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REVIEW

Radiofrequency ablation and thyroid nodules: updated systematic review

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Abstract

Purpose In the thyroid gland, radiofrequency ablation (RFA) is being applied to both benign nodules and cancers internationally, while interest is also growing in the West. Benign thyroid nodules (BTNs) may be candidates for intervention when symptoms develop. For differentiated thyroid cancers (DTC), surgery is currently the first-line treatment. However, for candidates with high surgical risk or those who refuse to undergo repeated surgery, newer techniques such as RFA are an option. Surgery is associated with complications including hypothyroidism, voice change, hypocalcemia, and a scar. RFA has been used in Asian and European institutions as an alternative to surgery, but is relatively new in North America. Although RFA is not associated with significant complications, few randomized control trials have assessed its efficacy. The studies to date suggest a low rate of severe complications and a small need for thyroid hormone replacement following RFA. Further large-scale studies focusing on a Western population are needed. The aim of this review is to evaluate the evidence with respect to the current studies and data about the safety and efficacy of radiofrequency ablation for the management of BTNs and DTC.

Methods We systematically searched the PubMed/MEDLINE, EMBASE, Clinical Queries, and Web of Science databases, for articles published up to April 30th, 2020.

Results Total of 75 studies that met the inclusion criteria were included in the review. Thirty-five studies focused on RFA use for solid nodules, 12 studies on predominantly cystic nodules, 10 for autonomously functioning thyroid nodules, and 18 studied were published on differentiated thyroid cancer.

Conclusions RFA seems to be an effective and safe alternative to surgery in high-risk surgical patients with thyroid cancers and for selected BTNs. Additional trials with longer follow-up in North American patients are needed to validate its full role in the armamentarium of thyroid ologists.

Keywords Papillary thyroid cancer · Radiofrequency ablation · RFA · Thyroid nodules · Levothyroxine

Introduction

The widespread use of thyroid ultrasound and other imaging modalities has led to increased detection of thyroid nodules, although only 10–20% are symptomatic [1–3]. Total or partial thyroidectomy has been the primary modality of treatment for differentiated thyroid cancer (DTC) as well as symptomatic benign thyroid nodules (BTNs). Surgery is associated with development of postsurgical hypothyroidism, as well as the occasional occurrence of intraoperative and postoperative complications. As an alternative to surgery, recent studies have shown that for papillary thyroid microcarcinomas (PTMC), observation might be enough in carefully selected cases [4, 5].

Post-surgical hypothyroidism is a common consequence of thyroid lobectomy and total thyroidectomy [6]. Levothyroxine (LT4) is prescribed after thyroidectomy as needed to achieve euthyroid status, but postoperative monitoring may be challenging [7].

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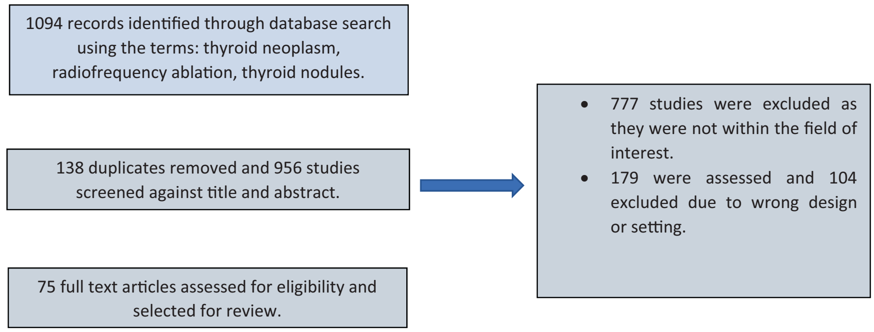

Fig. 1 Showing the search strategy

Because they are less invasive, thyroid conserving treatments such as radiofrequency ablation (RFA) have been gaining popularity [8–10]. RFA uses alternating current, with a frequency ranging between 200 and 1200 kHz, to generate local thermal energy [11]. This produces temperatures between 50 and 100 °C resulting in tissue necrosis [12]. The moving shot technique is commonly used with an internally cooled electrode of variable size [13]. The tip is generally inserted into the deepest part of the nodule and then gradually retracted to the superficial layers, protecting other structures including the vagus nerve, cervical ganglion, esophagus, trachea, and blood vessels by having a buffer of normal thyroid parenchyma or injected buffer (often lactated ringers or normal saline). RFA is terminated when the area of the nodule becomes hyperechoic on US or when impedances increases, or a combination of the two [14, 15].

RFA for thyroid pathology initially started as an alternate treatment for patients who were not surgical candidates due to medical co-morbidities [16]. It was introduced in the early 21st century for thyroid nodules, where it was associated with a volume reduction rate (VRR) of 80% in some cases [16, 17]. Published studies suggest that RFA has an excellent safety profile compared to existing management strategies [15]. In this study, we review studies that have investigated the efficacy and safety of RFA for BTNs and DTC. We further evaluate the effect of RFA on the need for post-procedural LT4 replacement.

