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Efficacy and Safety of Radiofrequency Ablation for Benign Thyroid Nodules: Initial Mongolian Experience

Otgonbayar Setevdorj [1, 2], Bayarmagnai Munkhjargal [2], Ishdorj Tsedenish [2], Yerkyebulan Mukhtar [3], Sergelen Orgoi [4]

[1]Department of General Surgery, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [2] Department of General Surgery, First Central Hospital of Mongolia; [3]Department of Epidemiology and Biostatistics, School of Public Health, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [4]Organ Transplantation Center, First Central Hospital of Mongolia, Ulaanbaatar, Mongolia

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Corresponding Author
Sergelen Orgoi,DMSc, Professor
Department of General Surgery,
First Central Hospital of Mongolia,
Ulaanbaatar 11000, Mongolia
Tel: +976-9903-9495
E-mail: otchigin9495@gmail.com

Objectives: To assess the efficacy and safety of thyroid radiofrequency (RF) ablation for benign thyroid nodules for a 24 months period. **Methods:** From 2019 to 2021, 485 nodules were from 183 patients (mean age 47.7 ± 11.2) who met eligibility criteria were enrolled from participants. At pre-ablation, the median volume was 0.371 mL (CI 95 %; 0.289 - 0.513). For 1, 3, 6, 12 and 24 months after treatment, 485 lesions, consisting of 258 (27 %) solid, 108 (11.3 %) predominantly solid, 47 (4.9 %) cystic, 25 (2.6 %) predominantly cystic and 47 (4.9 %) sponge were followed. RFA treatment was performed using two standard techniques (trans isthmic and moving-shot) and an RFA V-1000 cooling system. For 24 months, nodule size reduction was assessed. **Results:** At pre-ablation, the median volume was 0.371 mL (CI 95 % 0.289 - 0.513). For 1, 3, 6, 12 and 24 months after treatment, median volume reduction was 0.263 (CI 95 %; 0.205 - 0.325 $p < 0.000$), 0.163 (CI 95 %; 0.124 - 0.218 $p < 0.000$), 0.153 (CI 95 %; 0.074 - 0.194 $p < 0.000$), 0.148 (CI 95 %; 0.046 - 0.150 $p < 0.000$), and 0.062 (CI 95 %; 0.006 - 0.111 $p < 0.000$) respectively. Median volume statistically decreased significantly $p = 0.000$. Both mean symptom and cosmetic scores showed significant improvements ($p < 0.001$). All complications were also evaluated during the follow-up. **Conclusion:** Thyroid RF ablation is an effective and safe treatment modality in patients with benign thyroid nodules. RF ablation may be as effective as surgery if it is performed by experienced physicians in optimally selected patients.

Keywords: Radiofrequency Ablation, Thyroid, Nodule, Intervention, Tumor

Introduction

Thyroid nodules are widespread in the population. It has been demonstrated that approximately 15.8 % of the world's population has nodules and 7 % has palpable thyroid nodules [1]. Most nodules are benign and asymptomatic; however, ~5 % to 15 % can grow and cause compressive symptoms or cosmetic issues notably in women because palpable nodules are

5 times more prevalent in females compared to males [2, 3]. Large nodules may arise from nodular goiter, causing dysphagia, dyspnea, and dysphonia due to the local mass effect on important anatomical structures in the head and neck involved in swallowing, phonation and breathing. In extreme cases, nodular goiter may even lead to airway obstruction requiring emergent surgical intervention. Prevalence of compressive and cosmetic symptoms in patients with nontoxic goiter has been reported from 28 % to 36 % and 17 % to 69 %, respectively [4].

Hyperfunctioning nodules are relatively rare among benign nodules [5]; however, a subset may cause subclinical or overt hyperthyroidism [6]. Although the majority of patients are adequately controlled with currently available medical interventions, a small number may progress to hyperthyroidism. However, even subclinical hyperthyroidism may adversely affect the cardiovascular and skeletal systems, leading patients and physicians to employ definitive treatment with radioactive iodine and/or surgery [7]. Neither of these strategies, however, is without risks. Radioactive iodine (RAI) therapy specifically, when used to treat any cause of hyperthyroidism, may cause transient thyrotoxicosis, and although this risk can be ameliorated by pretreatment antithyroid medications, such a pretreatment regimen may also be associated with reduced RAI treatment success [8 - 10].

