

Efficacy and Safety of Radiofrequency Ablation Versus Surgery for Thyroid Nodules

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Objectives: To assess the efficacy and safety of radiofrequency (RF) ablation versus surgery for benign thyroid nodules for 24 months period. **Methods:** From January 2019 to January 2021, 200 patients with nodular goiters who underwent surgery (group A) and 183 patients treated by radiofrequency ablation (group B) were enrolled in this study. Inclusion criteria were the following: 1) cosmetic problem, 2) nodule-related symptoms, 3) refusal of surgery (for group B). An internally cooled radiofrequency ablation system and an 18 g internally cooled electrode were used. We compared the 2 groups in terms of efficacy, and safety during a 2-year follow-up. **Results:** Nodule type did not differ between groups, although in total 60.1 % were solid, 31.3 % were mixed, and 8.6 % were cystic. However, the number of nodules, median volume before surgery, and diameter of the nodule differed significantly. The median volume reduction was 34.6 % at 1 month, 56.1 % at 3 months, 70.6 % at 6 months, 73.9 % at 12 months, and 74.9 % at 24 months. Any volume reduction between follow-up intervals was statistically significant ($p < 0.000$). The most patients had no complications. However, surgical patients were more likely to have complications such as bleeding, hoarseness, and infection (14.5 %) than the RFA group (1.6 %). **Conclusion:** Surgical resection and radiofrequency ablation are both effective treatments of nodular goiter. Compared with surgery, the advantages of radiofrequency ablation include fewer complications, preservation of thyroid function, and fewer hospitalization days. Therefore, radiofrequency ablation should be considered a first-line treatment for benign thyroid nodules.

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

Introduction

Nodular goiter is the most common cause of thyroid disease in Mongolia, as in other countries. About 16 % of the world

population have thyroid nodules, of which 7 % are palpable nodules [1]. A small proportion of asymptomatic benign nodules increase in size and lead to compressive symptoms such as the sensation of pressure in the neck, and cosmetic changes such

as visible mass [2]. The prevalence of compressive and cosmetic symptoms in patients with non-functioning nodules has been reported to be up to 35 % and 70 %, respectively [3]. From a goiter, large nodules can develop, causing dysphagia, dysphonia, and dyspnea by compressing critical head and neck anatomical structures that are involved in breathing, phonation, and swallowing. The nodular mass can even lead to an obstructed airway, requiring urgent surgery.

Among benign nodules, hyperfunctioning nodules are generally rare [1], but some could progress to overt or subclinical hyperthyroidism [2]. Subclinical hyperthyroidism, manifested by low or normal thyroid stimulating levels may nevertheless cause significant cardiovascular abnormalities and loss of bone mineral density. Conventional medical therapy can adequately control thyroid disorders in most patients and recent guidelines suggest that asymptomatic nodules should be treated with watchful waiting; however, some patients require treatment due to compressive symptoms or cosmetic changes [3, 4]. There are several treatment options, but none are perfect. Although surgical resection is an established method with minimal complications, non-surgical options such as laser ablation therapy, percutaneous ethanol injection therapy, and ultrasound-guided RF ablation (RFA) therapy are available for those who are unable to undergo surgery or are contraindicated [5 - 7]. These methods have been shown to effectively reduce nodular volume whilst significantly improving cosmetic deformities and compressive symptoms [8, 9].

Ethanol injection is more effective in treating cystic thyroid nodules than solid ones and tends to progress locally, while RFA is useful in eradicating nodules of various sizes [10]. RFA is an outpatient procedure performed under local anesthesia. RFA induces rapid thermal damage to the target tissue by inserting an electrode needle that generates electrical currents in the range of radiofrequency waves. Coagulative necrosis is formed and is eventually replaced with fibrous tissue which leads to a reduction in nodule volume. The moving-shot technique is usually used in RFA treatment, in which the electrode tip is moved from the medial portions of the nodule to the lateral and superficial portions sequentially [11]. A volume reduction ratio demonstrated by the Korean and Italian teams was about 85 % and 80 %, respectively [12, 13]. Subsequent studies have published a wide range of volume reductions achieved by RFA (51 - 92 %) [8, 14, 15]. This variation may be explained by

several factors, such as ablation time and characteristics of the nodules treated [16, 17]. The rate of major complications of RFA therapy, such as damage to cervical structures or injury to the recurrent laryngeal nerve, has been reported to be as low as 1%, and the procedure is generally considered well-tolerated in previous large studies [18].

