Case Report

Radiofrequency ablation as a novel modality in the USA for treating toxic thyroid nodules: case series and literature review

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Background: Radiofrequency ablation (RFA) is widely accepted as a treatment for non-functioning benign thyroid nodules, mainly to reduce compressive symptoms. In addition to potential compressive symptoms, autonomously functioning thyroid nodules (AFTNs) can cause palpitations, weight loss, diarrhea, increased appetite, flushing, irritability, tiredness, poor sleep, and long-term cardiovascular and musculoskeletal consequences. Currently, there are no United States based RFA practice guidelines for the treatment of AFTNs. However, several reports from Asia and Europe have described the resolution of hyperthyroidism secondary to AFTNs with RFA.

Case Description: Three patients with toxic thyroid nodules presented with symptomatic hyperthyroidism, suppressed thyroid-stimulating hormone (TSH), and increased uptake on nuclear medicine thyroid scan. These patients were treated with RFA. At 3 months following ablation, TSH normalized to 2.09, 1.91, and 1.34 mIU/mL respectively. However, temporary hypothyroidism was encountered at 1 month following ablation. All patients discontinued their antithyroid medications following ablation. Nodules exhibited significant volume reductions of 38%, 32%, and 54% from the baseline at 1-month follow-up.

Conclusions: RFA potentiates as a safe and effective treatment of toxic thyroid nodules. Though it carries a risk of temporary hypothyroidism following ablation, long-term consequences appear to be minimal. Future study with larger sample size and longer follow-up are encouraged to identify factors predicting response.

Keywords: Radiofrequency ablation (RFA); hyperthyroidism; toxic thyroid nodule; case report

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Introduction

Radiofrequency ablation (RFA) of thyroid nodules involves the use of thermal energy to reduce nodular size, improve compressive symptoms, and ameliorate cosmetic concern. Though only recently approved by the United States (U.S.) Food and Drug Administration (FDA), RFA has been used for decades in Asia and Europe with impressive results. RFA has been shown to achieve volume reduction rates (VRRs) as high as 80% and 90% (1-5). Additionally, RFA has been shown to significantly improve compressive symptoms and patient satisfaction (6,7). Several studies of euthyroid patients receiving RFA for benign nodules have concluded that RFA does not typically affect thyroid function (8-10). While RFA is currently primarily used to reduce the size of benign, non-functional thyroid nodules, there are reports of its efficacy in the treatment of autonomously functioning thyroid nodules (AFTNs) (9-11). International guidelines, including those of Italy and Korea, allow RFA of AFTNs if a patient refuses first-line treatments [which include radioactive iodine (RAI) ablation and surgery] (1,12).

Given that the current definitive management of AFTNs is surgery or RAI ablation, the use of RFA could open a new frontier in AFTN treatment. Italian and Korean groups have published multiple multicenter primary studies and meta-analyses regarding the efficacy of RFA for AFTN. However, little data are available about its efficacy in North America. Here we report three different cases of hyperfunctioning thyroid nodules which did not respond well to medical treatment including antithyroid medications and were subsequently treated with RFA. We present the following article in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-35/rc).

Case presentation

Procedural details

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. RFA was performed as an outpatient procedure. The neck was prepared with povidone-iodine swabs and draped in standard surgical fashion to avoid the uncommon risk of infection or abscess. We utilized internally cooled 18-gauge STARmed (Seoul, Korea) catheters with a 7-mm tip size to thermally ablate each nodule. In each of the following cases we utilized the moving-shot technique along with a long-axis approach (13).

Case 1

An 81-year-old man was referred from his primary care physician for management of a symptomatic multinodular goiter with a left lower pole hyperfunctioning thyroid nodule as demonstrated on nuclear medicine thyroid scan, present for 1 year. The patient had a history of hyperthyroidism treated with methimazole 10 mg daily with no improvement and endorsed symptoms of hyperthyroidism including palpitations, weight loss, increased appetite, irritability, and poor sleep, but no compressive symptoms. At the time of presentation, laboratory workup showed thyroid-stimulating hormone (TSH) at 0.02 mIU/mL (normal range, 0.34–5.6 mIU/mL), T3 at 4.26 pg/mL (normal range, 2.5–3.9 pg/mL), free T4 at 0.99 ng/dL (normal range, 0.58–1.64 ng/dL), thyroglobulin antibody at <1 IU/mL (normal range, 0–0.9 IU/mL), and thyroglobulin at 10 IU/mL (normal range, 0–34 IU/mL). Neck ultrasound performed the day of the presentation showed four thyroid nodules (*Table 1*), the largest of which measured 2.74 cm × 2.08 cm × 1.87 cm (10.66 mL) localized to the left lower pole.

