Radiofrequency ablation for thyroid Bethesda III nodules: preliminary results

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Abstract

Purpose: The purpose of this study was to evaluate the feasibility of radiofrequency ablation (RFA) for thyroid nodules with cytological atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS, Bethesda III).

Materials and methods: A total of 28 adults presenting with 30 initial Bethesda III nodules underwent thyroid RFA at a single medical center. Thyroid nodules with Bethesda IV or V according to the second aspiration were excluded. All RFA procedures were performed using the free-hand, ‘moving-shot’ technique under local anesthesia. Clinical features and demographics, RFA details, nodule volume reduction rate (VRR), and complications were analyzed.

Results: The mean age of patients was 47.6 years, 82.1% of whom were females. Mean nodule volumes at pre-RFA, and at 6 months and 12 months post-RFA were 7.92, 2.42, and 1.25 mL, respectively, with a VRR of 77.9% at 6 months, and 87.4% at 12 months. Post-RFA complications were noted in two patients, one with transient vocal cord palsy and another with isthmus minor rupture.

Conclusion: RFA may be another safe alternative except for active surveillance or surgical excision for AUS/FLUS nodules with low-suspicion Thyroid Imaging Reporting and Data System features for patients who are unsuitable or strongly refuse surgery. Long-term results remain uncertain, thus further follow-up study is necessary.

Keywords

- thyroid nodule
- Bethesda III
- radiofrequency ablation
- ACR TI-RADS

Introduction

Thyroid nodules are a common and usually benign occurrence. Previous studies have reported prevalence rates of 2–6% with palpation, and 19–35% with ultrasound (1). With the current widespread use of ultrasound in clinical practice, thyroid nodules are being discovered with increasing frequency.

Thyroid fine needle aspiration cytology (FNAC) is the most accurate test for determining malignancy...
and is an integral part of current thyroid nodule evaluation procedures (2). The Bethesda System for Reporting Thyroid Cytopathology is widely accepted for determining standardized terminology with regards to thyroid FNAC. The atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) category, known as Bethesda category III, has been ascribed a malignancy risk of 5–15% (2, 3, 4, 5).

According to international guidelines, Bethesda III thyroid nodules are not considered an indication of radiofrequency ablation (RFA) (6, 7, 8). Patients with Bethesda III thyroid nodules or those undergoing regular follow-up, or even those undergoing repeated FNAC or core needle biopsy (CNB) examinations, may experience psychological stress and burden. Some patients may opt for surgical treatment (lobectomy or thyroidectomy) with associated surgical risks ranging from 7% to 40% (9, 10, 11). Thyroidectomy requires lifelong thyroid hormone supplementation, and even for patients undergoing lobectomy, there is a possibility of 10–44% needing thyroid hormone supplementation (12). Of note, the majority of such cases prove to have nodules of a benign nature (13). For patients with a benign disease, thyroid surgery is unnecessary. Due to these factors, the management of Bethesda III nodules remains a matter of controversy.

The purpose of this study was to evaluate the feasibility of RFA for AUS/FLUS (Bethesda III) thyroid nodules.

### Methods

This retrospective study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No.: 202200189B0), and each participants’ private information was protected. This study enrolled patients presenting with thyroid nodules with an initial AUS/FLUS diagnosis at a single medical center in Taiwan between September 2019 and September 2021. All nodules were submitted either to repeat FNAC or to CNB. Exclusion criteria were patients with (i) cardiac pacemaker, (ii) pregnancy, (iii) autoimmune thyroiditis, (iv) hyperthyroidism or subclinical hyperthyroidism, (v) follicular neoplasm, and (vi) malignancy discovered at the second diagnosis. A total of four thyroid nodules were excluded, three of which were determined as follicular neoplasm (Bethesda IV) upon repeat FNAC and one was determined to be papillary microcarcinoma upon repeat FNAC. After exclusion criteria and repeat biopsies, a total of 30 thyroid nodules with an initial AUS/FLUS diagnosis were confirmed in 28 patients. All patients had been referred to the thyroid surgery outpatient clinic for evaluation of surgical risks. They were fully informed about the benefits and risks of surgery, as well as the malignant risk associated with Bethesda III nodules and the current lack of RFA as an indication. Despite this, they were still not suitable candidates or declined surgery. The flowchart of patient selection is shown in Fig. 1.

