Safety and Efficacy of Radiofrequency Ablation for the Treatment of Thyroid Nodules: Review of the Literature

Kuo-Bin Tseng

Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital/I-Shou University, Kaohsiung, Taiwan

Abstract

Thyroid nodules (TNs) are frequently encountered in clinical practice; they are usually asymptomatic and, in recent years, appear to have increased in incidence as a result of the widely use of ultrasound (US). Most TNs are benign; therefore, they are usually monitored clinically until they start to cause compressive symptoms, become cosmetically problematic, develop autonomous functions, or prove to be cytological malignancies. Historically, surgery has been considered as the only therapeutic option for TNs. However, being an invasive procedure, surgery - even partial thyroidectomy - for such nodules is associated with minor risks of several complications, including iatrogenic hypothyroidism, scarring, hematoma, dysphonia, and injury to other structures. Thus, minimally invasive US-guided techniques, such as radiofrequency ablation (RFA), have recently been introduced to manage TNs, and shown promising results for volume reduction of TNs and the elimination of hyperthyroidism due to toxic nodules. In addition, RFA has a safety profile comparable in contrast with that of surgery. In summary, given its relatively low complication rate, minimally invasive nature, and thyroid function preservation—as well as the wide availability of radiofrequency generators—RFA is increasingly being applied for the management of thyroid diseases, particularly benign TNs. I present a review of the current literature regarding the feasibility, efficacy, and safety of RFA for the treatment of TNs.

Key Words: **Thyroid nodules; radiofrequency ablation; surgery; differentiated thyroid cancers; recurrent thyroid cancers; complications**

Introduction

The incidence of thyroid nodules (TNs) has increased in recent years due to widely use of ultrasound (US) and other highly sensitive imaging modalities in clinical practice. TNs are commonly benign, with 2% to 6% of TNs detectable through palpation, 19% to 35% detectable with US, and 8% to 65% showing in autopsy data[1], respectively. Nevertheless, some patients with TNs require treatment for compressive symptoms, cosmetic problems, or potentially malignant transformation. Once TNs have been confirmed as benign, conventional thyroid-stimulating hormone (TSH)-suppressive therapy and surgery are preferred for the treatment of enlarging benign TNs (BTNs); however, both these treatment methods have drawbacks. Previously, thy-

Reprint requests and correspondence：Kuo-Bin Tseng
Address：Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital/I-Shou University, Kaohsiung, Taiwan, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan, R.O.C.

roid-hormone-suppressive medication was used in the hope that such suppression would decrease the rate of growth of the BTN. However, the efficacy of this therapy remains controversial given that the therapy might lead to iatrogenic hyperthyroidism, decreased bone density, atrial fibrillation, or downstream cardiovascular effects[2,3]. Surgery is considered the optimal therapy for treating symptomatic BTNs, yet surgery may lead to iatrogenic hypoparathyroidism, scar formation, recurrent laryngeal nerve (RLN) damage, and injuries to adjacent structures[4]. Therefore, image-guided ablation techniques—such as radiofrequency ablation (RFA), microwave ablation (MWA), ethanol ablation (EA), and laser ablation (LA)—are gaining popularity for the treatment of BTNs.

RFA is one of the most commonly used thermal ablation (TA) techniques given that it is as a minimally invasive treatment with promising results, has fewer complications than surgery, is able to preserve thyroid function, and involves relatively few hospitalization days when used to treat BTNs[5,6]. TA is used in various countries to shrink BTNs through the induction of tissue heating and necrosis, which in turn alleviate associated symptoms and cosmetic problems[7]. RFA has been demonstrated having high efficacy in ablation of BTNs, and decreasing the nodular volume up to 84.8%[5,8]. Furthermore, the applications of RFA are gradually increasing in number; this therapy is now used to treat parathyroid hyperplasia, papillary thyroid microcarcinoma (PTMC), and metastatic lymphadenopathy. Although surgery is the priority therapeutic choice in taking into account of efficacy and prognosis for patients with these conditions, RFA should be considered a more favorable treatment in certain situations. In one meta-analysis of RFA for locally recurrent thyroid cancers (RTCs), the structurally curative success rate of RFA was 100% together with a 71.6% reduction in serum thyroglobulin[9]. The current review presents the latest research regarding the fundamentals of RFA and the devices, indications, and techniques especially designed to optimize thyroid RFA as well as the clinical outcomes and complications.

Fundamentals of RFA

In RFA, oscillating electrical currents are administered through an electrode at a frequency of 200 to 1200 kHz, causing ions in adjacent cells to continuously change direction to match the current-generated frictional heat (50 to 100 °C) and leading to coagulative necrosis within a few millimeters of the electrode[10,11]. In addition, conduction heat from the ablated area can damage adjacent tissue as the heat spreads outward[12]. This process of thermal injury secondary to friction and conduction heat is the fundamental principle behind RFA[10,13].

Radiofrequency signals are delivered to the target tissue through an internally cooled monopolar electrode, usually of 16 to 18 gauge. The procedure starts with a US-guided fixed ablation technique or a moving shot technique in which the electrode is inserted into the TN[14]. In the fixed ablation technique, a multi-tined expandable electrode is employed along the long axis of the nodule to create an ablation zone that forms a sphere[14]. By contrast, in the moving shot technique, an internally cooled electrode of variable size is commonly used; the needle is inserted through the isthmus, starting from the middle and heading in the lateral direction to reach the nodule, which is divided into small hypothetical zones. Each zone is ablated by the tip of the needle, which is moved from the deepest position upward to the most superficial part of the nodule[14]. This technique minimizes the risk of damage to adjacent structures.

The moving shot technique has many advantages over the fixed ablation technique[14]. First, it enables the ablation of ellipsoidal and exophytic areas, which are the most likely forms of TNs in routine practice. Second, the moving shot technique provides a spheroidal ablation area and therefore is safer and has fewer side effects than the fixed ablation technique owing to the relatively low level of exposure it gives and its continuous US monitoring of the RLN, which runs through the danger triangle of the trachea, esophagus, and thyroid gland[14]. Moreover, in the moving shot technique, the needle is stable and does not involuntarily move, even if the patient swallows or talks[14]. Using an ex vivo bovine liver tissue model, a study compared these 2 RFA techniques and found that the moving shot technique produced a considerably larger ablation volume than did the fixed ablation technique[15]. Hence, the moving shot technique is now the more popular procedure for RFA in the treatment of TNs.

Throughout use of the moving shot technique, the operator must interact with the patient by talking to them and instructing them to swallow, which enables continual assessment of the status of the RLN. If nerve damage is suspected, the ablation should be halted immediately, and the operator should consider injecting cold dextrose directly into the space where the damaged nerve or nerves are located until the symptoms have improved[16]. Finally, RFA should be terminated firstly if the entire area of the nodule presents hyperechoic signals and microbubbles on a US, and secondly the generator impedance increases as the tissue stiffens, indicating coagulative necrosis; or followed by the combination of these 2 phenomena occurs[11,17,18].

In addition to continued shrinkage of the nodule over months or years, immediate shrinkage will be appreciated. A 50% to 90% reduction in BTN volume is typically expected; such a reduction is variable depending on the tumor factor and operator[19-21]. A second ablation session is needed if a portion of the nodule is viable and has vascularity, as well as if there are ongoing symptomatic or cosmetic concerns; this is because the underablated portion with vascularity has considerable potential of regrowing[17]. After these procedures, US follow-up and clinical evaluations are suggested at 1, 3, 6, and 12 months and then annually up to 5 years postablation[22]. Moreover, the largest TN diameter, TN volume, TN vascularity, clinical complications, and cosmetic symptoms should be evaluated using data collected before and after the ablation[22]. Therapeutic success is defined as a 50% volume reduction at 12 months[22]. A delayed complication is defined as any complication detected at 1 month or more after RFA[23].

Pre-procedural Evaluation

US is the mainstay for detecting and characterizing a TN and providing guidance in a biopsy[24]. The size, shape, internal vascularity, echogenicity, margin, calcification, solid component proportion, and adjacent structures of each nodule should be carefully scrutinized in each TN case[24]. The nodule volume can be calculated using the following equation: $V = \pi abc / 6$, where V is the volume, a is the maximum diameter, and b and c are the 2 other perpendicular diameters; all 3 diameters should be measured through US[25].

Studies have suggested that, at least, twice US-guided fine needle aspiration (FNA) or core needle biopsies are required to confirm the TN to be benign before RFA is conducted[17,20,26-28]. Although slight differences exist in studies' recommendations for the treatment of autonomously functioning TNs (AFTNs), one FNA biopsy result is generally sufficient if the US indicates the presence of a benign feature, such as encapsulation, a cyst, a spongiform structure, no extrathyroidal extension, or lymphadenopathy[17,20,26-28]. A ^{99m}Tc pertechnetate or a ^{123}I thyroid scan can be used to differentiate AFTNs from autoimmune hyperthyroidism, especially in patients presenting with suppressed serum TSH[25]. The FNA biopsy should be repeated if suspicious or worrisome features show up on the US, even if the biopsy results were benign. Moreover, computerized tomography (CT) of the neck should be conducted if the TN volume has not been completely delineated through US or doubt exists regarding the extent of the nodule with respect to determining whether and the degree to which retrosternal extension is present and whether the patient is a suitable candidate for RFA[27].