Methods

A PubMed/MEDLINE search was done using the following terms (*Thyroid Nodule* OR *Thyroid Cancer* OR *Thyroid Carcinoma* OR *Thyroid Malignancy*) AND (*Radiofrequency Ablation* OR *Radiofrequency Ablation* OR *RF Ablation* OR *RFA*. For EMBASE, the search terms were ("*radiofrequency ablation*"/exp OR "*radiofrequency ablation*") AND the terms ("*thyroid*"/exp OR "*thyroid*")." ("*Radiofrequency Ablation and Thyroid*") were used in Clinical Queries. Web of Science search produced additional papers. We did not use any language restrictions. To expand our search, references of the retrieved articles were also screened for other data, and further literature search was done based on these results. We also searched previously published meta-analysis and systematic reviews on the topic and retrieved studies from those paper.

Study selection, eligibility criteria

Studies published until April 30th, 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) persons with DTC; (c) persons with benign functional or nonfunctional thyroid nodules (solid, mixed solid and cystic, or purely cystic. Exclusion criteria were (a) absence of outcomes (e.g., change in volume); (b) lack of explicit inclusion and exclusion criteria in the individual studies; (c) animal studies; (d) overlap in patient data.

Data extraction

Two authors (P.S. and H.M.) were involved in reviewing the literature from the screened title and abstract of the search results, and retrieved all potentially relevant reports. One author (J.R.) identified the suitable studies. Data synthesis and tabulation was done by the 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. The PRISMA search format is shown in Fig. 1. Any conflict was resolved by consensus. Duplicate studies, opinion pieces, commentaries, and reviews (except systematic reviews) were excluded.

Results

Literature search

The literature search from PubMed/MEDLINE, Web of Science, and EMBASE databases yielded 1094 studies (Embase 870, PubMed 200, and Web of Science 24).

Amongst 1094 studies, 138 duplicates removed, and 956 studies were screened against the title and abstract. After the initial search, 777 studies were excluded, and 179 studies were assessed for full-text eligibility. Amongst them, 104 studies were excluded due to poor study design. Finally, 75 studies were included in the systematic review. We used ("Radiofrequency Ablation and Thyroid") in Clinical Queries and got 17 meta-analysis which were screened for appropriate studies.

The flow chart of the search strategy is shown in Fig. 1.

Qualitative analysis

RFA as a modality for large benign solid nodules (BTNs)

Understandably, we identified more clinical studies that involved the use of RFA for BTNs. Of the identified studies, 13 were prospective, 4 were randomized controlled trials (RCTs), and 18 were retrospective. Follow-up ranged from 6 months to 5 years. The majority of the studies showed a VRR of >70%.

A large retrospective study by Che et al. comparing RFA ($n = 200$) and surgery ($n = 200$) for solid thyroid nodules demonstrated a VRR of 85% at 12 months follow-up for patients who underwent RFA. The overall cost of both procedures was similar. However, the surgery group had an increased rate of complication and postoperative LT4 use compared to the RFA group [18]. When factoring in the long-term need for levothyroxine post surgery, RFA had a much lower cost.

Baek et al. also validated the use of RFA in solid thyroid nodules, size greater than 2 cm in a prospective study, where 1 RFA session in the treatment group ($n = 15$) resulted in a mean VRR of 79.7% at 6 months, and significant improvement in symptoms and cosmetic score, compared to the control group ($n = 15$) that received no treatment [19].

With regards to the value of multiple ablative sessions, Huh et al. published a prospective study on solid nodules, size >2 cm, where a single RFA session in one group ($n = 15$) achieved VRR of 70.2% with an improved cosmetic score from 3.6 ± 0.6 to 2 ± 0.4 (cosmetic score defined as 1, if no palpable mass; 2, if no cosmetic problem but a palpable mass is present; 3, if the cosmetic difficulty on swallowing only). This was not significantly better than the second arm that received a second treatment of RFA [20].

Previous studies have reported malignancy rates ranging between 2 and 6% when cytopathology was done for BTN [21, 22]. 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 [15]. Therefore, multiple FNAB by experienced physicians should be sufficient before RFA. Studies have also shown that RFA does not disrupt the thyroid capsule and neither causes neoplastic changes in BTN [23, 24]. Consequently, in addition to not increasing the risk of malignancy, if need arises future surgery is also not affected by prior RFA. Thus, as noted by earlier guidelines and in our review, we agree that RFA for BTNs has been demonstrated to be a safe and effective for the relief of symptoms, and can be considered as a first-line therapy [15].

Table 1—shows the summary of the results of RFA in predominantly solid nodules [18–20, 25–56]

RFA and predominantly cystic nodules

With regards to predominantly cystic nodules, there were a total of 12 studies that were selected: three were prospective, seven were retrospective, and two were RCTs. Follow-up median range for most studies was from 6 to 12 months. The majority of patients received only one treatment session with RFA. A majority of studies reached a VRR of at least 70%.

A prospective multicenter study was done in Italy that included up to 30% cystic thyroid nodules. At 12 months follow-up, 70% VR was noted with marked improvement in compressive symptoms and no subsequent recurrence with no change in thyroid function [57]. These results were replicated by another single-center study done retrospectively by Cui et al. comprising of cystic thyroid nodules (73.7%). In this study, RFA resulted in VRR up to 83% in thyroid nodules greater than 2 cm. Nodules measuring less than 2 cm had a VRR 93.6%. Similar to the previous study, no change in thyroid function was reported. One patient had a reversible recurrent laryngeal nerve (RLN) paralysis which resolved spontaneously in 2 months [58].