### US risk stratification system

In the pre-RFA evaluation, ultrasound was performed to evaluate the risk of thyroid nodules in accordance with the American College of Radiology’s Thyroid Imaging Reporting and Data System (ACR TI-RADS) (14). The ACR TI-RADS is a point-based system which considers five US categories: composition, echogenicity, shape, margin, and echogenic foci. The classification system confers each nodule with a point ranging from 1 to 5: 1, benign; 2, not suspicious; 3, mildly suspicious; 4, moderately suspicious; and 5, highly suspicious.

### Pre- and post- RFA assessments

Prior to RFA, at least two US-guided FNAC or CNB were performed. All patients underwent lymph node evaluation by sonography before RFA, and the results were negative, indicating no suspicious lymph nodes. In the pre- and post-RFA evaluations, clinical assessments which included symptomatic and cosmetic scores were performed. The symptomatic score ranged from 0 to 5, with a point given for each positive symptom, including compression, cough, difficulty swallowing, voice change, and pain. The cosmetic score ranged from 0 to 3: 0, no palpable mass; 1, no cosmetic problem but palpable mass; 2, a cosmetic problem during neck extension and/or during swallowing; 3, readily detected cosmetic problem (15). Serum thyroid function levels were evaluated prior to RFA, and at 6 months after RFA. The US was evaluated in

**Figure 1**
Flowchart of patient enrolment.
all patients prior to RFA, and at 1, 3, and 6 months after the RFA procedure, and on an annual basis thereafter. The minor and major complications were assessed according to the rating system of the Society of Interventional Radiology (SIR), with classifications A–B (minor) and classifications C–F (major) (16).

**RFA devices and technique**

All patients in this study received single-session RFA. The RFA procedures were performed under local anesthesia and hydrodissection for critical structures with 5% dextrose water. RFA was performed using a free-hand, transisthmic approach, ‘moving-shot’ technique under US guidance, with an internally cooled 18G electrode of 7 cm in length, and with a 5-, 7-, or 10-mm active tip size, powered by an RF generator (VIVA, STARmed; or M2004, RF Medical). The choice of active tip length was determined according to nodule size and the relative position of the perithyroidal structures.

**Statistical analysis**

Clinical characteristics and serum data, nodule volume, and complications were analyzed by the Statistical Package for the Social Sciences Statistics (SPSS Version 23.0; IBM, Armonk, NY, USA) statistical software. Data measurements are expressed as mean, range, and s.d. Comparisons of the pre- and post-RFA data were analyzed with ANOVA. The threshold for statistically significant differences was defined as $P < 0.05$.

**Results**

**Clinical characteristics and imaging subgroups**

A total of 28 patients presenting with 30 thyroid nodules with an initial AUS/FLUS diagnosis were included in this study. The mean age of the patients was 47.6 years (range: 19–76; s.d. 13.4), with 23 female patients (82.1%) and five male patients (17.9%). The mean nodular volume was 7.92 mL (range: 0.08–62.93; s.d. 13.36), and the mean maximal diameter of the nodules was 2.83 cm (range: 0.7–7.6; s.d. 1.63). All these nodules are purely solid or predominantly solid. The reasons for refusing surgery are multifactorial, with the majority being concerned about surgical complications and long-term hormone supplementation after surgery. Patient demographic data and clinical characteristics are presented in **Table 1**.

