Review Article

Surgical perspective on radiofrequency ablation of thyroid tumors

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Abstract: Radiofrequency ablation (RFA) is a safe and effective, minimally invasive procedure that has been used for decades to treat various tumors in the body. More recently, RFA has been applied to the head and neck, namely the thyroid. Part of its appeal is the lack of a cervical incision, general anesthetic, or removal of the thyroid gland at all, making it an easy office procedure for ablation of benign or malignant tumors. For enlarged benign tumors causing compressive symptoms, RFA can provide a safe option without enduring potential hypothyroidism, or the downtown associated with surgical recovery. For autonomously functioning thyroid nodules (AFTN), RFA may produce modest results for improving symptoms of hyperthyroidism as well as compression, thus expanding the existing options of radioactive iodine (RAI) and anti-thyroidal medications. For the treatment of primary or recurrent thyroid cancer, surgery is the standard of care. However, not all patients are eligible for surgery and in certain instances, revision thyroid surgery for recurrent cancer can pose significant risk to the patient. Thus, the option of a minimally invasive nonsurgical technique for ablation can improve their quality of life and provide clinicians with an extra tool in their armamentarium. We review the literature of this novel procedure and the role RFA can play in treating benign tumors (nonfunctioning and functioning), primary and recurrent thyroid cancers for patients that do not wish to have surgery or are ineligible.

Keywords: Radiofrequency ablation (RFA); benign nodules; autonomously secreting thyroid nodules; primary and recurrent thyroid cancer

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Introduction

Ultrasound-guided radiofrequency ablation (RFA) is a minimally invasive nonsurgical procedure that has been used for decades to treat benign and malignant tumors of the liver, bone, kidney and lung as well as aberrant conduction pathways of the heart (1-7). Internationally, RFA has been shown to be safe and effective for treating thyroid conditions which include symptomatic benign thyroid nodules, as well as primary and recurrent thyroid cancer (8-17). In North America, surgery is the standard of care for removal of thyroid malignancy and the evidence for success of RFA in this population is limited. However, when we look at the success and ease of RFA treatment demonstrated among international circles, this treatment modality is a promising alternative to surgery for patients who pose risk due to their multiple medical comorbidities or those otherwise motivated to minimize the risks of treatment and the time of recovery.

RFA eliminates the need for an incision, removal of the thyroid as well as a general anesthetic, making this an attractive option for patients who pose surgical risk. With the use of local anesthetic or light sedation, the needle probe can be inserted into the midline of the anterior neck at the level of the isthmus, using ultrasound guidance, to avoid injuring nearby structures. Knowledge of the anatomy of the neck is essential for safety and is associated with low complication rate when performed by an experienced operator, surgeon or radiologist with ultrasound guidance. Because it does not require general anesthesia and can be completed in the office setting, there are other potential advantages even for patients who are not interested in the traditional surgical approach.

Herein, we review this novel nonsurgical approach, and the role RFA may play in expanding the treatment options for benign (non-secreting and secreting nodules) as well as primary or recurrent malignant tumors of the thyroid in patient's ineligible for surgery.

Benign tumors

Nonfunctioning tumors

Internationally, RFA is established as a safe and effective method for treating benign thyroid nodules (8,11-13,18-30). Enlarged thyroid nodules may cause compressive symptoms, globus sensation, and distortion or asymmetry of the neck, prompting patients to seek treatment. Traditionally, surgery has been the definitive treatment, but a cervical scar, potential hypothyroidism and a general anesthetic may be undesirable for some patients with a benign condition. RFA provides a minimally invasive, low risk procedure for reducing pressure symptoms while avoiding the need for a mid-cervical scar.