Beak et al. performed a single-blinded RCT on predominantly cystic nodules and at follow-up of 6 months reported a VR of 87% with no significant complications [59]. Sung et al. also showed similar results in a retrospective study on cystic nodules treated with RFA, achieving VR of 92.2% and significant improvement in symptoms with no change in thyroid function [60].

The utilization of ethanol for nodules that are primarily cystic is well supported, but RFA can be considered for recurrent cystic tumors or nodules that become solid after treatment with ethanol [15].

Table 2 shows the characteristics of the different studies performed to see the effects of RFA on nodules that are predominantly cystic [57–68].

RFA and autonomously functioning thyroid nodules (AFTNs)

Occasionally, patients with toxic solitary nodules or toxic multinodular goiter are not suitable candidates for surgery

Table 1 Showing the results of the systematic review for predominantly solid nodules

Authors	Design	Mean age (years)	Gender (F/M)	Sample size (n)	Follow-up (months)	RF session	VRR %	Volume at baseline (ml)/SD	Sonographic characteristics	Complications
Garino et al. [25]	Prospective	Na	Na	69	24	1	71.1	21.7	Mainly solid	None
Huh et al. [20]	Prospective	Group 1 (51:36) (M:F)	Group 1 (13:2)	15	6	1	70.2	13.3 ± 12.9	Solid >50%	Transient pain
		Group 2 (38)	Group 2 (15:0)	15		2	78.3	13 mL ± 6.8		–
Baek et al. [19]	Randomized trial	40.8	12/3	15	6	1	79.7	7.5 ± 4.9	Solid	Transient pain
Cervelli et al. [26]	Prospective	56.4	31/15	46	18	1	80–84	Na	Solid	Transient voice change ($n = 2$) Nodule abscess ($n = 1$)
Che et al. [18]	Retrospective	43.8 ± 12.7 52.4 ± 13.9	RFA 165/35 Surgery 154/46	200 200	12	1	84.8	5.4 ± 7.1 5.9 ± 6.4	Solid/mixed	Transient hoarseness ($n = 1$) Nodule rupture ($n = 1$)
Deandrea et al. [27]	Prospective	Na	Na	30	12	1	68.4	15.4	Solid	None
Deandrea et al. [28]	Prospective	66.8 ± 12.1	19/12	31	6	1	50.7	27.7 ± 21.5	Solid	Neck edema ($n = 3$)
Deandrea et al. [29]	Randomized trial	Group 1 39.5 ± 9.6 Group 2 54.3 ± 13.3	18/2 16/4	40	6	1	77 66	13.9 ± 3.1 15.0 ± 3.2	Solid	None
Spiezia et al. [30]	Prospective	72.5 ± 0.5	55/39	94	24	1	79.4	24.5 ± 2.1	Solid	Transient pain ($n = 13$)
Martinez et al. [31]	Prospective	50.1 ± 13.6	20/4	24	36	1	76.8	36.3	Solid >50%	Laryngeal nerve palsy ($n = 1$) Hematoma ($n = 3$)
Ahn et al. [32]	Retrospective	44.5	18/1	19	12	1–2	74.3	14.3 ± 13.4	Solid >50%	None
Hamidi et al. [33]	Retrospective	60	11/3	14	8.6	1	44.6	24.2	Predominantly solid	Hypotension ($n = 1$) Transient dysphagia ($n = 3$)
Ben Hamou et al. [34]	Retrospective	49.7 ± 12.2	80/19	99	18	1	75	20.4 ± 18.6	Mixed, solid >70%	Transient laryngeal nerve palsy ($n = 2$) Transient dysphonia ($n = 6$) Nodule rupture ($n = 2$) Transient Hyperthyroidism ($n = 3$)
Sambo Salas et al. [35]	Prospective	52.1	23/5	28	6	1	43.6 ± 16.2	24.4 ± 20.88	Solid	None
Dobnig et al. [36]	Prospective	52 ± 12.9	215/62	277	12	1	82	14.1 ± 16.5	Solid >70%	Subclinical hypothyroidism ($n = 1$)

Table 1 (continued)