Fine needle aspiration of the dominant left lower lobe nodule was performed and showed a benign adenomatoid nodule. Following current standards of practice, the patient was offered a thyroidectomy; however, he declined and noted he did not want to undergo surgery due to fear of complication. The patient requested a RFA procedure. After extensive discussion regarding the lack of conclusive data for RFA of AFTNs in the U.S. and the current standards of care, the patient elected to proceed with RFA. One month after the initial presentation, the patient underwent RFA of the left dominant thyroid nodule performed with an 18-gauge needle with a 7-mm active probe, impedance reached 600 ohms and energy reached 20–30 joules. The procedure was uneventful and lasted 5 minutes. The patient was discharged the same day and instructed to continue methimazole as prescribed. The patient was followed up at 1-, 3-, and 6-month. One month following the procedure, patient labs showed TSH levels of 13.6 mIU/mL (normal range, 0.34–5.6 µIU/mL), T3 of 76 ng/dL (normal range, 71–80 ng/dL), and free T4 of 0.55 ng/dL (normal range, 0.58–1.64 ng/dL). One-month post-ablation neck ultrasound showed a nodule measuring 2.37 cm × 1.96 cm × 1.42 cm (6.60 mL), representing a 38.11% volume reduction (*Figure 1*). The patient was able to discontinue methimazole at that time. Also, at the 1-month follow-up visit, the patient was counseled regarding symptoms of hypothyroidism and to return if suspected; however, he did not endorse any of these symptoms. TSH at 3-month follow-up was 2.09 µIU/mL.

Case 2

A 63-year-old man was referred from his primary care physician for surgical evaluation of hyperthyroidism and a dominant right thyroid nodule. He had been treated with methimazole 10 mg daily with no improvement. He endorsed compressive symptoms, including dysphagia, dyspnea, and intermittent hoarseness. A nuclear scan ordered by his primary care physician showed a hyperfunctioning hot nodule in the right lobe of the thyroid with suppression of the remaining thyroid tissue. At the

Table 1 Nodules criteria detected on neck ultrasound of the first case

Location	Size	Composition/echogenicity/ margins/echogenic foci	Shape	Vascularity	Elastography	ACR-TIRADS classification
Left lower pole	2.74 cm × 2.08 cm × 1.87 cm	Composition: solid Echogenicity: hypoechoic Margins: irregular Echogenic foci: none	Wider than tall	Absent Doppler flow	Mixed	TR4
Left mid pole	2.8 cm × 2.06 cm × 1.66 cm	Composition: solid Echogenicity: hypoechoic Margins: irregular Echogenic foci: none	Wider than tall	–	–	TR4
Left isthmus junction	1.33 cm × 1.05 cm × 0.77 cm	Composition: solid Echogenicity: hypoechoic Margins: irregular Echogenic foci: none	Wider than tall	Internal Doppler flow	Mostly Stiff	TR4
Right lower pole	2.69 cm × 1.56 cm × 1.32 cm	Composition: solid Echogenicity: hypoechoic Margins: ill defined Echogenic foci: none	Wider than tall	Absent Doppler flow	–	TR4

ACR-TIRADS, American College of Radiology-Thyroid Imaging Reporting and Data Systems.

time of presentation, laboratory workup showed a TSH of 0.06 mIU/mL (normal range, 0.34–5.6 mIU/mL), T3 of 3.36 pg/mL (normal range, 2.5–3.9 pg/mL), free T4 of 0.70 ng/dL (normal range, 0.58–1.64 ng/dL), thyroglobulin antibody of <1 IU/mL (normal range, 0–0.9 IU/mL), and thyroglobulin of 34.3 IU/mL (normal range, 0–34 IU/mL). Neck ultrasound showed two thyroid nodules (*Table 2*), the largest of which was in the right mid to lower pole and measured 4.22 cm × 1.73 cm × 1.67 cm (12.19 mL).

