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Update of Radiofrequency Ablation for Treating Benign and Malignant Thyroid Nodules. The Future Is Now

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Thermal and chemical ablation are minimally invasive procedures that avoid removal of the thyroid gland and target symptomatic nodules directly. Internationally, Radiofrequency ablation (RFA) is among one of the most widely used thermal ablative techniques, and is gaining traction in North America. Surgery remains the standard of care for most thyroid cancer, and in the right clinical setting, Active Surveillance (AS) can be a reasonable option for low risk disease. Minimally invasive techniques have emerged as an alternative option for patients deemed high risk for surgery, or for those patients who wish to receive a more active treatment approach compared to AS. Herein, we review the literature on the safety and efficacy of RFA for treating benign non-functioning thyroid nodules, autonomously functioning thyroid nodules, primary small low risk thyroid cancer (namely papillary thyroid cancer) as well as recurrent thyroid cancer.

Keywords: autonomously functioning thyroid nodules, benign thyroid nodules, recurrent thyroid cancer, thermal ablation, radiofrequency ablation, primary thyroid cancer

INTRODUCTION

New technologies are available to safely ablate thyroid nodules without removal of the gland itself. Laser Ablation (LA) and Radiofrequency ablation (RFA) are the most widely used thermal ablative treatments for solid nodules. High-Intensity Focused Ultrasound (HIFU) as well as Microwave Ablation (MA) are two other modalities that fall under the umbrella of thermal ablative techniques

and are gaining traction as longer-term data emerges (1, 2). Although, chemical ablation *via* percutaneous ethanol injection is cheaper and requires less costly equipment, it is considered the treatment of choice for cystic nodules and tends to be less effective for solid nodules (3–5). Each minimally invasive technique has its subtle differences and nuances, but they all share ease of use, effectiveness and safety.

RFA is an outpatient image-guided thermal ablative procedure that is a potential alternative to surgery for treating symptomatic benign nodules (6–39). This approach eliminates the need for general anesthesia, incision, or removal of the thyroid gland, making it an attractive nonsurgical option. RFA has been offered in certain centers since 2000 for the treatment of primary and metastatic liver, lung, bone and kidney tumors and to ablate aberrant conduction pathways in the heart (40–45). Since the Korean guidelines for the ablation of the thyroid with RFA in 2009 and its revised versions in 2012 and in 2017, various international societies have established their own recommendations (17, 22, 36, 46–48). The American Head and Neck Society has initiated a global collaborative consensus guideline which will be published soon.

With the use of local anesthesia and/or sedation, the RFA probe is introduced into the midline of the anterior neck at the level of the isthmus (called the trans-isthmic approach) and the nodule is targeted using the “moving shot technique” where the operator moves the RFA needle back and forth in the nodule while visualizing the hyperechoic changes in the tissue during ultrasound guidance (18, 45, 48). The heat from the electrode tip causes tissue necrosis and fibrosis by introducing a high-frequency alternating current, which raises tissue temperatures to 60 to 100 degrees Celsius (19). Lidocaine injection can be used prior to ablation to anesthetize the thyroid capsule to hydro-dissect, which provides greater distance from the active RFA needle tip and vital surrounding structures and also provides a heat sink around the nodule to prevent injury to these structures. A solution of 5% dextrose (D5W) may be used to hydro-dissect and to create an aqueous barrier for areas that should remain sensate, such as the trachea, nerves or other vital structures.

Once the tissue is ablated, there are obvious sonographic features available to guide the operator in real-time. These include hyperechoic signals and ‘micro-bubbling’ as well as an increase in the generator impedance as the tissue stiffens, indicating coagulative necrosis (17, 23, 49). The operator approaches the tissue as “subunits” from the deepest to the most superficial portion of the nodule. Care is taken to avoid extending the probe beyond the posterior or lateral thyroid capsule to avoid injury to nearby structures, particularly within the “danger triangle” where the recurrent laryngeal nerve is tethered to the trachea close to the posterior-medial aspect of the thyroid (49). Immediate shrinkage of the nodule is appreciated as well as continued progressive shrinkage over a period of months to years. In benign nodules, the volume of the nodule is expected to typically decrease between 50–90%, which can vary due to both operator and tumor factors (7, 20, 21, 30, 34, 35).