For treatment, surgery is the traditional method. However, numerous studies have been presented recently that thermal ablations including radiofrequency (RFA), laser (LA), as well as ultrasound (HIFU) have achieved a robust improvement of nodule-related symptoms and cosmetic problems by reducing the nodule volume [11 - 14]. Especially, RFA is safe, reasonable, and effective in the treatment of thyroid nodules, and does not require hospital admission, general anesthesia or skin incision. Technically, an electrode-needle generating an alternating electric field (in case of RFA), is inserted into the nodule under ultrasound (US) guidance, to induce rapid heating and destruction of the target zone. Treatment is accompanied by the formation of coagulative necrosis, and, over time, by fibrotic changes and progressive nodule shrinkage. For patients with benign nonfunctioning thyroid nodules, current recommendations for radiofrequency (RFA) ablation in Korea and Italy indicate treatment when patients complain of nodule-related compressive symptoms or cosmetic deformity [11, 12]. RFA is generally performed with the moving shot technique, whereby the tip of the electrode is sequentially moved from the medial and deepest part of the nodule to its most superficial and lateral parts [15]. Indeed, the volume reduction ratio (VRR) has been reported to be 84.1 % and 79.4 % by Korean and Italian groups, respectively [16, 17]. In subsequent studies, wide ranges of volume reduction (51 – 92 %) achieved by RF ablation have been published [13, 18, 19].

Despite the RFA procedures that have been reported as well tolerated in large retrospective series, with a risk of major complications (recurrent laryngeal nerve injury or damage to cervical structures) lower than 1 % [20 - 22], significantly different aesthetic outcomes of the RFA could be the result of several factors, such as characteristics of the treated nodules or ablation time [20, 21]. Some studies even concluded that although RFA is an effective and safe treatment, the VRR and clinical efficacy of RFA remain unclear. Moreover, recent study by Zheng et al. showed that single-session RFA was more cost-effective, however, patients with two-session RFA had less hypocalcemia, especially those with high alkaline phosphatase [23]. Marginal regrowth of the incompletely treated nodule, described in the 4-year follow-up study [24], showed that more than two session may be necessary to maintain long-term efficacy of the RFA. For these reasons, in the present study, we have aimed to establish a mini-invasive single-session radiofrequency (RF) technique, with a feature of short-duration ablation using relatively low watts, on different sizes and types of nodules, such as cystic, solid, and mixed, in the Mongolian population. The thyroid disease prevalence rate increased from 33.5 to 90.3 per 10.000 population in Mongolia between 2011 and 2020 respectively. In our country, about 500 thyroid surgeries are performed annually. Non-surgical small nodular goiter accounts for the majority of total goiter, but to date, these patients have no treatment options other than control and sclerosis (ethanol 95 – 99 %, aethoxysklerol 3 %). This is the first study in Mongolia to be conducted in one specialist center to evaluate single-session RFA with relatively low watts in patients with thyroid nodules.

In this study, we assess the efficacy and safety of thyroid radiofrequency (RF) ablation for benign thyroid nodules for a 24 months period.

Materials and Methods

Research design

The retrospective study was conducted from 9th Jan 2019 to 15th

Oct 2021, with 485 nodules from 183 patients (M: F = 9:174; mean age ± SD = 47.7 ± 11.2 years) who met the eligibility criteria and provided written informed consent and who were enrolled at the First Central Hospital of Mongolia. Nodules were assessed repeatedly pre-treatment and at 1st, 3rd, 6th, 12th, and 24th months post-treatment. Nodule volume, symptomatic and cosmetic assessment scores were recorded at each time point.

The inclusion criteria were as follows: patients with symptomatic problems due to a thyroid nodule; patients with cosmetic thyroid problems; cytological confirmation of a benign thyroid nodule on FNAB [23, 24]; no malignant US findings; solid (> 50 % solid components) and predominantly cystic (10 % < solid components < 50 %) thyroid nodules; cystic nodules (< 10 % solid components) and serum thyroid hormone and thyrotropin levels within normal range.

The exclusion criteria were follicular neoplasm or primary thyroid cancer; history of neck radiation therapy; pregnancy [24].