Precautious remind, prior to the ablation of RTCs, tumor recurrence should be confirmed through positive US-guided FNA cytology and measurements of washout thyroglobulin concentration[25]. US is the mainstay for assessing recurrent tumors and their critical surrounding structures, i.e., the size and characteristics of a recurrent tumor should be evaluated through US[25]. In addition, CT of the neck may be selectively used to evaluate a recurrent tumor prior to RFA[25].

RFA and Nonfunctioning BTNs

Several studies have demonstrated the efficacy and safety of RFA for volume reduction and symptomatic and cosmetic improvement with respect to nonfunctioning BTNs[29-33]. A short-term prospective cohort study indicated that the mean volume reduction ratio (VRR) of RFA for the treatment of nonfunctioning BTNs (60 solid nodules, 16 predominantly cystic nodules, and 2 cysts) was 41.5% and 64.7% at the 1-month and 3-month follow-ups, respectively[29]. Moreover, the corresponding therapeutic success rate in the same study was 30.8% at the 1-month and 84.6% at the 3-month follow-ups, respectively[29]. Similarly, a recent study evaluated 45 BTNs in 40 patients treated with RFA and obtained a mean (standard deviation) VRR of 58.4 at 1 month, 73.3 at 3 months, and 82.5 at 6 months ($p < 0.001$)[30]. Next, a meta-analysis of 5 studies that analyzed 956 nonfunctioning BTNs treated with RFA revealed a VRRs of 56.0% and 80.8% at the 3-month and 6-month follow-ups, respectively[31]. Another review suggested that the short-term (6 to 12 months) efficacy of RFA for treating nonfunctioning solid BTNs ranged between 50% and 80% (mean VRR)[32]. Regarding predominantly cystic TNs, a recent review of 12 studies indicated VRRs ranging between 70% and 97.5%, with most patients having undergone only one RFA treatment session at a median follow-up time point between 6 and 12 months[33].

Long-term data have been obtained related to the assessment of RFA efficacy and safety in treating nonfunctioning BTNs[19,21,34]. A meta-analysis of 12 studies on RFA assessed 1,186 nonfunctioning solid BTNs and obtained VRRs of 68%, 75%, and 87% at the 6-month, 12-month, 24-month, and 36-month follow-ups, respectively[21]. Moreover, the outcomes were more favorable for nodular volume smaller than 30 mL in comparison with larger ones (p < 0.05). In addition, significant improvement in compressive symptoms (p < 0.00001) and cosmetic problems (p < 0.00001) were discovered after RFA[21]. Moreover, a retrospective study of 216 patients with BTNs assessed the long-lasting effects of a single round of RFA treatment and obtained a median VRR of 77% after 5 years[19], and only 12% of these patients were retreated, together with regrowth in only 20% of patients[19]. Similarly, a long-term study of 215 patients with BTNs reported that the most favorable outcomes were observed in nodules smaller than 10 mL after a single round of RFA treatment (79% early reduction and 81% reduction after 5 years)[34]. To sum up, an overall VRR of 67% was observed with progressive shrinkage after 5 years of follow-up (p < 0.0001) alongside the maintenance of improved compressive symptoms and cosmesis[34].

Some US features may be predictive of RFA outcomes; for example, a nodule with a spongiform structure and intense intra-nodular and peri-nodular vascularity is more likely to shrink after treatment, whereas the presence of spot coarse calcifications does not constitute a concern in terms of RFA[35]. Furthermore, outcomes were less satisfactory for larger nodules likely because of the smaller amounts of energy delivered during the treatment of such nodules[35]. Several studies have demonstrated that smaller nodules (volume < 10 mL) have the most favorable VRR after RFA treatment and also that this success is maintained for up to 2 years[27]. Additionally, in one study, larger nodules (volume > 30 mL) had a significantly lower VRR than did smaller ones at 6-month and 12-month follow-ups (57% vs. 69% and 63% vs. 75%, respectively)[36]. Generally, larger TNs tend to require more than one RFA session[27]. In one study, the regrowth rate after an average follow-up period of 39 months was 24.1%[37]. Regrowth is directly associated with the effectiveness of the first ablation session and the initial size of the nodule[36].

Notably, heterogeneity in the volumes of treated nodules across studies, the technical expertise of the operators involved, the amount of energy delivered to nodules, and the learning curve associated with achieving ablation of the nodule margin all appear to have positive treatment effects given the results reported in the literature[38]. These results may serve as key guidelines for the counselling of patients regarding the long-term effectiveness of RFA and for the provision of information regarding the potential need for retreatment to maintain desired outcomes.

RFA and Functioning BTNs

An AFTN is a predominantly benign neoplasm that presents as a solitary hyperfunctioning nodule that can cause functional abnormalities at a prevalence of 0.9% to 9% of all TNs[39,40]. Although some initial studies focused on nonfunctioning BTNs and RTCs[41,42], over time, the use of RFA to treat AFTNs has proven suitable, especially for patients with subclinical or excessive hyperthyroidism[43]. Several prospective studies have demonstrated the effectiveness of RFA in achieving a long-term cure in patients with AFTNs (Table 1)[44-56]. Cesareo et al. had reported 29 patients with AFTNs that small nodules (<12 mL) were associated with higher incidence of normalization of thyroid function comparing to were medium-sized nodules (>12 mL; 86% vs. 45%; $p < 0.001$)[44]. In addition, de Boer et al. analyzed 21 patients with AFTNs and reported that 21 of them (71%) exhibited TSH normalization after RFA at the 12-month follow-up[45]. Sung et al. analyzed 44 patients (23 with AFTNs and 21 with pretoxic nodules) and reported a significant decrease in mean nodule volume from 11.8 to 4.5 mL ($p < 0.001$) after RFA , and 81% of those patients had restored euthyroidism at the final follow-up[46]. In the same study, after ablation, 35 patients had cold or normal thyroid scintigraphy results, whereas the remaining 9 patients had hot nodules[46]. These findings were consistent with those of Baek et al., who analyzed 9 patients (4 with AFTNs and 5 with nontoxic nodules) [47]. Similar results have been obtained in various studies investigating AFTNs in which a single session of RFA was applied, namely significant volume reductions and the restoration of euthyroidism at the 12-month follow-up, with the VRR ranging between 73% and 86% and degree of TSH normalization ranging between 50% and 94%[48-51].

A meta-analysis of 14 studies (involving patients with 411 AFTNs) revealed that RFA had high efficacy, namely a VRR of 69.4% and degree of TSH normalization of 71.2% after a mean follow-up duration of 12.8 months[52]. Moreover, none of those patients had developed hypothyroidism or major complications at the aforementioned follow-up[52]. Similarly, a significantly high VRR (79%) was discovered at the 12-month follow-up in a meta-analysis of 8 studies (involving 205 AFTNs)[53]. However, RFA was found to have only moderate efficacy in achieving TSH normalization (57%) after follow-up durations ranging from 6 to 24 months[53].

Notably, the correlation between the baseline nodule volume and treatment response in patients with AFTNs is still controversial. In a systematic review, subgroup analyses performed in accordance with nodule volume (15, 18, and 20 mL) found no

Table 1. Summary of Studies for Evaluating the Efficacy of RFA for Treating AFTNs

Authors	**Study design**	**Mean age (years)**	**Simple size (n)**	**RF sessions**	**Follow-up (months)**	**Nodular type**	**Mean initial volume (mL)**	Mean final volume (mL)	Thyroid function normalization at last follow-up (%)	Mean VRR at last follow-up (%)
Cesareo et al.[44]	Prospective	51	15 (A)* 14 (B)#	1	24	Solid	5.2±1.8 (A) 18.3±4.7 (B)	0.8±0.4 (A) 5.7±3.3 (B)	86.0% (A) 45.0% (B)	84±6% (A) 68±11% (B)
De Boer et al.[45]	Retrospective	52.8	21	1±1	12	Solid	9.8	Not reported	71.0%	Not reported
Sung et al.[46]	Retrospective	43	44	1.8 ± 0.9	19.9 ± 12.6	Soild/mixed	18.5 ± 30.1	4.5 ± 9.8	81.8%	81.7 ± 13.6%
Baek et al.[47]	Retrospective	47	9	2.2 ± 1.0	11 ± 4.2	Solid/mixed/cystic	14.98 ± 25.53	7.57 ± 19.99	55.6%	70.7 ± 22.9%
Bernardi et al.[48]	Prospective	69	30	1	12	Solid/mixed	17.12 ± 2.39	4.29 ± 0.61	50.0%	74.8 ± 3.0%
Dobnig et al.[49]	Prospective	52	32	1	12	Solid/mixed	8.7 ± 7.0	2.1 ± 4.7	84.0%	86.1 ± 13.4%
Cappelli et al.[50]	Retrospective	45	17	1	12	Solid/mixed	7.2 ± 5	1.8 ± 1.2	94.1%	72.9 ± 18.1%
Cervelli et al.[51]	Retrospective	52	22	1	12	Solid/mixed	14.3 ± 17.2	2.55 ± 2.06	90.0%	76.4 ± 17.0%
Deandrea et al.[54]	Retrospective	67	23	1	6	Soild/mixed	22.5 ± 16.3	11.6 ± 10.7	24.0%	52.1 ± 16.1%
Faggiano et al[55]	Prospective	58	20	1	12	Solid	13.3 ± 1.8	1.8 ± 0.3	40.0%	86.0%
Spiezia et al.[56]	prospective	72.5	28	1±2	24	Solid	24.5 ± 2.1	4.97 ± 1.9	78.6%	77.0 ± 6.0%

