Radiofrequency Ablation Is a Thyroid Function–Preserving Treatment for Patients with Bilateral Benign Thyroid Nodules

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ABSTRACT

Purpose: To evaluate the efficacy and safety of radiofrequency (RF) ablation for treatment of bilateral thyroid nodules as well as preservation of thyroid function.

Materials and Methods: Between January 2007 and October 2012, 18 patients (16 women and 2 men; mean age, 49.9 y; median age, 44 y; age range, 27–81 y) with bilateral thyroid nodules treated by RF ablation were included in this study. The inclusion criteria included bilateral thyroid nodules, pressure symptoms or cosmetic problems, cytologic confirmation of benignancy without atypical cells, and patient refusal of surgery. We used an RF generator (Cool-tip RF system [Covidien, Boulder, Colorado] or SSP-2000, Taewoong Medical Co, Ltd [Gyeonggi-do, Republic of Korea]) and an 18-gauge internally cooled electrode with 1-cm active tips (Cool-tip [Covidien] or Well-Point RF electrode [Taewoong Medical Co, Ltd]). RF ablation was conducted using the moving shot technique and a trans-isthmic approach. RF ablation was performed in separate sessions for nodules in each lobe. Follow-up ultrasound examinations were performed at 1–6 months, 6–12 months, and during the last month of follow-up. The diameter and volume of the nodule and clinical problems including cosmetic and symptom scores were evaluated before and after the procedure.

Results: The mean initial nodule size was 4.1 cm ± 1.9, although there was a significant decrease by the time of the last follow-up examination (range, 1–48 mo; mean, 18.1 mo ± 12.8; \( P < .001 \), 2.5 cm ± 1.4). The initial nodule volume was 24.4 mL ± 32.2 and was decreased at the last follow-up (6.3 mL ± 19.0, \( P < .001 \)), with a mean volume reduction of 75.9% ± 19.0. The symptom (\( P < .001 \)) and cosmetic (\( P < .001 \)) scores were decreased. Serum hormone levels did not differ significantly before treatment and at the last follow-up (\( P > .05 \)).

Conclusions: RF ablation improves cosmetic problems and symptoms and preserves thyroid function in patients with bilateral thyroid nodules.

ABBREVIATION

TPO = thyroid peroxidase

Thyroid nodules are a common problem and are found in 10%–41% of the general population by ultrasound (US) (1). Although most thyroid nodules are benign and do not require treatment, some patients with benign nodules may require treatment for nodule-related symptoms and cosmetic problems (2). Surgery and radioiodine therapy have been used for patients with symptomatic thyroid nodules, although both surgery and radioiodine therapy can cause complications, such as voice change or hypothyroidism. For patients with bilateral thyroid nodules, permanent hypothyroidism is inevitable after total thyroidectomy. In cases of unilateral lobectomy, subclinical or clinical hypothyroidism also can develop...
Nonsurgical treatment is an option to avoid hypothyroidism in patients who are averse to surgery. Nonsurgical therapy options, including US-guided procedures, are presently being investigated. Radiofrequency (RF) ablation has been proposed for thyroid lesions, and clinical trials have shown that it is effective in reducing nodule volume and reducing nodule-related symptomatic and cosmetic problems. Some studies have reported transient hyperthyroidism or permanent hypothyroidism in a few patients after RF ablation. However, the reason for permanent hypothyroidism was unclear owing to the elevated levels of antibodies to thyroid peroxidase (TPO) before ablation. Although thyroid function seems to be influenced only rarely by RF ablation, it is unclear whether RF ablation affects thyroid function in patients with bilateral, benign thyroid nodules. The purpose of this study is to evaluate the efficacy and safety of RF ablation for treatment of bilateral thyroid nodules as well as preservation of thyroid function.

MATERIALS AND METHODS

Patients
This retrospective study was approved by our institutional review board, and informed procedural consent was obtained from all patients before each procedure. Between January 2007 and October 2012, 692 patients received RF ablation for benign thyroid nodules at Asan Medical Center. Among these patients, 30 were treated for bilateral benign thyroid nodules. Of these patients, 12 who did not have baseline laboratory data (n = 4), follow-up laboratory data (n = 4), US follow-up (n = 1), measurement of the diameter of the nodule on US (n = 1), or records of cosmetic and symptom scores (n = 2) were excluded from the study. The study included 18 patients (36 nodules) with bilateral thyroid nodules (16 women and 2 men; mean age, 49.9 y; median age, 44 y; range, 27–81 y). All of the enrolled patients fulfilled the following criteria: (i) bilateral thyroid nodules, (ii) nodule-related symptoms or cosmetic problems, (iii) at least two cytologic confirmations of benignancy without atypical cells, and (iv) refusal to undergo surgery (Fig 1).