Fine needle aspiration of the dominant right lobe nodule was performed and showed a benign follicular nodule with cystic degeneration. The patient denied surgical intervention and consequently RFA of the right dominant thyroid nodule ensued using an 18-gauge needle with a 7-mm active probe. RFA was uneventful, with impedance reaching 400 ohms and energy reaching 20 joules. To ensure adequate ablation, treatment targeting the medial and lateral side of the nodule proceeded from deep to superficial. The patient was discharged the same day and instructed to continue their methimazole as prescribed. At 1-month follow-up, the patient had relief of compressive symptoms and was found on laboratory analysis to have a TSH of 7.23 µIU/mL (normal range, 0.34–5.6 µIU/mL), T3 of 1.18 ng/mL (normal range, 0.58–1.59 ng/mL), and free T4 of 0.52 ng/dL (normal range, 0.58–1.64 ng/dL). Notably, thyroid function tests normalized within the following two weeks. Ultrasound showed that the ablated nodule shrunk to 2.79 cm × 1.80 cm × 1.64 cm (8.24 mL), demonstrating a 32.45% volume reduction (*Figure 2*). The patient was able to discontinue methimazole at that time. Also, at the 1-month follow-up visit, the patient was counseled regarding symptoms of hypothyroidism and to return if suspected; however, he did not endorse any of these symptoms. TSH at 3 months was 1.91 µIU/mL.

Case 3

A 51-year-old woman who was previously hospitalized in 2014 for high blood pressure, tachycardia, and confusion with subsequent diagnosis of hyperthyroidism and of a multinodular goiter presented to our clinic. The patient had been placed on methimazole briefly, as an allergic reaction quickly led to propylthiouracil as replacement. On physical

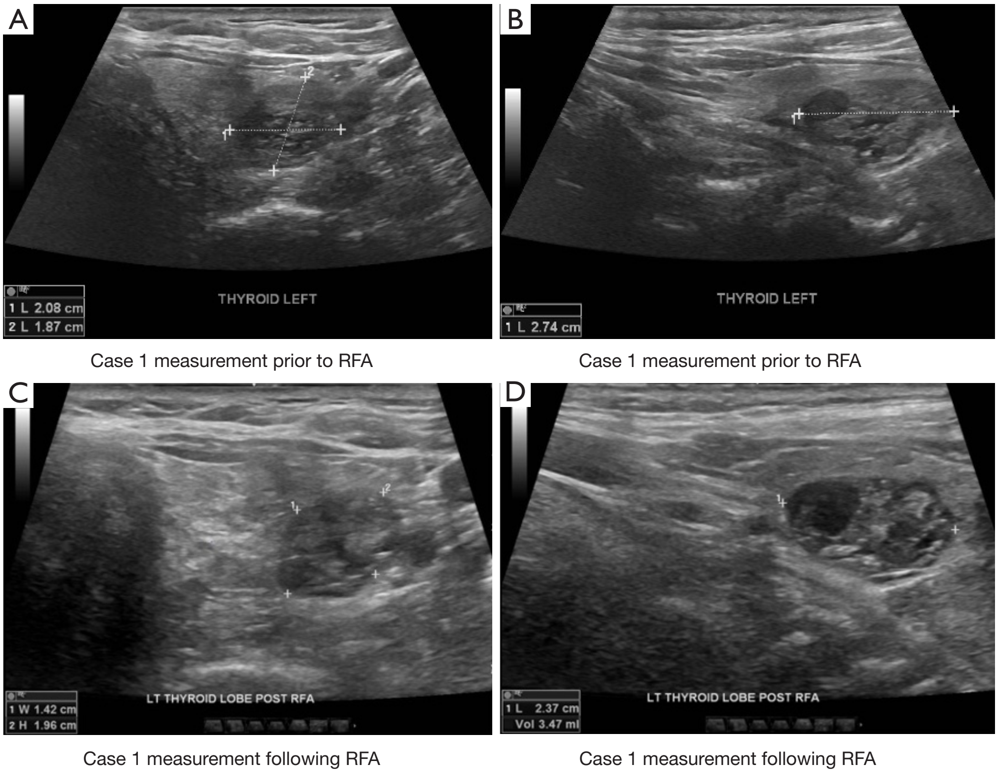

Figure 1 Sonographic images of case 1 prior to and one month following RFA. Volume decreased from 10.66 to 6.60 mL, indicating a 38.11% volume reduction rate. RFA, radiofrequency ablation.

