In the past decade, there has been a shift from treating all thyroid cancer surgically, to favoring less aggressive approaches for low-risk thyroid cancer. Surgery was historically the treatment of choice for most thyroid cancer. Active surveillance has emerged as an alternative for low-risk thyroid cancer in select patients. This approach has been accepted worldwide, and sound evidence supports its oncological safety in carefully selected patients. However, not all patients want to undergo lifelong monitoring, and some patients may wish to treat their cancer in a minimally invasive manner. Thermal ablation has developed as a minimally invasive alternative to surgery and active surveillance for well selected patients with thyroid malignancy. Herein, we review the role of thermally ablative techniques, specifically radiofrequency ablation, for the treatment of small primary thyroid cancers, recurrent thyroid cancer, and lymph node metastases.

There is a growing interest in the use of radiofrequency ablation (RFA) for the treatment of thyroid cancer. RFA is a minimally invasive procedure that uses heat to destroy cancer cells. It is performed by inserting a needle into the tumor, which is then heated to a high temperature to destroy the cancer cells. RFA is effective for the treatment of small primary thyroid cancers, recurrent thyroid cancer, and lymph node metastases.

Clinical Evaluation of the Patient

Ultrasound is the procedure of choice for delineating the size and extent of nodules in the thyroid, determining the
proximity of the nodules to important neurovascular structures, and evaluating the lateral neck compartments for metastatic lymph nodes. If there is clinical concern that a nodule extends below the clavicles or is locally invasive of the visceral, axial imaging such as a contrast enhanced CT scan can be performed.

If the cytopathology from a fine needle aspiration reveals a new diagnosis of papillary thyroid cancer, or other forms of well-differentiated thyroid cancer, surgical referral is generally recommended unless the patient has a low-risk PTMC. However, if a biopsy proven recurrent papillary thyroid cancer is present, the patient should first undergo multidisciplinary review to discuss treatment options.

An important consideration for determining whether a patient is a candidate for thermal ablation include the absence of a family history of thyroid cancer. Certain histopathological variants of thyroid cancer are associated with familial tumor syndromes and are likely better served by surgery. For example, the cribriform-morular variant of papillary carcinoma is seen in patients with familial adenomatous polyposis. Others, such as PTEN hamartoma tumor syndrome is associated with papillary or follicular thyroid cancer as well as benign and malignant tumors of the breast, endometrium, and colon hamartomas. Furthermore, patients who have had prior radiation to their head and neck or environmental exposure (eg Chernobyl) would likely benefit from surgical resection instead of RFA given their increased risk of developing additional tumors.

Active Surveillance for Low Risk Primary Thyroid Cancer

Over the last few decades, there has been a push toward active surveillance of papillary thyroid microcarcinoma (PTMC) in select patients. The World Health Organization (WHO) defines PTMC as a small papillary thyroid cancer (≤ 10 mm in greatest dimension). The American Joint Committee on Cancer (AJCC) TNM system classifies T1 category (T1a: ≤ 2 cm into T1a: ≤ 1 cm and T1b: ≤ 2 cm). Several studies have demonstrated that the distinction between a T1a and T1b is minimal in terms of prognosis in the absence of high risk pathological features or extrathyroidal extension. Currently, the ATA guidelines recommend AS for T1aN0 and potentially for T1bN0 low risk thyroid cancer.

Patients with small papillary microcarcinomas that are intrathyroidal, lack aggressive cytopathology, and lack local invasion or clinically detectable metastases are candidate for AS. Various prospective studies have been conducted for AS of low-risk (T1aN0M0) PTMC since the 1990s demonstrating favorable outcomes that include a low rate of growth, rare regional or distal lymph node metastases, and low mortality. In a systematic review and meta-analysis, Cho et al., found the pooled proportion of tumor size enlargement (defined as 3 mm or more) occurring at 5 years was 5.3% (95% confidence interval (CI), 4.4%-6.4%), and the pooled proportion of 5-year lymph node metastasis was only 1.6% (CI, 1.1%-2.4%).

While active surveillance makes sense from a population health perspective, it can be burdensome on patients and it does not address patient anxiety. Many patients who live in rural areas and are not prepared to commute to a large city center for regular surveillance. Cho et al. demonstrated the main reason for patients undergoing surgery at a later date instead of ongoing active surveillance (32%-69%) was due to patient anxiety rather than disease progression. The key concerns from the AS group were the risks of surgery, the possibility of having to take thyroid hormone treatment, and the potential impact on quality of life, making thermal ablation an attractive option.

Indications for Radiofrequency Ablation

Low Risk Primary Thyroid Cancer

Currently, the recommendations for treatment with RFA in primary thyroid carcinoma are low risk papillary thyroid cancer patients who would be otherwise eligible for AS or refuse surgery. The majority of studies have demonstrated the efficacy and safety of thermal ablation for low-risk papillary thyroid microcarcinoma (PTMC) as well as for smaller papillary thyroid carcinoma (PTC) less than 2 cm. In a long-term retrospective study, Cho et al. found complete disappearance rates of 98.8% at 24 months and 100% at 60 month follow-up after RFA of 84 PTMC’s. After more than 5 years of follow-up, there was no local progression, regional or distant metastases, delay in surgery or procedure related death found.