Preparation and Participation
Before RF ablation, clinical evaluation for symptoms and cosmetic problems, US imaging, and laboratory data were obtained for all patients. US and US-guided fine-needle aspiration were performed by two radiologists (J.H.B. and J.H.L.) using a linear probe (5–14 MHz) with a US system (EUB-7500; Hitachi Medical Systems, Tokyo, Japan, or iU22; Philips Healthcare, Bothell, Washington). The three diameters of each nodule (ie, the largest diameter and two other perpendicular diameters) were measured by US, and the nodule volumes were calculated using the following equation: volume = \( \pi abc/6 \) (where a is the largest diameter, and b and c are the other two perpendicular diameters). In cases of multiple nodules in each lobe, the single dominant nodule was measured and treated. At the time of their enrollment, patients rated their symptoms on a 10-cm visual analog scale (range, 0–10). The nodule size was represented by its largest diameter. Physicians recorded the cosmetic score (1, no palpable mass; 2, no cosmetic problem but a palpable mass; 3, a cosmetic problem on swallowing only; and 4, a readily detected cosmetic problem). The baseline laboratory data included serum thyrotropin, free thyroxine, and triiodothyronine. The serum levels of antibodies against TPO and thyroglobulin were evaluated in all patients.

RF ablation was performed by two staff radiologists (J.H.B. and J.H.L.) using previously described techniques. We used an RF generator (Cool-tip RF system; Covidien, Boulder, Colorado, or SSP-2000, Taewoong Medical Co, Ltd, Gyeonggi-do, Republic of Korea) and an 18-gauge internally cooled electrode with 1-cm active tips.

![Figure 1. Flow chart of patient enrollment.](image-url)
electrode; Taewoong Medical Co, Ltd). After sterilization of skin and application of local anesthesia, an electrode was inserted. The thyroid nodules were treated using the moving shot technique (Videos 1, 2 [available online at www.jvir.org]). Baek et al. (10) suggested dividing thyroid nodules into multiple, small conceptual ablation units and performing RF ablation unit-by-unit, by moving the electrode. The conceptual units are smaller at the periphery of a nodule and large in the center of a nodule or in regions remote from critical structures (10). The conceptual ablation unit area is displayed as a white and round area in the flash file (Video 1 [available online at www.jvir.org]) and as a transient, hyperechoic zone during the electrode movement in the US file (Video 2 [available online at www.jvir.org]). The electrode tip is initially positioned in the deepest, most remote portion of a nodule to allow the tip to be easily monitored in the absence of any disturbance caused by a transient hyperechoic zone (10). When a transient echogenic area appears in the targeted unit, the RF power is decreased, and the electrode tip is moved to an untreated area. The electrode is continuously moved both backward and in the superficial direction within the thyroid nodule. The video files (Video 1 [available online at www.jvir.org]) also show that the electrode is continuously “moving” both backward and upward in the superficial direction within the thyroid nodule, and we have defined this as “moving.” While the electrode is moving, a transient hyperechoic zone, indicated by a popping sound, appears in the treated portion of the nodule. A popping sound was defined as an audible sound or tactile vibration detected by the operator during RFA (14) and was described as a “shot.” RF ablation was performed on different days for the larger nodules and then for the contralateral thyroid nodules. Possible complications were evaluated by monitoring the clinical signs and symptoms during the procedure. Hematoma formation was evaluated by US monitoring and according to the patient’s coughing, pain, skin burn, and voice change, all of which were evaluated by monitoring the patient’s symptoms and clinical signs. Complications were classified as major and minor based on the Society of Interventional Radiology (SIR) (6). A major complication was defined as one that, if left untreated, might be life-threatening, could lead to substantial morbidity or disability, or could result in a lengthened hospital stay (6). All other complications were considered minor. Pain was defined as any kind of pain that resulted in inadequate ablation despite medication and that persisted for >3 days after ablation (6). Other types of pain were regarded as side effects (6). Tolerable pain immediately after RF ablation was not regarded as a complication or side effect (6). Patients were discharged after 1–2 hours of observation. US examinations with size measurement and volume calculation were performed at 1–6 months, 6–12 months, and during the last month of follow-up. Clinical evaluation including cosmetic and symptom scores and laboratory tests including serum thyrotropin, free thyroxine, triiodothyronine, and serum levels of antibodies against TPO and thyroglobulin were evaluated at 6 months and during the last month of follow-up.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows (Version 18.0; SPSS, Inc, Chicago, Illinois). Variables were compared using Wilcoxon signed rank test at the time of each patient’s enrollment and at the last follow-up examination. The significance level was defined as \( P < .05 \).

