Efficacy and Safety of Radio Frequency Ablation for Benign Thyroid Nodules: Initial Clinical Experience in United Arab Emirates

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Abstract

Objectives Radio frequency ablation (RFA) to treat thyroid nodules is well known as one of alternative therapeutic modalities. This study aimed to investigate the efficacy and complications of RFA to treat symptomatic benign thyroid nodules in United Arab Emirates.

Materials and Methods Eight-nine benign thyroid nodules of 63 patients were enrolled, who were treated by percutaneous ultrasound (US)-guided RFA from 2017 to 2020, and had following US examinations during 12 months after RFA procedure. Symptomatic score with 10-cm visual scale, cosmetic score with four-point scale, and US findings (nodule diameter, volume, composition and vascularity) were compared before and after RFA procedures. RFA-related complications (hematoma, voice change, hypothyroidism, and hyperthyroidism) were assessed.

Statistical Analysis Paired t test was applied to compare laboratory findings before and after RFA procedure. Multiple linear regression analysis was applied to determine significant factors to predict the efficacy of RFA. One-way analysis of variance was applied to compare volume reduction rate (VRR) at 3, 6, and 12 months.

Results Symptomatic and cosmetic scores were significantly improved (pre-RFA vs. post-RFA: 6.07 ± 1.89 vs. 2.06 ± 1.09, 2.94 ± 0.84 vs. 1.27 ± 0.51, p < 0.001). Nodule diameter (cm), volume (mL) at pre-RFA, post-RFA 3 months, 6 months, and 12 months were 3.86 ± 1.26, 2.64 ± 1.14, 2.06 ± 1.09, 1.82 ± 1.14, and 18.8 ± 18.79, 8.82 ± 12.42, 4.47 ± 5.59, 4.11 ± 9.17 (p < 0.001). VRR (%) was 52.81 ± 23.48 at post-RFA 3 months, 79.77 ± 16.91 at 6 months, and 82.08 ± 19.54 at 12 months. Composition of solidity was a significant predictive factor, related to VRR at post-RFA 12 months (p = 0.003). Complication rate was 12.7% (8 of 63 patients). Major complications did not occur.

Conclusion RFA can be an effective and safe alternative modality to treat benign thyroid nodules, and be preferable to treat symptomatic cystic thyroid nodules in Middle East population.

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Introduction

Thyroid nodule is one of common disease entities in head and neck. It can be detected in 4 to 8% of adults on palpation, and in 10 to 41% on ultrasound (US) examination.1,2 Although most thyroid nodules are asymptomatic, 5 to 15% of thyroid nodules cause compressive symptom and cosmetic problem.3,4 US-guided radio frequency ablation (RFA) has been developed to treat symptomatic thyroid nodules as a minimally invasive alternative treatment to thyroid surgery in the recent decade, by Korean and Italian study groups.5,6 The clinical outcome of RFA has been promising, ranging from 51 to 92% volume reduction after procedure.5,7–10 It has also been a safe therapeutic modality that showed low complications rate, such as local pain, hemotoma, and transient hypothyroidism.11 The clinical application of RFA for treating benign thyroid nodules has been spread worldwide to other European countries and North America recently.3,12,13 However, RFA for thyroid nodules has not been introduced to United Arab Emirates. The purpose of this study is to investigate the initial clinical outcome of the efficacy and safety for RFA to treat benign symptomatic thyroid nodules in United Arab Emirates.

Patients and Methods

This retrospective study from a single institution was approved by the institutional review board. Informed consent of patients was waived. Individual procedure consent was obtained to explain the method and expected complications of thyroid RFA, before procedure. All demographic and US findings were retrospectively reviewed based on electronic medical chart.

Study Population

From March 2017 to September 2020, US-guided RFA for thyroid nodules had been performed for 101 thyroid nodules from 75 patients (male: female = 10:65, mean age: 40.65 years ± 11.7, range: 20–67). Inclusion criteria are as follows; (i) subjective symptomatic or cosmetic problem, caused by thyroid nodules (palpable mass, neck pain, dysphagia, dyspnea, voice change or radiating pain to shoulder or arm); (ii) benign pathologic examination before RFA procedure, which was confirmed by at least twice fine-needle aspiration or at least once core needle biopsy, as recommended from the guideline published by Korean Thyroid Radiology Society14 and (iii) no malignant findings on US examinations before RFA (hypochochogenicity, irregular margin, taller than wide orientation, and microcalcification). Exclusion criteria are as follows: (i) inconclusive result on pathologic examination, including nondiagnostic/unsatisfactory, atypia of undetermined significance/follicular lesion with undetermined significance, follicular neoplasm/suspicious follicular neoplasm, suspicious malignant and malignant and (ii) the loss to follow-up, by 12 months after RFA procedure.