Prior to RFA of a benign nodule, at least two benign biopsy results should be done (either FNA or core biopsy) (17, 22, 36, 46–48). For AFTN, the societies differ slightly in their

recommendations, but generally one FNA result can suffice if the ultrasound features are consistent with benign ultrasound results (spongiform, cystic, encapsulated, no evidence of extrathyroidal extension or lymphadenopathy) (17, 22, 36, 46–48). If there are worrisome or suspicious sonographic features, but the biopsy result is benign, the FNA should be repeated. Furthermore, if the volume of the thyroid nodule is not completely delineated on ultrasound or doubt exists regarding the extent of the nodule, a CT scan of the neck can help to determine if and how much retrosternal extension is present and whether the patient is an appropriate candidate for RFA.

BENIGN NON-FUNCTIONING THYROID NODULES

Many reports have established the short-term efficacy (6–12 months) and safety of RFA for reducing the volume of benign nonfunctioning nodules (50–85%) (18, 20, 21, 26, 30, 50–52). Long-term data are starting to emerge with recommendations for the number of treatments required to maintain volume reduction of benign nodules. Lim et al. demonstrated up to 93.4% volume reduction rate at 4 years post RFA treatment for benign nonfunctioning nodules as well as improved local symptoms and cosmesis (6). In their series, only 5.6% of the nodules demonstrated regrowth, which tended to be at the peripheral margin (6).

Several papers have shown that RFA has the best reduction rate for smaller nodules (volume < 10 mL), with maintained success for up to 2 years (6, 9, 10, 28–31, 53). Deandra et al. found in their long-term series of 215 patients, that the best response was seen in nodules less than 10 mL, showing an 81% volume reduction rate at 5 years after one RFA procedure (31). Progressive shrinkage over time was noted through the five-year follow-up as well as maintenance of improved compressive symptoms and cosmesis (31). Similarly, in a retrospective multi-institutional trial, Bernardi et al. demonstrated in a series of 216 patients a long-lasting effect of a single RFA treatment with a median volume reduction rate of 77% after 5 years (7). Only 12% underwent a second treatment, and regrowth was noted in 20% of treated patients (7). As opposed to smaller nodules, larger benign nodules tend to require more than one treatment. The variability between the results in the literature can likely be attributed to the heterogeneity of nodule size treated across studies, the energy delivered to nodules, the technical expertise of the operator and the learning curve associated with achieving ablation of the nodule margin (54). These important studies provide a framework for counselling patients regarding the long-term effectiveness of RFA as well as the importance of discussing the potential need for retreatment to maintain the desired effect.

AUTONOMOUSLY FUNCTIONING THYROID NODULES

Benign autonomously functioning thyroid nodules (AFTN) tend to be more variable than for benign non-functioning nodules

likely due to the increased vascularity present in AFTNs and the increased possibility for leaving viable remnant tissue at the margin. The literature demonstrates that achieving euthyroidism post RFA is more consistent when the pretreatment volume of the AFTN is small and more homogeneous ultrasonographically. Cesareo et al. compared the reduction in medium sized nodules (>12 mL, n=14) versus smaller sized nodules (< 12 mL, n=15), and found that euthyroidism was achieved in 86% of small nodules versus 45% in medium size nodules (10). Similarly, Cappelli et al. report a volume reduction rate of 73% with TSH normalization in 94% of 17 patients treated with RFA with nodules of an average 7 mL (11). After one RFA session, Cervelli et al. demonstrated a volume reduction rate of 76.4% +/- 16.9% with a 91% (20/22 patients) TSH normalization at 12-month follow-up in 25 AFTNs that were homogenous in volume and of smaller pretreatment size (55). However, Cesareo et al. found only modest results (57%) of TSH normalization post RFA treatment in a systematic review covering 8 studies on 205 AFTNs (12).

