Review Article

Radiofrequency ablation of thyroid nodules: a clinical review of treatment complications

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Abstract: Radiofrequency ablation (RFA) is a minimally invasive ablative modality for the treatment of thyroid nodules. Reports of RFA use have demonstrated an impressive safety profile and excellent volume reduction rates between 60–90%. Given its increased popularity in the United States as well as globally, numerous recent works have been published and a discussant of relevant complications incorporating recent insight may assist practitioners in minimizing complications and optimizing patient outcomes. Herein, we provide a comprehensive and updated review of the reported complications and side effects following RFA, summarizing their frequency and clinical presentation. We also describe a means of minimizing such complications and/or side effects. Overall, the safety profile of RFA is impressive and superior to that of thyroid surgery. The overall risk of complication is reportedly 2–3%. The risk of permanent complication or severe injury is very unlikely, below 1%. Complications are infrequent, but may be nerve-related, endocrine-related, or iatrogenic-related, and consequences of localized heat delivery. The vast majority of complications related to RFA can be managed conservatively, without need for invasive measures. This review will assist surgeons and clinicians in recognizing and treating the various complications and side effects in clinical practice.

Keywords: Radiofrequency ablation (RFA); complication; review

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Introduction

The incidence of thyroid nodules has risen in past decades secondary to increased surveillance and detection (1). Though the majority of thyroid nodules are benign, their increased detection rates have allowed thyroid cancer to be the fastest-growing cancer (2). Non-surgical management of non-functional thyroid nodules includes anti-thyroid medications and radioactive iodine ablation. Treatment by anti-thyroid drugs can be considered if the patient is in a hyperthyroid state, secondary to an autonomously functioning thyroid nodule, for example. For indications such as remnant ablation of benign tissue, adjunctive treatment, or treatment of a known disease, radioactive iodine ablation may be considered (3,4). Yet, radioactive iodine ablation is associated with hypothyroidism and radiation exposure, and higher doses of radiation tends

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Table 1 Complications following RFA and their reported incidence rates

Complication	Incidence rate
Transient recurrent laryngeal nerve palsy	0.86–1.02%
Permanent recurrent laryngeal nerve palsy	0.00–0.17%
Brachial plexus injury	0.07%
Horner syndrome	0.13%
Nodule rupture	0.19–2.5%
Hematoma	0.9–2.1%
Hypertension	0.46%
Vasovagal reaction	0.34%
Fever	0.3–6.0%
Skin burn	0.27%
Edema	1.00%
Pain	0.8–15.7%
Vomiting/nausea	0.62%
Permanent hypothyroidism	0.07%
Cough	1.26%

Incidence rate values taken from large multi-institutional works and/or meta-analyses. RFA, radiofrequency ablation.

to confer a greater risk for the development of solid cancers (5). Consequently, radioactive ablation may not be an attractive treatment modality for patients with a previous malignancy or large thyroid glands. Importantly, radioactive iodine ablation and methimazole, the most commonly prescribed anti-thyroid medication, are both contraindicated in women who are either pregnant or breastfeeding. Surgical management has been the classic management modality of symptomatic thyroid nodules, especially if malignant (6). Yet, surgical intervention carries with it the risk of nerve palsy, hypothyroidism, and hypoparathyroidism. Considering some of these concerns, percutaneous minimally invasive technologies have risen as attractive treatment modalities including microwave, laser, and radiofrequency ablation (RFA).

Ultrasound-guided RFA utilizes a percutaneous electrode to deliver a uniform centrifugal zone of thermal energy (7). Soft tissue ablation by RFA has been implicated in cardiovascular and vascular settings, as well as tumor ablation including those of the liver, lung, bone, adrenal, parathyroid, and thyroid. In specific, RFA of thyroid nodules has been shown to be quite successful, achieving volume reduction rates between 65–90%, with an impressive safety profile (8,9). In this review, we discuss the pertinent complications following RFA of thyroid nodules (*Table 1*).

Overall

According to the most recent, comprehensive meta-analysis, 2,786 nodules with a mean volume of 10.3 mL (range, 0.05–27.7 mL), had an overall complication rate of 2.38% following RFA. The authors reported the rate of major and minor complications to be 1.47% (41/2,786) and 1.72% (48/2,786), respectively (10). Of the nodules studied, 91.2% were benign thyroid nodules and 8.8% were malignant. The authors noted a significantly higher (P=0.0038) major complication rate in malignant versus benign thyroid nodules (10).

