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Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients

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Abstract This study evaluated the safety and volume reduction of ultrasonography (US)-guided radiofrequency ablation (RFA) for benign thyroid nodules, and the factors affecting the results obtained. A total of 302 benign thyroid nodules in 236 euthyroid patients underwent RFA between June 2002 and January 2005. RFA was carried out using an internally cooled electrode under local anesthesia. The volume-reduction ratio (VRR) was assessed by US and safety was determined by observing the complications during the follow-up period (1–41 months). The correlation between the VRR and several factors (patient age, volume and composition of the index nodule) was evaluated. The volume of index nodules was 0.11–95.61 ml (mean, 6.13±9.59 ml). After ablation, the volume of index nodules decreased to 0.00–26.07 ml (mean, 1.12±2.92 ml) and the VRR was 12.52–100% (mean, 84.11±14.93%) at the last follow-up. A VRR greater than 50% was observed in 91.06% of nodules, and 27.81% of index nodules disappeared. The complications encountered were pain, hematoma and transient voice changes. In conclusion, RFA is a safe modality effective at reducing volume in benign thyroid nodules.

Keywords Radiofrequency ablation · Thyroid nodule · Thyroid ultrasound · Intervention

Introduction

Thyroid nodules were found in 4–8% of adults by means of palpation, in 10–41% by means of ultrasonography (US), and in 50% by means of a pathologic examination at autopsy [1]. Most thyroid nodules are benign [2] but some nodules require treatment for cosmetic reasons, subjective symptoms or anxiety about a malignant change [3, 4]. The treatment for benign thyroid nodules consists of two parts: surgery and levothyroxine medication However, both surgery and medication have drawbacks. Although surgery is curative, it has problems, including general anesthesia, scar formation and iatrogenic hypothyroidism. In addition, the efficacy of thyroid hormone-suppressive therapy is still controversial [5]. Therefore, non-surgical minimally invasive modalities, such as ethanol ablation and interstitial laser photocoagulation (ILP), have been attempted, yielding good results [6–20].

Radiofrequency ablation (RFA) is a minimally invasive technique that has been used to treat benign and malignant

tumors [21–24]. In the thyroid gland, RFA has been applied to a recurrent thyroid cancer [23] and benign thyroid nodules [25].

This study evaluated the safety and effectiveness of RFA at reducing volume in benign thyroid nodules.

Materials and methods

Patients

A total of 302 benign thyroid nodules in 236 euthyroid patients were treated with US-guided RFA between June 2002 and January 2005. This study population consisted of 211 females and 25 males, aged 13–75 (mean age, 40.9 years).

The patients were referred to the radiology interventional department at our thyroid center for RFA. The patients had refused surgery and requested non-surgical treatment.

This study is a retrospective study design. IRB approval and a written informed consent document was obtained from all patients before the procedure. The consent document contained the following: (1) the expected number of RFA sessions and the possibility of recurrence; (2) possible complications (superior and recurrent laryngeal nerve injury, pain, hemorrhage, skin burn to the neck and pad attachment sites, tracheal injury, esophageal injury, vessel injury, infection, abscess formation, hypothyroidism, hypoparathyroidism); (3) medication history (particularly anticoagulant drugs) or prior surgery; (4) after the procedure, 1-day admission for an evaluation of the complications.

The inclusion criteria of this study were as follows: (1) the presence of subjective symptoms (foreign body sensation, neck discomfort or pain, compressive symptom) or cosmetic problems; (2) a poor surgical candidate or refusal to undergo surgery; (3) fine-needle aspiration cytology and US findings that were compatible with a benign nodule; (4) anxiety about a malignancy.

The exclusion criteria were as follows: (1) a nodule less than 5 mm in size; (2) follicular neoplasm or malignancy on fine needle aspiration cytology (FNAC); (3) a nodule with the sonographic criteria for a malignancy (taller than wide, marked hypoechoic, microcalcifications, ill-defined margins), although FNAC was a benign result; (4) previous radiation or operation history to the head and neck; (5) previous sclerosing therapy.

Pre-ablation assessment

The US examination, laboratory data, and FNAC were performed with all patients. Two radiologists (J.H.B. and Y. S.K.) carried out the US examination and FNAC. The size, characteristics, composition, intra-nodular vascularity, and the presence of abnormal lymph nodes in the neck were evaluated using a 10-Mhz linear probe on a real-time us system (Prosound SSD-5000, Aloka, Wallingford, Conn., USA; Aplio SSA-770A, Toshiba, Otawara-shi, Japan).