When the volume of a nodule is reduced by > 80%, Cesareo et al. found a greater chance for thyroid function normalization and symptom resolution (10, 15). In a multicenter trial, Sung et al. demonstrated this concept with a significant reduction in nodule volume from a pretreatment mean nodule volume of 18.5 ± 30.1 mL to 4.5 ± 9.8 mL ($p < 0.001$) post RFA treatment in a series of 23 AFTNs (44 patients, 23 with AFTN and 21 with a pretoxic nodule) (13). This significant change in nodule volume and thus vascularity resulted in a significant improvement of triiodothyronine, free thyroxine, and thyrotropin in the final follow up (19.9 ± 12.6 months) (13). TSH levels normalized in 81.8% of the study patients without the development of hypothyroidism post RFA. These findings are congruent with those of Baek et al. in a series of 9 patients (4 AFTN and 5 pretoxic nodules) (14).

Even though several studies support targeting smaller AFTNs to ensure success, the correlation between pretreatment nodule size and treatment outcome of AFTNs is still controversial. A recent meta-analysis highlights the efficacy of RFA treatment on TSH normalization (71.2% of patients) and a volume reduction rate of 69.4% at a mean follow-up of 12.8 months. However, in a subgroup analysis, there was no significant difference in TSH normalization or volume reduction rate (VRR) between small or large nodules when divided into groups of 15mL, 18mL and 20 mL (56). Similarly, Bernardi et al. in their series of 30 patients found no significant correlation between baseline volume and treatment response after RFA (15). Thus, it seems that the rate of reduction of the nodule post RFA plays a more important role in the success of achieving euthyroidism rather than the pretreatment nodule size. However, smaller AFTNs seem to be overall most effectively treated and therefore maybe best for the novice operator to initiate RFA treatment. Due to the variability of results with AFTNs, the international guidelines are more cautious when recommending RFA as curative for AFTNs (17, 22, 36, 46, 47). Accumulating evidence from prospective studies will help in the pretreatment counseling of this patient population.

SURGERY VERSUS RADIOFREQUENCY ABLATION FOR BENIGN NODULES

For symptomatic benign thyroid nodules, an open thyroidectomy is the standard of care. However, surgery may not always be the best choice, particularly for older patients who are not ideal surgical candidates or for patients who do not wish to risk hypothyroidism, scarring, hoarseness or surgical recovery time especially for benign disease. In a meta-analysis comparing thermal ablation with conventional thyroidectomy, thermal ablation was safer and had significantly lower incidence of hoarseness, hypothyroidism and postoperative pain ($p < 0.05$) (57). After thermal ablation, patients had significantly better postoperative cosmetic outcome and shorter hospitalization time compared with conventional thyroidectomy ($p < 0.05$) (57). However, in terms of symptom improvement, both options were equally favorable, with no statistical difference between thermal ablation and conventional thyroidectomy ($p = 0.58$), thus showing RFA as a promising treatment option (57).

Other trials, such as the one by Jin et al. found that thermal ablation is superior to conventional thyroidectomy for benign nodules in terms of patient satisfaction, post-operative quality of life, and shorter hospital stay (58). Although both options were found to have similar complication rates, thermal ablation can take longer to achieve the desired volume reduction than a definitive surgical approach. In a telephone survey of 126 patients treated with RFA and 84 treated with surgery for a single benign thyroid nodule, Bernardi et al. compared patient satisfaction (8). Overall, 94% of patients that underwent surgery were fully satisfied with the outcome and resolution of their nodule related symptoms or hyperthyroidism. For nonfunctioning thyroid nodules, RFA was as effective as surgery in patient satisfaction with resolution of nodule-related symptoms. On the other hand, for AFTN, surgery relieved 95.8% of patient's hyperthyroid symptoms whereas RFA was effective in 52.9% patients resulting in withdrawal of their antithyroid drugs. In terms of complications, however, RFA was superior to surgery and no cases of hypothyroidism were identified, whereas 37.5% of patients after surgery required thyroid replacement therapy (8).