The prevalence of thyroid disease in Mongolia increased three-fold since 2010. About 500 thyroid surgeries are performed annually in the country. Non-surgical small nodular goiter accounts for the majority of total goiter, but to date, limited treatment options are available to these patients. Most patients with thyroid nodules were managed with medications or underwent surgery, and no alternative treatment options were offered previously. Fortunately, the first radiofrequency ablation of the thyroid gland was performed in the First Central Hospital of Mongolia on January 9, 2019. To date, no studies exploring the efficacy of RFA in comparison to general surgery were conducted in Mongolia. Therefore, this is the first study in Mongolia conducted in a specialized single center to evaluate the mini-invasive technique of single-session RFA, with a feature of short duration ablation with relatively low wattage, in different sizes and types of benign thyroid nodules, such as cystic, solid, and mixed.

The objective of this study was to assess the efficacy and safety of radiofrequency (RF) ablation versus surgery for benign thyroid nodules for 24 months period.

Materials and Methods

Study design and sample

This retrospective study was conducted from January 2019 to January 2021, and 200 patients with nodular goiters who underwent surgery (group A) and 183 patients treated by RFA (group B) were enrolled. The inclusion criteria involved patients with thyroid nodules confirmed by biopsy, with the significant cosmetic issue, compressive symptoms, and in group B patients, refusal of surgery. The exclusion criteria were patients with a follicular neoplasm or primary thyroid cancer, a history of neck radiation therapy, and pregnancy. Repeated measurement was carried out to evaluate the volume reduction of the RFA procedure, after 1 month, 3 months, 6 months, and 12 months, as well as 24 months.

The study was approved by the Research Ethics Committee

of the Mongolian National University of Medical Sciences and informed consent was obtained from all participants before surgery and the RFA procedure.

Pre-Ablation Assessment

All participants underwent clinical examination, laboratory testing, ultrasound (US), and US-guided fine-needle aspiration biopsy (FNAB). RFA was performed using a real-time US system and linear probe (7 - 15 MHz) (Mindray M7, China). The proportion of solid components and three orthogonal diameters of each nodule (the longest diameter and two other perpendicular ones) were measured (12). The formula for calculating the nodule volume is 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) [13]. Thyroid function markers such as free thyroxine, total triiodothyronine, and thyrotropin were measured along with blood coagulation tests and platelet counts. Furthermore, a visual 10 cm scale (0 - 10 cm) was used to evaluate the patient's symptoms associated with the nodules. In clinical examination, the thyroid gland was assessed to determine a cosmetic grading score: 0 for no palpable mass; 1 for no cosmetic issues but palpable; 2 for cosmetic issues if present only on swallowing; and 3 for a visible cosmetic issue [19].

Procedure

The patients in group A underwent surgery under general anesthesia. Surgery was performed by endocrine surgeons with 8 - 25 years of clinical experience. The surgery was performed by the traditional Nikolaev OV and Kocher methods.

In group B patients, US-guided RFA was performed on an outpatient basis. We used a modified, straight electrode with internal cooling for the RFA system (Cool-Tip RF System, M-1000, RF Medical, Korea). Depending on nodule size and physician choice of modality, an internally cooled 18-gauge electrode with 0.3-, 0.5-, 0.7-, and 1-cm active tips were used. A trans-isthmic approach and the moving-shot technique were used, which are described in further detail below [20, 21]. To avoid blood loss, the access route and adjacent vessels were rigorously evaluated by the US. Local anesthesia of the puncture site was achieved by injecting 1 - 2 % lidocaine around the thyroid gland. In the trans-isthmic approach, the electrode is inserted through the short axis of the thyroid nodule to be treated, enabling passing through an adequate amount of the thyroid parenchyma. This

US-guided trans-isthmic approach helps minimize the risk of the electrode tip injuring the esophagus and the recurrent laryngeal nerve as the interstitial space is well monitored throughout the procedure. In addition, needle movement is restricted during patient swallowing or talking and avoids fluid leaks outside the thyroid gland from the cystic nodule [22].