Three orthogonal diameters of the tumors (the largest diameter and two other perpendicular ones) were measured by US immediately before RFA. The volume of the tumor was calculated using the following equation: $V=\pi abc/6$ (V: volume, a: the largest diameter, b and c: the other two perpendicular diameters).

The composition of the nodules was assessed subjectively by an US examiner, and was classified as mainly solid, mainly cystic and mixed type. The nodules that had a solid portion greater than 80% were defined as mainly solid type ($n=164$, Fig. 1), those that had a cystic portion greater than 80 % were defined as mainly cystic type ($n=49$, Fig. 2), and the others were defined as a mixed type if they were neither mainly solid nor cystic ($n=89$, Fig. 3).

The laboratory studies included a thyroid function test (TSH, triiodothyronine, free thyroxine), complete blood count, and a blood coagulation test (prothrombin time, activated partial thromboplastin time).

Procedure

Before ablation, an intravenous route was made via the antecubital vein of the arm; however, pre-medication was not administered. The patients were placed in the supine position with the neck extended. Two grounding pads were attached to both thighs. Under the US examination, the above-mentioned observers determined the approach route for the electrode. An RF generator (Cool-tip RF system, Radionics, Valleylab, Colo., USA) and an internally cooled electrode (17 gauge, with 1-cm active tip) were used. The following two aspects were considered before deciding the appropriate approach route for the electrode: (1) the transisthmic approach, passing through enough thyroid parenchyma, which prevents a change in the position of the electrode tip during swallowing and the leakage of hot fluid in case of a cystic nodule, and (2) a careful observation of the vessels along the approach route was made to prevent serious hemorrhage. RFA was delayed for 1 or 2 weeks if there was serious hemorrhage.

The patients were treated with 2% lidocaine (Huons, Hwasung, South Korea) for the local anesthesia of the puncture site and around the thyroid gland. The skin was not incised so as to prevent unnecessary scar formation. An electrode was inserted into the thyroid nodule under US guidance along the short axis of the nodule. Initially, the electrode tip was positioned in the deepest and most remote portion of the nodule. Ablation began with 30 W of power. However, the power was reduced to 20–25 W if the patient could not tolerate the pain during ablation.

If the formation of a transient hyperechoic zone at the electrode tip did not appear within 10 s, power was