Pre - ablation assessment

All patients were evaluated by US examination, US-guided FNAB, blood tests, and clinical examinations. US, US-guided FNAB, and RF ablation were performed using a 10 – 16 MHz linear probe and a real-time US system (Mindray M7, China). For each nodule, three orthogonal diameters (the largest diameter and two perpendicular diameters) and the proportion of the solid components were measured. The volume of each nodule was calculated as follows: $V = \pi abc / 6$ (where V is the volume, a is the largest diameter, and b and c are the two perpendicular diameters) [11, 20]. Laboratory examinations included measurements of serum thyrotropin, total triiodothyronine, free thyroxine, platelet counts, and blood coagulation tests that included prothrombin time and activated partial thromboplastin time [11]. At the time of enrollment, the patients were asked to rate their nodule-related symptoms on a 10 -cm visual analog scale (0 – 10 cm) and a cosmetic grading score was assessed by the physician (0, no palpable mass; 1, no cosmetic problem but a palpable mass; 2, a cosmetic problem on swallowing only; and 3, an easily detected cosmetic problem) [25].

Procedures

All procedures were performed under US guidance on an outpatient basis by a physician. The RF device used was a cool-tip RF system with a straight-type modified internally cooled electrode: RF generators (Cool-Tip RF system, M-1000, RF Medical, Seoul, Korea) and an 18-gauge internally cooled electrode (RF Medical, Seoul, Korea) with 0.3, 0.5, 0.7, and 1 cm active tips, depending on the size of the nodule and the preference of the physicians.

A trans-isthmic approach method and the moving-shot technique were used [11, 26]. To prevent hemorrhage, vessels along the approach route were carefully evaluated using Doppler US. Patients were managed with 1 – 2 % lidocaine around the thyroid gland for puncture site anesthesia. A trans-isthmic approach allows the electrode to pass through a sufficient amount of thyroid parenchyma by insertion of the electrode through the short axis of the target nodule from the isthmus. This method has several advantages as it can prevent movement of the needle or electrode when the patient swallows or talks during ablation and it can also prevent fluid leakage (i.e., ablated hot fluid of the thyroid nodules' cystic portion) outside the thyroid gland. Moreover, this approach also allows continuous US monitoring of the nodule as well as of the space between the electrode tip and the expected location of the recurrent laryngeal nerve, thereby minimizing the risk of injury to the nerve and/or the esophagus. The electrode was inserted into the thyroid nodule under US guidance [27].

Initially, the electrode tip was positioned in the deepest and most remote portion of the nodule. Ablation was initiated with RF power ranging from 20 W to 50 W according to the electrode tip size: 0.7 cm, 15 – 30 W; 1 cm, 30 – 70 W. If a transient hyperechoic zone did not form at the electrode tip within 5 – 10 seconds, the RF power was increased in 5 – 10 W increments, up to 120 W according to the electrode as follows: 0.7 cm, 40 – 70 W; 1 cm, 55 – 90 W. When a transient hyperechoic zone appeared at the periphery of the nodule (usually within 5 – 10 seconds), the electrode tip was moved backward for the prevention of heat transmission to the perithyroidal tissue. In the nodule's central areas, the electrode was moved to an untreated area if the transient hyperechoic zone expanded around the electrode tip. This technique was termed the "moving-shot technique," in contrast to the "fixed-needle technique" that is normally used to treat hepatocellular carcinoma [28]. Before ablation, the nodule was divided into multiple predicted ablation units. These units were designed to be smaller in the periphery of the nodule and its portion adjacent to critical structures of

the neck, but much larger in the nodule's central portion. Next, the nodule was treated "unit by unit" using the moving-shot technique. If the patient could not tolerate the pain during the ablation, the power was either turned off for several minutes or lidocaine was injected around the thyroid capsule. The ablation procedure was terminated when the entire nodule had become hyperechoic.

Potential complications were evaluated according to clinical signs and symptoms both during and immediately after the procedure. Complications and side effects were defined according to the quality improvement guidelines of the Society of Interventional Radiology and a prior multicenter evaluation of complications. After RF ablation, each patient was observed in the hospital for 1 day.

Follow-ups

Patients were followed up by US and clinical evaluations at 1, 3, 6, 12, and 24 months. The thyroid nodule volume and cosmetic as well as symptom scores were evaluated in the same manner before and after ablation.