Authors	Design	Mean age (years)	Gender (F/M)	Sample size (n)	Follow-up (months)	RF session	VRR %	Volume at baseline (ml)/SD	Sonographic characteristics	Complications
Mauri et al. [37]	Retrospective	55.8 ± 14.1	48/11	59	12	1	74 ± 14	32.7 ± 19.5	Solid	None
Jung et al. [38]	Prospective	46.0 ± 12.7	302/43	345	5 Years	1–2	95.3	14.2 ± 13.2	Predominantly solid	Transient voice change ($n = 2$) Hyperthyroidism ($n = 1$)
Jeong et al. [39]	Retrospective	40.9	211/25	236	41	1–6	84.1	6.1 ± 9.5	Predominantly solid	Transient voice change ($n = 3$), hematoma ($n = 5$), and pain ($n = 13$)
Ugurlu et al. [40]	Prospective	–	8/25	33	6	1	74	7.3 ± 8.3	Solid	Transient pain ($n = 4$)
Yue et al. [41]	Retrospective	46.4 ± 13.3	75/27	102	10.7 ± 5.1	1	83.6 ± 5.2	5.7 (3.8–10.3)	Solid	None
Lim et al. [42]	Retrospective	37.9 ± 10.6	101/10	111	49.4 ± 13.6	2.2 ± 1.4	93.4 ± 11.7	9.8 ± 8.5	Solid	Transient voice change ($n = 1$), brachial plexus injury ($n = 1$)
Li et al. [43]	Prospective	42.7 ± 14.9	27/8	35	6	1	>50	8.8 ± 8.6	Solid/cystic	None
Cesareo et al. [44]	Randomized trial	56 ± 14	27/15	42	6	1	>62.8	24.5 ± 19.6	Solid	Permanent vocal cord paralysis ($n = 1$), transient voice change ($n = 2$)
Bernardi et al. [45]	Retrospective	58.3 ± 3.6	25/12	37	12	1	70	12.4 ± 2.5	Solid	Transient voice change ($n = 1$) and thyroiditis with no hypothyroidism ($n = 1$)
Valcavi et al. [46]	Retrospective	54.9 ± 14.3	35/5	40	24	1	80	30.0 ± 18.2	Solid	Nodule rupture ($n = 1$), pseudo cystic change ($n = 1$), transient pain ($n = 7$)
Sim et al. [47]	Retrospective	44.1 ± 13.2	49/5	54	39.4 ± 21.7	1	97	14.0 ± 12.7	Solid >70%	Voice change for 3 months ($n = 1$)
Kohlhase et al. [48]	Retrospective	50	14/4	18	3	1	56 6 ± 17.9	8 (0.48–62)	Solid >80%	None
Jawad et al. [49]	Retrospective	50.9	39/7	46	6	1	67 ± 17.6	25.9 ± 27.7	Solid >50%	None
Deandrea et al. [50]	Retrospective	66	182/33	215	5 Years	1	66.9	20.9 (15–33)	Solid >70%	Transient hematoma ($n = 6$), transient cutaneous edema ($n = 12$)
Turtulici et al. [51]	Retrospective	44 ± 16	34/11	45	6	1	72.6 ± 11.3	13.5 ± 6.7	Solid	None
Rabuffi et al. [52]	Retrospective	57.5 ± 15.5	55/22	77	12	1	70.9 ± 20.8	17.9 ± 15.6	Solid	Transient pain ($n = 6$) and transient hematoma ($n = 2$)
	Prospective	57.2 ± 17.1	22/10	32	12	–	73.56	18.36 ± 10.82	Solid	Transient hematoma ($n = 4$)

Table 1 (continued)

Authors	Design	Mean age (years)	Gender (F/M)	Sample size (n)	Follow-up (months)	RF session	VRR %	Volume at baseline (ml)/ SD	Sonographic characteristics	Complications
Feroci et al. [53]										
Cesareo et al. [54]	Randomized	53.3	–	30	6	1	64.30	26	–	Transient pain ($n = 6$), thyrotoxicosis $n = 1$) and hematoma ($n = 3$)
Korkusuz et al. [55]	Retrospective	47	22/18	40	3	1	50	6.5	Solid	Transient mild hematoma ($n = 26$)
Zhao et al. [56]	Retrospective	45 ± 15	49/20	69	6	1–2	81.9 ± 6.8	6.35 ± 5.66	Solid/cystic	None

or radioiodine therapy. Some studies have shown the benefit of RFA in this small subset of patients, especially in patients with nodules less than 12 ml in volume [69]. We have included six retrospective and four prospective studies in Table 3. Sung et al. included 44 patients and showed a marked decrease in mean nodule volume from 11.8 ± 26.9 to 4.5 ± 9.8 mL and significant improvement in thyroid function, at last follow-up [70]. When thyroid scintigraphy was done to identify treatment efficacy, 35 nodules did not have uptake (i.e., cold nodules), and the rest ($n = 9$) showed decreased uptake [70]. Cervelli et al. compared RFA with Radioiodine (RAI) for AFTNs, and although there was no significant difference in VR% between the two groups, euthyroidism was achieved in 90.9% ($n = 20/22$) of patients treated with RFA compared to 72% (18/25) in RAI group. None of the patients developed hypothyroidism in the RFA group (compared to the RAI group, where five persons developed post-ablative hypothyroidism) [71].

A prospective study by Faggiano et al. enrolled 40 patients with nodules larger than 4 cm. Of these, there were 22 nontoxic and 18 autonomous functioning nodules that were randomized into two groups. One group ($n = 20$) received a single session of RFA, and the other group ($n = 20$) received no treatment. At a median follow-up of 9 months, nodular volume in the RFA group decreased substantially (84.9 ± 1.5). It was associated with complete recovery from hyperthyroidism in toxic nodules as demonstrated by euthyroidism after methimazole withdrawal in 40% ($n = 4/10$) of the patients and improved in 40% ($n = 4/10$) who required reduced dose of methimazole. Unfortunately, mean reduced dose was not reported in the study and the maximum follow-up period was just 12 months. Thus, it cannot be inferred from the data if some of these patients resumed methimazole therapy in future or required another session of RFA. In comparison, the control group showed worsening compressive symptoms and persistent hyperthyroidism in all patients (100%) [72].