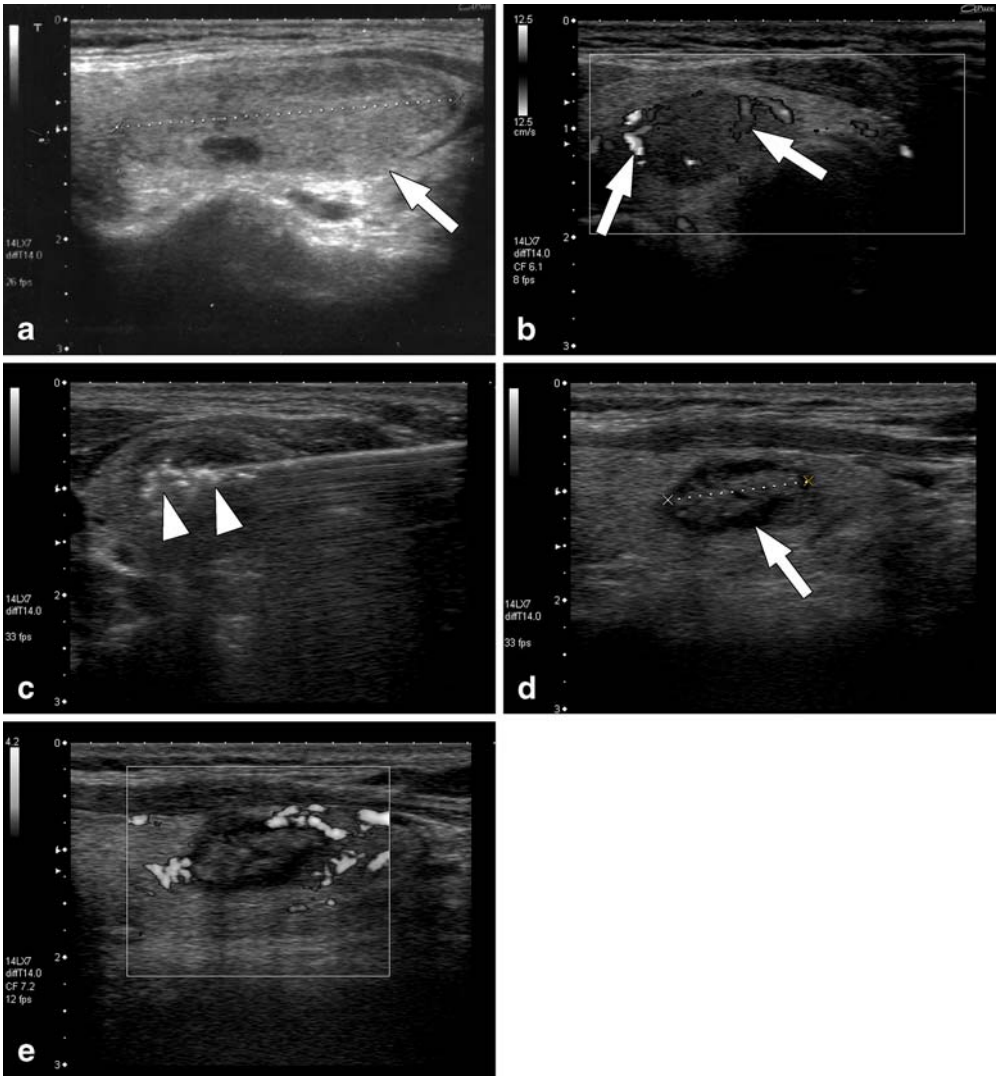

Fig. 1 A 33-year-old woman had a solid nodule in the right lobe of her thyroid gland. **a** US examination showed a mainly solid and isoechoic nodule (*arrow*), and the volume of index nodule was approximately 2.27 ml. **b** On the Doppler study, slightly increased vascularity in the nodule was also noted (*arrows*). **c** During the procedure, an internally cooled electrode was inserted into the thyroid nodule. Multiple echogenic micro-bubbles (*arrowheads*) around the electrode tip were noted. **d** Six months after ablation, the volume of the nodule decreased to 0.37 ml. **e** The Doppler US taken at 6 months after ablation showed that the vascularity in the nodule had disappeared

increased in 5-W increments up to 70 W. When a transient hyperechoic zone appeared at the periphery of the nodule (usually within 5–10 s), the electrode tip was moved backward in order to prevent heat transmitting to the perithyroidal tissue. In the more central areas of the nodule, if the transient hyperechoic zone expanded around the electrode tip, the electrode was moved to an untreated area. This technique was named the "moving-shot technique" in contrast to the "fixed-needle technique" normally used to treat hepatoma. Before ablation, we divided the nodule into multiple imaginary or supposed ablating units. We made these units smaller on the periphery of the nodule as well as

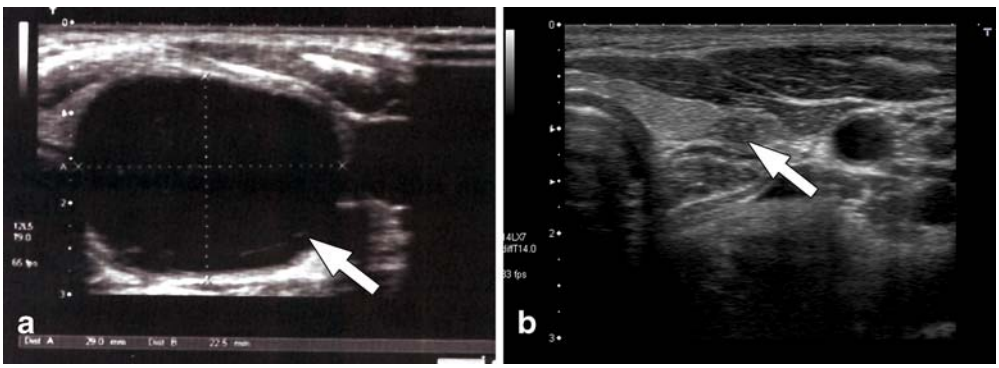

Fig. 2 A 44-year-old woman had a mainly cystic nodule in the left lobe of her thyroid gland. **a** The US examination revealed the cystic nodule (*arrow*) to be 14.66 ml in volume. The nodule was treated with one RFA session. **b** After 19 months, the nodule had contracted to less than 0.4 ml, and changed to a hypoechoic lesion (*arrow*)