**ACR TI-RADS subgroups of Bethesda III nodules**

Repeat FNAC is recommended by the Bethesda system for reporting thyroid cytopathology and is used to assist in the clinical decision-making process for AUS/FLUS nodules. Of the 30 nodules which underwent repeat FNAC, the second FNAC was unsatisfactory (Category I) in 13.3% (4/30), benign (Category II) in 70% (21/30), and AUS/FLUS (Category III) in 16.7% (5/30) (Fig. 2). The results of the second cytology after the initial Bethesda III diagnosis, in accordance with the ACR TI-RADS sublevel criteria, are shown in **Table 2**.

**RFA Efficacy**

The median power was 30 W, median total delivered energy 14,287 J and median delivered energy per volume 3186.3 Joule/mL. All nodules were almost completely treated during RFA with very few residual tissues. The mean post-RFA nodule volume and maximal diameter at 6 months and at 12 months were 2.42 and 1.25 mL ($P<0.001$), and 1.60 and 1.18 cm ($P<0.001$), respectively, with a volume reduction rate (VRR = [(initial volume – final volume)/initial volume] × 100) of 77.9% at 6 months and 87.4% at 12 months ($P<0.001$). There were

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**Table 1** Clinical characteristics and RFA effects.

<table>
<thead>
<tr>
<th>RR</th>
<th>Pre-RFA</th>
<th>Post-RFA at 6 M</th>
<th>Post-RFA at 12 M</th>
<th>Post-RFA Overall</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule diameter (cm)</td>
<td>2.83 ± 1.63</td>
<td>1.60 ± 1.07</td>
<td>1.18 ± 0.83</td>
<td>0.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nodule volume (cm³)</td>
<td>7.92 ± 13.36</td>
<td>2.42 ± 3.83</td>
<td>1.25 ± 2.13</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume reduction rate (%)</td>
<td>–</td>
<td>77.9 ± 13.8</td>
<td>87.4 ± 10.8</td>
<td>0.000</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic scale</td>
<td>0.7 ± 1.0</td>
<td>0.1 ± 0.4</td>
<td>0.1 ± 0.4</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cosmetic scale</td>
<td>2.1 ± 1.3</td>
<td>1.1 ± 1.1</td>
<td>0.6 ± 0.9</td>
<td>0.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T3 (ng/dL)</td>
<td>64–152</td>
<td>95.86 ± 9.93</td>
<td>95.39 ± 12.66</td>
<td>0.872</td>
<td>–</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>0.70–1.48</td>
<td>0.99 ± 0.08</td>
<td>1.03 ± 0.09</td>
<td>0.101</td>
<td>–</td>
</tr>
<tr>
<td>TSH (µIU/mL)</td>
<td>0.35–4.9</td>
<td>1.55 ± 0.92</td>
<td>1.52 ± 0.77</td>
<td>0.643</td>
<td>–</td>
</tr>
</tbody>
</table>

M, months; max., maximal; RR, reference range.
Results of second cytology after initial Bethesda III diagnosis.

Table 2
Various TI-RADS classifications of features for nodules initially diagnosed as AUS/FLUS in the first FNAC, as well as the outcomes of the second FNAC and post-RFA FNAC. Notably, eight nodules with a diameter larger than 1cm 6 months post-RFA underwent repeat FNAC and the only nodule that exhibited an AUS/FLUS result after RFA was a TI-RADS 4 nodule. The delivered energy and VRR for both TR1-2 and TR3-4 are also presented in this table.