Almost all studies showed that dosage of antithyroid drugs either stopped or reduced over time after the procedure. However, there was great variability ranging between 23 and 94.1% amongst studies with respect to normalization of thyroid function post RFA. This might be due to difference in nodule size, type of technique used and heterogenicity in the follow-up periods. In conclusion our review suggests that RFA for AFTN may lead to a VRR, but this may not be clinically meaningful for all patients. As such, RFA can be considered for patients who are highly motivated, but may not be appropriate as a first-line therapy for patients seeking definitive intervention. Nevertheless, prospective studies with longer follow-up comparing size and nature (pre toxic vs. toxic) of the nodules are warranted to establish RFA's efficacy for AFTN.

Table 2 Showing the results of the systematic review for predominantly cystic nodules

Authors	Design	Mean age (years)	Gender (F/M)	Sample size (n)	Follow-up (months)	RF session	VRR%	Mean volume at baseline (ml)/SD	Sonographic characteristics	Complications (n)
Kim et al. [61]	Prospective	39.1	28/2	30	13.5	1	88.2	6.3	Cystic/solid	Vocal cord palsy ($n = 1$), transient hematoma ($n = 1$), burn ($n = 1$) and pain ($n = 1$).
Aysan et al. [62]	Prospective	44.5	78/22	100	6	1	97.5	32.4	Cystic/solid	Temporary hoarseness ($n = 1$), skin edema ($n = 1$)
Baek et al. [59]	Randomized trial	47.6	19/3	22	6	1	87.5 ± 11.5	8.6 ± 9.4	Cystic	None
Cui et al. [58]	Retrospective	52 ± 14	109/28	137	6	1	83.1	8.25 ± 11.7	Cystic 73%	Temporary hoarseness ($n = 1$)
Dobnig et al. [63]	Retrospective	53 ± 13	119/39	158	12	1	76% (Solid) 90% (Cystic)	21.3 ± 23.6	Cystic/solid	Reversible hoarseness
Hong et al. [64]	Retrospective	49.9	16/2	18	12	1	76	24.4 mL ± 32.2	Cystic/solid	None
Deandrea et al. [57]	Prospective	55	253/84	337	12	1	70	20.7	Cystic <30% predominantly solid	Voice change ($n = 1$), nodule infection ($n = 1$)
Vuong et al. [65]	Retrospective	43.9 ± 12.8	153/31	184	12	1	81	Na	Solid/cystic	Transient voice change ($n = 2$)
Sung et al. [60]	Retrospective	42.5	18/3	21	12	1–3	92.1 ± 14.6	10.1 ± 7.01	Cystic >90%	None
Sung et al. [66]	Randomized	44.9 ± 10.6	22/3	25	6	1	93.5% ± 5.3	9.3 ± 11.7	Cystic	None
Lee et al. [67]	Retrospective	38	22/5	27	6	>1	92.0 ± 6.2	4.2 ± 5.3	Cystic	Hematoma ($n = 1$)
Yoon et al. [68]	Retrospective	47.1	8/3	11	11.4 ± 6.7	1–3	81	17.1 ± 16.9	Cystic	None

Table 3 Showing the results of the systematic review for autonomously functioning thyroid nodules

Authors	Design	Mean age (years)	Gender (F/M)	Sample size (n)	Follow-up (months)	Thyroid function normalization at last follow-up (%)	Patients (n) requiring thyroid drugs post RFA	VRR%	Volume at baseline (ml)/SD	Complications (n)
Sung et al. [70]	Retrospective	43 ± 14.7	40/2	44	19.9 ± 12.6	81	2	81.7 ± 13.6	18.5 ± 30.1	None
Cervelli et al. [71]	Retrospective	52 ± 13.9	20/2	22	12	91	None	76.4	14.3 ± 17.2	None
Faggiano et al. [72]	Prospective	58.3 ± 4.3	16/4	20	12	40	4	85	13.3 ± 1.8	None
Baek et al. [73]	Retrospective	47 ± 17	8/1	9	6 to 17	67	1	70.7 ± 23	14.98 ± 25.53	None
Cesareo et al. [69]	Prospective	–	18/11	29	24	65	None	77 ± 11	11.5 ± 7.5	None
Deandrea et al. [28]	Retrospective	66.8 ± 12.1	NA	23	6	23	18	52.1 ± 16.1	22.5 ± 16.3	Neck edema ($n = 3$) requiring steroid.
Spiezia et al. [30]	Retrospective	72.5 ± 0.5	NA	28	24	78.6	6	77 ± 6	32.7 ± 5.4	None
Bernardi et al. [74]	Prospective	69.1 ± 2.0	20/10	30	12	50	15	74.7 ± 3.0	17.1 ± 2.3	Transient voice change ($n = 1$)
Dobnig et al. [1]	Prospective	52 ± 12.9	NA	32	12	84.3	NA	86.1 ± 13.4	86.1 ± 13.4	–
Cappelli et al. [75]	Retrospective	45.3 ± 18.0	11/6	17	12	94.1	1	72.9 ± 18.1	7.2 ± 5.0	Transient hematoma ($n = 1$)

Table 3 shows the characteristics of the different studies performed to see the effects of RFA on autonomous thyroid nodules [1, 28, 30, 69–75].