Abbreviations: AFTN, autonomously functioning thyroid nodule; RF, radiofrequency; RFA, radiofrequency ablation; VRR, volume reduction ratio.
*(A) represents small AFTNs (<12 mL).
#(B) represents medium-sized AFTNs (>12 mL).

Table 2. Summary of Studies for Evaluating the Efficacy of RFA for Treating DTCs

Authors	Study design	Mean age (years)	Simple size (n)	Tumor nodule (n)	Tumor type	Follow-up (months)	VRR (%)	Tumor disappeared at last follow-up (%)	Complications (n)
Lim et al.[65]	Retrospective	46±12	133	152	PTMC†	39±25	100%	91.4%	Hematoma (n = 2) Transient voice change (n = 1)
Zhang et al.[66]	Prospective	44.7±10.7	92	98	PTMC†	7.8±2.9	95.8%	10.2%	Transient voice change (n = 4) Neck pain (n = 1)
Ding et al.[67]	Retrospective	45.1 ± 12.9	37	38	PTMC†	N/A (1-18)	99.3±3.5%	97.4%	None
Yan et al.[68]	Retrospective	43.4 ± 9.3	47	100	PTMC†	47.8 ± 11.5	99.9%	92.0%	None

Authors	Study design	Mean age (years)	Simple size (n)	Tumor nodule (n)	Tumor type	Follow-up (months)	VRR (%)	Tumor disappeared at last follow-up (%)	Complications (n)
Kim et al.[69]	Retrospective	72	6	6	PTMC†	48.5±12.3	98.5±3.3%	66.7%	Transient hypertension (n = 1) Neck pain (n = 1)
Cho et al.[70]	Retrospective	46±12	74	84	PTMC†	72±18	100%	100%	Hematoma (n = 2) First-degree burn (n = 1) Transient voice change (n = 1)
Yan et al.[71]	Retrospective	43.6±9.8	414	414	PTMC†	42.1±11.9	98.8±6.4	88.4%	Neck pain (n = 16)
Zhang et al.[72]	Retrospective	45.4±10.8	94	94	PTMC†	64.2±2.8	N/A	99% (no recurrence)	None
Choi et al.[73]	Meta-analysis	range, 42.2 to 59.5	195	201	PTMC†	N/A	99.3%	65.2%	Transient voice change (n = 5) Neck pain (n = 3)
Tong et al.[74]	Meta-analysis	range, 42.2 to 72.0	697	767	PTMC†	>7.8	−1.35 SMD	76.2%	Voice hoarseness (n = 5) Hypothyroidism (n = 3) Neck pain (n = 1) Bleeding (n = 2) Skin burn (n = 1)
Xiao et al.[84]	Retrospective	41.0 ± 9.2	66	66	PTC#	20.5 ± 7.4	99.1 ± 2.4%	57.6%	Neck pain (n = 2)
Cao et al.[85]	Retrospective	46±11	847	847 (T1a: 673) (T1b: 174)	PTC#	22 ± 13	68.2%	69% (T1a group) 64% (T1b group)	Transient voice change (n = 24) Hematoma (n = 3) Cough (n = 1) High fever (n = 1)
Cao et al.[86]	Retrospective	46 ± 14	172	172 MWA (n = 123) RFA (n = 49)	PTC#	24.9 ± 14.1	89.8%	61.6%	Transient voice change (n = 8) High fever (n = 1)
He et al.[88]	Retrospective	43.94	94	94	PTC#	36	< 45 yrs: 100% ≥ 45 yrs: 99.7%	< 45 yrs: 95.7% (no tumor progression) ≥ 45 yrs: 95.7% (no tumor progression)	Transient voice change (n = 1) High fever (n = 1)
Ha et al.[95]	Retrospective	45.1±10.5	10	10	Follicular neoplasm	66.4±5.1	99.5±1.0%	80%	Transient neck pain (n = 6)
Lin et al.[96]	Retrospective	39.6±10.5	22	22	Follicular neoplasm	10.1	73.3% ± 17.7%	N/A	Transient vocal cord palsy (n = 1)

Authors	Study design	Mean age (years)	Simple size (n)	Tumor nodule (n)	Tumor type	Follow-up (months)	VRR (%)	Tumor disappeared at last follow-up (%)	Complications (n)
Monchik et al.[42]	Retrospective	53	16	16	Locoregional recurrent PTC or FTC	40.7	N/A	87%	Permanent vocal cord paralysis (n = 1) Skin burn (n = 1)
Lim et al.[75]	Retrospective	52.8±16.7	39	61	Locoregional recurrent PTC	26.4±13.7	95.1±12.3 %	82%	Transient vocal cord palsy (n = 3)
Chung et al.[76]	Retrospective	51.8±14.7	29	46	Locoregional recurrent PTC	80±17.3	99.5%±2.9%	91.3%	None
Baek et al.[77]	Retrospective	44.8	10	12	Locoregional recurrent PTC	23 ± 5.5	93%±15%	50%	Permanent dysphonia (n = 1)
Guenette et al.[78]	Retrospective	N/A	14	21	Locoregional recurrent PTC or FTC	61.3	N/A	100%	Permanent vocal cord paralysis (n = 1)
Chegeni et al.[79]	Retrospective	N/A	48	103 (81 DTC, 22MTC)	Locoregional recurrent DTC or MTC	range,12-37	91%	62.1%	Transient vocal cord palsy in DTC group (n = 3) None in MTC group
Lee et al.[80]	Retrospective	53	32	35 (34 PTC, 1 MTC)	Locoregional recurrent PTC or MTC	30	96.4%	94%	Permanent voice change (n = 1)
Kim et al.[81]	Retrospective	42.3±10.2	27	36	Locally recurrent PTC (<2 cm)	36	>70%	86%	Hoarseness (n = 2)
Choi et al.[82]	Retrospective	45.4±13.6	70	70	Locally recurrent PTC	76.8 ± 23.7	>90%	100%	Transient voice change (n = 6)

Abbreviations: DTC, differentiated thyroid cancer; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; MWA, microwave ablation; NA, not applicable; RFA, radio-frequency ablation; PTMC, papillary thyroid microcarcinoma; PTC, papillary thyroid carcinoma; VRR, volume reduction ratio; SMD, standardized mean difference.
† PTMCs are restricted to cases of T1aN0M0 only.
# PTCs are restricted to cases of T1bN0M0 only.

significant differences in the degree of TSH normalization ($p = 0.54$) or VRR ($p = 0.94$) [52]. Similarly, Bernardi et al. recruited 30 patients with AFTNs and reported no significant correlation of pretreatment nodule size with post-RFA response[48]. Hence, the VRR of a nodule after RFA appears to play a more crucial role in the achievement of TSH normalization than does the baseline nodule volume. However, a meta-analysis suggested that the baseline nodule volume was associated with the rate of TSH normalization[53]. However, further prospective studies with longer follow-up periods investigating the relationships between nodule volume and treatment outcomes for patients with AFTNs are warranted to establish the efficacy of RFA.

RFA versus Surgery for BTNs

Surgery has long served as the standard therapeutic method for treating symptomatic BTNs; however, surgery may not always be the optimal choice, particularly for patients for whom iatrogenic hypoparathyroidism, scar formation, RLN damage, or injury to another structure is a concern. Jin et al. reported that TA is preferable to receive surgery because of BTN management with respect to patient satisfaction, postoperative quality of life, and hospitalization duration[57]. However, although the complication rates of TA and surgery are similar, compared with surgery, TA requires more time to achieve the desired volume reduction[57]. A meta-analysis comparing TA with surgery for the treatment of BTNs demonstrated that TA resulted in lower incidences of hoarseness (odds ratio [OR] = 0.33), hypothyroidism (risk difference = 0.31), and postoperative pain (OR = 0.35) and shorter hospitalization durations (standard mean difference = 4.01) [58]. Moreover, TA had more favorable postoperative cosmetic outcomes compared with surgery ($p < 0.05$); however, the difference in symptom improvement between these 2 options was not significant ($p = 0.58$)[58]. In summary, RFA seems to be a promising therapeutic choice for BTNs.