The international literature supports RFA as an effective method for relieving compressive symptoms for benign nodules (18,19,31-35). Over time, RFA can reduce the size of a nodule by 33–58% after one month, by 51–85% after 6 months, and by 93% after 4 years (28,36). Worldwide, RFA is one of the more common ablative procedures that utilizes thermal energy, for reducing the volume of predominantly benign solid nodules (35,37). However, in long-term follow up, Lim *et al*. demonstrated a well-maintained volume reduction in size of over 93% in benign nodules regardless of whether they were cystic or solid (28). A recent study by Bernardi *et al*. demonstrated a significant sustained reduction in the nodule volume (85%) after 5 years post-treatment (35). The "moving shot" technique with a heated electrode may explain why RFA is effective: the tumor margins may be included in the ablation after protecting surrounding critical structures with an aqueous buffer, thereby maximizing the surface area the electrode reaches and preventing marginal regrowth (28,37).

For benign non-secreting nodules causing pressure or compression on the trachea, surgery is definitive. However, RFA has not been shown to be inferior to the surgical option and effectively reduces nodule volume. In a meta-analysis, Trimboli *et al*. demonstrate a significant reduction in the volume of RFA treated nodules, compressive symptoms and cosmetic scores with sustained nodule reduction for up to 2–3 years in nodules smaller than 30 mL (38). Bernardi *et al*. demonstrated a significantly reduced nodule volume for up to 5 years post treatment that was maintained in 85% of RFA treated patients with a benign nodule with only 12% requiring retreatment (35). Generally, RFA has the best reduction rates for smaller nodules (volume <10 mL), with success for up to 2 years (23,28,29,38-41). Lim *et al*. is one of many to demonstrate that larger nodules (>20 mL) require repeat RFA treatment compared with smaller nodules in order to achieve a similar volume reduction during a 4-year follow up (28). A consensus regarding the definition of small, medium and large nodules is still lacking, including the number of RFA sessions required to achieve desired results (42).

Sensory nerves present around the thyroid capsule are anesthetized with lidocaine injection. Different techniques have been described for nodule ablation; the Korean Guidelines, the Italian society and the Italian working group on Minimally Invasive Treatments of the Thyroid (MITT), the European thyroid association clinical guidelines, as well as the Austrian society recommend using the "moving shot" technique once the probe has advanced into the thyroid nodule (18,19,31-33,43). The probe introduces a high-frequency alternating current that causes localized coagulative necrosis and cell death through high temperatures of 60 to 100 degrees Celsius (44). As a result, slowly and over time, the nodule reduces in size. Sustained nodule reduction has been achieved along with reduced complications and recovery time compared to surgery (22,23). Furthermore, the "moving shot" technique (trans-isthmic approach) has been shown to minimize potential thermal injury to the recurrent laryngeal nerve (13).

Almost a decade ago, the Korean Guidelines published strong evidence that RFA is a safe, well tolerated procedure with a low incidence of complications (1,8,13,18,19,45-48). Over time, various international societies have produced additional guidelines which endorse RFA as a safe and effective treatment for benign nodules. These guidelines include the Korean society of thyroid radiology, the Italian Working Group on Minimally Invasive Treatments of the Thyroid (MITT), the European Thyroid Association Clinical Practice Guidelines, the United Kingdom's National Institute for Health and Clinical Excellence (NICE), as well as the Austrian thyroid association (18,19,31-34,43). The international societies all agree that RFA is safe for benign symptomatic nodules or cosmetic concerns once the nodule is confirmed to be cytopathologically benign on at least two FNA or core biopsies (18,19,31-33,49).

For treatment of benign nodules, the overall complication rate is 2.11% [95% confidence interval (95% CI): 1.15–3.06], whereas the overall complication rate for recurrent thyroid cancers is higher at 10.98% (95% CI: 4.82–17.15) (13). No life- threatening complications are reported, and minor complications include pain, skin burn, and hematoma (19). The most common major complication noted is voice change, with an incidence of 0.94% for benign nodules, and an exceedingly low incidence of permanent changes (13). Nodule rupture is the second most common major complication after RFA treatment (0.17%, 4/2421) (13). Patients may present with sudden neck bulging and pain at the RFA site due to delayed hemorrhage, however the incidence remains low. Additionally, different trials reported the most common complication was temporary pain (10,20,50,51).