Table 2 Nodules criteria detected on neck ultrasound of the second case

Location	Size	Composition/echogenicity/margins/echogenic foci	Shape	Vascularity	Elastography	ACR-TIRADS classification
Right mid to lower pole	4.22 cm × 1.73 cm × 1.67 cm	Composition: solid Echogenicity: isoechoic Margins: irregular Echogenic foci: microcalcifications	Wider than tall	Peripheral Doppler flow	Mixed	TR5
Left lower pole	0.79 cm × 0.70 cm × 0.60 cm	Composition: solid Echogenicity: hypoechoic Margins: irregular Echogenic foci: none	Wider than tall	Peripheral and internal Doppler flow	Mixed	TR4

ACR-TIRADS, American College of Radiology-Thyroid Imaging Reporting and Data Systems.

examination, two right thyroid nodules about 2.50 cm each were detected. They were confirmed to be benign by fine needle aspiration. Thyroid uptake scan had demonstrated each to be hyperfunctioning right thyroid nodules. The patient had a history of abnormal wound healing, with "hypertrophic scarring" and wished to avoid surgery. Four years prior, one nodule underwent ethanol ablation which was immediately aborted due to uncontrolled pain. The patient decided to undergo RFA for her still hyperfunctioning thyroid nodule. Thyroid function tests 1-month pre-

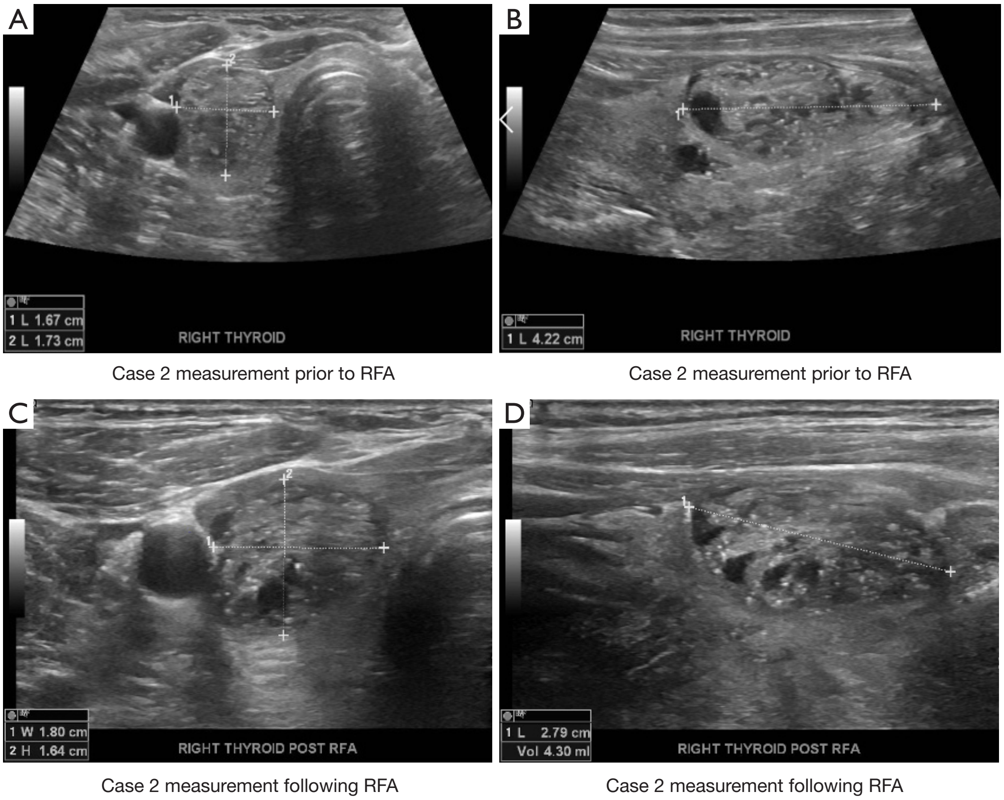

Figure 2 Sonographic images of case 2 prior to and one month following RFA. Volume decreased from 12.19 to 8.24 mL, indicating a 32.45% volume reduction rate. RFA, radiofrequency ablation.

ablation demonstrated a TSH of <0.005 mIU/mL (normal range, 0.34–5.6 mIU/mL), T4 of 7.4 ng/mL, and T3 of 2.9 ng/mL (normal range, 0.58–1.59 ng/mL). Ultrasound assessment of the neck revealed a right upper pole thyroid nodule measuring 0.82 cm × 0.75 cm × 0.62 cm (0.38 mL) and a right mid-pole thyroid nodule measuring 3.57 cm × 3.96 cm × 2.87 cm (40.57 mL). The patient maintained her prescription of propylthiouracil up until the day prior to surgery.