First, the electrode was inserted into the nodule in the midline-to-lateral approach through the isthmus, into the deepest part. Depending on the size of the electrode tip, ablation began with a power between 20 W and 50 W: 15 - 30 W for 0.7 cm; 30 - 70 W for 1 cm. In less than ten seconds, a transient hyperechoic zone should form. If it failed to do so, we increased the power of RFA in increments (5 - 10 W) under the electrode tip. When a transient hyperechoic zone appeared, the electrode tip was moved backward from the nodule's periphery to avoid heat transmission to adjacent tissue. When an expansion of the hyperechoic zone was observed, the electrode was shifted back to the central portions of the nodule, a technique called the "moving-shot technique" [23]. Ablation units were determined before RFA and were ideal to be larger in the central portion of a nodule but smaller in the periphery to prevent injury to other important anatomical structures. Subsequently, the nodule was treated "unit by unit" with the moving-shot technique. In case the patient had difficulty tolerating pain during the treatment, the thyroid capsule was injected with more anesthetic or the current application was interrupted for some time. In case the nodule was completely hyperechoic, the procedure was stopped entirely.

Side effects and complications were constantly monitored, evaluated during and post-procedure, and a multicenter assessment of complications was performed beforehand. The patients remained in the hospital for one day after RFA therapy.

Follow-Up

In group A, an examination of thyroid function was performed to adjust the optimal dosage of levothyroxine (Euthyrox) 1 month after the thyroid resection. Surgical complications were monitored immediately after thyroid surgery and during the follow-up period.

The 2 groups were assessed before treatment and at 1-, 3-, 6- and 12-month follow-ups. Nodules volume and symptomatic and cosmetic assessment scores were recorded at each time point. The primary endpoint was the volume reduction ratio

(percentage) at 1-, 3-, 6- and 12-month follow-ups. Secondary endpoints included therapeutic success rate, improvement of symptoms and cosmetic problems, and several major complications.

The volume reduction ratio was calculated according to the formula: Volume reduction ratio = $([\text{initial volume} - \text{final volume}] \times 100) / \text{initial volume}$ [11]. It was possible to repeat the procedure if the symptoms or cosmetic issues were not resolved to the patient’s satisfaction or if a visible nodule was detected in the US.

Statistical analysis

For categorical variables, Chi-square and Friedman’s test was used to compare six repeated measurements of treatment. The Wilcoxon signed-rank test was used when comparisons were needed between the two repeated measurements. For continuous variables, one-way ANOVA was carried out followed by Tukey test as multiple comparisons. To reveal the predictors for a volume reduction, we did the multiple linear regression model and all predictors enter the regression equation at once. The result was considered statistically significant if $p < 0.05$. Data analysis was performed on IBM SPSS, version 25 (IBM

Corp., Armonk, NY, USA).

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.

Result

From January 2019 to January 2021, 183 patients with nodular goiter underwent RFA (mean age 45.74 ± 12.45 years) and 200 patients who were treated surgically (mean age 36.52 ± 9.61 years) were enrolled in this study. Nodules were examined before treatment and 1, 3, 6, and 12 months after treatment. Nodule volume, symptomatology, and cosmetic evaluation were assessed at each time interval. The primary endpoint was percent volume reduction at follow-up at 1, 3, 6, and 12 months. Secondary endpoints included therapeutic success rate, improvement in symptoms and cosmetic problems, and number of serious complications. The treatment characteristics of the patients are shown in (Table 1). In terms of demographic

Table 1. Demographic characteristics of the experimental subjects prior either RFA or surgery.

Variables	Surgery (n = 200)	RFA (n = 183)	Total (n = 383)	p-value*
Age	N (%)	N (%)	N (%)	
< 34	22 (11.0)	20 (10.9)	42 (11.0)	0.039
35 - 39	25 (12.5)	22 (12.0)	47 (12.3)	
40 - 44	24 (12.0)	30 (16.4)	54 (14.1)	
45 - 49	23 (11.5)	34 (18.6)	57 (14.9)	
50 - 54	28 (14.0)	21 (11.5)	49 (12.8)	
55 - 59	26 (13.0)	31 (16.9)	57 (14.9)	
> 60	52 (26.0)	25 (13.7)	77 (20.1)	
Gender				
Female	186 (93.0)	174 (95.1)	360 (94.0)	0.091
Male	14 (7.0)	9 (4.9)	23 (6.0)	
Composition of nodules				
Solid	123 (61.5)	107 (58.5)	230 (60.1)	0.074
Mixed	57 (28.5)	63 (34.4)	120 (31.3)	
Cyst	20 (10.0)	13 (7.1)	33 (8.6)	
No. of nodules				
Single	200 (100.0)	76 (41.5)	276 (72.1)	
Multiple	-	107 (58.5)	107 (27.9)	

*p < 0.05. RFA, radiofrequency ablation

Table 2. Median level of volume reduction following RFA procedure.