Generally, one treatment with RFA maintains effective volume reduction (11,12), however other studies have shown with follow-up longer than 3 years, more than two session of RFA may be necessary to maintain long-term volume reduction (12,28,39). Larger nodules (>20 mL) are more likely to require two sessions of RFA instead of the one treatment that has successfully ablated smaller nodules (40). Studies have demonstrated that RFA reduces nodule volume, relieves local symptoms and cosmetic concerns as effectively as thyroid lobectomy (22,23).

Autonomously functioning tumors

The American Thyroid Association (ATA) Guidelines outline that surgery or radioactive iodine (RAI) treatment is effective for the treatment of autonomously functioning thyroid nodules (AFTN) (52,53). These two options are not always acceptable for patients since RAI involves receiving radiation which is controversial in women of childbearing age (53). Both treatments have potential complications such as hypothyroidism. Even with lobectomy, surgery confers roughly a 30% chance of hypothyroidism, which is generally avoided in RFA-treated patients (54,55). RFA may gain favor with patients wishing to avoid developing post-operative hypothyroidism (10,20,23,50,56,57).

Many trials have demonstrated efficacy and safety of treating AFTN with RFA (10,20,23,50,56,57). However, compared with benign non-secreting nodules, the volume reduction and normalization of thyroid function in AFTN tends to be more variable (50,57). An important factor that can affect whether euthyroidism is achieved post RFA is the nodule size. When the pretreatment volume of the AFTN is small and homogeneous, the outcome tends to be more consistent. Cesareo *et al.* compared the reduction between medium sized nodules (18 mL) versus smaller sized nodules (5 mL), and found that euthyroidism was achieved 86% in small nodules versus 45% in medium size nodules (58). Similarly, Cappelli *et al.* report a volume reduction rate of 73% with TSH normalization in 94% of patients treated with RFA with nodules an average of 7 mL (59). After one session of RFA, Cervelli *et al.* demonstrated a volume reduction rate of 76% with a 91% TSH normalization at 12-month follow up in AFTN that were homogenous in volume and pretreatment size (60). However, in a systematic review, Cesareo *et al.* found only modest results with TSH normalization post RFA treatment (61). Further work done by Cesareo *et al.* found that when the volume of a nodule was reduced by >80%, the greater the chance of thyroid function normalization and symptoms resolution (58,61). Due to the variability in results with AFTN, all guidelines take a more cautious tone when recommending RFA as curative for AFTN (19,31,32-34,43).

Other large multicenter trials and systematic reviews provide promising results for the treatment of AFTN with RFA. Sung *et al.* demonstrated improved symptoms of hyperthyroidism along with normalized TSH levels in 81.8% of study patients without the development of hypothyroidism post RFA (56). In a systematic review, more than 50% of patients after RFA could discontinue their anti-hyperthyroid medications after RFA (32,42). Additionally, patients that received RFA found significant improvement in their compressive symptoms due to the reduced nodule volume (mean volume reduction ratio, 81.7% during the mean follow-up period of 19.9 months). No major complications were reported in this trial (32,42). Progression of hypothyroidism, if any, after treatment may be better explained by the progression of autoimmune thyroiditis associated with preexisting thyroid antibodies.

The Korean Guidelines and various authors suggest that follow up post RFA should be based on ultrasonographic features and TSH of the AFTN (19,56,57). This will determine whether the patient's anti-thyroidal medications can be stopped or if they require another treatment with RFA. Previous studies report a mean number of RFA treatment sessions to be 1.8–2.2 (1–6 sessions) for AFTN (20,62). Previous reports show that single session RFA allowed withdrawal of ATD in 22–50% of patients (50,57). Further, the dose of methimazole was reduced after RFA in 78% of patients (50). The improvement in thyroid function is seen over time after RFA treatment, with 50% remission 12 months after the procedure (57). While RFA for benign nodules is certainly effective and beneficial for most symptomatic patients, the results of RFA for AFTN are more variable.