Nerve injury

Recurrent laryngeal nerve palsy

Recurrent laryngeal nerve palsy is a major complication encountered by patients undergoing RFA. One study of 1,543 benign thyroid nodules reported voice change with a frequency of 1.02% (15 cases), all cases reported thyroid nodules close to the recurrent laryngeal nerve (11). Similarly, Kandil *et al.* led the largest North American multi-institutional experience with RFA and reported only 2 cases of temporary voice change (2/233, 0.86%) and no incidences of permanent voice change (12). Patients experiencing nerve palsy typically present with hoarseness of voice during or immediately following the procedure. Vocal cord palsy can be confirmed by a post-procedural laryngoscope. Importantly, nerve palsy is typically transient with symptoms resolving passively within 2 to 3 months (13), though cases of permanent voice change have been reported (10,14-16). One work described permanent ipsilateral laryngeal nerve paralysis in two separate patients, both of whom had nodules that were paratracheally located (15). Aldea Martínez *et al.* reported only a single permanent complication in their series of 24 benign thyroid nodules, in which the patient experienced laryngeal nerve palsy (16).

In order to minimize the risk of nerve palsy, anatomical mastery of vital neck structures is required by practitioners. Though the path of the recurrent laryngeal nerve is quite variable (17), it typically courses within the 'danger zone', which is both deep and medial, lying near the tracheoesophageal grooves. Considering this, practitioners should either ablate the medial portion of the nodule with extreme care or not at all (12). Potential avenues of minimizing nerve palsy include rescue hydrodissection, the injection of dextrose in 5% water (D5W) medial to the nodule, and utilizing the 'moving shot technique'. The moving shot technique conceptualizes the thyroid gland into many spherical units which would be ablated. This is fitting as RFA delivers localized heat and allows for controlled ablation sessions (18). The use of intraoperative nerve monitoring is a tool frequently used in the operating room for surgeons to localize and ensure the functional integrity of the vagus nerve and its branches, including the recurrent laryngeal nerve (19). Recently, a prospective case series including 20 benign thyroid nodules reported similar laryngeal adductor reflex amplitudes before and after RFA during continuous intraoperative nerve monitoring (20). In addition, with the patient under local anesthesia, intermittent conversations with the patient allows for real-time feedback on intraoperative nerve integrity. If nerve injury is noted intraoperatively, rescue hydrodissection should ensue and the nerve should be bathed with chilled D5W (21).

Brachial plexus injury

Injury to the brachial plexus is rare following RFA due to its anatomical location deep in the neck. However, penetration of the electrode through or outside of the thyroid capsule can lead to nerve injury (13). Only one brachial plexus nerve injury following RFA of a thyroid nodule is discussed in the literature. Baek *et al.* present a brachial nerve injury (1/1,459, 0.07%), reporting a patient who displayed symptoms of numbness and decreased sensation in the fourth and fifth fingers of the left hand shortly after ablation therapy (11). The patient gradually recovered over the subsequent 2 months. This complication substantiates the importance of adequate visualization of the entire length of the electrode tip with ultrasound to prevent penetration beyond desired tissue (11,22). Additionally, a comprehensive understanding of surrounding anatomy to prevent damage to adjacent nerve structures (vagus nerve, phrenic nerve, sympathetic chain ganglion, and brachial plexus) is necessary for prevention.

Horner syndrome

Horner syndrome manifests in patients who have sustained damage to sympathetic nerves and is a fearful yet rare complication of ultrasound-guided neck procedures. Patients present with a clinical diagnosis of a well-known triad: ptosis, facial anhidrosis, and miosis ipsilateral to the affected side (23). An early predictive sign of Horner syndrome may be pain associated with an eye or conjunctival redness, warranting immediate evaluation. Typically, deeper dissections to the anterior cervical spine or cervicothoracic junction can cause Horner syndrome (24). Still, one study of 746 patients undergoing ultrasound-guided RFA reported only a single case of Horner syndrome, an incidence of 0.13% (25). This patient with a benign thyroid nodule complained of left ocular discomfort and reddened left conjunctiva immediately following the procedure (25). They later developed progressive left ptosis, miosis, and anhidrosis with little improvement over 6 months (25). Damage to the middle cervical sympathetic ganglion, located deep in the anterior neck and adjacent to the thyroid, can bring about Horner's syndrome. These nerves can be confused with surrounding structures such as thyroid nodules or lymph nodes (25,26). The connection of the middle cervical sympathetic ganglion to surrounding sympathetic nerves can be utilized on ultrasound to differentiate this ganglion from surrounding lymph nodes (27). The middle cervical sympathetic ganglion can only be visualized 41% of the time on ultrasound, and its detection and subsequent avoidance during RFA is crucial in minimizing nerve injury and symptomatic sequelae (27).