Variable	Repeated measurements by months						*p-value
	First	Third	Sixth	One year	Two years	Total	
A volume reduction ^{a,b,c}	34.6 ± 14.4	56.1 ± 11.6	70.6 ± 0.9	73.9 ± 10.1	74.9 ± 15.6	62.01 ± 18.4	0.047

One-way ANOVA, multiple comparison: ^aFirst vs. One year, p-value 0.005; ^bSixth vs. One year, p-value 0.014; ^cThird vs. Two years, p-value 0.031;

Table 3. Efficacy and complications of RFA and surgery.

Variables	Surgery (n = 200)	RFA (n = 183)	Total (n = 383)	p-value*
	Mean ± SD	Mean ± SD	Mean ± SD	
Mean hospitalization (days)	4.2 ± 1.1	1 ± 0.0	2.7 ± 1.1	0.084
Composition of nodules	N (%)	N (%)	N (%)	
Solid	123 (61.5)	107 (58.5)	230 (60.1)	0.342
Mixed	57 (28.5)	63 (34.4)	120 (31.3)	
Cystic	20 (10.0)	13 (7.1)	33 (8.6)	
TSH				
Normal	172 (86.0)	183 (100.0)	355 (92.7)	
Elevated	21 (10.5)	-	21 (5.5)	
Decreased	7 (3.5)	-	7 (1.8)	
Postoperative pain				
Yes	164 (82.0)	3 (1.6)	164 (42.8)	0.000
No	36 (18.0)	180 (98.4)	219 (57.2)	
Cosmetic issue				
Yes	200 (100.0)	1 (0.5)	200 (52.2)	
No	-	182 (99.5)	183 (47.8)	
Complication				
Yes	171 (85.5)	180 (98.4)	351 (91.6)	0.000
No	29 (14.5)	3 (1.6)	32 (8.4)	
Postoperative medication				
Yes	75 (37.5)	183 (100.0)	258 (67.4)	
No	125 (62.5)	-	125 (32.6)	

* p < 0.05. TSH, thyroid stimulating hormone; RFA, radiofrequency ablation

characteristics, there were significant differences between age at surgery and RFA, but not in gender. Nodule type did not differ between groups, although in total 60.1 % were solid, 31.3 % were mixed, and 8.6 % were cystic. However, the number of nodules, median volume before surgery, and diameter of the nodule differed significantly. Most surgical candidates had single thyroid nodules, whereas RFA candidates had multiple. The median volume before surgery and diameter was higher in the surgical patients.

Efficacy and safety

The changes in nodule volume and percent volume reduction between baseline and the next measurement for RFA are shown in (Table 2). The median volume reduction was 34.6 % at 1 month, 56.1 % at 3 months, 70.6 % at 6 months, 73.9 % at 12 months, and 74.9 % at 24 months. Any volume reduction between follow-up intervals was statistically significant (p < 0.000). (Table 3) shows the results and complications in the two groups. After the procedures, thyroid-stimulating hormone (TSH) levels were significantly normal in both groups. Postoperative pain was more

Table 4. Multiple regression for a volume reduction.

Variables	Betta	SE	t	p-value	95%CI
Age	0.84	0.21	1.81	0.421	-0.44 - 7.63
Mean hospitalization (days)	0.01	0.23	0.29	0.712	0.06 - 0.61
Gender	1.91	2.91	2.38	0.818	-0.14 - 13.31
Composition of nodules	3.15	2.03	1.79	0.231	-0.45 - 7.68
No. of nodules	0.72	1.84	3.51	0.921	0.74 - 5.35

F = 5.42; R² – 0.15; Adjusted R² – 0.09

likely to be observed in the surgical group (82.0 %), whereas the RFA group reported little pain (1.6 %). All surgical patients had a significant cosmetic problem due to scarring, while 99.5 % of RFA patients had no visible problems. Most patients in both groups experienced no complications. However, surgical patients were more likely to have complications such as bleeding, hoarseness, and infection (14.5 %) than the RFA group (1.6 %). There was a significant difference in medication use after treatment, with the surgical group taking more medications. The mean hospitalization days were significantly higher in those undergoing surgery (p < 0.000) than in the RFA group.