Malignant tumors

Primary tumors

Papillary thyroid cancer, the most common subtype of thyroid cancer has an excellent prognosis once treated surgically (52). For primary thyroid cancer, surgery is the standard of care, followed by RAI and thyroid replacement therapy (52). Contrary to "one size fits all" approach where all patients presenting with thyroid cancer receive total thyroidectomy, the recent ATA guidelines have recommended thyroid lobectomy or even active surveillance for low-risk cancers (52). This paradigm shift in patient care is supported by large international trials that demonstrate the indolence of papillary thyroid cancer (63,64). This point of departure from the traditional approach is where RFA may be best suited.

In international circles, patients with primary low risk thyroid cancer are offered active surveillance of low-risk thyroid cancer or RFA as an alternative if they are ineligible for surgery (65). The indications for RFA in primary tumors have not been clearly established. Alternative treatments are reserved for patients that clinically require treatment but are too high risk to have repeat surgery, or who refuse surgery (52). Although, the data in North America for this treatment is limited, the Korean Guidelines have provided sound evidence that prove the safety and long-term efficacy of treating low risk papillary thyroid microcarcinomas (PTMC) with success (16,17,65-68). Additionally, for patients that are ineligible for surgery, Kim *et al*. demonstrated a significant mean volume reduction (98.5%±3.3%) with a disappearance rate of 66.7% of primary low risk papillary thyroid cancer during 4 years of follow up (66). The international societies are divided on the use of RFA for primary thyroid cancer, such as papillary and follicular cancer (32). RFA may provide a promising therapeutic option for primary papillary microcarcinoma provided there is no multifocality or nodal metastasis present (32).

Zhang *et al*. demonstrated favorable oncological outcomes in the long term follow up (5 years) for patients treated with RFA for low risk PTMC (65). In their comparison of patients treated with RFA versus surgery, they found a higher quality of life, fewer complications and decreased cost was associated with the RFA treated group. Although papillary thyroid cancer tends to be indolent regardless of the strategy implemented, patients wishing to have treatment without the risks of surgery can undergo RFA safely in very select patients with oncological effectiveness (65).

RFA is effective for treating of papillary thyroid cancer, however more aggressive carcinomas such as anaplastic or medullary have shown mixed results (69,70). Jeong *et al*. demonstrated that RFA reduces tumor size in patients with well differentiated thyroid cancer regardless of whether the tumor is micro- or macro-carcinoma (69). However, when the histology is anaplastic (poorly differentiated), several RFA treatments are required with only minimal improvement in compressive symptoms, likely due to the rapid doubling time of this cancer (69). Thus, RFA is not accepted as primary treatment for aggressive cancers and may be used in palliative situations when all other treatments are exhausted.

Follicular neoplasm, which accounts for 10–20% of malignant thyroid nodules, is best treated with surgery, according to ATA, and and the various international guidelines (19,31,32-34,52). Often, a diagnostic dilemma exists when diagnosing follicular cancer due to the low sensitivity of FNA (71). In order to make a definitive diagnosis of follicular carcinoma, surgical resection is required to detect vascular or capsular invasion (72). For patient's ineligible for surgery, alternatives like RFA are a possibility, however currently, there is a paucity of literature to support this practice. Ha *et al*. reported promising results for patients with follicular neoplasms less than 2 cm (73). Over a 5-year follow up, 8/10 follicular neoplasms disappeared, 2/10 patients had more than 97% volume reduction, and none of the patients developed recurrences or distant metastatic disease (73). Currently, many of the international societies do not support RFA for the treatment of a follicular neoplasm.