Che et al. reported that RFA and surgery were both effective treatments for BTNs; however, the incidence of complications due to RFA was significantly lower than that due to surgery (1.0% vs. 6.0%; $p = 0.002$)[5]. Moreover, in comparison with surgery, RFA resulted in lower incidences of hypothyroidism (0.0% vs. 71.5%), RLN injury (0.5% vs. 3.0%), and hypoparathyroidism (0.0% vs. 3.0%)[5]. However, no significant differences in recurrence were discovered between RFA and surgery (0.05% vs. 2.5%; $p = 0.100$)[5]. Similarly, Bernardi et al. demonstrated RFA to be almost as effective as surgery for eliminating nodule-related symptoms in patients with nonfunctioning BTNs (84.6% vs. 100.0%)[59]. Besides, RFA led to fewer complications than did surgery, and none of the patients who underwent RFA developed hypothyroidism, whereas 37.5% of those who underwent surgery subsequently required levothyroxine treatment. Regarding cosmetic outcomes , no differences between RFA and surgery were reported; both were highly effective treatment methods for the vast majority of patients[59]. Notably, RFA revealed significantly less effective than surgery for the treatment of AFTNs (33.3% vs. 100.0% success, respectively)[59].

In summary, RFA constitutes an effective alternative for surgery, and leads to fewer complications than does surgery in the treatment of BTNs. However, RFA has some limitations when treating BTNs. First, RFA is not suitable for all types of TNs, particularly large BTNs, substernal nodules, and deeply located nodules[27]. Moreover, RFA requires months or even years to sufficiently reduce the volume of a large BTN. Furthermore, some BTNs may exhibit incomplete responses and local regrowth during follow-up and therefore may require repeat ablation or surgery, whereas some nodules shrink slowly but fail to completely recede[27]. Finally, pathology cannot be carried out with RFA intervention, and no long-term follow-up data regarding the use of RFA for treating BTNs harboring malignant cells are available. Therefore, the controversy of post-procedural monitoring remains undetermined[59].

Combined Approach for Large Toxic Goiters and Large BTNs

Surgery is considered the standard treatment method for large toxic goiters and large BTNs, and the current guidelines do not endorse RFA as a primary treatment method for either of these conditions. However, an approach that combines these 2 therapies may be an innovative solution and rapidly reduce the nodular volume as well as restore euthyroidism[17,20,26]. Mader et al. reported that a combination of RFA and radioiodine therapy (RIT) led to significantly greater thyroid volume reduction ($p < 0.05$) compared with RIT alone[60]. Moreover, all the patients analyzed in that study exhibited clinical euthyroidism after the treatment, and no major complications or instances of discomfort were observed[60]. Similarly, a series of studies investigating large toxic nodular goiters and BTNs treated with local US-guided ablative approaches combined with RIT obtained generally favorable outcomes from LA[61], EA[62], and MWA[63]. Moreover, significant volume reductions alongside the restoration of euthyroidism and no severe complications were observed in all those studies[60-63].

In summary, combination of different modalities appears to reduce the required dose of RIT and provide effective and rapid relief of compression-based symptoms. However, although ablative approaches appear to be appropriate complementary therapies alongside RIT, the most effective ablative procedure has yet to be determined

RFA and Malignant TNs

Surgery has long been considered the standard treatment for well-differentiated thyroid cancers (DTCs); however, surgery carries the risk of postoperative hypothyroidism, anesthetic-related complications, or injury to the RLN or parathyroid glands[64]. Recent studies have demonstrated the efficacy and safety of RFA for treating primary PTMCs[65-74] and RTCs[42,75-82]. However, few studies have investigated the application of RFA for the treatment of papillary thyroid carcinomas (PTCs)[69,83-88]. For medullary thyroid carcinomas (MTCs), surgery remains the main treatment modality; however, few case studies have shown RFA to be effective and safe for treating non-metastatic MTCs in patients who are not suitable for surgery[89] or those with local recurrence after surgical resection of their MTC[90]. Hence, future studies should explore the efficacy and safety of RFA for treating patients with MTCs.

The treatment of inoperable anaplastic thyroid carcinomas with RFA is still controversial, and preliminary research is yet to reveal any benefits for treating such aggressive cancers with RFA[91].

The characteristics of variously relevant studies are summarized in Table 2.

RFA for Primary PTMCs (T1aN0M0)

Several studies have obtained promising results for treating primary PTMCs with RFA[65-74]. First, Lim et al. investigated the efficacy of RFA in 133 patients with 152 PTMCs and reported a 91.4% rate of complete disappearance of ablated tumors after a mean follow-up duration of 39 months[65]. Furthermore, no regrowth of residual ablated tumors was reported among the patients whose tumors did not completely disappear during the follow-up period, and no local recurrence, lymph node (LN) metastasis, or distant metastasis was detected[65]. Next, Zhang et al. reported a mean VRR of 95.8% at 12 months and a complete disappearance rate of 10.2 % in 92 patients with 98 PTMCs after a follow-up of 7.8 months[66]. Moreover, no local recurrence or LN metastasis was detected[66]; however, it should be noted that that study had a short follow-up duration. Ding et al. demonstrated that RFA could effectively treat low-risk PTMCs, with 97.4% of the analyzed nodules completely disappearing without recurrence or hypothyroidism after a mean follow-up duration of 6 months[67]. On the basis of a mean follow-up duration of 48 months, Yan et al. suggested that RFA can effectively ablate bilateral PTMCs; the mean VRR was 99.9% and the complete disappearance rate was 92.0% without delayed or immediate complications[68]. Although 2.1% of the patients in that study developed LN metastases and 4.3% had PTMCs after follow-up, additional RFA was performed for all recurrent lesions, and all of them subsequently completely disappeared[68]. Similar results were reported by Kim et al. in a case series analyzing patients with small low-risk PTCs; at the 48-month follow-up after RFA, the mean VRR was 98.5%, and the complete disappearance rate was 66.7%[69].

Cho et al. investigated the long-term efficacy of RFA in 74 patients with 84 PTMCs[70]. The complete disappearance rate at the 24-month and 60-month follow-ups was 98.8% and 100.0%, respectively. In addition, 4 newly developed cancers found in 3 patients were also ablated with RFA and subsequently completely disappeared[70]. During the 60-month follow-up period, no local tumor progression, LN metastasis, or distant metastasis was discovered, and no patients underwent delayed surgery[70]. Similarly, Yan et al. evaluated the long-term outcomes of RFA in 414 patients with unifocal low-risk PTMCs[71]. After 42 months of follow-up following RFA, the complete disappearance rate was 88.4%, and the mean VRR was 98.8%, indicating long-term efficacy in this large cohort[71]. Furthermore, the mean duration until recurrent PTMC development was 27.6 months, the overall incidence rate of such development was only 3.6%, and in almost all cases of such development, the patient underwent additional RFA, after which the nodules completely disappeared during the follow-up[71]. Next, Zhang et al. investigated the oncological efficacy of RFA compared with that of thyroidectomy over a 60-month follow-up period for patients with low-risk PTMCs[72]. That study found that RFA was not inferior to surgery with respect to oncological outcomes and was associated with higher quality of life, fewer complications, and lower overall cost. Furthermore, a new lesion (in the remaining ipsilateral lobe) developed in only 1 of the 94 patients in the RFA group (1.1%), and no LN metastasis was identified in the RFA group[72]. However, although these studies obtained promising results for the treatment of PTMCs, further research involving longer follow-up periods is required to further validate the efficacy and safety of RFA.

In a meta-analysis, Choi et al. assessed the efficacy and safety of all known TA techniques for treating PTMC; the results revealed that RFA resulted in the highest mean VRR (99.3%), followed by MWA (95.3%) and then LA (88.6%; $p < 0.001$)[73]. Although the inter-assay heterogeneity was significant, the pooled proportions of complete disappearance and recurrence of PTMC were only 57.6% and 0.4%, respectively ($p < 0.001$)[73]. Moreover, the pooled proportions of overall and major complications for all TA techniques were 3.2% and 0.7%, respectively, indicating the high safety of all such techniques for treating PTMCs[73]. Similarly, in a meta-analysis of 12 studies, Tong et al. investigated the efficacy and safety of RFA, MWA, and LA for treating 1187 patients with 1284 PTMCs[74]. All 3 modalities resulted in significantly high VRRs ($p < 0.05$). Although MWA had higher efficacy than the other 2 approaches, the difference was not significant.

Moreover, the pooled proportions of complete disappearance after RFA, MWA, and LA were 76.2%, 62.9%, and 57.3%, respectively, and a lower proportion of recurrence was detected after RFA (0.01%) than after MWA (0.85%) or LA (1.9%)[74]. Finally, no distant metastasis was detected during the follow-up in any of the analyzed studies, and the pooled proportions of complications encountered were low and similar among the 3 therapeutic methods ($p > 0.05$)[74].