Pre-RFA Assessment

Before RFA procedure, symptomatic score, related to thyroid nodules, was assessed at the initial outpatient visit, using a 10-cm visual scale (0–10 cm). Cosmetic score was assessed on physical examinations, using a four-point scale; grade I: impalpable or invisible mass, grade II: a palpable mass without cosmetic problem, grade III: a palpable mass with cosmetic/symptomatic problem during swallowing or sleep, and grade IV: a palpable mass with an easily detected cosmetic/symptomatic problem. Laboratory blood test was performed for all candidates of RFA, which was thyroid function test, platelet count, and coagulation test, including prothrombin time and activated partial thromboplastin time, before procedure of RFA. Thyroid function test included thyroid-stimulating hormone (TSH, normal range: 0.27–4.2 μIU/mL), free thyroxine (T4, normal range: 0.93–1.7 ng/dL).

US examination was performed for thyroid nodules, which was supposed to be targeted for RFA procedure, using a 6 to 9 MHz or 6 to 15 MHz linear transducer (Logiq E9, GE healthcare, Milwaukee, Wisconsin, United States). Orthogonal diameters of thyroid nodules were measured; the longest diameter (a) and two perpendicular diameters (b, c). Volumetric measurement (V) of each nodule was performed, using the equation; \( V = \frac{abc}{6} \). Composition of solidity for thyroid nodules was classified using three-point scale as follow—grade I: predominantly cystic that was more than 80% cystic component of the nodule, grade II: mixed cystic and solid that was from 20 to 80% solid component of the nodule, and grade III: predominantly solid that was more than 80% solid component of the nodule. Vascularity of thyroid nodule on power Doppler examination was classified using four-point scale as follows—grade I: absence of perinodular or intranodular vascularity, grade II: presence of perinodular vascularity only, grade III: intranodular vascularity of less than 50% portion of the nodule with or without perinodular vascularity, and grade IV: intranodular vascularity of more than 50% portion of the nodule with or without perinodular vascularity.15

RFA Procedure

All procedures were selectively performed either at outpatient or inpatient department of day care unit by a 7-year experienced head and neck radiologist. Local anesthesia using 1 to 2% lidocaine was applied for all cases. Monitored anesthesia care was selectively applied by an anesthesiologist for pain-sensitive cases. A cool-tip radio frequency system was used with an 18 gauge straight-type internally cooled electrode (Radio Frequency Thyroid-RF Electrode, RF medical, Seoul, Korea).

Under real-time US guidance, transisthmic approach method was performed for target thyroid nodules. Skin puncture of RF electrode was done at the opposite side of target thyroid nodule through thyroid isthmus to maintain sufficient amount of thyroid parenchyma through electrode track, to minimize perithyroidal hemorrhage or nodule rupture. Initially, electrode was deployed at the deepest and most remote portion of target nodule. Ablation was initiated to make transient focal hyperechoic ablation zone around active tip of electrode for 5 to 20 seconds. After the initiation of ablation, electrode was a little withdrawn medially and anteriorly, so-called “moving shot technique,”
to prevent conductive thermal damage to adjunct vital structures including carotid artery, esophagus, trachea, and recurrent laryngeal nerve. The electrode was subsequently moved toward nonablated area on unit-by-unit basis, when transient hyperchoic ablation zone was expanded around electrode tip. Active tip of electrode was from 0.5 to 1 cm, according to target nodule size. Applied maximal power for ablation was from 25 to 50 W. Mean ablation time was 23.4 minutes ± 15.7, range: 5 to 70. Just after procedure, US investigation was performed for the whole neck area to detect immediate procedure-related hematoma. Before patient’s discharge, patients were asked to detect voice change.

Post-RFA Assessment
The follow-up strategy was outpatient visit at 3, 6, and 12 months after RFA procedure. During follow-up, thyroid function test and US examination were repetitively performed. The repeat assessment of symptomatic and cosmetic score was done at follow-up of 12 months. On following US examination, the volume of ablated thyroid nodule was measured, using same manner. The volume reduction rate (VRR) was calculated using this equation; VRR = (\(\frac{\text{pre-RFA volume} - \text{post-RFA volume on follow-up}}{100}\))/pre-RFA volume. The therapeutic success was defined as more than 50% of VRR at 12 months. The complications related to RFA procedure such as hematoma, skin burn, voice change, hypothyroidism, or hyperthyroidism were evaluated at follow-up period.