RESULTS

Relevant clinical data are summarized in Table 1. The data at enrollment and last month of follow-up are summarized in Table 2. The mean initial nodule size was 4.1 cm ± 1.9 (range, 1.2–10.0 cm). The mean follow-up period was 18.1 months ± 12.8 (range, 1–48 mo). No patient was lost to follow-up in this study. After RF ablation, the mean nodule size was decreased significantly at 1–6 months (3.3 cm ± 1.4, \( P < .001 \)), 6–12 months (2.8 cm ± 1.5, \( P < .001 \)), and the last follow-up (2.5 cm ± 1.4, \( P < .001 \)) (Fig 2a–d). The mean initial nodule volume was 24.4 mL ± 32.2 and was decreased significantly at 1–6 months (11.2 mL ± 13.7, \( P < .001 \)), with a mean volume reduction rate of 48.0% ± 20.5%. The mean nodule volume was also decreased significantly at 6–12 months (9.2 mL ± 12.3, \( P < .001 \)) and at the last follow-up (6.3 mL ± 19.0, \( P < .001 \)), with a mean volume reduction rate of 70.3% ± 16.2% and 75.9% ± 19.0%. The mean symptom (3.8 ± 0.5 vs 2.5 ± 1.0, \( P < .001 \)) and cosmetic (2.4 ± 2.0 vs 1.4 ± 1.3, \( P < .001 \)) scores were decreased significantly at the last follow-up (Fig 3a, b). The serum levels of thyrotropin (\( P = .687 \)), free thyroxine (\( P = .382 \)), and triiodothyronine (\( P = .170 \)) were not significantly changed at the last follow-up compared with values before treatment. In addition, no patients developed hypothyroidism during the follow-up period. The mean time interval between the first and second treatments was 3.3 months ± 2.9 (range, 1–11 mo).

Before RF ablation, two patients showed positive thyroid antibodies. One patient was positive for the anti-TPO antibody, and one was positive for the antithyroglobulin antibody. The follow-up periods of these two patients were 11 months and 12 months. After RF ablation, thyroid antibodies were not evaluated in these two patients. Among five patients with follow-up antibody testing, none of them developed thyroid antibodies during the follow-up period. During the follow-up period, there were no major or minor complications, such as voice change or unbearable pain. None of the patients required surgery because of insufficient nodule...
DISCUSSION

The present study demonstrated that RF ablation did not affect thyroid function for patients with bilateral thyroid nodules during a mean follow-up period of 18.1 months. In addition, there were no major complications. RF ablation achieved improvement of symptoms and cosmetic problems by reduction of the nodule volume. No patients required additional surgery or other treatment during the follow-up period because of recurrence or incompletely resolved clinical problems. These results revealed that RF ablation is a safe and effective treatment for patients with bilateral thyroid nodules.

Although surgery is a curative method for treating bilateral thyroid nodules, permanent hypothyroidism is inevitable after total thyroidectomy. In addition, unilateral lobectomy can cause subclinical or clinical problems.
hypothyroidism (3). The three most common complications of thyroid surgery are vocal cord palsy, postoperative hemorrhage, and hypoparathyroidism (16). More recent studies have reported an incidence of permanent, recurrent laryngeal nerve palsy of 0.3%–1.7% and of permanent hypoparathyroidism of 0.7%–3% after total thyroidectomy for benign thyroid nodules (17). Every effort should be made to preserve the parathyroid glands with their own blood supply; however, this may be insufficient to prevent the occurrence of transient hypoparathyroidism (16). Delbridge et al (18) determined that transient hypoparathyroidism should be regarded as an acceptable outcome of bilateral thyroid surgery rather than as a complication. Surgery also has other drawbacks, including general anesthesia and cosmetic scar formation. The optimal treatment strategy for bilateral thyroid nodules and the associated clinical problems often poses a dilemma for physicians. However, RF ablation preserves thyroid function while minimizing complications (7,10,19). Several studies have