Other studies have compared the complication rates of surgery and RFA for benign nodules and found a higher rate of complications in the surgical group compared to RFA (9). Che et al. compared complications after open surgery versus RFA and found that 71.5% versus 0% had hypothyroidism, 3% versus 0.5% had recurrent laryngeal nerve palsy, and 3% versus 0% had hypoparathyroidism (9). For the accurate calculation of post-surgical recurrent laryngeal nerve injury rates both the American Academy of Otolaryngology and the American Thyroid Association have recommended laryngeal exam postop given the known disparity between vocal cord paralysis and vocal symptoms (59, 60). When we compare surgery to RFA complications moving forward we will need to be steadfast in ensuring that laryngeal exam is preformed uniformly in both treatment groups.

One of the key benefits of RFA compared with surgery is the reduced chance of causing post-treatment hypothyroidism. Surgery involves removing the gland with the nodule and the normal

parenchyma, whereas RFA targets the nodule alone, leaving the normal tissue protected and preserving thyroid function (9). Whether RFA changes the tissue planes, making it more difficult to resect surgically at a later date remains to be determined.

Nevertheless, some limitations of RFA should be mentioned. RFA is not suitable for all types of thyroid nodules, particularly for large benign nodules when patients expect rapid results, substernal nodules, and deeply located nodules. Additionally, there are still some nodules with incomplete response and local regrowth in the follow-up period, which require repeat ablation or surgery, and some nodules which shrink slowly but fail to completely recede (61).

COMBINED THERMAL ABLATION AND RADIOACTIVE IODINE TREATMENT

The guidelines are more cautious when recommending treatment of large benign goiters, and more than one treatment is expected for larger sized nodules (17, 22, 36, 46, 47). The use of one treatment modality exclusively may only partially give a desired effect for benign large toxic nodules, however evidence for combining thermal ablation with radioactive iodine (RAI) has been promising. Even though surgery is considered the first line treatment, and current international guidelines do not endorse RFA as primary treatment for large toxic goiters, a combined approach may be an innovative safe solution for reducing the dose of RAI and rapidly controlling local symptoms of hyperthyroidism and compression without undergoing surgical removal of the gland (62). In a pilot study by Chianelli et al., combined LA therapy with RAI treatment induced faster and greater improvement of local and systemic symptoms compared to RAI alone (63). Korkusuz et al. found similar success with combined therapy using MA with RAI for Graves' disease and large toxic nodular goiters (64). A significant reduction in size was appreciated with restoration of euthyroidism and a reduced dose of RAI (64). Even though MA and LA have proven effective, RFA is more widely disseminated and is better studied to date (62).

Thermoablative procedures can be useful in older patients for providing relief at a rate that may be faster than RAI alone. There are limitations for each treatment modality, however when RAI and RFA are combined, the volume of the nodule is reduced more rapidly. Mader et al., used combined therapy (RAI and RFA) for large goiters which led to a significant reduction in thyroid volume ($p < 0.05$) compared to the control group (RAI mono therapy) (62). However, by three months post treatment the volume reduction did not differ between the two groups ($p > 0.05$). All patients became euthyroid after treatment and no complications or discomfort were noted (62). With future work, combined therapy may limit the dose of RAI and provide fast relief in patients who refuse or have contraindications to surgery.

MALIGNANT THYROID NODULES

Recent studies have demonstrated the efficacy and safety of thermal ablation for low-risk papillary thyroid microcarcinoma

(PTMC) (65–76) as well as for recurrent thyroid cancer where the risks of surgery outweigh the benefits or in patients who refuse repeat surgery (77–90). However, it should also be recognized that RFA for low-risk PTMC must be considered in the appropriate context, as many studies demonstrate excellent outcomes and minimal growth with simple active surveillance in this patient population. Preliminary work has not shown benefit for poorly differentiated aggressive tumors such as anaplastic carcinoma (69). For medullary thyroid cancer (MTC), surgery remains the treatment of choice. Few case reports have demonstrated RFA to be a safe and effective option for early MTC in patient's ineligible for surgery (91) or for patients with a regional recurrence after surgical resection of their MTC (92). However, the data is somewhat limited for MTC and remains controversial.