RFA for indeterminate nodules and differentiated thyroid cancer

RFA has been performed in four categories of the patient population with DTC: (1) Persons with previous surgery in whom repeat surgery was higher risk because of risks associated with reoperation, (2) Persons who are poor surgical candidates, (3) Persons who refused surgery due to unexplained reasons, and (4) Persons who have microcarcinomas and were candidates for observation. The studies were mostly retrospective, and only three of them had a prospective study design. Duration of follow-up after RFA ranged from 6 months to 5 years. RFA sessions ranged from 1 to 3 sessions. Post-RFA, VRR percentage was higher than 50% in all the studies, with some studies reporting almost 99% reduction in VRR. Most studies showed a greater than 80% decrease in size of the tumor after RFA.

In a single-center study by Baek et al. ten patients with metastatic DTC who all had previous surgery (mean operations = 1.5) were treated with RFA. At last follow-up of >24 months, treatment resulted in >90% VRR with complete disappearance of nearly 50% of the tumors. In this study theraupetic success was defined as VRR >50% and all patients achieved it except one who developed dysphonia during RFA and refused further treatment. This same patient developed new metastatic lesions and was referred for repeat surgery [76]. Though, RFA appears to be really effective with no tumor recurrence at 2 years, however we should not ignore the fact that the mean time between last operation and RFA was 41 months. Thus, the interpretation will be biased if the theraupetic success of these treatment options is compared due to difference in follow-up period. Furthermore, this study did not evaluate the quality of life, long-term recurrence of tumor and survival of the patients. Similarly a larger study was done by Lee et al. [77] evaluating 35 recurrent thyroid cancers (34 papillary, one medullary), the majority of which had been previously treated with surgery. Post RFA (performed for loco-regional recurrence), 9 lesions had a subsequent second recurrence, requiring another session of RFA ($n = 8$) and/or surgery ($n = 1$). Upon follow-up, 7 of these tumors had complete resolution, and one lesion required third session of RFA. At last follow-up, 94% of tumors had disappeared entirely and rest had a VRR of 96.4%. This study had a longer follow-up period of 30 months and post RFA biopsy was performed with additional RFA sessions to control the tumor [77]. Therefore in conclusion RFA may be suggested for DTC with closer follow-up by performing routine biopsies and US. However as these tumors may have slow growth, RCTs with longer follow-up are needed before RFA is established as the standard of treatment.

Patients with indeterminate nodules who refuse surgery or are poor surgical candidates may opt for RFA. These patients are limited by the inability to obtain a definitive diagnosis without surgery. Now, follicular carcinoma contributes 10–20% of all thyroid malignant nodules [78]. However, due to the low specificity of fine needle aspiration cytology, diagnostic lobectomy is necessary for definitive analysis [79]. Ha et al. published a study of ten patients with follicular tumors <2 cm in size who were treated with RFA as an outpatient and followed for up to 5 years. Mean VRR was 99%, with 80% of tumors showing complete disappearance and none of the patients undergoing surgery. Mild neck pain was the only complication that was reported, and no recurrence of the nodule was noted at follow-up [80]. Thus, RFA might be an option for small follicular neoplasms in persons with co-morbidities. The risk of under-diagnosing a malignancy must be carefully discussed with the patients. However, we do not routinely support this option in patients who are acceptable surgical candidates.

RFA has also been studied on aggressive thyroid cancers. In a retrospective study where tumors were divided into three groups: (1) anaplastic carcinoma (ATC), (2) papillary microcarcinoma, and (3) papillary microcarcinoma, it was shown that post RFA, there was clinical improvement in group 2 (VRR >99%) and 3 (VRR >45%). However, two patients with anaplastic thyroid carcinoma (ATC) (group 1) showed no improvement in symptoms and had a poor prognosis. This was not surprising considering the generally poor prognosis associated with ATC. No significant complications were reported in any of the groups [81].

Treatment options for low risk cancer specially PTMC have been debatable. The 2015 ATA guidelines suggested active surveillance as the first-line for low risk PTMC [82]. Although, it can help reduce overtreatment and unnecessary surgery. However, a small percentage of PTMC (defined as <1 cm) may progress to be aggressive cancer and surveillance alone may pose a psychological burden on patients until a definitive treatment is offered. Studies have shown efficacy of RFA when used for PTMC. In a recent study, 94 patients post-RFA were followed for 64.2 months and 93 (98.9%) showed no recurrence. In addition, better quality of life, no use of LT4, and reduced cost compared to surgery was reported [83]. Similar results were shown in a case series where mean VRR was 98.5%, and no metastasis at follow-up was reported [84]. Contrary to this, some physicians have debated that thermal ablation may lead to incomplete treatment. Kim et al. has published a case report where subsequent surgery was required for PTC due to incomplete RFA treatment [85]. Recently Ma et al. reported three cases of PTMC treated with RFA and later underwent surgery showing histological evidence of residual tumor [86]. Therefore, although RFA seems a more attractive alternative than surveillance for PTMC, care should be taken that it is performed by experts with close pre-evaluation of the lesion. In addition newer adjuncts such as US elastography (USE) and contrast-enhanced US (CEUS) should be used to identify the completeness of the procedure. Thus, though it is early to say but RFA seems to have the potential to replace surgery in carefully selected patients.