Statistical Analysis
Statistical analysis was performed using MedCalc (version 19.5.1, MedCalc Software, Ostend, Belgium). The p-value of < 0.05 was considered as statistically significant. Paired t test was applied to compare the changes of TSH, T4, thyroid nodule diameter, volume, symptomatic score, and cosmetic score before and after RFA procedure. Multiple linear regression analysis was applied to determine significant factors to predict the efficacy of RFA; the relation with VRR at 12 months and predictive factors, which were nodule diameter, volume, composition, vascularity, symptomatic and cosmetic scores. One-way analysis of variance (ANOVA) was applied to compare VRR at 3, 6, and 12 months, according to significant predictive factor.

Results
Of 75 patients who underwent percutaneous US-guided RFA for benign thyroid nodules, 12 patients were excluded: suspicious follicular neoplasm on pathologic examination (n = 1) and the insufficient follow-up period by 12 months (n = 11). Finally, 63 patients with 89 thyroid nodules were enrolled in this study (male:female = 7:56, mean age: 41.02 years ± 11.03, age range: 20–66). Patients represented symptoms of palpable mass (n = 32), dysphagia (n = 15), dyspnea (n = 9), voice change (n = 4), localized neck pain (n = 2), and radiating pain to shoulder (n = 1). A single thyroid nodule was treated by RFA (n = 44), two nodules were treated (n = 15), and three nodules were treated (n = 5). All patients underwent one session of RFA procedure during 12 months follow-up.

The mean ± standard deviation (SD) of symptomatic score before RFA procedure was 6.07 ± 1.89, range: 3 to 8, and that after RFA was 2.06 ± 1.09, range: 1 to 6. The mean ± SD of cosmetic score before RFA was 2.94 ± 0.84, range: 2 to 4 and that after RFA was 1.27 ± 0.51, range: 1 to 3 in -Table 1. Symptomatic and cosmetic scores were significantly improved at 12 months after RFA (p < 0.001). The mean ± SD of T4 before RFA was 1.17 ± 0.99, range: 0.01 to 5.35 and that after RFA was 1.71 ± 1.35, range: 0.3 to 7.24 (p < 0.001). The mean ± SD of T4 was 1.61 ± 2.65, range: 0.9 to 3.3 and that after RFA was 1.21 ± 0.22, range: 0.9 to 2.54, (p = 0.051).

On US examination, the mean ± SD of the longest diameter of target thyroid nodule was 3.86 cm ± 1.26, range: 2.1 to 7.5 before RFA procedure, 2.64 cm ± 1.09, range: 1.2 to 6.5 at 3 months, 2.06 cm ± 1.09, range: 0.7 to 5 at 6 months and 1.82 cm ± 1.14, range: 0.01 to 6.9 at 12 months after RFA (p < 0.001) in -Table 1. The mean ± SD of volume of target thyroid nodule was 18.8 mL ± 18.79, range: 3.2 to 95.79 before RFA procedure, 8.82 mL ± 12.42, range: 0.72 to 61.5 at 3 months, 4.47 mL ± 5.59, range: 0.54 to 51.2 at 6 months and 4.11 ± 9.17, range: 0.01 to 76.78 at 12 months after RFA (p < 0.001). The mean ± SD of VRR of target thyroid nodule

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The efficacy of RFA for 89 thyroid nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics (unit)</td>
<td>Pre-RFA (n = 89)</td>
</tr>
<tr>
<td></td>
<td>3 months (n = 67)</td>
</tr>
<tr>
<td>Symptomatic score</td>
<td>6.07 ± 1.89</td>
</tr>
<tr>
<td>Cosmetic score</td>
<td>2.94 ± 0.84</td>
</tr>
<tr>
<td>TSH (μIU/ml)</td>
<td>1.17 ± 0.99</td>
</tr>
<tr>
<td>T4 (ng/dl)</td>
<td>1.61 ± 2.65</td>
</tr>
<tr>
<td>Diameter (cm)</td>
<td>3.86 ± 1.26</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>18.8 ± 18.79</td>
</tr>
<tr>
<td>VRR (%)</td>
<td>52.81 ± 23.48</td>
</tr>
<tr>
<td>Success rate (%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: n, number; RFA, radio frequency ablation; T4, free thyroxin; TSH, thyroid-stimulating hormone; VRR, volume reduction rate.
Efficacy and Safety of RFA for Benign Thyroid Nodules