Careful evaluation of the desired nodule is required before ablation to ensure a successful outcome for the patient and to avoid delay for possible surgery. The main indications include: a) cytopathology confirmed papillary thyroid carcinoma (PTC) without evidence of aggressiveness b) single PTC without extrathyroidal extension c) no metastatic tumors at the time of treatment and d) ineligibility for surgery (78). The operator should note key features during evaluation, such as capsule invasion or lymph node metastases, and whether an aggressive variant of PTC is present. These features should prompt surgery instead of RFA. Currently, the Italian society does not recommend RFA for first line treatment of primary thyroid cancer, however emerging evidence has shown benefits, safety and efficacy for treatment of low-risk tumors (46).

RFA FOR PAPILLARY MICROCARCINOMA (T1AN0M0)

Detection of smaller thyroid cancers, namely PTMCs, is increasing in part because of increased medical imaging and accounts for 50% of papillary thyroid cancers (93). The World Health Organization (WHO) defines PTMC as a small papillary thyroid cancer or < 10 mm in greatest dimension (93). The American Joint Committee on Cancer (AJCC) TNM system classified T1 category ($T1: \leq 2$ cm) into T1a: ≤ 1 cm and T1b: ≤ 2 cm (94). Although the 2015 American Thyroid Association guidelines (ATA) do not recommend biopsy of nodules less than 1 cm unless high risk features are present, these small indolent cancers are often incidentally detected (59). On one hand, while surgery is an option, it is an invasive approach for removal of such small indolent lesions that likely would otherwise not have caused significant morbidity. On the other end of the treatment spectrum, several landmark trials have shown no increase in mortality of patients undergoing active surveillance (AS) for small papillary thyroid cancers compared to those who underwent immediate surgery with 10 years of follow up (95, 96). Thus, the optimal management for PTMC is controversial. Some patients may be reluctant to undergo AS with a proven diagnosis of cancer, regardless of its indolence. The unnecessary anxiety of having a cancer diagnosis may make

some patients feel more comfortable actively treating their cancer without surgery or observation. Mounting evidence has established short term safety and efficacy of thermal ablation for PTMC (65–73). In addition to surgery and AS, thermal ablative techniques, such as RFA may bridge the gap in treatment options for patients wishing to have their PTMC managed in a minimally invasive way.

Several trials have demonstrated promising results for treating primary PTMC with RFA. Ding et al. used RFA to treat 38 PTMC in 37 patients with a low power setting of 20 W (65). All treated nodules achieved complete ablation, no complications occurred, and no hypothyroidism was encountered. After 12 months post treatment 37 of the 38 nodules were completely resolved with no evidence of nodule recurrence in 37 patients (65). Similarly, Zhang et al. demonstrated safety and efficacy in RFA-treated PTMCs over a 18-month follow-up (66). After treating the lesion(s) with 3-5W of power, a significant volume reduction rate was noted within the first 6 months follow up ($p < 0.01$) but not after the 12 months follow up (66). Of the 98 nodules (92 patients), 10 resolved after six months, and 23 resolved in 12 months. All patients post RFA demonstrated no evidence of residual tumor on ultrasound or histological pathology after US guided biopsy (66). Again, no major complications were noted.