Immediate effects

Fever

Intraoperative febrile events have been reported in patients undergoing RFA of thyroid nodules. Of the febrile events reported in the literature, this side effect occurs with a frequency of 0.3–6%, with patients commonly reaching up to 38 ℃ (11,28-30). One study details that in all 5 of their febrile patients, the fever spontaneously resolved 24–36 h post-RFA treatment (29).

Skin burn

Skin burns following ablation have been reported. In one study, 4 of 1,459 patients (0.27%) developed first-degree burns at the puncture site (11). All four reported mild pain and skin color changes at the burn site, with symptom resolution within 7 days (11). Most skin burns mentioned in the literature following RFA are minor, first-degree burns with uneventful clinical sequelae and resolution 7–10 days post RFA (11,25,31). However, one study reported a case of a full-thickness burn that took 3 weeks to heal and resulted in scar formation (32). Thus, the degree of burn should be acknowledged with clinical follow-up as needed. Importantly, the use of a bipolar electrode may minimize this complication and is accordingly especially recommended in pregnant patients or those with electrical cardiac devices (33).

Pain and/or heat

Pain is common after any procedure. For RFA procedures, it is one of the most commonly reported side effects. Pain is reported at a rate of 0.8–15.7% in patients, with symptoms often resolving spontaneously in 1–2 days (11,25,29,34). In their experience, Jeong *et al.* report that 13 patients (5.5%) complained of pain for longer than 2 days and required acetaminophen to control the pain (35). Importantly, this pain can be intolerable, with one study of 875 subjects reporting 7 patients who developed pain during the procedure which prompted treatment termination. These patients' complaint of pain persisted for more than 3 days post-operatively despite medical therapy (25).

Vomiting/nausea

Post-operative nausea is a well-known side effect of most procedures. One study reported that 9 of their 1,459 patients developed vomiting after RFA but recovered within 1–2 days (11). Similarly, another study of 875 subjects discussed 4 patients who developed vomiting as a side effect of RFA (25). Antiemetics can be administered in these patients post-operatively (13).

Cough

Patients may complain of cough following RFA. For example, Kim *et al.* reported that 11 patients (1.26%, 11/875 patients) developed 10–30 s coughing spells postoperatively. All patients recovered without any significant complication (25). Coughing can be triggered intraoperatively as well. A prospective study of 40 patients reported that two patients developed coughing during the procedure (28). Coughing during RFA may occur while ablating nodules close to the trachea, thus special care must be taken ablating nodules in this region (13,25). Utilization of the trans-isthmic approach, whereby the electrode is inserted into the isthmus with the electrode resting on the trachea, may minimize the risk of cough development as well as improve electrode stability in the event the patient does cough (22).

Vasovagal reaction

A vasovagal reaction or vasovagal syncope occurs when heart rate and blood pressure suddenly drop (13). Vasovagal reactions also include difficulty breathing, vomiting, and defecation. Vasovagal reactions are often triggered by a strong emotional response or pain. It has also been postulated that these reactions occur if the vagus nerve is stimulated during the ablation of a nodule in its immediate proximity (13). In one study, 5 of 1,459 patients (0.34%) developed a vasovagal reaction after RFA, but recovered within one day, without any sequelae (11). Another study reported that 7 of 875 patients (0.80%) developed a vasovagal reaction in response to RFA, which resolved within 10 min, either by discontinuing the procedure or elevating the patient's legs (25).

Hypertension

Hypertension has been reported to occur during the RFA procedure. It is thought to occur as thyroid hormone is released from thyroid tissue that is being ablated or in response to pain associated with the ablation (25). One study demonstrated that 4 of 875 patients (0.46%) had increases in blood pressure greater than 40 mmHg compared to baseline measurements, requiring medical therapy (25). Notably, these 4 patients also had underlying hypertension. Surgeons should be aware of this possible complication, especially when treating patients with poorly controlled hypertension. Though continuous blood pressure monitoring is not widely exercised, it is recommended by the Korean guidelines (36). Patients with hypertensive urgency should likely not be treated by RFA until their blood pressure has been adequately treated.

Diffuse glandular hemorrhage

Hemorrhage of the thyroid gland post-RFA can present with acute voice changes, severe pain, and pressure on the neck. These symptoms occur during the procedure and require mild compression of the neck and direct vessel ablation (11,25). Of note, hematoma development adjacent to critical structures can lead to transient dysphonia (25). Hemorrhaging can be prevented with careful inspection of the perithyroidal vessels and anterior jugular vein with ultrasound, and swift insertion of the RFA electrode. Additionally, the use of a small-bore electrode (18 gauge) can minimize the risk of vessel damage and hemorrhagic sequelae, when compared to large-bore electrodes (11,37).