Table 2. Changes in Nodule Size, Volume, Symptom and Cosmetic Scores, and Serum Levels of Hormones after RF Ablation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enrollment 1–6 Months</th>
<th>6–12 Months</th>
<th>Last Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (cm)</td>
<td>4.1 ± 1.9</td>
<td>3.3 ± 1.4 (P &lt; .001)</td>
<td>2.8 ± 1.5 (P &lt; .001)</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>24.4 ± 32.2</td>
<td>11.2 ± 13.7 (P &lt; .001)</td>
<td>9.2 ± 12.3 (P &lt; .001)</td>
</tr>
<tr>
<td>Symptom score</td>
<td>2.4 ± 2.0</td>
<td></td>
<td>1.4 ± 1.3 (P &lt; .001)</td>
</tr>
<tr>
<td>Cosmetic score</td>
<td>3.8 ± 0.5</td>
<td></td>
<td>2.5 ± 1.0 (P &lt; .001)</td>
</tr>
<tr>
<td>Thyrotropin (mU/mL)</td>
<td>1.0 ± 0.6</td>
<td></td>
<td>1.3 ± 1.1 (P = .687)</td>
</tr>
<tr>
<td>fT4 (ng/dL)</td>
<td>1.3 ± 0.3</td>
<td></td>
<td>1.3 ± 0.2 (P = .382)</td>
</tr>
<tr>
<td>Triiodothyronine (ng/dL)</td>
<td>152.5 ± 18.6</td>
<td></td>
<td>143.0 ± 16.5 (P = .170)</td>
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</tbody>
</table>

Note.—Each value is the mean ± SD.

fT4 = free thyroxine; RF = radiofrequency.

Figure 2. A 48-year-old woman presented with bilateral thyroid nodules. (a) Transverse US imaging performed before RF ablation shows a right solid and cystic nodule. The arrows indicate the margin of the nodule. (b) Transverse US image obtained before RF ablation shows a left solid and cystic nodule. The arrows indicate the margin of the nodule. (c) Marked volume reduction of the treated nodules is noted on 12-month follow-up US image. The arrows indicate the margin of the right thyroid nodule. (d) Marked volume reduction of the left nodule is noted on US image obtained 12 months after RF ablation. The arrows indicate the margin of the right thyroid nodule.
suggested that RF ablation is an effective and safe alternative to surgery for treating benign thyroid nodules (5,7,10). Lim et al (20) reported that after RF ablation of one nodule in most patients (ie, 126 nodules of 111 patients), no patient showed hypothyroidism. Ha et al (21) demonstrated that RF ablation does not affect thyroid function in patients who have undergone previous lobectomy. However, preservation of thyroid function after treatment of bilateral nodules has not yet been verified after either RF ablation or other minimally invasive treatments such as laser, ethanol, and microwave ablation and high-intensity focused ultrasound. Our study demonstrates the ability of RF ablation to preserve thyroid function after treatment of bilateral thyroid nodules. We believe that RF ablation can successfully treat thyroid nodules, while minimizing normal thyroid parenchyma injury during the ablation. For this reason, RF ablation can preserve thyroid function even though bilateral thyroid nodules were treated. However; given the small population of the present study, confirmation of these results in a study with a large population is necessary.

Although various complications of RF ablation have been reported, including pain, voice changes, thyroid function abnormalities, hematoma, and skin burns, there have been no reports of procedure-related deaths, and only a few cases of adverse sequelae have been reported (2). The present study showed no procedure-related complications. There have been a few reported cases of hypothyroidism after RF ablation (6,7). The cause of hypothyroidism is still unclear, although several studies have suggested some general trends. Most patients had thyroid antibodies before treatment (6,7,19,22–25), and some developed them after treatment (19,26). When considering these close relationships between the thyroid antibody and hypothyroidism, the development of hypothyroidism seems to be associated with preexisting thyroid antibodies (23). However, Valcavi et al (27) reported that two patients (1.6%) became hypothyroid and two patients (1.6%) became hyperthyroid after laser ablation.

Regarding volume reduction, the present study is comparable to other published studies. In the previous studies, the mean baseline nodule volume ranged from 9.8–24.5 mL, and the mean volume reduction ranged from 78.6%–89.9% at 1 year of follow-up (20,28). Our study showed a 75.9% ± 19.0% volume reduction during a mean follow-up period of 18.1 months after treatment compared with the baseline nodule volume of 24.4 mL ± 32.2.

The present study has several limitations. First, a small number of cases was included, and the follow-up period was limited. The second limitation is the retrospective study design and performance of the study at a single medical center. Third, RF ablation is not the standard of care for the treatment of thyroid nodules. Fourth, fine-needle aspiration after RF ablation can demonstrate atypical cells; however, this is very rare in routine clinical practice. The fifth limitation is that the cosmetic score was recorded subjectively. Finally, follow-up antibody tests were not evaluated in two patients with preexisting thyroid antibodies.

In conclusion, RF ablation improves cosmetic problems and symptoms and preserves thyroid function in patients with bilateral thyroid nodules. Although the present study revealed well-preserved thyroid function in all of the patients with bilateral thyroid nodules treated by RF ablation, validation of these results with a study using a large population is necessary.

REFERENCES