Careful evaluation by ultrasound is paramount to rule out aggressive sonographic characteristics that may prevent delay for patients who would be better served with surgery. The cytopathology should confirm classic variant of PTC without evidence of histological aggressiveness that is associated with the tall cell variant, hobnail variant, or the columnar cell variant. The tall cell variant has a higher rate of recurrence, poorer survival compared with the classical variant, and a BRAF mutation (associated with extrathyroidal extension and lymph node metastases) in up to 80% of these tumors. The hobnail variant and the columnar cell subtype are associated with frequent distant metastases (typically to the lung) and increased risk of tumor-related death. Other variants of papillary carcinoma such as the solid variant and diffuse sclerosing variant are also associated with a less favorable outcomes however the data is conflicting. The presence of TERT promoter and TP53 mutations are contraindications to the use of thermal ablation. Although the combination of BRAF and TERT promoter mutation is very rare, the two are associated with a poorer prognosis in PTC. Tumor location is also an important consideration. A more superficial location makes a tumor more amenable to RFA as there is more distance from the trachea and the recurrent laryngeal nerve. Tumors that abut the trachea carry a higher risk of invasion, particularly if no rim of normal thyroid tissue is observed.
Follicular and Medullary Thyroid Ablation Cancer

The use of RFA is controversial for the treatment of follicular neoplasms (Bethesda III/IV) and is not endorsed by the various international societies nor the American Thyroid Association guidelines (ATA) due to the lack of evidence showing long-term treatment benefit. Although up to 80% of follicular neoplasms are benign, an fine needle aspiration resulting in follicular neoplasm does not decryster between a benign or malignant lesion.35 Lobectomy is the treatment of choice to be informed of their treatment options including RFA.1,9 While best cared for in a multi-disciplinary manner, and should be treated surgically, RFA has been shown to be effective at local control.36,37 For patients deemed to be high risk candidates for recurrent laryngeal nerve and the parathyroid glands due to replacement, and/or external beam radiotherapy and chemotherapy depending on the extent of regional or distant disease.1 Revision surgery is fraught with risk, particularly to the exclusion of vascular or capsular invasion and to definitively diagnose whether the nodule is a follicular adenoma or a carcinoma.1 Without long-term data, RFA for follicular carcinoma is not recommended at this time since incomplete treatment could potential lead to distant metastasis years later.

For medullary thyroid cancer (MTC), aggressive surgery remains the treatment of choice. Only a handful of case reports have evaluated RFA for early MTC in patients ineligible for surgery or for patients with a regional recurrence after surgical resection of their MTC.36,37 Similarly, for inoperable poorly differentiated tumors such as anaplastic carcinoma, RFA has a questionable clinical benefit beyond palliation.

Recurrent Thyroid Cancer or Metastatic Lymph Nodes

The standard of care for recurrent thyroid cancer is surgery, followed by radioactive iodine treatment (RAI) for cancers that demonstrate iodine avidity, suppressive thyroid hormone replacement, and/or external beam radiotherapy and chemotherapy depending on the extent of regional or distant disease.1 Revision surgery is fraught with risk, particularly to the recurrent laryngeal nerve and the parathyroid glands due to scarring in the thyroid bed. For patients deemed to be high surgical risk or for those who do not wish to undergo revision surgery, RFA has been shown to be effective at local control.1

Patients presenting with recurrent thyroid carcinoma are best cared for in a multi-disciplinary manner, and should be informed of their treatment options including RFA.1,9 While the indications for RFA ablation of recurrent thyroid carcinoma have not been clearly established in the United States, several studies have indicated that if the treatment is intended to be curative, RFA is most effective for patients with small indolent metastases (≤10 mm) and ≤ 3-4 loci of recurrent thyroid cancer in the neck and without metastatic cancers beyond the neck.9,38-40 However, when 3-4 metastases are present, the likelihood of subclinical regional or distant metastases is increased. In these cases, RFA could be used for local control if surgery or RAI are not feasible. For patients with unresectable primary9 or recurrent cancer, RFA may be used in a palliative fashion.9

RFA has been demonstrated to be effective for small localized recurrent thyroid cancer.1,9-42 Choi et al. compared RFA to surgery for small localized recurrent thyroid cancer and found comparable recurrence-free survival rates between both groups (P = 0.2) with no significant differences in mean serum thyroglobulin levels and the mean decrease after treatment between the groups (P = 0.891 and P = 0.963).43 Although this retrospective study shows promising results, we do not know the true long-term outcome of this approach beyond the five of years of available data.

Two meta-analyses support the effectiveness of RFA treatment for patients with locally metastatic recurrent well-differentiated PTC who refused surgery or were ineligible in terms of significant volume reduction as well as reduced biomarker levels (thyroglobulin) post treatment. Zhao et al. examined nine articles including 189 patients (54 male, 135 female) with 255 tumors treated with RFA, and follow up for more than six months.41 Their results showed that tumor volume, largest diameter, and thyroglobulin level were decreased after RFA. In a second meta-analysis, Suh et al. included ten studies with a 270 patients and 415 locally recurrent papillary thyroid cancers.42 The volume reduction ratio was more than 50% after RFA in 100% of patients, and the pooled proportion of recurrence after RFA was 0%. Both studies show promising short-term data, however larger trials with longer term data beyond 5 years is necessary and patients should be counselled appropriately.