In a meta-analysis examining the efficacy and safety of all ablation techniques for PTMC, RFA showed the highest mean volume reduction rate (99.3%) compared to other thermal ablation techniques such as MA (95.3%) and LA (88.6%) ($p < 0.001$) (75). Although significant heterogeneity between studies is noted, the pooled proportions of complete disappearance of PTMC was 57.6% (95% CI:35.4-79.8) and recurrence was 0.4% (95% CI:0-1.1) (75). Furthermore, the pooled proportions of overall and major complications for all thermal approaches were 3.2% (95% CI:1.1-5.2) and 0.7% (95% CI:0-1.5) demonstrating the safety of these techniques for PTMC (75).

A recent meta-analysis of 12 studies on the efficacy and safety of thermal ablation by RFA, MA or LA included 1,187 patients with 1,284 papillary microcarcinomas. All modalities induced reduction in nodule volume. MW achieved the highest standard mean deviation (-3.82; 95% CI -7.02; -0.63) than RFA (-1.35; 95% CI -1.62; -1.09) and LA (-1.80; 95% CI -2.75; -0.85), but the difference was not statistically significant. Complete disappearance pooled proportion was 76.2%, 62.9% and 57.3% after RFA, MW and LA treatments, respectively. There was a lower proportion of recurrence after RFA (0.01%) than after MA (0.85%) and LA (1.87%). However, the differences were not statistically significant. The rates of complications observed were also low and similar between the compared techniques (97).

Zhang et al. compared RFA with surgery for patients with a low-risk PTMC, and followed them for five years (67). After 5-year follow-up, RFA was not found to be inferior to surgery with respect to oncological efficacy. Only one patient in the RFA group developed a new lesion (1 of 94) (1.1%) arising in the remaining ipsilateral lobe and none of the RFA group developed lymph node metastases (67). When compared with RFA, surgery

took longer, had a longer hospitalization time, and was more costly ($p < 0.001$). The surgical group had a lower thyroid-related quality of life, as well as more complications (2.5% recurrent laryngeal nerve palsy, 1.3% hypoparathyroidism) compared to neither of these complications in the RFA group ($p = 0.095$) (67).

Yan et al. examined the long-term oncological efficacy of RFA in 414 PTMC patients after 42.15 ± 11.88 (range 24 – 69 months) months (76). After RFA, 366 out of 414 tumors (88.41%) completely disappeared, with a volume reduction rate of $98.81 \pm 6.41\%$ demonstrating long-term efficacy in this large cohort (76). The incidence of lymph node metastases post RFA was 0.97% (ipsilateral neck in three patients, and one in the central compartment), all of which underwent additional RFA with complete disappearance of the node during follow-up. Recurrent PTMC was found in 10 patients (2.42%); seven were in the contralateral lobe and three in the ipsilateral lobe, which were successfully treated with a second RFA procedure. The mean time of recurrent PTMC development was 27.60 ± 12.71 months (range, 6 – 48 months) (76). Similar to other trials, Yan et al. found no delayed or immediate complications.

As the field of minimally invasive techniques continue to grow, more long-term data will emerge and may substantiate the oncologic effectiveness of thermal ablation for primary microcarcinoma.

RFA FOR PAPILLARY THYROID CANCER (T1BN0M0)

Little evidence exists for thermal ablation of T1bN0M0 cancers, particularly with RFA, compared with T1aN0M0 PTC. The distinction between T1a and T1b is minimal, and the prognosis does not differ significantly between these two subdivisions as demonstrated by previous studies (98, 99). Xiao et al. compared surgery and RFA in patients with T1bN0M0 PTC (91 patients in each group) and found no significant difference between the two groups in local tumor progression and complications (74). In the RFA group, four patients had local tumor progression (4.4%, three persistent PTC and one develop lymph node metastases). Whereas in the surgery group, two patients (2.2%) developed lymph node metastases, and no new or persistent PTC was noted. When the complication rates were compared, the surgery group had four patients with permanent hypoparathyroidism (4.4%) after total thyroidectomy, meanwhile the RFA group developed no major complications, and only two patients experienced moderate pain (74). Even though the mean follow-up time was 25 months, the results are promising. In future studies comparison should be made between RFA treated patients and unilateral thyroid surgery as opposed to total thyroidectomy.