In summary, several certain studies have indicated the feasibility of RFA for the treatment of primary PTMCs, but some evidences still have shown probably incomplete treatment[92-94]. Kim et al. reported a patient with primary PTC who underwent RFA before reliably cytological evidence with subsequently surgery because of incomplete RFA treatment[92]. In addition, Sun et al. reported that in 6 of 11 cases of PTMCs (54.5%) treated with RFA, and surgery was later done with pathological evidence of residual LN metastasis[93]. Similarly, Ma et al. reported 3 cases of PTMCs that required surgery because of residual tumors revealed through histopathology after incomplete RFA treatment[94]. Although prior RFA study shows promising results for the treatment of PTMCs, caution should be exercised during the evaluation of lesions before RFA. New adjuncts, such as US elastography and contrast-enhanced US, should be employed to determine the completeness of such procedure[33].

RFA for PTCs (T1bN0M0)

Although RFA has yielded promising results for the treatment of primary PTMCs[65-74], few studies have investigated the application of RFA to the management of T1bN0M0 PTCs. One possible explanation for this research gap is the higher risk of recurrence of DTCs (T1b) compared with that of DTCs (T1a)[83]. In one meta-analysis of 21 studies that analyzed 219,291 patients with welldifferentiated thyroid cancers, Zhang et al. reported that DTCs (T1b) had higher risks of recurrence (OR = 1.520; $p < 0.05$) and mortality (OR = 1.504; $p < 0.05$) than did DTCs (T1a)[83]. Moreover, when DTCs were divided into subcategories titled S1 (≤1 cm) and S2 (1 to 2 cm), S2 was associated with more aggressive histological features than was S1, including extrathyroidal extension (OR = 2.575 ; $p < 0.05$), bilateral extension (OR = 2.278; $p < 0.05$), vascular invasion (OR = 4.494 ; $p < 0.05$), and LN metastasis (OR = 1.12; $p < 0.05$)[83]. Hence, further prospective research is required to determine whether tumor size is related to the prognosis of DTCs.

Although a few studies have investigated the efficacy of RFA for treating PTCs, a growing body of research suggests that RFA obtains promising results for treating patients with PTCs (T1bN0M0), particularly those who are ineligible for or unwilling to undergo surgery[69,84-88]. First, Kim et al. reported that RFA is an effective and safe modality for controlling not only PTMCs but also low-risk small PTCs. However, it should be noted that the patients in that study were elderly and ineligible for surgery and that only 2 of the analyzed PTCs were larger than 1 cm in diameter[69]. Xiao et al. analyzed 66 patients with PTCs (T1bN0M0) who were ineligible for surgery and reported that RFA had high efficacy (97.0%), with the mean VRR being 99.1% and with 57.6% of the analyzed tumors having disappeared at the 30-month follow-up[84]. Next, Cao et al. studied 847 patients with solitary PTCs (T1N0M0); of these patients, 202 underwent RFA, 645 underwent MWA, and complete disappearance of their tumors was achieved in 68% (69.0% in the T1a group and 64% in the T1b group; $p < 0.001$) [85]. Moreover, the disease progression rate was 1.1 % after ablation (0.9% in the T1a group and 1.7% in the T1b group; $p = 0.54$)[85]. In another study, Cao et al. analyzed 172 patients with PTCs (T1bN0M0) treated with RFA and reported that over a mean follow-up duration of 24.9 months, the complete tumor disappearance rate was 61.6%[86]. Moreover, the LN metastasis rate was only 0.6%, and the new tumor rate was only 1.2%[86].

Additionally, Xiao et al. compared RFA with surgery in 182 patients with solitary PTCs (T1bN0M0) and reported no significant differences between the 2 treatment groups in terms of local tumor progression or complications[87]. Moreover, 4.4% of the patients in the RFA group developed local tumor progression (3 persistent PTCs and 1 LN metastasis), whereas in the surgery group, 2.2% of the patients had LN metastases. No recurrent or persistent PTCs had been discovered over a mean follow-up duration of 25 months[87]. Regarding complications, 4.4% of the patients in the surgery group developed permanent hypoparathyroidism, whereas no major or minor complications were observed in the RFA group[87]. These findings were consistent with those of He et al., who investigated a series of 204 patients[88]. Hence, RFA appears to be a feasible, effective, and safe treatment option for patients with solitary PTCs (T1bN0M0) who are ineligible for or unwilling to undergo surgery. However, further research is required to compare RFA with unilateral or total thyroidectomy in patients with PTCs (T1bN0M0).

RFA for Follicular Thyroid Neoplasm

The use of RFA for treating follicular thyroid neoplasm is currently controversial because surgical resection remains the standard treatment for eliminating the presence of vascular or capsular and thus reaching a definitive diagnosis. According to the guidelines of the American Thyroid Association[3] and the Korean Society of Thyroid Radiology[7], RFA is not recommended for the management of follicular neoplasm because no evidence suggests that it has clinical benefits in this respect. Moreover, the amount of clinical research on RFA for the treatment of follicular neoplasm remains limited. One study that analyzed 10 patients with follicular neoplasm less than 2 cm in size reported that RFA may be an effective and safe treatment method for such cases and that no recurrence was observed within a mean follow-up duration of 5 years[95]. Furthermore, the mean VRR was 99%, and 80% of the ablated tumors in that study disappeared completely during the follow-up[95]. A recent 10-month study employing positron emission tomography and involving 28 patients with follicular neoplasm reported that RFA was an effective and safe alternative treatment option for selected patients with a low standard uptake score[96]. Another study suggested that RFA may be suitable for patients at low risk of follicular neoplasm so long as they are observed closely given the minor risk of cancer involved[97]. Nevertheless, the number of studies that have determined that a minimally invasive treatment such as RFA is effective for treating follicular neoplasm remains insufficient. Similar to most preliminary conclusion, further research is required to clarify whether RFA should be recommended as a treatment for patients with follicular neoplasm.

RFA for RTCs

DTC tends to have a positive prognosis; however, the incidence of local or distant recurrence has been 30% in some series and depends on patient- and tumor-related risk factors[98]. Such recurrence necessitates further surgical treatment followed by cycles of RAI therapy, external beam radiotherapy, or chemotherapy[3]. Repeat surgery to treat RTC can be challenged because edematous change, scarring, and the friability of tissue alongside distortion of landmarks made such repetition more hazardous[99]. Hence, instead of revision surgery, which may result in severe complications, minimally intensive techniques, such as RFA, can be used instead as substitutive approaches for patients who are ineligible for surgery or unwilling to undergo another surgery.

Lim et al. reported that RFA was effective for the treatment of loco-regionally recurrent PTCs, obtaining a mean VRR of 95.1% and the complete disappearance of 82.0% of the treated tumors after a mean follow-up duration of 26 months[75]. Next, Chung et al. reported long-term efficacy of RFA for treating locally recurrent PTCs; the mean VRR was 99.5%, and 91.3% of the treated tumors completely disappeared[76]. Baek et al. showed RFA to be effective for treating metastatic well-differentiated thyroid cancers (WDTCs), obtaining a mean

VRR of 90% and the complete disappearance of approximately 50% of the treated tumors[77]. This finding was similar to those results from Monchik et al.[42] and Guenette et al.[78] Similarly, Chegeni et al. assessed the efficacy of RFA for treating 103 RTCs (81 DTCs and 22 MTCs) and reported a mean VRR of 91% and the complete disappearance of 62.0% of the treated tumors after a mean follow-up duration of 23 months[79]. Moreover, the recurrence-free survival rate was 77.1% (11 recurrences: 7 DTCs and 4 MTCs), and the overall mean recurrence-free survival duration was 34.6 months[79]. Likewise, Lee et al. evaluated the efficacy of loco-regional recurrence of WDTCs (34 PTCs and 1 MTC) and reported a mean VRR of 96.4% and the complete disappearance of 94.0% of the treated tumors after a mean follow-up duration of 30 months[80].

Studies have shown that the effectiveness levels of RFA and repeat surgery for the treatment of local RTCs are comparable. Kim et al. evaluated RFA for locally recurrent PTCs smaller than 2 cm by comparing these PTCs with others treated with repeat surgery. The recurrence-free survival rates at the 1-year and 3-year follow-ups were comparable (p = 0.681) for RFA (96.0% and 92.6%, respectively) and repeated surgery (92.2% and 92.2%, respectively)[81]. Moreover, after treatment, the hoarseness rates were similar for RFA (7.3%) and repeated surgery (9.0%; p = 0.812); however, hypocalcemia developed only in the repeated surgery group (11.6%) and not in the RFA group (0%; p = 0.083)[81]. Similar results were reported by Choi et al., who compared the efficacy and resulting complications of RFA and repeated surgery in patients with locally recurrent PTCs. After propensity score matching, the recurrence-free survival rates were similar between the 2 groups (p = 0.2), and the 3- and 6-year recurrence-free survival rates were 100% and 97.9% for the RFA group, and 100% and 97.8% for the surgery group, respectively [82]. Moreover, the major complications in the RFA group was smaller than that in the surgery group (3.1% vs. 31.2%; $p < 0.001$)[82]. Hence, compared with reoperation, which may lead to severe complications, RFA could be a favorable alternative that yields similar or favorable results for the treatment of local RTCs. However, larger-scale prospective studies with longer follow-up periods are needed to validate RFA's superiority over surgery in patients with local RTCs.