Technical Considerations for RFA of Malignant Tumors

The electrode active tip length is chosen based on the size of the tumor and how close the tumor sits in relation to surrounding critical structures. For PTMC, a smaller tip that is no more than 7 mm is the norm. Generally, a monopolar electrode with a smaller tip (5 mm) can safely and effectively treat tumors that are adjacent to neurovascular structures.

RFA is attractive to patients and providers because of the ability to ablate tumors in an outpatient setting, without an incision or a general anesthetic. Appropriate positioning is important, especially for patients who have had prior surgery, because good ultrasound visualization is key for safe RFA. Local anesthetic is typically adequate for small tumors, although patients with larger tumors undergoing palliative treatment may require conscious sedation.

Once the patient is anesthetized locally, typically the “trans-isthmic approach” and the “moving shot technique” are used, as for benign nodules. It should be noted that smaller tumors may be treated at a lower wattage with only a single slow pull back. By using lower wattage, there is increased thermal spread which can effectively treat the entire nodule with just one pass in some cases. Based on tumor size, location, and vascularity, advanced ablation techniques may be necessary to fully treat thyroid tumors. As opposed to benign nodules, extending the ablation margin several millimeters beyond the tumor border will reduce the risk of recurrence. For malignant tumors that are close in proximity to vital structures, hydrodissection should be used by injecting 5% dextrose solution (D5W) between the thyroid capsule and critical structures to create a thermal barrier.44 Vascular ablation techniques (artery first ablation or marginal venous ablation) are often unnecessary for small tumors as ablation will simultaneously treat the tumor and thrombose the vascular supply. However, for
patients with larger tumors who are being treated with RFA due to high surgical risk or palliation, these vascular ablation techniques may be beneficial.

**Recognizing and Treating Complications**

Although multiple studies have established that RFA has an excellent safety profile, recurrent malignant nodules tend to have a higher complication rate compared with primary benign nodules shown in a systematic review (10.98% vs 2.11%). One of the more common minor complications reported for recurrent thyroid cancer include voice change which is 7.95% (14/176) compared with 0.94% (21/2245) for benign nodules. This can be mitigated by carefully evaluating the proximity of the tumor to the danger triangle on ultrasound, reducing the power of the generator if the patient reports pain, and performing hydrodissection to provide a thermal buffer. If a nerve injury is detected, the nerve should be bathed with chilled D5W (rescue hydrodissection) until symptoms resolve. It should be noted that postoperative patients can have distorted anatomy and a high degree of skill both with ultrasound and RFA combined with knowledge of normal and postsurgical anatomy is necessary to minimize complications.

**Clinical Follow Up and Post Procedural Evaluation**

As with thermal ablation of benign nodules, close clinical follow up after the procedure is critical. Cho and colleagues demonstrated that after RFA, PTMC will likely increase in volume for the first 3-6 months, but may disappear in the following 12-18 months. This is due to ablation of a margin of normal tissue around the tumor, and can give the false impression that the tumor is progressing. The postoperative evaluation should include a physical exam, an ultrasound evaluation, TSH, and thyroglobulin. While the optimal follow up schedule remains to be determined, many providers will see patients back at 1, 3, 6, and 12 months, and every 6 months thereafter. Post-procedural recommendations gleaned from the Korean Society of Interventional Radiology and the European Thyroid Association guidelines include:

1) Pre- and Post-procedural symptom score profiles are filled out by patients using a grade 0 to 10 scale. In addition, a cosmetic score is measured by a physician according to the following grades: 1, no palpable mass; 2, a palpable mass without cosmetic problems; 3, a cosmetic problem on swallowing only, 4 – visible cosmetic problem.

2) The volume reduction ratio (VRR) which is measured pre- and post-operatively on ultrasound. The VRR is equal to: (Initial volume – Final volume x 100/Initial volume).

3) Blood work to measure TSH pre- and post-operatively, and if indicated, thyroglobulin in recurrent thyroid cancer.

4) Long term follow up is recommended (greater than 5 years) until further studies on larger cohorts of patients are done to better understand the risk of disease recurrence and metastatic spread after RFA.

**Conclusions**

RFA has been shown to be safe and effective for long-term local tumor control for low-risk PTMC in patients ineligible for surgery or those who do not wish to undergo active surveillance. In certain clinical situations, RFA may be used for local control in small recurrent tumors or to palliate symptoms in unresectable cancer. Further studies are ongoing to better define the role of thermal ablation for the treatment of malignant thyroid tumors.

**References**

1. 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. 26:1-133, 2016


Anderson KL, Youngwirth LM, Scheri RP, et al: T1a versus T1b differentiated thyroid cancers: do we need to make the distinction? Thyroid 8:1046-1052, 2008


Ito Y, Miyachi A, Kihara M, et al: Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 24:27-34, 2014