Table 4 shows the characteristics of the studies involving RFA for DTC/Follicular Neoplasms [76, 77, 80, 81, 83, 84, 87–98].

RFA-related complications

Though RFA is a relatively safe technique, some complications have been observed. Voice change is an untoward event that occurs due to thermal injury and/or compression from hemorrhage of the RLN or the vagus nerve [99]. 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 [100].

Kim et al. did a retrospective study that evaluated the complication rate in 746 patients who underwent RFA for BTNs. The study reported a transient voice change ($n = 5$, 0.7%), nodule rupture requiring drainage ($n = 1$, 0.1%), Horner syndrome ($n = 10.1$%), transient hypothyroidism ($n = 10.1$%), hematoma ($n = 6$, 0.8%), pain ($n = 5$, 0.7%), and development of hypertension treated with medication ($n = 4$, 0.4%) as some of the complications [101]. A similar pattern was seen in our review, where transient pain was the most common complication [19, 20, 30, 40, 61]. One study reported permanent laryngeal nerve injury in a solitary patient ($n = 1$, total $n = 24$) [31]. In a slightly larger study, Cesareo et al. also reported permanent vocal cord paralysis ($n = 1$, total $n = 42$) [44]. However, transient laryngeal nerve injury was reported by Hamou et al. in a small number of patients ($n = 2$, 2%) [34]. Three studies reported nodule rupture in one patient, each that required no further treatment [18, 34, 46]. Another study noted a nodular abscess that required aspiration and management with antibiotics ($n = 1$, 1/46) [26]. Hematoma may be more common, but rarely requires intervention and generally resolves with time [30, 39, 61, 67]. Mild, temporary neck swelling and edema requiring steroid were reported by Deandrea et al. in another small number of patients ($n = 3$, 3/31) [28]. Subclinical hypothyroidism ($n = 1$) in a single patient was found in one study [36]. Thus, the overall

Table 4 Showing the results of the systematic review for differentiated thyroid cancer (DTC)

Authors	Design	Sample (n)	Gender (F/M)	Age (years)	Follow-up (months)	VRR%	Tumor[a] disappeared (n)/%	Tumor type	Complications (n)
Lim et al. [87]	Retrospective	39	25/14	52.8 ± 16.7	26.4 ± 13.7	95.1 ± 12.3	50/82.0%	Papillary thyroid carcinoma	Transient voice change (3)
Mazzeo et al. [88]	Prospective	13	4/9	70 ± 7	11.2 ± 4.6	80.8 ± 23.1	1/7%	Papillary, medullary and follicular	Permanent laryngeal nerve paralysis ($n = 2$)
Ha et al. [80]	Retrospective	10	46/8	45.1 ± 10.5	66.4 ± 5.1	99.5 ± 1.0	8/80%	Follicular neoplasm	Transient neck pain ($n = 6$)
Jeong et al. [81]	Retrospective	8	6/2	64 ± 17	19.3	48–99	–	Papillary macro-carcinoma papillary microcarcinoma anaplastic carcinoma	None
Kim et al. [84]	Retrospective	6	4/2	72	48.5 ± 12.3	98.5 ± 3.3	4/66.7%	Small papillary carcinomas	Transient hypertension ($n = 1$), neck pain ($n = 1$)
Kim et al. [89]	Retrospective	27	20/7	42.3 ± 10.2	36	>70	31/86%	Papillary thyroid carcinoma	Hoarseness ($n = 2$)
Lee et al. [77]	Retrospective	32	25/7	53	30	96.4	31/94%	Papillary and medullary	Permanent voice change ($n = 1$)
Baek et al. [76]	Retrospective	10	6/4	44.8	23 ± 5.5	93% ± 15%	6/50%	Papillary thyroid carcinoma	Permanent dysphonia ($n = 1$)
Choi et al. [90]	Retrospective	70	53/17	45.4 ± 13.6	76.8 ± 23.7	>90%	100%	Papillary thyroid carcinoma	Transient voice change ($n = 6$)
Chung et al. [91]	Retrospective	29	17/12	51.8 ± 14.7	80 ± 17.3	99.5% ± 2.9%	42/91.3%	Papillary thyroid carcinoma	None
Ding et al. [92]	Retrospective	37	29/8	45.1	>12	99.3 ± 3.49%	37/97%	Papillary thyroid carcinoma	None
Monchik et al. [93]	Retrospective	16	12/4	53	40.7	–	14/87%	Papillary thyroid carcinoma medullary carcinoma	Permanent vocal cord paralysis ($n = 1$), skin burn ($n = 1$)
Park et al. [94]	Prospective	11	8/3	69	6	50.9	–	Papillary and follicular carcinoma	Skin burn ($n = 1$), neck swelling ($n = 11$)
Dupuy et al. [95]	Prospective	8	5/3	59	10.3	–	25%	Papillary and follicular carcinoma	Skin burn ($n = 1$), permanent laryngeal nerve paralysis ($n = 1$)
Zhang et al. [83]	Retrospective	94	70/24	45.4 ± 10.8	64.2 ± 2.8	–	99% (No recurrence)	Papillary	None
Xu et al. [96]	Retrospective	35	20/15	43.49 ± 13.01	2 Weeks	–	–	Papillary	Transient voice change ($n = 2$)
Lim et al. [97]	Retrospective	133	114/19	46 ± 12	39 ± 25	100%	139/91.4%	Papillary	Transient voice change ($n = 1$) and hematoma ($n = 2$)
Guenette et al. [98]	Retrospective	14	7/7	–	61.3	–	21/100%	Papillary and and follicular	Vocal cord paralysis ($n = 1$)