Adverse Events Due to RFA

Compared with surgery, RFA leads to fewer complications and shorter hospitalization durations and is less likely to result in post-procedural thyroid hormone replacement in certain patients[5]. It should be noted that some complications associated with RFA have been observed, but these complications can usually be managed conservatively through the administration of analgesics or antibiotics.

In a retrospective study, Kim et al. evaluated the complication rate in 875 patients who underwent RFA for BTNs (746 patients; 83.5%) or RTCs (129 patients; 14.7%). The overall complication rate was 3.5%, and the major complication rate was 1.6%. Furthermore, the major complication rate in the RTC group was significantly higher than that in the BTN group (5.4% vs. 0.9%; p = 0.002); these major complications included transient voice change (0.8% vs. 0.7%), permanent voice change (2.3% vs. 0.0%), nodule rupture requiring drainage (0.0% vs. 0.1%), Horner syndrome (0.0% vs. 0.1%), and spinal accessory nerve injury (2.3 % vs. 0.0%). However, no significant differences were discovered in the minor complication rate[100]. Similarly, in a systemic review, Chung et al. reported that RFA had an overall complication rate of 2.48% and a major complication rate of 1.35%, with voice change being the most common major complication (1.44%, 35/2421 patients), followed by post-RFA nodule rupture (0.17%, 4/2421 patients)[101]. Additionally, a subgroup analysis in the same study revealed that the overall and major complication rates for RTCs were significantly higher than the corresponding rates for BTNs ($P = 0.0011$ and 0.0038, respectively)[101].

Finally, a systemic review of 32 studies covering 3,409 patients revealed that the most common minor complications included transient pain, the incidence of which was 2.6% to 17.5 %[102]. Other reported minor complications—including transient thyroiditis, skin burns, hematoma, and vomiting—were also observed, albeit less frequently[100-102].

In summary, although RFA can cause various complications, severe adverse complications appear to be rare. To minimize the incidence of complications and sequelae, the broad spectrum of possible complications must be understood, and all available preventative techniques must be considered.

Conclusion

The current scientific literature indicates that RFA could be considered as an effective, safe, and efficient treatment in terms of goiter volume reduction, compressive symptom resolution, and cosmetic improvement for both BTNs and AFTNs. However, nodular regrowth remains poor understood and continuous monitoring of ablated nodules after the initial procedure is warranted. Moreover, a final pathology test will not be available, while no long-term follow-up data regarding the use of RFA to treat BTNs harboring malignant cells are available; therefore, how best to monitor such cases remains undetermined. Additionally, RFA has been demonstrated to be effective and safe for long-term local tumor control for primary PTMCs in patients who do not wish to undergo active surveillance or who are ineligible for surgery. Currently, not much evidence sheds light on the effectiveness of RFA for PTCs. In certain clinical situations, RFA may be used in patients with small PTCs or those with recurrent DTCs in the neck who are unwilling to undergo repeat surgery or have high surgical risk. Of course, further research is required to better define the role of RFA for the treatment of malignant TNs.

References

1. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab 2008;22(6):901-11.
2. Bandeira-Echtler E, Bergerhoff K, Richter B. Levothyroxine or minimally invasive therapies for benign thyroid nodules. Cochrane Database Syst Rev 2014;2014(6):CD004098.
3. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26(1): 1-133.
4. Rosato L, Avenia N, Bernante P, et al. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg 2004;28(3):271-6.
5. Che Y, Jin S, Shi C, et al. Treatment of benign thyroid nodules: comparison of surgery with radiofrequency ablation. Am J Neuroradiol 2015;36(7):1321-5.
6. Cesareo R, Palermo A, Pasqualini V, et al. Efficacy and safety of a single radiofrequency ablation of solid benign non-functioning thyroid nodules. Arch Endocrinol Metab 2017;61(2):173-9.
7. Baek JH, Lee JH, Valcavi R, Pacella CM, Rhim H, Na DG. Thermal ablation for benign thyroid nodules: radiofrequency and laser. Korean J Radiol 2011;12(5): 525-40.
8. Deandrea M, Sung JY, Limone, P, et al. Efficacy and safety of radiofrequency ablation versus observation for nonfunctioning benign thyroid nodules: a randomized controlled international collaborative trial. Thyroid 2015;25(8):890-6.
9. Suh CH, Baek JH, Choi YJ, Lee JH. Efficacy and safety of radiofrequency and ethanol ablation for treating locally recurrent thyroid cancer: A systematic review and meta-analysis. Thyroid 2016;26(3):420-8.
10. Rhim H, Goldberg SN, Dodd GD, et al. Essential techniques for successful radio-frequency thermal ablation of malignant hepatic tumors. Radiographics. 2001;21 Spec No:S17-35.
11. Park HS, Baek JH, Park AW, Chung SR, Choi YJ, Lee JH. Thyroid radiofrequency ablation: updates on innovative devices and techniques. Korean J Radiol 2017;18(4):615-23.
12. Shin JH, Baek JH, Ha EJ, Lee JH. Radiofrequency ablation of thyroid nodules: basic principles and clinical application. Int J Endocrinol 2012;2012:1-7.
13. Goldberg SN. Radiofrequency tumor ablation: principles and techniques. Eur J Radiol 2001;13(2):129-47.
14. Barile A, Quarchioni S, Bruno F, et al. Interventional radiology of the thyroid gland: critical review and state of the art. Gland Surg 2018;7(2):132-46.
15. Ha EJ, Baek JH, Lee JH. Moving-shot versus fixed electrode techniques for radiofrequency ablation: comparison in an ex-vivo bovine liver tissue model. Korean J Radiol 2014;15(6):836-43.
16. Chung SR, Choi YJ, Lee JH. Management strategy for nerve damage during radiofrequency ablation of thyroid nodules. Int J Hyperthermia. 2019;36(1):203-9.