The patient underwent an uneventful single-session RFA with impedance reaching 400 ohms. At 1-month follow-up, the patient denied hoarseness of voice or pain when swallowing. The patient reported satisfaction with her result and mentioned improved cardiovascular health according to her cardiologist. The patient was asked to withhold propylthiouracil completely. One-month post-ablation TSH levels were 2.37 µIU/mL (normal range, 0.34–5.6 µIU/mL) while her T4 and T3 were both within normal limits. Ultrasound of the right middle-pole thyroid nodule measured 3.7 cm × 2.48 cm × 2.02 cm (18.54 mL) with only slight vascularity along the anterior capsule of the thyroid. The patient had a VRR of 54.32% from baseline (*Figure 3*). TSH was 1.34 µIU/mL at 3-month follow-up.

Discussion

RFA has been demonstrated to be an effective treatment for benign, non-functional thyroid nodules, and was recently approved in the USA for this purpose. A study of 111 patients with benign, non-functional thyroid nodules treated with an average of 2.2 RFA sessions, demonstrated that nodule volume was significantly reduced, and cosmetic appearance was significantly improved. The overall success rate, defined as at least a 50% volume reduction, was 98.4%, with a complete disappearance rate of 18.3% and a recurrence rate of 5.6%. These results were maintained for up to 3 years post-procedure (14). Corroborating this, another study reported a significant mean VRR (67%) in 215 patients at a 1-year follow-up (15). Finally, a 2018 study demonstrated an average 80.3% volume reduction at a 1-year follow-up in 345 patients who received RFA of a benign thyroid nodule. The overall therapeutic success rate

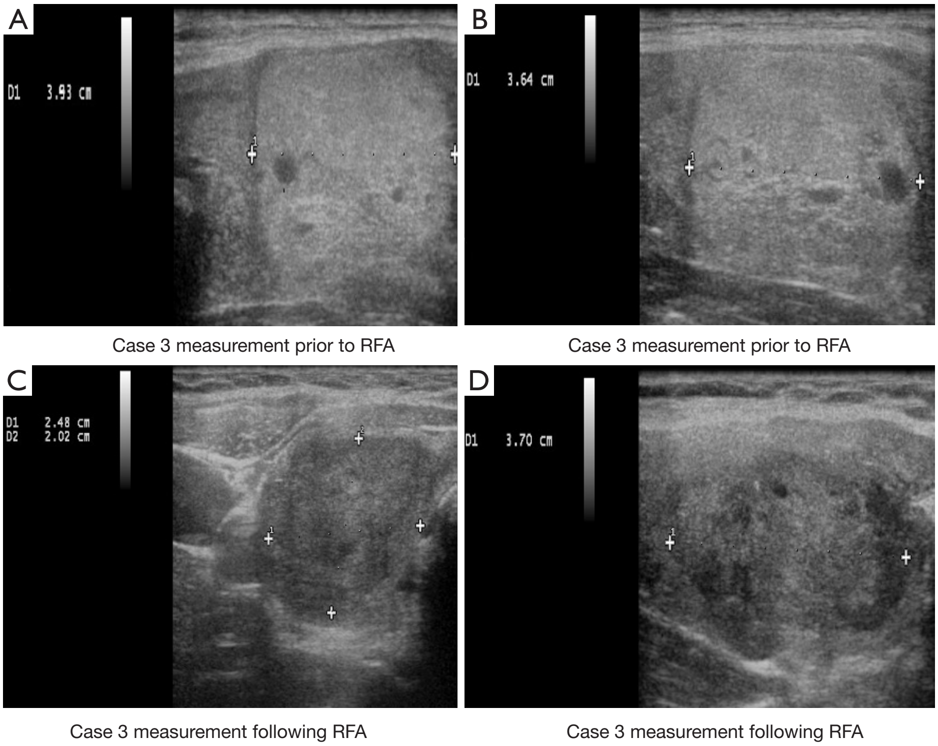

Figure 3 Sonographic images of case 3 prior to and one month following RFA. Volume decreased from 40.57 to 18.54 mL, indicating a 54.32% volume reduction rate. RFA, radiofrequency ablation.

in this study was 97.8% (16). A systematic review of RFA for benign, non-functional thyroid nodules concluded that RFA allowed significant volume reduction, evident as early as 6 months post-procedure. RFA can result in a substantial decrease in compressive symptoms and improvement in cosmesis. The mean volume reduction at 6 months is approximately 68%, whereas, at 24 months, this number increases to 87% (17).