[a]Number and percentage of tumor nodules that disappeared on last follow-up post RFA

complication rate of RFA for BTNs is variable and highly dependent on the skill of the performing physician and institutional safeguards. However the complications were relatively minor in most series.

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 [87, 90]. Permanent laryngeal nerve injury and voice change were reported in studies with a frequency of occurrence between 6 and 15% [77, 88, 93, 95, 102]. Kim et al. reported transient hypertension in patients [84]. Mild skin burn was also reported in some studies [93–95]. 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.

Levothyroxine (LT4) and BTNs

Postsurgical hypothyroidism after partial thyroidectomy varies from 5 to 49% [103]. RFA has shown a minimal effect on thyroid function. In a retrospective study, Ha et al. reported no change in thyroid function post-RFA at 43.7 months of follow-up [104]. Similar results have been reported in other studies [29]. Interestingly, transient hyperthyroidism has been reported in some patients [39, 61]. About 10% of the population appear to require LT4 supplementation eventually [105].

Overall, RFA is significantly favorable when compared to surgical options in avoiding post-procedural hypothyroidism and long-term levothyroxine replacement. Anecdotally in our practice, this is a significant concern to many patients who are motivated to undergo RFA.

Discussion

RFA may be used as an effective alternative to surgery for carefully selected thyroid cancer patients and a vast majority of BTNs, while AFTNs may be more likely to have an incomplete response. The immediate future will likely see further interest in RFA for the management of all thyroid nodules. The desire to avoid the morbidity of surgery and the possible postsurgical hypothyroidism will likely continue to drive this trend. While complications are all also possible with RFA, the incidence appears favorable when compared to surgical series. It is likely that RFA will become another tool in the kit of thyroid interventionalists, along with surgery and radioactive iodine. There is limited evidence suggesting that operating on the thyroid that has been treated with RFA is more challenging. Surgery performed after prior RFA has been successful with good outcomes [24].

Our study has some limitations. First, a metanalysis could not be performed in this systematic analysis due to the heterogeneity of the included studies, lack of a control population in many studies, and differences in inclusion and exclusion criteria. Second, many of the studies were retrospective with a small follow-up duration (around 1 year). Third, the exact breakdown of nodules based on US features was not mentioned in majority of the studies. Fourth, most of the studies were based in Asia or Europe. Differences in the BMI, neck circumference etc between the North American population and the rest of the world, might play a role in changing the patient selection, outcomes, and complications of RFA [106]. Potentially, differences in body habitus could make the initial treatment more challenging, subsequent follow-up less precise, and might be associated with more aggressive tumors for which surgery should have been the preferred modality of treatment [107, 108]. Finally, publication bias was not assessed in our review paper.

Despite these concerns, RFA is promising due to the significant prevalence of BTNs and the low prevalence of aggressive DTCs. In the future, surgery could be substituted with RFA for NIFTP (noninvasive follicular thyroid neoplasm with papillary like nuclear features) or other indeterminate nodules if technical and other limitations improve or in carefully selected patients who are highly motivated and able to undergo close surveillance. Similarly, PTMC is generally indolent and could be considered as treatment targets if the technique of RFA evolves. While the current state of thyroidology does not allow complete prognostication of indeterminate, indolent (PTMC, NIFT-P) or malignant tumors based on cytology or molecular markers, RFA could be a safe alternative than overtreating many in the population who are diagnosed with small tumors that are likely never to cause harm. RFA could help to reduce the treatment burden for these patients. For the time being, the lack of definite histopathological information in the absence of diagnostic surgery is a significant impediment. RFA with associated low morbidity can also play a beneficial role in patients with nonaggressive tumors who do not fit the criteria for surgery due to the presence of comorbidities. RFA may also be an excellent option for many BTNs due to the low risk of complications, a VRR of >80%, and high patient satisfaction.

In conclusion, RFA seems to be an effective and safe alternative to surgery in high-risk surgical patients with thyroid cancers and for selected BTNs. Additional trials with longer follow-up in North American patients are needed to validate its full role in the armamentarium of thyroidologists.

Compliance with ethical standards

Conflict of interest Author H.M. declares that he has no conflict of interest. Author P.S. declares that he has no conflict of interest. J.O.R. is a consultant for Baxter Health Corp.

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