In the multiple linear regression model, R² and adjusted R² were 0.15 and 0.09, respectively. None of the predictors for a volume reduction were statistically significant (Table 4).

Discussion

RFA therapy of thyroid nodules is demonstrated to be the best thermo-ablative method with minimal disadvantages. The therapy is widely practiced in some countries, and formal guidelines have been developed in China, Italy, Korea, and Austria. Since the first publication on RFA in 2006, several interventional studies have been conducted [24 - 28]. The limitations and complications of RFA were also previously investigated and provided a better treatment strategy [29]. The Italian and Korean research groups laid the foundation for RFA therapy, and many more centers added to the evidence that RFA efficiently and safely reduces benign thyroid nodules and achieves euthyroidism, particularly in solid, compressive nodules. However, thyroid nodule RFA therapy as part of standard management has been indicated and developed in only a few guidelines internationally [30]. Efficacy is evaluated by several indicators, including the proportion of completely destroyed or reduced nodules, the percentage of

volume reduction, and the reduction of compressive symptoms [30].

Our prospective study was conducted by a trained endocrine surgeon by applying techniques and equipment like previous studies and demonstrated RFA safety and efficacy. The reduction of nodule volume (74.9 %) was similar to the previous research (50 - 93.3 %), with a comparable minimal complication (2% - 3.6 % in large studies) [28 - 30].

The complication rate was 2.18 % (4/183) overall. The rate of major complications was 2 (2.03 %), and the rate of minor complications was 1 (0.54 %). When Chung et al (2017) systematically reviewed multiple studies in which benign and malignant thyroid lesions were treated with mostly one session in 2421 participants, there was less than 3 % of overall complication rate and around 1 % of major complication rate [30].

There were no fatal complications or sequelae among the patients. Based on the available international guidelines and interventional studies providing evidence on the efficacy and safety of RFA with a trans-isthmic approach, our surgical team applied this method along with the moving-shot technique [23]. In the present study, we achieved a volume reduction compared to the previously published literature from Korea and Italy with similar efficacy [12,13]. According to previous studies, the pre-treatment nodule volume, follow-up duration, and the proportion of solid components are important factors associated with successful volume reduction in patients.

In comparison, power level, and proportion of solid components were primarily associated with a reduction in volume in our patients. Higher wattage may be required to achieve adequate volume reduction in larger solid nodules, and the solid component proportion could be an essential predictor of the choice of treatment modality.

Another crucial aspect of our finding was that independent

predictors of the outcome were determined from the nodule US features. It has been previously reported that cystic and spongiform nodules tend to reduce in size better than solid nodules with homogenous US characteristics, particularly in the laser-ablation technique [30]. As previously demonstrated, we observed a higher likelihood of volume reduction in spongiform nodules when treated with RFA. In vascularization patterns, highly vascularized nodules or in the peripheral portions were more likely to shrink after RFA treatment. This phenomenon also occurs with other procedures that involve thermal injury, such as laser ablation and high-intensity focused ultrasound, which was explained by the additional steam produced by nodule components with fluid inside and increased thermocoagulation.

Our study has several limitations. Patients were followed up for 24 months, and our short-term follow-up data were unable to assess long-term outcomes and nodule recurrence rates after the procedure. Continued long-term monitoring to compare long-term recurrence, outcomes, and satisfaction with other methods would expand the scope of the study. In general, volume reduction is minimal 3 months after RFA. More studies are needed to evaluate the RFA therapy in different age and gender groups, considering different ablation duration, power settings, nodal nodule vascularization, nodular type, and size in a larger sample size. Further, multiple linear regression was conducted to predict the value of a volume reduction on the age, mean hospitalization, gender and composition of nodules as well as number of nodules. Unfortunately, none of the predictors were statistically significant with the outcome variable. Follow-up studies of nodule recurrence or regrowth of nodules in a longer-term are also recommended. We believe that the current study may serve Mongolian physicians and surgeons as a primary guideline for future RFA procedures.

Conclusions

Surgical resection and radiofrequency ablation are both effective treatments of nodular goiter. Compared with surgery, the radiofrequency ablation has the advantages of fewer complications, preservation of thyroid function and fewer hospitalization days. Therefore, radiofrequency ablation should be considered a first-line treatment for benign thyroid nodules.

Conflict of Interest

The authors state no conflict of interest.

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