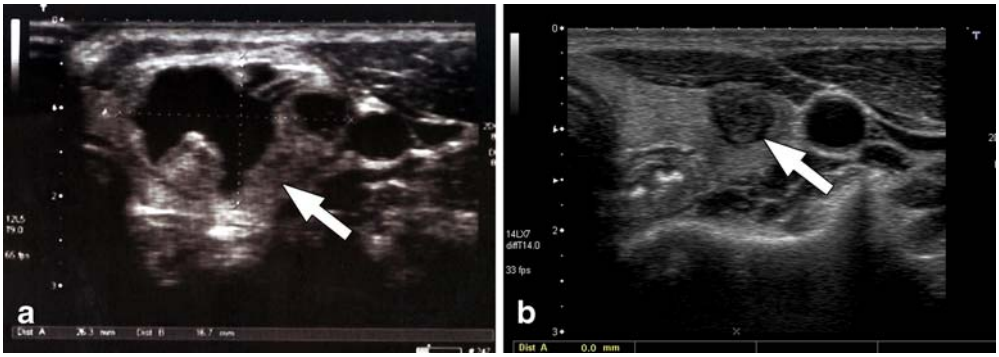

Fig. 3 A 33-year-old woman had a mixed solid and cystic nodule in the left lobe of her thyroid gland. **a** US examination showed a mixed solid and cystic nodule (*arrow*) measuring 9.66 ml in volume. The nodule was treated with three RFA sessions. **b** After 19 months, the nodule had changed into a small hypoechoic nodule (*arrow*), and the volume was approximately 0.5 ml

in the portion of the nodule adjacent to the critical structures of the neck. The units were much larger in the central portion of the nodule. The nodule was then treated unit by unit using the moving shot technique. During ablation, both thighs were checked frequently to prevent skin burn. The ablation time and power ranged from 5 to 30 min (mean, 14 min) and 20–70 W, respectively. Ablation was terminated when all units of the nodule had changed to transient hyperechoic zones.

However, an untreated portion was left in some cases for the following reasons: (1) intractable pain; (2) tumor size was too large to be ablated completely in one session; (3) edema or hematoma developed in the thyroid gland and the extra-thyroidal soft tissue.

The patients were treated in the afternoon and admitted for 1 day. After ablation, oral analgesics (acetaminophen) were prescribed. If the patient complained of pain into the next day, additional oral analgesics were prescribed and it was recorded as a minor complication.

Follow-up evaluation, assessment of safety and volume-reduction ratio (VRR)

The US examination, laboratory data, and complications were all evaluated. A follow-up US examination was performed immediately after ablation and on the first postoperative day. US examinations were also preformed at 1, 3, and more than 6 months after ablation (range, 1–41 months). Changes in size, echogenicity, and intra-nodular vascularity were all evaluated.

The VRR was assessed by US imaging and was calculated by the following equation: volume reduction ratio (%)={[initial volume (ml) – final volume (ml)]× 100}/initial volume. The thyroid function test (TFT) was carried out one day after ablation. If the TFT was abnormal, the test was confirmed at the next follow-up (1 month).

The complications during or after the procedure were also evaluated by the clinical signs and symptoms.

Additional ablation was performed for the following reasons: (1) a viable portion (same echogenicity with index nodule and the presence of intra-nodularvascularity) of the nodule was detected on the follow-up US; (2) The VRR was less than 50%.

Evaluation of factors that affect the result of treatment

The relationship between the VRR and several factors (patient's age, the volume and composition of index nodule) was evaluated.

Analysis and statistics

Statistical analyses were performed using SPSS for Windows (version 13.0; SPSS, Chicago, Ill., USA). Multiple linear regression analysis of the VRR of the ablated nodule, the patient's age and volume of the index nodule were performed. One-way ANOVA was used to examine the correlation between the VRR and the composition of the nodule. One-way analysis of variance (ANOVA) was used to examine the relationship between the volume percentages of the remnant nodules (100 - volume reduction ratio of the nodule) and composition at each follow-up period (after 1 month, n=247; 3 months, n=155; more than 6 months, n=140). A P value <0.05 was considered significant.