<table>
<thead>
<tr>
<th>ACR TI-RADS</th>
<th>n (%)</th>
<th>Consecutive Bethesda III in 2nd FNAC</th>
<th>Post-RFA FNAC</th>
<th>Median total energy (J)</th>
<th>Median energy per volume (J/ml)</th>
<th>VRR at 12M (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR 1</td>
<td>1 (3.3%)</td>
<td>0/1 (0%)</td>
<td>0/3</td>
<td>15,008</td>
<td>3,296.5</td>
<td>89.5%</td>
</tr>
<tr>
<td>TR 2</td>
<td>12 (40.0%)</td>
<td>3/12 (25.0%)</td>
<td>0/3</td>
<td>13,646</td>
<td>3,020.8</td>
<td>85.4%</td>
</tr>
<tr>
<td>TR1 + TR2</td>
<td>13 (43.3%)</td>
<td>3/12 (25.0%)</td>
<td>0/3</td>
<td>13,646</td>
<td>3,020.8</td>
<td>85.4%</td>
</tr>
<tr>
<td>TR 3</td>
<td>8 (26.7%)</td>
<td>0/8 (0%)</td>
<td>0/1</td>
<td>14,287</td>
<td>3,186.3</td>
<td>87.4%</td>
</tr>
<tr>
<td>TR 4</td>
<td>9 (30.0%)</td>
<td>2/9 (22.2%)</td>
<td>1/4</td>
<td>14,287</td>
<td>3,186.3</td>
<td>87.4%</td>
</tr>
<tr>
<td>TR3 + TR4</td>
<td>17 (56.7%)</td>
<td>5/30 (16.7%)</td>
<td>1/8</td>
<td>14,287</td>
<td>3,186.3</td>
<td>87.4%</td>
</tr>
</tbody>
</table>

Discussion
This is the first study demonstrating the safety and efficacy of the RFA procedure to treat patients with thyroid nodules.
Molecular testing, including markers such as BRAF, RAS, RET/PTC, and PAX8-PPARγ, has been shown to enhance the accuracy of preoperative FNAC for cases with indeterminate thyroid FNA samples (5, 20, 21). However, due to its cost and limited routine use in our hospital, we could not include this data in our study, which should be considered when interpreting our results. As a workaround, the inclusion of AUS/FLUS nodules with low-suspicion TI-RADS features for ablation might have been a practical approach. Studies have shown that the sensitivity and specificity of ACR TI-RADS are 61–79% and 85–92%, respectively (22, 23). There is a correlation between TI-RADS ultrasound classification and Bethesda cytology, especially for benign nodules. The malignancy risk stratification with TI-RADS is more accurate for nodules classified according to the Bethesda system (18, 24, 25, 26, 27). In our study, there were no malignant findings in the post-RFA FNAC results. The sole nodule displaying an AUS/FLUS outcome post-RFA was categorized as a TI-RADS 4 nodule, indicating that RFA might be less suitable for nodules with higher ACR TI-RADS levels. Indeed, nodules classified as low TI-RADS levels exhibit low malignancy rates, making conservative management with follow-up ultrasound a viable approach. For Bethesda III nodules with low-suspicion TI-RADS features, clinical observation can be advantageous (26, 28, 29), and the potential benefits of RFA may further enhance the treatment options.

RFA is more favored in Asian societies for its less invasion. According to 2017 KSThR guidelines, RFA is indicated for benign thyroid nodules, and may also be used for recurrent thyroid cancer for high surgical risk patients or who refuse surgery (6). The indications of RFA for Bethesda III or IV nodules are not yet established, but studies show it can be safe and effective for small follicular neoplasms or low 18F-fluorodeoxyglucose uptake follicular neoplasms (30, 31). The current study adds evidence to the safety and effectiveness of RFA for treating Bethesda III nodules, supporting its role in nodule management based on the Bethesda System.