The volume reduction ratio was calculated as follows: volume reduction ratio = ([initial volume - final volume] x 100) / initial volume [11]. Additional treatment was allowed if the follow-up the US showed a remaining viable portion of the nodule and if the patient complained of incompletely (< 50 %) resolved symptomatic or cosmetic problems.

All complications were also evaluated during the follow-up [17].

Statistical analysis

The Fisher's exact test was carried out for categorical variables. The Friedman's test was carried out to compare the study groups. The Nemenyi test was applied for multiple comparisons after the Bonferroni corrections. A critical p-value of < 0.05 was used. Data were analyzed using IBM SPSS, version 25 (IBM Corp., Armonk, NY, USA). Friedman's test was used to compare six repeated measurements of treatment.

Ethical statement

The study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences) (No 2019/9-05). All patients provided written informed consent before participating in the study.

Results

From 9th Jan 2019 to 15th Oct 2021, 485 nodules from 183 patients (M:F = 9:174; mean age ± sd = 47.7 ± 11.2 years). Nodules were assessed pre-treatment and at 1, 3, 6, 12, and 24 months post-treatment. Nodules volume, symptomatic and cosmetic assessment scores were recorded at each time point.

Treatment characteristics of our study patients are summarized in Table 1. RFA ablation one session 482 (99.4 %), second session 3 (0.6 %). The mean time to RF ablation was 2.28 (0.05 - 17.34). Needle size was 0.66 cm. Among the 485 treated thyroid nodules, there were 258 (53.2 %) solid, 108 (22.3 %) predominantly solid, 47 (9.7 %) cystic, 25 (5.2 %) predominantly cystic, and 47 (9.7 %) sponge nodules. There were 210 (43.3 %) left, 258 (53.2 %) right and 17 (3.5 %) isthmus.

Figure 1 shows nodule volume at the 24 months follow-up after RFA; completely destroyed 53 (12.6 %), volume decreased 343 (81.5 %), volume increased 25 (5.9 %). Completely destroyed at the 1, 3, 6, 12 and 24 months after RFA; 4 (1.1 %), 5 (1.4 %), 23 (12.4 %), 14 (8.5 %) and 7 (18.9 %) respectively.

In other words, Table 2 shows the median volume reduction rates at the 1, 3, 6, 12, 24-months follow-ups were 34.6 %, 56.1 %, 70.6 %, 73.9 %, 74.9 %, respectively. Between 1 - 24 months period of follow up, statistically significant decreased $p = 0.004$.

The median volume reduction of follow-ups is summarized in Figure 2. At pre - ablation, the median volume was 0.37 mL (CI 95 % 0.29 - 0.51). For 1, 3, 6, 12 and 24 months after treatment, median volume reduction were 0.26 (CI 95 %; 0.21 - 0.33, $p < 0.000$), 0.16 (CI 95 %; 0.12 - 0.22 $p < 0.000$), 0.15 (CI 95 %; 0.07 - 0.19, $p < 0.000$), 0.15 (CI 95 %; 0.05 - 0.15, $p < 0.000$), 0.06 (CI 95 %; 0.01 - 0.11, $p < 0.000$), respectively. Median volume statistically decreased significant $p = 0.000$.

Complications and side effects are summarized in Table 3. The overall complication rate was 4 (2.18 %). All complications were also evaluated during the follow-up. Major and minor complication rates were 2 (2.03 %) and 1 (0.54 %), respectively. Almost all study subjects recovered without sequelae. No patient experienced a life-threatening or delayed complication during the follow-up.

Table 1. Demographic characteristics of enrolled patients.