Hematoma

Post-operative hematoma following RFA of thyroid nodules has been reported. Hematomas occur in about 0.9–2.1% of cases (13,35,38). Although hematomas are often seen post-operatively, Rabuffi *et al.* discuss a sudden presentation of a neck hematoma during the procedure upon insertion of the electrode, necessitating immediate cessation of the operation (38). Typically, hematomas present as perithyroidal, subcapsular, or intranodular due to injury to the anterior jugular vein or perithyroidal vessels (39). Conservative treatment is often recommended with mild neck compression for 5–10 min and complete resolution with time, often within 1 to 2 weeks (39,40). Hemorrhaging can be prevented during RFA with a detailed understanding of the neck anatomy for careful examination of perithyroidal vessels and anterior jugular veins (11).

Hypothyroidism

Although rare, there have been a few reports of hypothyroidism following RFA (34). One study involving 1,459 patients revealed that 1 patient developed permanent hypothyroidism (11). Pre- and post-RFA labs in this patient revealed elevated anti-TPO antibodies, suggesting an autoimmune disorder (11). Another study demonstrated that 1 of 875 patients developed transient hypothyroidism in the immediate postoperative period, within 24 h of the RFA (25). While the etiology remains unclear, both studies suggest the progression of autoimmune thyroiditis may cause hypothyroidism to develop after RFA (11,34). The presence of pre-existing anti-thyroid antibodies may put patients at increased risk for developing hypothyroidism. In consequence, it has been suggested that all patients undergoing RFA treatment have pre-procedure thyroid function tests to evaluate for the presence of anti-thyroid antibodies (11,13,34), which could potentially predict post-procedural hypothyroidism. To treat hypothyroidism, patients may receive levothyroxine therapy post-operatively (13).

Needle tract seeding

During a needle biopsy, tumor cells can be implanted along the needle tract and go on to seed surrounding structures. This rare, iatrogenic phenomenon has been cited as a risk of fine needle aspiration (FNA) and core needle biopsy procedures but is an unlikely, but notable complication when considering RFA (41-43). A single case of needle tract seeding has been reported in the literature, describing a 19-year-old female who was treated twice by RFA and subsequently developed a subplatysmal mass. The patient's second mass took 2 years to develop and was successfully treated by thyroidectomy (18). Beyond the thyroid gland, certain factors have been shown to increase the risk for seeding, including an increased diameter of the needle, multiple passes to collect biopsy, and large tumor size (41,44-47).

Misdiagnosis of a parathyroid adenoma

Intrathyroidal parathyroid adenomas are the third most common location for ectopic parathyroid adenomas (18% of ectopic adenomas), occurring with a frequency of 1.4% to 4.0% of all patients with parathyroid adenomas (48-53). While purposeful ablation of a parathyroid adenoma is not a complication, the ablation of a parathyroid adenoma misdiagnosed as a thyroid nodule can be considered as such. This has been reported once in the available literature (54). The case describes a 53-year-old female whose 2.3×1.3 cm nodule was misdiagnosed as a thyroid nodule on preoperative fine-needle aspiration. The nodule was treated by RFA, did not diminish in volume, and subsequently grew over the next two years. Finally, a Tc99-Sestamibi scan determined the nodule to be a parathyroid adenoma, after the patient presented with a primary hyperparathyroidism sequela: weakness, hypercalcemia, and spondylolisthesis. The patient was successfully treated by parathyroidectomy shortly after, yet the case underscores the importance of clinical reasoning. In most cases, this ectopia is found in one of the inferior parathyroid glands with a highly variable diagnostic sensitivity detecting between 25% to 67% of cases on the ultrasound (48,53,55). Thus, these nodules can be easily mistaken for thyroid nodules.

Muscle twitching

Muscle twitching has been reported as a side effect of RFA. One study demonstrated that 1 of 875 patients (0.11%), developed muscle twitching in response to RFA (25). The authors postulate that muscle twitching occurred because of lidocaine toxicity (25).

Tracheal/esophageal injury

Tracheal and esophageal injury occur when the trachea or esophagus are perforated and ablated during RFA. Two independent series of 1,543 nodules and 302 nodules reported zero incidences each (35). This serious and life-threatening complication may be prevented by maintaining a safe distance between the electrode tip and the trachea.