This study reports on the efficacy and safety of the RFA procedure, nonetheless several limitations exist. First, this was a retrospective study involving a small number of cases observed within a 1-year follow-up period. A future longitudinal follow-up study involving a larger patient number could be designed to more accurately evaluate long-term outcomes. Secondly, as mentioned above, compared to surgical excision, noninvasive treatments lack the definitive pathology

<table>
<thead>
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<th>Table 3</th>
<th>RFA effects in different cytology subgroups.</th>
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<tbody>
<tr>
<td><strong>Pre-treatment cytology</strong></td>
<td><strong>Bethesda subgroups</strong></td>
</tr>
<tr>
<td></td>
<td>[II+I]</td>
</tr>
<tr>
<td>n*</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Pre-RFA max. diameter</td>
<td>2.73 ± 0.97</td>
</tr>
<tr>
<td>Pre-RFA volume</td>
<td>6.57 ± 5.47</td>
</tr>
<tr>
<td>VRR at 6 months (%)</td>
<td>82.0 ± 9.8</td>
</tr>
<tr>
<td>VRR at 12 months (%)</td>
<td>88.6 ± 6.8</td>
</tr>
</tbody>
</table>

*Total n = 30.

initial AUS/FLUS nodules while revealing the categories of ACR TI-RADS and the second cytology after the initial Bethesda III diagnosis. Of those nodules with two consecutive AUS/FLUS diagnoses which underwent RFA, a post-RFA FNAC with a consecutive AUS/FLUS diagnosis was only noted in one TR 4 nodule. The RFA treatment achieved a significant VRR of 75.5% and 87.4% at 6 and 12 months, respectively. Post-RFA complications were noted in one patient with transient vocal cord palsy and another with an isthmus minor rupture. It is important to note that no long-term complications were reported in this study.

In the current study of 30 nodules, 16.7% were diagnosed as consecutive AUS/FLUS and 70% were benign nodules in the second FNAC. Previous studies have reported a consecutive AUS/FLUS diagnosis in 38.5% of patients, while 42.7–63.5% of repeat FNACs were found to be benign (13, 17). The risk of malignancy (ROM) in thyroid nodules classified as Bethesda III (AUS/FLUS) is 10–30%, while ROM in patients with consecutive AUS/FLUS FNACs is 13.5–26.3% (5, 17, 18, 19). Of note, most surgical specimens from benign nodules with AUS/FLUS cytopathology consist of nodular hyperplasia (13). Thus, although Bethesda III nodules are at risk of malignancy, surgical excision is not necessary for all Bethesda III nodules based on clinical risk factors, sonographic pattern, and patient preference (5). In this article, we have elucidated the efficacy of RFA in the treatment of thyroid AUS/FLUS nodules. Although the potential malignant risks associated with these nodules cannot be entirely ruled out, not all nodules of this nature require surgery, and when compared to active surveillance, RFA has shown therapeutic benefits. RFA provides another choice for patients especially those who are anxious about the Bethesda III nodules but also concerned about the surgical risks.
report that comes after the excision. Therefore, the potential malignant risks associated with the nodules cannot be entirely ruled out, which is a limitation of noninvasive treatments. Additionally, the absence of data on molecular testing through FNAC is another limitation. As a result, thorough preprocedural evaluations and long-term active surveillance are crucial.

In conclusion, RFA appears to be another active surveillance or surgical excision for AUS/FLUS nodules with low-suspicion TI-RADS features, especially for patients who are unsuitable for or strongly opposed to surgery. This approach allows for organ preservation while avoiding surgical risks. However, it is important to note that RFA has its limitations and carries a risk of malignancy when compared to surgical excision. As these findings are preliminary, longer-term follow-up is required to establish the safety of RFA in treating Bethesda III thyroid nodules.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research received no specific grant from any funding agency.

Author contribution statement

P-L. Chiang: analysis and interpretation of data; major contributor in writing the manuscript; S-D. Luo, Y-H. Chang, C-K. Chou, S-Y. Chi, Y-F. Chan: acquisition of data; Wei-Che Lin: design and revision of the study.

Acknowledgements

We thank Thyroid Head and Neck Ablation Center of Kaohsiung Chang Gung Memorial Hospital and all the subjects who participated in this study.

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Received 24 May 2023
Accepted 11 September 2023
Available online 11 September 2023
Version of Record published 9 October 2023