17. Kim JH, Baek JH, Lim HK, et al. 2017 Thyroid radiofrequency ablation guideline: korean society of thyroid radiology. Korean J Radiol 2018;19(4):632-55.
18. Gharib H, Hegedus L, Pacella CM, Baek JH, Papini E. Clinical review: Nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. J Clin Endocrinol Metab 2013;98(10):3949-57.
19. Bernardi S, Giudici F, Cesareo R, et al. Five-year results of radiofrequency and laser ablation of benign thyroid nodules: a multicenter study from the Italian minimally invasive treatments of the thyroid group. Thyroid 2020;30(12):1759-70.
20. Dobnig H, Zechmann W, Hermann M, et al. Radiofrequency ablation of thyroid nodules: good clinical practice recommendations for Austria: an interdisciplinary statement from the following professional associations: Austrian Thyroid Association (Osdg), Austrian Society for Nuclear Medicine and Molecular Imaging (Ognmb),Austrian Society for Endocrinology and Metabolism (Oges), Surgical Endocrinology Working Group (ACE) of the Austrian Surgical Society (Oegch). Wien Med Wochenschr 2020;170(1-2):6-14.
21. Trimboli P, Castellana M, Sconfienza LM, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: a systematic review and meta-analysis. Endocrine 2020;67(1):35-43.
22. Jung SL, Baek JH, Lee JH, et al. Efficacy and safety of radiofrequency ablation for benign thyroid nodules: a prospective multicenter study. Korean J Radiol 2018;19(1):167-74.
23. Baek JH, Lee JH, Sung JY, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology 2012;262(1):335-42.
24. Moon WJ, Baek JH, Jung SL, et al., Ultrasonography and the ultrasound-based management of thyroid nodules: consensus statement and recommendations. Korean J Radiol 2011;12(1):1-14.
25. Na DG, Lee JH, Jung SL, et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J Radiol 2012;13(2):117-25.
26. Papini E, Monpeyssen H, Frasoldati A, Hegedus L. European thyroid association clinical guideline for the use of image-guided ablation in benign thyroid nodules. Eur Thyroid J 2020;9(4):172-85.
27. Tufano RP, Pace-Asciak P, Russell J, et al. Update of radiofrequency ablation for treating benign and malignant thyroid nodules. The Future is Now. Front Endocrinol (Lausanne) 2021;12;698689.
28. Mauri G, Pacella CM, Papini E, et al. Image-guided thyroid ablation: proposal for standardization of terminology and reporting criteria. Thyroid 2019;29(5):611-8.
29. Nguyen VB, Nguyen TX, Nguyen VVH, Nguyen HT, Nguyen DT, Le CV. Efficacy and safety of single-session radiofrequency ablation in treating benign thyroid nodules: a short-term prospective cohort study. Int J Endocrinol 2021;2021: 7556393.
30. El-Galil MSA, Ali AH, Botros RM, EI-Khaleq YIA, Hetta OMA. Efficacy and safety of ultrasound (US)-guided radiofrequency ablation of benign thyroid nodules. Egypt J Radiol Nucl Med 2021;52:57(2021).
31. Guo DM, Chen Z, Zhai YX, Su HH. Comparison of radiofrequency ablation and microwave ablation for benign thyroid nodules: a systematic review and meta-analysis. Clin Endocrinol 2021;95:187-96.
32. Muhammad H, Santhanam P, Russell JO, Kuo JH. RFA and benign thyroid nodules: Review of the current literature. Laryngoscope Investig Otolaryngol 2021;6(1):155-65.
33. Muhammad H, Santhanam P, Russell JO. Radiofrequency ablation and thyroid nodules: updated systematic review. Endocrine 2021;72(3):619-32.
34. Deandrea M, Trimboli P, Garino F, et al. Long-term efficacy of a single session of RFA for benign thyroid nodules: a longitudinal 5-year observational study. J Clin Endocrinol Metab 2019;104(9):3751-6.
35. Deandrea M, Garino F, Alberto M, et al. Radiofrequency ablation for benign thyroid nodules according to different ultrasound features: an Italian multicentre prospective study. Eur J Endocrinol 2019;180(1):79-87.
36. Rangel LG, Volpi E, Steck JH, et al. Radiofrequency for benign thyroid nodules—critical review of the literature. Ann Thyroid 2021;6:2.
37. Sim JS, Baek JH, Lee J, Cho W, Jung SI. Radiofrequency ablation of benign thyroid nodules: depicting early sign of regrowth by calculating vital volume. Int J Hyperthermia 2017;33(8):905-10.
38. Trimboli P, Deandrea M. Treating Thyroid Nodules by Radiofrequency: Is the Delivered Energy Correlated With the Volume Reduction Rate? A pilot study Endocrine 2020;69(3):682-7.
39. Hegedüs L. Clinical practice. The thyroid nodule. N Engl J Med 2004;351(17):1764-71.
40. Burch HB, Shakir F, Fitzsimmons TR, Jaques DP, Shriver CD. Diagnosis and management of the autonomously functioning thyroid nodule: the Walter Reed Army Medical Center experience, 1975-1996. Thyroid 1998;8(10):871-80.
41. Jeong WK, Baek JH, Rhim H, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur. Radiol 2008;18(6):1244-50.
42. Monchik JM, Donatini G, Iannuccilli J, Dupuy DE. Radiofrequency ablation and percutaneous ethanol injection treatment for recurrent local and distant well-differentiated thyroid carcinoma. Ann Surg 2006;244(2):296-304.
43. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26(10):1343-421.
44. Cesareo R, Naciu AM, Iozzino M, et al. Nodule size as predictive factor of efficacy of radiofrequency ablation in treating autonomously functioning thyroid nodules. Int J Hyperthermia 2018;34(5):617-23.
45. de Boer H, BomW, Veendrick P, Bom E, van BorrenM, Joosten F. Hyperactive thyroid nodules treated by radiofrequency ablation: a Dutch single-centre experience. Neth J Med 2020;78(2):64-70.

46. Sung JY, Baek JH, Jung SL, et al. Radiofrequency ablation for autonomously functioning thyroid nodules: a multicenter study. Thyroid 2015;25(1):112-7.
47. Baek JH, Moon WJ, Kim YS, Lee JH, Lee D. Radiofrequency ablation for the treatment of autonomously functioning thyroid nodules. World J Surg 2009;33(9):1971-7.
48. Bernardi S, Stacul F, MichelliA, et al. 12-month efficacy of a single radiofrequency ablation on autonomously functioning thyroid nodules. Endocrine 2017;57(3):402-8.
49. Dobnig H, Amrein K. Monopolar radiofrequency ablation of thyroid nodules: a prospective Austrian single-center study. Thyroid 2018;28(4):472-80.
50. Cappelli C, Franco F, Pirola I, et al. Radiofrequency ablation of functioning and non-functioning thyroid nodules: a single institution 12-month survey. J Endocrinol Invest 2020;43(4):477-82.
51. Cervelli R, Mazzeo S, Boni G, et al. Comparison between radioiodine therapy and single-session radiofrequency ablation of autonomously functioning thyroid nodules: a retrospective study. Clin Endocrinol(Oxf) 2019;90(4):608-16.
52. Kim HJ, Cho SJ, Baek JH, Suh CH. Efficacy and safety of thermal ablation for autonomously functioning thyroid nodules: a systematic review and meta-analysis. Eur Radiol 2021;31(2):605-15.
53. Cesareo R, Palermo A, Benvenuto D, et al. Efficacy of radiofrequency ablation in autonomous functioning thyroid nodules. A Systematic review and meta-analysis. Rev Endocrine Metab Disord 2019;20(1):37-44.
54. Deandrea M, Limone P, Basso E, et al. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. Ultrasound Med Biol 2008;34(5):784-91.
55. Faggiano A, Ramundo V, Assanti AP, et al. Thyroid nodules treated with percutaneous radiofrequency thermal ablation: a comparative study. J Clin Endocrinol Metab 2012;97(12):4439-45.
56. Spiezia S, Garberoglio R, Milone F, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid 2009;19(3):219-25.
57. Jin H, Lin W, Lu L, Cui M. Conventional thyroidectomy vs thyroid thermal ablation on postoperative quality of life and satisfaction for patients with benign thyroid nodules. Eur J Endocrinol 2021;184(1):131-41.
58. Guan SH, Wang H, Teng DK. Comparison of ultrasound-guided thermal ablation and conventional thyroidectomy for benign thyroid nodules: a systematic review and meta-analysis. Int J Hyperthermia 2020;37(1):442-9.
59. Bernardi S, Dobrinja C, Fabris B, et al. Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. Int J Endocrinol 2014; 2014:934595.
60. Mader A, Mader OM, Groner D, et al. Minimally invasive local ablative therapies in combination with radioiodine therapy in benign thyroid disease: preparation, feasibility and efficiency – preliminary results. Int J Hyperthermia 2017;33(8):895-904.
61. Chianelli M, Bizzarri G, Todino V, et al. Laser ablation and 131-iodine: a 24-month pilot study of combined treatment for large toxic nodular goiter. J Clin Endocrinol Metabol 2014;99(7):E1283-6.
62. Zingrillo M, Modoni S, Conte M, Frusciante V, Trischitta V. Percutaneous ethanol injection plus radioiodine versus radioiodine alone in the treatment of large toxic thyroid nodules. J Nucl Med 2003;44(2):207-10.
63. Korkusuz H, Happel C, Koch DA, Gruenwald F. Combination of ultrasound-guided percutaneous microwave ablation and radioiodine therapy in benign thyroid disease: a 3-month follow-up study. RoFo 2016;188(1):60-8.
64. Zanocco KA, Hershman JM, Leung AM. Active surveillance of low-risk thyroid cancer. JAMA 2019;321(20):2020-1.
65. Lim HK, Cho SJ, Baek JH, et al. US-guided radiofrequency ablation for low-risk papillary thyroid microcarcinoma: efficacy and safety in a large population. Korean J Radiol 2019;20(12):1653-61.
66. Zhang M, Luo Y, Zhang Y, Tang J. Efficacy and safety of ultrasound-guided radiofrequency ablation for treating low-risk papillary thyroid microcarcinoma: a prospective study. Thyroid 2016;26(11):1581-7.
67. Ding M, Tang X, Cui D, et al. Clinical outcomes of ultrasound-guided radiofrequency ablation for the treatment of primary papillary thyroid microcarcinoma. Clin Radiol 2019;74(9):712-7.
68. Yan L, Zhang M, Song Q, Xiao J, Zhang Y, Luo Y. The efficacy and safety of radiofrequency ablation for bilateral papillary thyroid microcarcinoma. Front Endocrinol (Lausanne) 2021;12:663636.
69. Kim JH, Baek JH, Sung JY, et al. Radiofrequency ablation of low-risk small papillary thyroid carcinoma: preliminary results for patients ineligible for surgery. Int J Hyperthermia 2017;33(2):212-9.
70. Cho SJ, Baek SM, Lim HK, Lee KD, Son JM, Baek JH. Long-term follow-up results of ultrasound-guided radiofrequency ablation for low-risk papillary thyroid microcarcinoma: more than 5-year follow-up for 84 tumors. Thyroid 2020;30(12):1745-51.
71. Yan L, Lan Y, Xiao J, Lin L, Jiang B, Luo Y. Long-term outcomes of radiofrequency ablation for unifocal low-risk papillary thyroid microcarcinoma: a large cohort study of 414 patients. Eur Radiol 2021;31(2):685-94.
72. Zhang M, Tufano RP, Russell JO, et al. Ultrasound-guided radiofrequency ablation versus surgery for low-risk papillary thyroid microcarcinoma: results of over 5 years' follow-up. Thyroid 2020;30(3):408-17.
73. Choi Y, Jung SL. Efficacy and safety of thermal ablation techniques for the treatment of primary papillary thyroid microcarcinoma: a systematic review and meta-analysis. Thyroid 2020;30(5):720-31.
74. Tong M, Li S, Li Y, Li Y, Feng Y, Che Y. Efficacy and safety of radiofrequency, microwave and laser ablation for treating papillary thyroid microcarcinoma: a systematic review and meta-Analysis. Int J Hyperthermia 2019;36(1):1278-86.
75. Lim HK, Baek JH, Lee JH, et al. Efficacy and safety of radiofrequency ablation for treating locoregional recurrence