Other

Nodule rupture

Thyroidal nodule rupture occurs when the thyroid capsule breaks down allowing for extravasation of intrathyroidal fluids (10,11). Nodule rupture can most often be managed conservatively (analgesics, antibiotics), yet may require invasive measures such as aspiration or surgical intervention (debridement/lobectomy). On ultrasound, thyroid nodules at risk of rupture typically gradually decrease in size. Surgical intervention/drainage is indicated when an abscess forms (36). The complication rate for nodule rupture ranges between 0.19–2.5%, often presenting as a sudden painful, edematous neck (11,25,28,56-59). Symptoms present months after RFA treatment, with one study that described 26 patients with ruptured nodules reporting an average of 54.8±43 days (56). Thyroid nodules are more likely to rupture through the anterior part of the thyroid capsule (83%, 25/30) and are depicted as a bulging heterogeneous density of soft tissue on an ultrasound (11,56,57,59). This is thought to be due to intra-nodular hemorrhage causing the subsequent formation of fluid surrounding the intra- and extra-thyroidal tissue (56). Bleeding within the thyroid nodule may be due to microvascular leakage within the tumor, patient hypervascularity, tearing of the tumor wall and thyroid capsule, or massaging/excessively moving the neck after the procedure (59,60). Knowledge of these potential causes for nodular rupture may minimize risk. Invasive management is sometimes necessary (45%, 15/33) (11,13,57,59), and is recommended if the nodule was initially greater than 4.5 cm in diameter (56). For smaller nodules, conservative management, such as a course of antibiotics, might be administered first before drainage. As aforementioned, however, detection of thyroid abscess requires surgical intervention/drainage (36).

Edema

Mild post-operative edema at the site of electrode insertion is fairly common, and if severe, can be treated with anti-inflammatory medication. One study of 31 patients reported that most patients had mild edema after ablation, but often resolved spontaneously within 24 h. Three of their 31 patients were treated with a single dose of 1.5 mg betamethasone to reduce the swelling (61). A retrospective study of 100 patients reported 1 patient that not only developed edema of the thyroid tissue post-operatively but also a painful swelling of the skin (62). The authors of this study reported complete resolution of the edema in 12 days with anti-inflammatory therapy (62).

Pseudocystic transformation (colliquation)

Often compared to nodular rupture in presentation, pseudocystic transformation is rarely reported. This transformation causes leakage of fluid into the neck muscle fascia. Valcavi *et al.* discuss the presentation of a patient with pain and sudden swelling in their neck 3 weeks after RFA (13,28). The resolution of symptoms and clinical outcome was not mentioned. Diagnosis of this complication can be made with ultrasound though the normal appearance of post-RFA thyroid nodules (hypoechogenicity, heterogenicity, and irregular margins) can be misinterpreted as a pseudocystic transformation (13). The prevalence of pseudocystic transformation is reportedly variable, from 0.3–4.9% of patients after undergoing RFA on thyroid nodules (11,28,59,63). Understanding the signs and symptoms at presentation can assist surgeons in clinically recognizing and treating pseudocystic transformation. Since patients typically report pain and sudden swelling, these patients can be treated with oral corticosteroids (28).

Considerations

The incidence of complication is significantly higher in malignant as compared to benign lesions. For example, a 2017 meta-analysis reported an overall complication rate of 10.98% as compared to 2.11% in malignant versus benign lesions (P=0.001). Investigating only major complications, they accordingly reported 6.71% and 1.27% complication rates (P=0.003) (10). With respect to tumor type, papillary thyroid carcinomas are typically indolent in nature and have impressive volume reduction rates. A recent meta-analysis of 1,770 papillary thyroid microcarcinoma patients reported that 79% of all tumors completely disappeared (64).

The complication rate of other minimally invasive ablative techniques are comparable to RFA. For example, laser ablation can be used to treat thyroid nodules and has a reported complication rate of 0.5% rate for voice change (65), which is similar to RFA. It is worth noting that RFA was shown to be superior with respect to volume reduction [RFA: 77.8%, 95% confidence interval (CI): 67.7–88.0% compared to laser ablation (LA): 49.5%, 95% CI: 26.7–72.4%], though this work was published in 2015 (66). Microwave ablation is another thermal technique used to treat thyroid nodules. Cheng *et al.* reported that microwave ablation and RFA had comparable rates of complication, at 6.63% and 4.78%, respectively. The authors also reported similar volume reduction rates with either modality, with 57.9% using microwave ablation and 64.5% using RFA (P>0.05) (67). Minimally invasive ablative techniques such as RFA, laser ablation, and microwave ablation, in general, have similar complication rates which are less than that of traditional thyroidectomy.

Conclusions

Understanding the complications of RFA therapy for the treatment of thyroid nodules is important for the prevention and early recognition of symptoms for treatment. Our review provides an updated, comprehensive summary of possible complications following RFA for surgeons and clinicians alike to better optimize the best management and surgical practices.

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Footnote

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