Results

In most patients (n=260, 86.1%), one nodule was treated. More than two nodules (2–6 nodules) were treated in 42 patients (13.9%). Most nodules (n=212, 70.2%) were treated in a single session but 90 nodules (29.8%) required more than two sessions (two times, n=63; three times, n=20; four times, n=4; five times, n=2; six times, n=1). On the follow-up US examination, the echogenicity of the nodule was lower than that observed before ablation, and the intra-nodular vascularity had disappeared (Fig. 1b and e).

Table 1 The changes in volume before RFA and at each follow-up

	Initial	1 month later	3 months later	6 months later	Last follow-up
No. of nodules	302	247	155	140	302
Volume (ml)[a]	0.11–95.61 (6.13±9.59)	0.00–40.30 (2.53±4.40)	0.00–24.17 (2.00±3.24)	0.00–30.11 (1.54±4.38)	0.00–26.07 (1.12±2.92)
Largest diameter (cm)[a]	0.6–10.00 (2.44±1.36)	0.00–7.00 (1.73±1.03)	0.00–5.20 (1.60±0.97)	0.00–6.00 (1.26±1.07)	0.00–5.70 (1.01±1.00)
Volume reduction rate (%)		58.20	74.41	84.79	84.11

[a]Mean ±standard deviation *in parentheses*

VRR

Before ablation, the largest diameter recorded was 0.6–10 cm (mean, 2.44±1.36 cm) and the volume of index nodules was 0.11–95.61 ml (mean, 6.13±9.59 ml). After ablation, the largest diameter recorded was 0.00–5.70 cm (mean, 1.01±1.00 cm) and the volume of the nodules was 0.00–26.07 ml (mean, 1.12±2.92 ml) at the last follow-up. The VRR was 12.52–100% (mean, 84.11±14.93%) at the last follow-up. The mean VRR at 1, 3 and 6 months after ablation was 58.20%, 74.41% and 84.79%, respectively. The changes in the volume of the nodule before ablation, and at each follow-up are summarized in Table 1.

A volume reduction greater than 50% was observed in 91.06% (n=275), and 84 (27.81%) index nodules had disappeared on the follow-up US. There was no patient in which the volume increased after ablation at the last follow-up.

Safety

The patients complained of various degrees of pain at the ablated site, or pain radiating to the head, ear, shoulder, or teeth. The pain decreased when the generator output was reduced or turned-off during ablation and was easily controlled by oral analgesics during admission. However, 13 patients (5.5%) required analgesics for more than 2 days.

Immediately after ablation, extra-thyroidal hematoma developed in five patients (2.1%) but was resolved within 1 month using conservative treatment. There was no intra-thyroidal or intra-nodular hematoma formation. Three patients (1.3%) complained of voice changes, all recovering within 2 months without specific treatment. There were no serious complications, such as esophageal perforation, tracheal injury or skin burn. One day after ablation, thyroid function tests were performed on all patients. The serum triiodothyronine and free thyroxine were within normal limits, but the TSH had decreased in three patients 1 day after ablation without any thyrotoxicosis symptoms (0.017, 0.087, and 0.053, respectively; normal range 0.4–4 mU/l). However, they had normalized at the subsequent 1-month follow-up.

Factors related to the VRR

Multiple linear regression analysis between the VRR and the patient's age and index volume showed that the correlation coefficient was 0.036 (P=0.884), and the P value of these factors was 0.891 and 0.623, respectively. Therefore, the VRR was not associated with the patient's age or index volume statistically.

One and three months after ablation, the mainly cystic nodules decreased in size more than the other types (P=0.000 and 0.007, respectively) but there was no significant difference between the types of nodules at the 6-month follow-up (P=0.621). There was no correlation between the VRR and the composition of the nodule after 6 months (Fig. 4).