Table 2: Multiple linear regression analysis: the relation with VRR at 12 months and demographic, US findings

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Coefficient (β)</th>
<th>Standard error</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic score</td>
<td>-4.377</td>
<td>2.376</td>
<td>0.07</td>
</tr>
<tr>
<td>Cosmetic score</td>
<td>4.843</td>
<td>4.737</td>
<td>0.311</td>
</tr>
<tr>
<td>Diameter</td>
<td>2.589</td>
<td>3.415</td>
<td>0.453</td>
</tr>
<tr>
<td>Volume</td>
<td>-0.174</td>
<td>0.192</td>
<td>0.366</td>
</tr>
<tr>
<td>Composition</td>
<td>-9.851</td>
<td>3.175</td>
<td>0.003</td>
</tr>
<tr>
<td>Vascularity</td>
<td>-3.419</td>
<td>3.39</td>
<td>0.317</td>
</tr>
</tbody>
</table>

Abbreviations: US, ultrasound; VRR, volume reduction rate.

was 52.81% ± 23.48, range: 7.7 to 95.91 at 3 months, 79.77% ± 16.91, range: 22.7 to 98.7 at 6 months and 82.08% ± 19.54, range: 20.1 to 99.7 at 12 months after RFA (p < 0.001). Therapeutic success rate was 97.75% (87 of 97 treated thyroid nodules). Composition of solidity showed grade I in 11 nodules (12.4%), grade II in 14 nodules (15.7%), and grade III in 64 nodules (71.9%). Vascularity showed grade I in 5 nodules (5.6%), grade II in 30 nodules (33.7%), grade III in 49 nodules (55.1%), and grade IV in 5 nodules (5.6%).

In multiple linear regression analysis between VRR at 12 months and predictive factors of demographic and US findings, the composition of solidity was statistically significant (coefficient: -9.851, standard error: 3.175, p-value = 0.003) in Table 2. The other factors were not statistically significant. In one-way ANOVA, according to composition of solidity, the mean ± SD of VRR at each follow-up of predominantly cystic thyroid nodules, mixed cystic, and solid nodules and predominantly solid nodules was 82.19% ± 11.92, 64.95% ± 25.81, 53.71% ± 22.07 at 3 months (p = 0.005), 91.95% ± 7.99, 91.31% ± 3.99, 71.1% ± 17.03 at 6 months (p < 0.001), and 97.63% ± 2.26, 93.7% ± 6.4, 76.87% ± 20.59 at 12 months after RFA (p < 0.001) in Fig. 1.

Complications related to RFA procedure are demonstrated in Table 3. Overall complication rate was 12.7% (8 of 63 patients). Intrathyroidal or perithyroidal hemorrhage on treated thyroid lobe was detected during procedure for five patients (7.9%). All have recovered within 2 weeks with conservative management (sand bag compression or ice packing). Subclinical hypothyroidism without subjective symptoms occurred at 3 or 6 months after RFA in two patients (3.2%). One of them has recovered spontaneously within following 3 months without thyroid hormone replacement therapy, but the other has not recovered until 12 months of follow-up. Subclinical hyperthyroidism occurred at 3 months after RFA for one patient (1.6%) without thyrotoxic symptoms. She has spontaneously recovered without antithyroid medication within following 3 months. Major complications including clinical hypothyroidism, hyperthyroidism, and voice change were not occurred.

Discussion

This study initially presented the efficacy and safety of RFA for treating symptomatic benign thyroid nodules from United Arab Emirates. The mean VRR of all treated nodules in this study was 82.08% at 12 months after RFA, which was

Table 3: Complications of RFA for benign thyroid nodules for 12 months follow-up

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. of complications (%)</th>
<th>Detection time</th>
<th>Recovery time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>5 (7.9%)</td>
<td>1 days</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Skin burn</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclinical hypothyroid</td>
<td>2 (3.2%)</td>
<td>3, 6 months</td>
<td>3–6 months</td>
</tr>
<tr>
<td>Subclinical hyperthyroid</td>
<td>1 (1.6%)</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Major complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voice change</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical hypothyroid</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical hyperthyroid</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8 (12.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RFA, radio frequency ablation.