RFA FOR FOLLICULAR THYROID NEOPLASM

RFA treatment for follicular neoplasm is more controversial than PTC since surgical resection is required to exclude the presence

of vascular or capsular invasion to definitively diagnose whether the nodules is a follicular adenoma compared with a carcinoma. However, a recent 5-year study including 10 patients with follicular neoplasm < 2 cm in size found on thyroid biopsy reported that RFA is safe and effective in the short-term for such cases. Ha et al. demonstrate a significant reduction in the mean volume ($99.5 \pm 1.0\%$) of lesions, with eight ablated lesions (8/10, 80%) disappearing completely after single treatment on follow-up and no recurrences noted (range: 60-76 months) (100). Further large-scale trials are required to confirm effective oncological control, as it is unclear if sonographically invisible carcinomas still have metastatic potential.

RECURRENT THYROID CANCER

While the mortality rate for well-differentiated thyroid cancer tends to be favorable, the risk of recurrent PTC can range from 20 – 59% depending on patient and tumor risk factors (78). The mainstay of recurrent thyroid cancer is surgery, followed by RAI therapy and suppressive thyroid hormone replacement treatment, external beam radiotherapy and/or chemotherapy (59). Revision surgery for recurrent disease is not without its challenges due to scarring in the tissue bed, which can make identification and preservation of the RLN and parathyroid glands difficult. Various thermal ablative techniques (RFA, LA or MA) and chemical ablative approaches (ethanol ablation) can be used as an alternative method in patients deemed to be at high surgical risk, those in whom the surgeon deems non-operable or for those refusing to undergo repeat surgery. In each situation, a tailored and multi-disciplinary approach is imperative, as recurrent carcinomas can present in myriad presentations.

In patients treated with lobectomy, total thyroidectomy, and/or neck dissection as their primary surgery, Choi et al. examined patients with local recurrences and compared the efficacy and complication rate between the RFA group and repeat surgery group (77). After propensity score adjustment, the recurrence-free survival rates were comparable between the two groups ($p=0.2$), including the decrease in the mean serum thyroglobulin levels post treatment (RFA $p=0.891$ and surgery $p=0.963$) (77). Additionally, overall complications were noted more frequently in the surgery group, compared with the RFA group, particularly for hypocalcemia (surgery $n=27$; RFA, $n=7$; $p<0.001$) (77), which was similar to the findings of Kim et al. (78).

Various studies have looked at possible parameters to measure the efficacy after RFA for recurrent PTC. Most of these studies have looked at the short-term results (over 6 months), leaving the long-term outcomes still to be determined. Jeong et al. reviewed the literature (79) and found the mean reduction in tumor volume ranging from 50.9% to 8.4% (80–82); with complete disappearance noted in 25-94% of cancers (80, 81, 83–85); therapeutic success rates in 75% - 97% (80, 83, 86, 87); with symptom improvement observed in 64% of patients (82); and a decrease in serum thyroglobulin concentration in most patients signifying therapeutic success (80, 82–84). One study on

seventy-three patients reported the mean volume reduction rate of recurrent tumors to be $98.4\% \pm 6.2\%$, and the complete disappearance rate 86.1% (78). Furthermore, two meta-analyses including one hundred and eighty-nine patients (87) and two hundred and seventy patients (88) with a local recurrence of their thyroid cancer found a significant decrease in volume and largest diameter of the tumor as well as thyroglobulin level before and after RFA treatment (87, 88).

Longer term data are beginning to emerge, with promising results for treating locally recurrent PTC with US-guided RFA. Chung et al. found after a mean follow up of 80 ± 17.3 months (range, 60-114 months), in a series of twenty-nine patients (forty-six recurrent PTC), that the tumor volume decreased significantly ($p < 0.001$) with a mean volume reduction of $99.5\% \pm 2.9\%$ and significant thyroglobulin decrease ($p < 0.001$), and complete tumor disappearance of 91.3% by the final evaluation with no delayed complications noted (89).