from papillary thyroid cancer. Eur Radiol 2015;25(1):163-70.
76. Chung SR, Baek JH, Choi YJ, Lee JH. Longer-term outcomes of radiofrequency ablation for locally recurrent papillary thyroid cancer. Eur Radiol 2019;29(9):4897-903.
77. Baek JH, Kim YS, Sung JY, Choi H, Lee JH. Locoregional control of metastatic well-differentiated thyroid cancer by ultrasound-guided radiofrequency ablation. AJR Am J Roentgenol 2011;197(2):W331-6.
78. Guenette JP, Monchik JM, Dupuy DE. Image-guided ablation of postsurgical locoregional recurrence of biopsy-proven well-differentiated thyroid carcinoma. J Vasc Interv Radiol 2013;24(5):672-9.
79. Chegeni H, Ebrahiminik H, Mosadegh Khah A, et al. Ultrasound-Guided Radiofrequency Ablation of Locally Recurrent Thyroid Carcinoma. Cardiovasc Intervent Radiol 2022;45(5):677-84.
80. Lee SJ, Jung SL, Kim BS, et al. Radiofrequency ablation to treat loco-regional recurrence of well-differentiated thyroid carcinoma. Korean J Radiol 2014;15(6):817-26.
81. Kim JH, Yoo WS, Park YJ, et al. Efficacy and safety of radiofrequency ablation for treatment of locally recurrent thyroid cancers smaller than 2 cm. Radiology 2015;276(3):909-18.
82. Choi Y, Jung SL, Bae JS, et al. Comparison of efficacy and complications between radiofrequency ablation and repeat surgery in the treatment of locally recurrent thyroid cancers: a single-center propensity score matching study. Int J Hyperthermia 2019;36(1);358-66.
83. Zhang TT, Li CF, Wen SS, et al. Effects of tumor size on prognosis in differentiated thyroid carcinoma smaller than 2 cm. Oncol Lett 2019;17(5):4229-36.
84. Xiao J, Zhang M, Zhang Y, et al. Efficacy and safety of ultrasonography-guided radiofrequency ablation for the treatment of T1bN0M0 papillary thyroid carcinoma: a retrospective study. Int J Hyperthermia 2020;37(1):392-8.
85. Cao XJ, Wang SR, Che Y, et al. Efficacy and safety of thermal ablation for treatment of solitary T1N0M0 papillary thyroid carcinoma: a multicenter retrospective study. Radiology 2021;300(1):209-16.
86. Cao XJ, Liu J, Zhu YL, et al. Efficacy and safety of thermal ablation for solitary T1bN0M0 papillary thyroid carcinoma: a multicenter study. J Clin Endocrinol Metab 2021;106(2):e573-81.
87. Xiao J, Zhang Y, Zhang M, et al. Ultrasonography-guided radiofrequency ablation vs. surgery for the treatment of solitary T1bN0M0 papillary thyroid carcinoma: a comparative study. Clin Endocrinol (Oxf) 2021;94(4):684-91.
88. He H, Wu R, Zhao J, Song Q, Zhang Y, Luo Y. Ultrasound-guided radiofrequency ablation versus surgical resection for the treatment of T1bN0M0 papillary thyroid carcinoma in different age groups. Front. Endocrinol (Lausanne) 2021;12:734432.
89. Biamonte E, Solbiati L, Ierace T, et al. Medullary thyroid carcinoma treated with percutaneous ultrasound-guided radiofrequency ablation. Endocrine 2019;65(3):515-9.
90. Tong MY, Li HS, Che Y. Recurrent medullary thyroid carcinoma treated with percutaneous ultrasound-guided radiofrequency ablation: a case report. World J Clin Cases 2021;9(4):864-70.
91. Jeong SY, Baek JH, Choi YJ, et al. Radiofrequency ablation of primary thyroid carcinoma: efficacy according to the types of thyroid carcinoma. Int J Hyperthermia 2018;34(5):611-6.
92. Kim HY, Ryu WS, Woo SU, et al. Primary papillary thyroid carcinoma previously treated incompletely with radiofrequency ablation. J Cancer Res Ther 2010;6(3):310-2.
93. Sun W, Zhang H, He L, et al. Surgery after ultrasound-guided radiofrequency ablation for papillary thyroid carcinoma in 21 patients: a retrospective study from a single center in China. Med Sci Monit 2020;26:e928391.
94. Ma B, Wei W, Xu W, et al. Surgical confirmation of incomplete treatment for primary papillary thyroid carcinoma by percutaneous thermal ablation: a retrospective case review and literature review. Thyroid 2018;28(9):1134-42.
95. Ha SM, Sung JY, Baek JH, et al. Radiofrequency ablation of small follicular neoplasms: initial clinical outcomes. Int J Hyperthermia 2017;33(8):931-7.
96. Lin WC, Tung YC, Chang YH, et al. Radiofrequency ablation for treatment of thyroid follicular neoplasm with low SUV in PET/CT study. Int J Hyperthermia 2021;38(1):963-9.
97. Gulcelik NE, Gulcelik MA, Kuru B. Risk of malignancy in patients with follicular neoplasm: predictive value of clinical and ultrasonographic features. Arch Otolaryngol Head Neck Surg 2008;134(12):1312-5.
98. Medas F, Canu GL, Boi F, Lai ML, Erdas E, Calò PG. Predictive factors of recurrence in patients with differentiated thyroid carcinoma: a retrospective analysis on 579 patients. Cancers (Basel);2019;11(9):1230.
99. Johnson S, Goldenberg D. Intraoperative monitoring of the recurrent laryngeal nerve during revision thyroid surgery. Otolaryngol Clin N Am 2008;41(6):1147-54.
100. Kim C, Lee JH, Choi YJ, et al. Complications encountered in ultrasonography-guided radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers. Eur Radiol 2017;27(8):3128-37.
101. Chung SR, Suh CH, Baek JH, Park HS, Choi YJ, Lee JH. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. Int J Hyperthermia 2017;33(8):920-30.
102. Wang JF, Wu T, Hu KP, et al. Complications following radiofrequency ablation of benign thyroid nodules: a systematic review. Chin Med J 2017;130(11):1361-70.

運用射頻消融術來治療甲狀腺結節之安全性及效能：文獻回顧

曾國賓

義大癌治療醫院　內科部內分泌暨新陳代謝科
義守大學醫學院

摘要

甲狀腺結節常見於臨床實務中，它們通常是無症狀；同時，這幾年來由於超音波的廣泛運用之結果，使得甲狀腺結節發現率似乎有增加的趨勢。大多數的甲狀腺結節是良性的，因此，它們在臨床上通常被嚴密監控直到開始出現有壓迫症狀、產生美觀問題、發展出自主性甲狀腺機能亢進或者在細胞學上被證明是惡性腫瘤為止。從歷史角度，手術切除曾被認為是治療甲狀腺結節的唯一選項。然而，作為一種侵入性治療方式，手術切除甲狀腺結節即便只是部分甲狀腺切除，仍然會出現許多輕微的併發症之風險，譬如說醫源性甲狀腺機能低下、疤痕、血腫、發音困難以及其它結構上的受傷等等。因此，利用超音波為導引的微創技術，譬如射頻消融術，近來已被引進來治療甲狀腺結節，已顯示包括在甲狀腺結節容積之縮減、毒性結節性甲狀腺腫引起的機能亢進之消除和甲狀腺結節壓迫引起的症狀之改善;而且，射頻消融術在安全性方面則與手術治療相當。總而言之，由於相對上有較低的併發症之機率、微創之特性和保存正常甲狀腺機能加上射頻消融產生器的廣泛可取得性，射頻消融術已逐漸被運用來治療甲狀腺疾病，特別是良性甲狀腺結節的治療上。本篇論文旨在回顧當前文獻來討論運用射頻消融術來治療甲狀腺結節之可行性、效能和安全性。