Variables	Male (n = 183)	Female (n = 174)	Total (n = 357)	p-value
Age	N (%)	N (%)	N (%)	
Under 34	2 (22.2)	18 (10.3)	20 (10.9)	
35 – 39	2 (22.2)	20 (11.5)	22 (12.0)	
40 – 44	1 (11.1)	29 (16.7)	30 (16.4)	
45 – 49	2 (22.2)	32 (18.4)	34 (18.6)	
Above 50	2 (22.2)	75 (43.1)	77 (42.1)	
Session				
One time	181 (98.9)	8 (91.0)	172 (98.0)	0.394
Two times	2 (1.1)	1 (9.0)	3 (2.0)	
Composition of nodule				
Cyst	13 (7.1)	2 (22.2)	11 (6.3)	
Predominant cyst	16 (8.7)	1 (11.1)	15 (8.6)	
Predominant solid	24 (13.1)	1 (11.1)	23 (13.2)	
Solid	107 (58.5)	2 (22.2)	105 (60.3)	
Sponge	23 (12.6)	3 (33.3)	20 (11.5)	
Location				
Isthmus	4 (2.2)	1 (11.1)	3 (1.7)	
Left	131 (71.6)	5 (55.6)	126 (72.4)	
Right	48 (26.2)	3 (33.3)	45 (25.9)	
Ablation Watt				
20 - 30 W	96 (52.5)	2 (22.2)	94 (54.0)	0.138
31 W <	87 (47.5)	7 (66.7)	80 (46.0)	
Duration time (second)				
0.5 - 1.5	165 (92.2)	7 (77.8)	70 (90.7)	0.167
Above 1.5	18 (7.8)	2 (22.2)	16 (9.2)	
Needle size, mm				
0.3	2 (1.1)	1 (11.1)	1 (0.6)	
0.5	55 (30.1)	2 (22.2)	53 (30.5)	
0.7	115 (62.8)	4 (44.4)	111 (63.8)	
1.0	11 (6.0)	2 (22.2)	9 (5.2)	

Table 2. Treatment outcomes between baseline to next measure of volume reduction (%).

	A volume reduction			
Months [a, b, c, d]	Median	95 % CI	IQR	p-value*
1st month	34.6	31.0 - 37.4	8.2 - 56.4	0.000
3rd months	56.1	51.1 - 59.4	31.3 - 74.7	
6th months	70.6	64.0 - 74.9	47.8 - 87.8	
12th months	73.9	68.7 - 78.2	53.8 - 89.5	
24th months	74.9	65.2 - 90.1	49.8 - 98.6	

*Friedman's test; multiple comparisons: [a]1st vs. 3rd, $p < 0.000$; [b]1st vs. 6th, $p < 0.000$; [c]1st vs. 12th, $p < 0.000$; [d]1st vs. 24th, $p < 0.000$.

Table 3. Complications.

Complications	Number of Complications (%)	Time of Detection (Days)	Time to Recovery (Days)
Major complications (n = 3)			
Transient voice change	2 (1.09)	1	60
Hypothyroidism	1 (0.54)	30	30
Minor complications (n = 1)			
Hematoma	1 (0.54)	1	7
Total	4 (2.18)	1–30	1–60

Table 4. Integrated results.

Volume	n (%)	Initial volume Median	Latest volume Median	Reduction Median
Destroyed	53 (12.6)	0.08	-	100
Decreased	343 (81.5)	0.71	0.17	67.9
Not changed	-	-	-	-
Increased	25 (5.9)	0.05	0.09	29.0

Table 4 shows destroyed 53 (12.6), volume decreased 343 (81.5), volume increased 25 (5.9), there are no nodules whose volume has not changed.

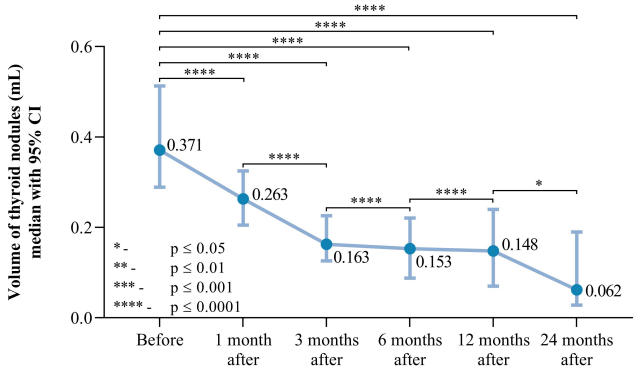

Figure 1. Treatment outcomes.