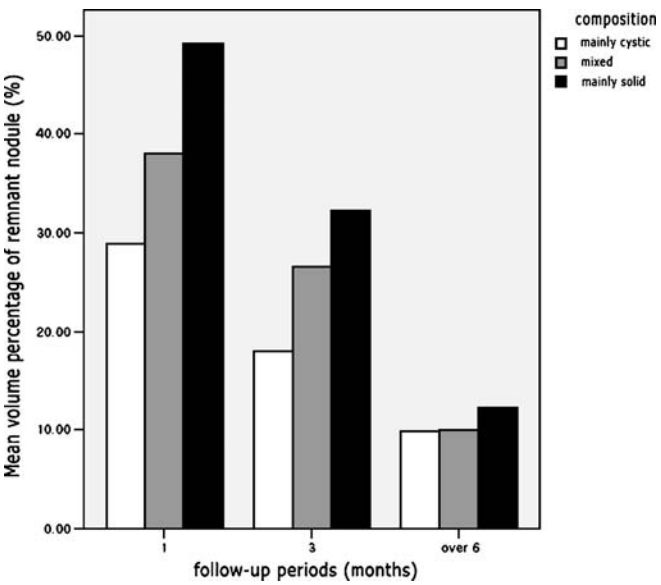

Fig. 4 Graph shows the correlation between mean volume percentage of remnant nodule and composition of the thyroid nodule at 1, 3 and over 6 months after RFA

Discussion

Since Rozman et al. [26] performed the first ethanol ablation in thyroid cysts in 1989, it has been used as an alternative therapeutic procedure in various benign thyroid diseases. They reported the mean VRR ranged from 36 to 91% of the original volume at a 4.4- to 24-month follow-up [8, 27–30].

However, ethanol ablation has some drawbacks. Multiple treatment sessions are needed to achieve a total cure. An increased number of sessions appear to be related to an increased risk of complications. Another considerable drawback is the difficulty in predicting the area of the tissue damage due to uneven distribution [11, 16].

Recently, ILP was introduced for benign thyroid nodules [9–11, 19, 20]. These studies reported that the mean VRR was 44–82% at the 6- to 12-month follow-up. ILP was performed in one to three sessions for one nodule.

Kim et al. [25] reported their initial experience of RFA for benign thyroid nodules, and showed that the residual volume after thyroid RFA was approximately 11.8% at the 9- to 18.5-month follow-up. The patients had only one ablation session for a single nodule.

In this study, the mean VRR was 84.79% and 84.11% at the 6-month and last follow-up, respectively. Volume reduction greater than 50% was observed in 91.06% (n=275), and 27.81% (n=84) of index nodules had disappeared. These RFA results are similar to those for ethanol ablation, ILP and other RFA reports.

Lee et al. [12] reported that ethanol ablation is more effective on solid nodules. However, Kim et al. [8] reported that the mean volume reduction of a cystic lesion (65%) was superior to that of solid lesions (38.3%). They suggested that a solid nodule is more resistant to the diffusion of ethanol and the abundant vascularity of a solid nodule favors the drainage of ethanol. Regarding RFA, Kim et al. [25] reported that mixed and mainly cystic tumors showed a significantly better response than mainly solid tumors. This might be due to the homogeneous conduction of heat and the absence of a heat sink effect [31]. According to our analysis, 1 and 3 months after ablation, the mainly cystic nodules decreased in size more than other nodules, but there was no significant difference between the nodules after the 6-month follow-up. In our opinion, the mainly cystic tumor decreased rapidly in volume due to the even conduction of heat and removal of the cystic component. Also, mainly solid tumors decreased in volume sufficiently if the tumor was completely ablated. Therefore, there is no difference in volume reduction between them after 6 months.

Recurrent laryngeal nerve injury is a serious complication. Recent reports by thyroid surgeons show that the incidence of recurrent laryngeal nerve injury in a thyroidectomy was 0.2%–1.1% [32–34]. Transient or permanent nerve injury was reported in up to four percent of cases of ethanol ablation and ILP [6, 8–11, 17–19, 29, 30, 35–38]. Kim et al reported that the incidence of recurrent laryngeal nerve injury after RFA was 3.3% [25].

In this study, three patients (1.3%) complained of transient voice changes, which were resolved within 2 months without specific treatment. The rate (1.3%) noted in this study is similar to that of other modalities. We did not encounter any serious complications such as esophageal perforation or tracheal injury. In summary, Kim and co-workers reported positive results for 30 cases of RFA in benign thyroid nodules as an initial trial. Our study confirmed those results using a larger series of 302 cases.

Conclusion

Thyroid nodule RFA appears safe and imaging follow-up confirms volume reduction, however its efficacy and safety needs to be verified through long-term follow-up.

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