RFA may be a useful alternative to surgery for patients with isolated AFTNs. There are several studies of RFA for the treatment of AFTNs performed outside of the U.S. In a study of 30 patients with hyperfunctioning thyroid nodules treated with a single RFA session, almost half had resolution of their hyperthyroid state by 1-year post-procedure. Notably, there was an incremental increase in the number of patients with full resolution of their hyperthyroidism with time. There was no significant relationship between nodule characteristics on imaging (baseline nodule volume, volume reduction, vascularity) and the likelihood of remission after RFA (11). Another study of 9 patients with single benign AFTNs, who received one to four RFA sessions 1–2 months apart, found that between 6 and 17 months post-procedure, serum TSH normalized in 5 of 9 patients, rose above normal level requiring thyroid hormone supplementation in one patient, and continued to experience hyperthyroidism in only three patients. The change in TSH levels were not significantly associated with any nodule characteristics (18). In 2020, Cappelli *et al.* found that, in 17 patients with AFTNs, 3 of which were being treated with methimazole, 16 patients became euthyroid within 6 months after RFA. Notably, there was no significant difference in nodule size reduction between patients with hyperfunctioning and non-functioning nodules (19). In contrast, a study of 24 AFTNs found small nodules (<12 mL) responded better to RFA than do medium-sized nodules (>12 mL) (20).

In a study of 23 patients with AFTNs who underwent RFA, five patients became euthyroid, and 16 improved but remained hyperthyroid at a three-month follow-up (21). A study including 32 hyperthyroid patients who received a single session of RFA showed that 27 became euthyroid by 1-year follow-up, while four were sub-clinically hyperthyroid. One became sub-clinically hypothyroid (22). Faggiano *et al.* conducted a study of 18

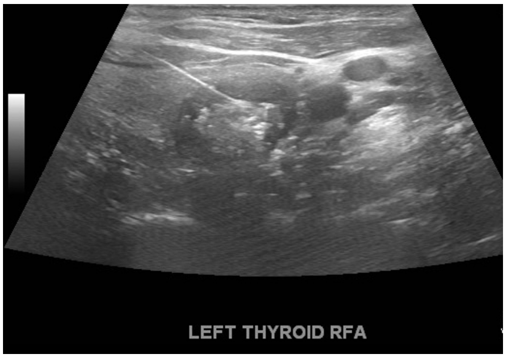

Figure 4 Ultrasound guided radiofrequency ablation of a toxic nodule. RFA, radiofrequency ablation.

hyperthyroid patients treated with methimazole, in which treatment with a single RFA session resulted in complete remission of hyperthyroidism in 40% of patients at 1-year follow-up (23). Another study of six patients with AFTNs found that a single RFA session resulted in euthyroidism in five patients (24). In a 2009 study of 28 patients with hyperfunctioning thyroid nodules, 79% were able to stop methimazole therapy at a 1-year follow-up after a single RFA session (10). In 44 hyperthyroid patients who underwent RFA, nine remained hyperthyroid, though they were improved from baseline, and 35 became either euthyroid or hypothyroid (25). Finally, in a study of eight patients with AFTNs who received RFA, 50% were euthyroid at a 6-month follow-up (26). All of these studies were done outside the U.S.

Within the U.S, there are currently two studies which have reported the efficacy and safety of RFA treatment on AFTNs. Hussain *et al.* reported the largest American study including 24 AFTNs which were ablated without major complication, achieving mean TSH and free T4 levels within normal range and a 71.1% VRR after a median of 87 days (27). The other U.S.-based work, a work describing only a single patient, was found to have normal thyroid function 4 months post-ablation (9). Overall, this data highlighted the ability of RFA to restore euthyroid status for a significant number of hyperthyroid patients (28,29). A recent meta-analysis published by Cesareo *et al.* investigated the association between the baseline toxic nodules volume and rate of post ablation TSH normalization. The authors reported that smaller nodules had a higher chance to be treated with TSH normalization than larger ones (29).