Discussion

Monopolar radiofrequency ablation (RFA) is presently the best-documented thermo-ablative method. Its availability, however, remains restricted, offered mainly by a few research groups worldwide (largely located in South Korea, Italy, and China) that since 2006 have reported at least 18 interventional studies on the effects of a single treatment course with a monopolar, internally cooled system [29 - 33]. Other studies addressing complications and limitations of RFA complete the picture of this systematically evolving method over time [34]. Many series have described the efficacy and safety of minimally invasive techniques such as RFA in its application to solid and compressive benign thyroid nodules. The results of Korean and Italian pioneering centers stand out in this respect. Nevertheless, RFA has not yet been unanimously included in all international guides on the standard management of thyroid nodules [35]. The efficacy of RFA can be assessed based on different parameters such as percentage volume reduction, the proportion of nodules with therapeutic success (volume reduction > 50 %), and the reduction or disappearance of compression symptoms [36].

Our prospective study was performed by a trained endocrine surgeon using similar techniques and devices, which demonstrated the efficacy and safety of RF ablation. The volume reduction achieved in our study (74.9 %) is comparable to other studies published in the literature (50 % - 93.3 %), with a similar low complication rate (reported to be 2.4 % - 3.5 % in larger studies) [37 - 40].

The overall complication rate was 2.18 % (4 / 183). Major and minor complication rates were 2 (2.03 %) and 1 (0.54 %), respectively. A systematic review carried out by Chung et al. in 2017 analyzed 24 studies including 2786 nodules (benign and recurrent thyroid cancers) in 2421 patients with a mean of 1.5 sessions in 91.7 % of studies. The overall complication rate was 2.38 % with a major complication rate of 1.35 % [41].

All study subjects recovered without sequelae. Moreover, there were no life-threatening complications. We employed a similar method that involved a trans-isthmic approach and the moving-shot technique [28]. Regarding efficacy, the volume

reduction achieved in the present study is comparable to those of previous studies from Korea [16] and Italy [17] with 236 and 94 patients, respectively. Regarding the factors related to volume reduction, earlier RF research suggested that variables such as the initial nodule volume, the proportion of solid components, and the follow-up period are related to volume reduction. In contrast, our analyses found that initial solidity and applied energy were independent predictors of nodule volume reduction. Lim et al. previously suggested that a solid nodule or larger initial volume requires more energy for sufficient volume reduction. Recently, Ha et al. reported that the proportion of solid components is important for the treatment modality selection [26].

Another issue in the present study, and perhaps the most important, is that we were able to identify some US features of the nodules that can be predictive of the outcome. As a matter of fact, microcystic nodules (also called spongiform) and the grossly cystic ones shrank better than the nodules with a homogeneous solid US pattern: although a similar finding was previously reported by Valcavi et al. [42] and by Negro et al. [43 - 45] in nodules treated by laser, to our knowledge this is the first clear demonstration of a correlation between spongiform structure and volume reduction in RF-treated nodules. As to the predictive value of the pattern of vascularisation, literature data reported conflicting results; we showed that intense peripheral or peripheral and intranodular vascularisation can predict a better response to treatment. The possible explanation of our observation is that heating produces more steam in the case of tissue with a large fluid component, colloid, or blood and that the steam enhances the thermocoagulation process in the treated nodule. This mechanism may be shared by all thermo-ablative techniques, whatever the heating source: LA, RFA, HIFU, microwaves, and so on.

Our study has several limitations. The follow-up period was limited to 24 months and our short-term follow-up data could not evaluate the long-term outcome and recurrence of treated nodules. The cost-effectiveness was not evaluated and only the results of the work performed by the single physician were shown. Continuous long-term monitoring to compare long-term relapses, outcomes, and satisfaction with other methods and to expand the scope of the study are needed. However, a previous RF study showed that volume reduction is usually minimal after 3 months. Further studies exploring the RF technique among diverse groups of age, gender, while considering the different ablation durations, setting, nodular vascularization, nodular type and size in a larger sample size are needed. Also, long-term follow-up studies on the relapse and regrowth of nodules are recommended. We believe that the current study could serve as a primary guideline for future RF procedures among Mongolian physicians and surgeons.

In summary, the results of the present study are consistent with the existing literature and confirm the safety of RFA in general and the efficacy of a single treatment course of monopolar RFA in a large central European cohort. The results also provide some potentially significant data for future discussions regarding possible selection criteria for patients with thyroid nodules that could be treated with RFA.

Conclusions

Thyroid RFA is an effective and safe treatment modality in patients with benign thyroid nodules. RFA may be as effective as surgery if it is performed by experienced physicians in optimally selected patients.

Conflict of Interest

The authors state no conflict of interest.

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