Fig. 1 Bar graph shows the correlation with composition of thyroid nodules and volume reduction rate at 3, 6, and 12 months after radio frequency ablation procedure.
comparable with that reported in the previous studies with large population: 80.3% at 12 months follow-up by Korean group and 78.6% at 12 months follow-up by Italian group.\textsuperscript{5,6} The mean VRR of predominantly cystic nodules in this study was 97.63% at 12 months after RFA, which could be more efficient than that reported in previous systemic review about RFA for cystic nodules: 70 to 97.5% at 6 to 12 months follow-up.\textsuperscript{16} The mean VRR of predominantly solid mass in this study was 76.87%, which was comparable with that reported in previous systemic review about RFA for solid nodules: 50 to 83.6% at 6 to 12 months follow-up.\textsuperscript{16} The success rate of RFA in this study was 97.75% at 12 months, which was also comparable with that reported in previous study: 97.8% at 12 months follow-up in Korean group.\textsuperscript{5}

Approximately 50 countries have a Muslim-majority population in the world, which were mostly located in Middle East area and North Africa. Alcohol drinking is prohibited or restricted by Islamic law or civil policy in many Muslim-majority countries.\textsuperscript{17,18} On outpatient department, many Muslims tend to refuse to have alcohol ablation (ethanol sclerotherapy), when they have symptomatic cystic or predominantly cystic nodules, arising from thyroid gland. They seem to abstain from any kinds of alcohol intake, not only because it is illegal in some countries, but also because it makes them the guilty conscience from their religion, although alcohol ablation is the first-line to treat symptomatic thyroid nodules.\textsuperscript{17} Thyroid hormone replacement therapy and surgery (thyroid lobectomy or total thyroidectomy) can be alternatively applied for cystic thyroid nodules. However, thyroid hormone replacement therapy is still controversy to make side effects for reducing bone density and aggravating atrial fibrillation under lifelong hormonal suppression. Although thyroid surgery is a curative treatment for thyroid nodules, it can create complications such as high risk of recurrent laryngeal nerve injury, iatrogenic hypothyroidism, and postoperative cosmetic problem. Therefore, RFA can be preferable as the first-line therapeutic option to treat symptomatic cystic thyroid nodules for patients, who refuse alcohol ablation in Muslim-majority countries.

To evaluate safety of RFA procedure for thyroid nodules, the overall complication rate has been reported as 3.3%, ranging from 0 to 10%, and major complication rate was 1.4% in the multicenter study.\textsuperscript{11} In this study, overall complication rate was 12.7% (8 of 63 patients). All patients with hematoma have spontaneously improved within 2 weeks without intervention or surgery to evacuate hematoma. Patients with transient subclinical hypothyroidism or hyperthyroidism were asymptomatic. Any major complications such as recurrent laryngeal nerve damage and permanent thyroid dysfunction were not occurred.

This study has several limitations. First, this is the retrospective study, based on medical chart review and investigator’s opinion. To detect procedure-related complications could be underestimated without systemic approach. Second, all RFA procedures were performed by one experienced head and neck radiologist. The clinical outcome could be variable, depending on operator’s knowledge, experience, and skill. To validate these results, multicenter study is required involved in many well-trained and experienced operators, who can do RFA procedure from Middle East area. Third, follow-up period was limited up to 12 months for all patients. To validate the efficacy of thyroid RFA, the study with long-term follow-up is required.

In conclusion, RFA is an effective and safe alternative modality to treat benign symptomatic thyroid nodules for the population in United Arab Emirates, demonstrating comparable clinical outcome with previous published data. RFA can be a preferable therapeutic modality to treat symptomatic cystic thyroid nodules in Muslim-majority countries, where the patients refuse alcohol ablation.

**Authors’ Contributions**

K.H.L. and E.Y.J. conceptualized and designed the study. K.H.L. and S.J.J. acquired the data. K.H.L. and E.Y.J. analyzed and interpreted the data. K.H.L. was involved in drafting of the manuscript. E.Y.J. and S.J.J. critically revised the manuscript. S.J.J. was also involved in statistical analysis. K.H.L. and E.Y.J. contributed to study administration and supervision.

**Ethical Approval**

This study was approved by Ministry of Health and Prevention Research Ethics Committee (MOHAP/DXB-REC/OOO/No.110/2021).

**Note**

The first prize of oral presentation at Pan Arab Interventional Radiology Society (PAIRS), 2020, Dubai, United Arab Emirates.

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None.

**Conflict of Interest**

None declared.

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