When recurrences in the central compartment occur, invasion of surrounding structures such as the trachea, esophagus, RLN, and parathyroid glands are more likely, making reoperation in a previously operated tissue bed with a recurrence very challenging. Chung et al. reviewed a series of patients with RFA-treated recurrent thyroid cancer in the central compartment after total thyroidectomy. The mean volume reduction rate was $81.2\% \pm 55.7\%$, and complete disappearance of the tumor 72% after a mean follow-up of 47.0 ± 35.4 months (90). The lower rate of tumor disappearance for RFA-treated recurrences in the central compartment can likely be explained by the narrow working space and important neighboring structures. Treatment efficacy was significantly higher for tumors that were not in contact with the trachea, and unsurprisingly, lowest for tumors invading the trachea (90). Thus, the long-term efficacy of RFA treated recurrent papillary thyroid cancer is promising in the right clinical situation. As we anticipate future guidelines in North America, RFA treatment may be indicated for early localized disease to prevent progression into the neighboring vital structures in patients who are poor operative candidates or have other reasons to avoid surgery.

COMPLICATIONS OF RFA

Though multiple studies have demonstrated that thermal ablation is a safe technique, there are some associated complications which are mostly minor. In a meta-analysis of 12 studies including RFA treated benign nodules with follow up for more than three years, Cho et al. found an overall complication rate of 4.6% and a major complication rate of 1.3% in the RFA group (34). In a systematic review including 2786 nodules (24 studies including both benign and recurrent thyroid cancers) the overall RFA complication rate was 2.38%, with 1.35% for major complications (35). On subgroup analysis, the overall and major complication rate was higher for recurrent malignant nodules (10.98%) compared with benign nodules (2.11%) (35).

TABLE 1 | Complications following RFA of benign thyroid nodules [from a systematic review of 3409 patients by Wang et al. (101)].

Complications	N° cases
Pain and sensation of heat	281
Voice changes	32
Hematoma/hemorrhage	31
Vasovagal reactions	19
Nodule rupture	14
Horner syndrome	14
Increase in blood pressure	12
Nausea/vomiting	11
Fever	11
Cough	10
Skin burn	6
Recurrent nerve injury	4
Hypothyroidism	3
Needle track seeding	2
Thyroiditis and thyrotoxicosis	1
Brachial plexus injury	1
Pseudocystic transformation	1

The most common minor complication include pain with an incidence that ranges from 2.6% to 17.5% in a systematic review that included 32 studies with 3409 patients (101). In a systematic review by Chung et al. transient voice change was one of the common minor complications post-RFA, with an incidence of 0.94% (21/2245 for benign nodules) compared with 7.95%, 14/176 for recurrent cancer (35). Skin burns, hematoma and transient thyroiditis can occur but less frequently (34, 35, 102) (**Table 1**).

Major complications such as permanent recurrent laryngeal nerve injury, nodule rupture, hematoma requiring surgical drainage, Horner's syndrome or injury to the adjacent esophagus or trachea are rare (39, 103).

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CONCLUSION

Given the accumulating international evidence, we anticipate that RFA will one day become routinely used for many benign and malignant conditions of the thyroid. We still require large prospective trials to be performed in diverse populations and with longer term data to substantiate oncologic efficacy. For the novice operator, comfort and ease results from a solid working knowledge of ultrasound guided FNA of the thyroid. Once this has been established, smaller benign nodules may be targeted first before treatment of larger or malignant nodules. Until more robust efficacy data is available for malignant thyroid nodules, RFA for malignant thyroid nodules should ideally be performed in a setting of prospective data analysis and/or clinical trials.

AUTHOR'S NOTE

This paper was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com).

AUTHOR CONTRIBUTIONS

Equal contributions were made by RT and PP-A for the writing of the initial manuscript. JR contributed to the manuscript edits and final review. Members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com) made contributions to the writing and editing of subsequent drafts of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: RT is a consultant for RGS Healthcare.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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