Dobrinja *et al*. have recommended that RFA is not used as first-line treatment for follicular neoplasm since it is unknown whether the heat from this modality may promote tumor progression and potentially delay surgery (74). Up to date, there has been no evidence to show that RFA may promote tumor progression. In a 2-year follow-up, patients with benign thyroid lesions had significant reduction in volume post RFA procedure, however in 2/6 patients with follicular neoplasm, with a Bethesda-3 or -4 and a tumor larger than 2 cm regrew after RFA and required surgery (74). It remains questionable whether there was a pre-existing undetected malignancy prior to RFA or whether the size of the treated tumor (>2 cm) played a role. The role of RFA for treating small thyroid malignancies remains to be fully elucidated but may be valuable for those who would otherwise be offered observation due to comorbidities or desire to avoid surgical intervention (e.g., PTMC).

Recurrent tumors

Even though the mortality rate for well differentiated thyroid cancer is less than 1%, recurrences can occur in up to 20% and 59% of patients with low- and high-risk papillary thyroid cancer, respectively (75). Surgical removal is the treatment of choice for locoregionally recurrent thyroid cancer and can improve long term survival (52). However, prior surgery is complicated by scar tissue and undefined tissue planes which can make identification of important structures like the parathyroid glands or the recurrent laryngeal nerve more difficult and potentially risky (76). RFA may be a suitable nonsurgical option for curative or palliative purposes in patients with recurrent thyroid cancer who carry high surgical risk or refuse surgery but clinically need treatment (19).

Various studies have demonstrated that RFA can be used for curative purposes in recurrent thyroid cancer smaller than 2 cm (14,15,77). Kim *et al*. found a disappearance rate of 86% and a low recurrence rate of 11.5% after 3 years of follow up in the RFA group which was similar to the re-operative group (15). When compared with the surgical group undergoing reoperation, the RFA group had fewer complications including vocal cord paralysis and hypocalcemia, demonstrating the safety of this alternative treatment (15). Similarly, Lim *et al*. found that RFA was safe and effective for controlling recurrent papillary thyroid cancer with a 95% volume reduction, as well as a complete disappearance of 82% of the treated tumors, and a significantly decreased serum thyroglobulin level post treatment (14). Additionally, two meta-analyses support ultrasound guided RFA as an effective and safe nonsurgical option for treatment of locally recurrent thyroid cancer (78,79). The therapeutic success rate is 89.5–100%, with a volume reduction rate of >50%, and complete resolution of 68.8% of lesions treated with RFA (78,79). Longer term effectiveness and safety of RFA (>5 years) for locally recurrent thyroid cancer has also been demonstrated, with complete disappearance of 91.3% treated tumors, a 99.5% volume reduction, and significantly decreased serum thyroglobulin levels (80).

In patients with inoperable recurrent thyroid cancer, RFA can be used to provide symptomatic relief due to volume reduction (19). Given the indolent nature of differentiated thyroid cancer, surgery may be too aggressive for patients at risk for recurrent laryngeal nerve palsy, hypoparathyroidism, or spinal accessory nerve palsy. Radiation treatment may benefit high risk patients but leaves patients with side effects that can be worse than the disease itself. RAI is not helpful for eradicating gross disease but can be combined with surgery and radiation for potential benefit. RFA is a safe alternative which has the potential to be combined with other therapies for palliative intent. Symptoms of dysphagia and hoarseness may be more difficult to relieve, however Park *et al*. reported 63.6% of patients experienced improvement in their symptoms of neck discomfort from their bulky tumor compressing the trachea post RFA (81). Lesions that are superficially localized are more effectively treated with RFA than deeper lesions that encase the carotid artery, the recurrent laryngeal nerve or esophagus (81). For the carefully selected recurrent carcinoma, RFA may provide some control without significantly increasing the risk profile.

Conclusions

The current ATA guidelines recommend surgery as the first line of treatment for benign symptomatic tumors, as well as primary and recurrent thyroid cancer. However, in select patients who do not wish to undergo the risks of surgery and a general anesthetic, RFA can be performed in an outpatient clinic with local anesthesia easily, repeatedly and safely. As we continue to accumulate evidence for RFA in the Western Hemisphere and internationally, we anticipate RFA will expand our clinical tools for treating patients and be offered to patients who prefer to avoid surgery.

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