Comparison of RFA with alternate treatments

The current standard of care for the definitive management of hyperthyroidism caused by AFTNs is surgery and RAI ablation. Thyroidectomy allows definitive cure, however it by default carries with it a relatively large risk of permanent hypothyroidism, recurrent laryngeal nerve injury, and hypoparathyroidism (30,31). RAI, while effective, treats a patient with exogenous radioactive elements which, according to a recent meta-analysis, displays a linear-dose response relationship with solid cancer mortality (32). Resultantly, the obvious benefits of RFA, including minimal risk of hypothyroidism and a lack of an incisional scar, may be an especially attractive therapy for patients with severe hyperthyroidism, previous malignancy, or cosmetic concern.

Additionally, both RAI ablation and thyroidectomy require starting medical treatment to control TSH levels preoperatively with methimazole or propylthiouracil, which are contra-indicated in pregnancy (33). The notion of achieving a euthyroid state prior to RFA for AFTNs is currently not discussed by recent guidelines (34). In addition, with respect to quality of life and cost, a Chinese study found that RFA patients had significantly better general and mental health than open surgery for benign thyroid nodules, though it was more costly (35). No studies from the U.S. investigate the cost effectiveness of RFA of toxic thyroid nodules. Depending on the patient population treated, these options may not be suitable or have inherent risks that are undesirable to the patient, suggesting RFA to be a potentially safe and effective approach for treating AFTNs (*Figure 4*) (36).

We found that RFA successfully reversed the thyroid function in one month for all three AFTNs. Yet, only a single patient had complete normalization of their thyroid function tests. Traditionally, RFA is considered less effective than surgery in curing hyperthyroidism, though our work and the work of other U.S.-based studies, albeit of small samples sizes, could suggest of comparable efficacy (6,27). Notably, patients with benign (non-functional) thyroid nodules undergoing surgery are significantly more likely to result in hypothyroidism than those undergoing RFA (37,38). In a large study of 1,459 patients, Beak *et al.* established that the rate of recurrent laryngeal nerve injury following RFA is 1.02% (39). Resultantly, RFA is recommended over surgical treatment for benign nodules in these risk-related circumstances (37). RAI ablation, an alternative therapy for AFTNs, was found to be of equal efficacy with RFA in a study of twenty-two patients with AFTNs. Yet, RAI ablation was more likely to result in hypothyroidism and persistence of the nodule, while RFA was more likely to result in a euthyroid state (40).

Two patients had temporary hypothyroidism at 1-month follow-up. These two patients had a long history of uncontrolled hyperthyroidism. Their disease was poorly controlled with no response to antithyroid medications. The temporary hypothyroidism can be explained by the successful ablation of the autonomous functioning tissue, with a potentially delayed response of the normal thyroid tissue.

Safety and future prospective of the RFA procedure

Overall, RFA for benign non-functioning thyroid nodules and AFTNs is a relatively safe procedure with potential to grow and will be widely implemented in the management of thyroid disease (41). A previous study of 1,459 patients undergoing RFA of benign thyroid nodules identified the complication rate as 3.3% (39). The most noted complications are pain, temporary voice changes, hematoma, and cutaneous burns (42). RFA procedures performed by experienced physicians resulted in significantly lower significant complication rates (18). Of note, there is a small risk of developing hypothyroidism after RFA.

Conclusions

RFA, while currently recommended in selected circumstances for the treatment of non-functioning thyroid adenomas for relief of compressive symptoms, has also shown promise in the treatment of AFTNs. The literature indicates that most hyperthyroid patients with AFTNs treated with RFA achieve a euthyroid state, though there is a risk of developing clinical or subclinical hypothyroidism, as described in 1 of 4 cases, yet long term laboratory values are not available at this time. Though more large-scale studies are needed in the U.S., currently available reports suggest that RFA can be considered in patients with AFTNs who wish to avoid surgery, who are not good surgical candidates and those wishing to avoid RAI.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-35/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-35/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-35/coif). EK serves as an Editor-in-Chief of *Gland Surgery* from May 2017 to April 2024. EK also serves as a consultant of STARmed. RPT serves as an unpaid editorial board member of *Gland Surgery* from May 2015 to August 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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