STUDY PROTOCOL

Official Title of the Study:
Radiofrequency Ablation for the Treatment of Benign Thyroid Nodules: A Prospective Study (RFAT)

Protocol Version:
Version 1.0

Document Date:
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1. Title of full study and this report

- Full study: Radiofrequency Ablation for the Treatment of Benign Thyroid Nodules: A Prospective Study
- This report: Radiofrequency Ablation for the Treatment of Benign Thyroid Nodules: A Prospective Study

2. Protocol Version

Version 1.0, Date: 10th Feb, 2023

3. Investigators

- **Principal Investigator**:
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4. Background and Rationale of this report

Benign thyroid nodules are prevalent. These nodules often cause compressive symptoms or cosmetic concerns, necessitating intervention. Radiofrequency ablation (RFA) has emerged as a promising alternative, particularly for nodules with significant solid components, due to its ability to target vascular structures and reduce recurrence risk. Previous studies have shown RFA achieves significant volume reduction rates (VRR), but data on single-session RFA for purely cystic and predominantly cystic thyroid nodules (PCTNs) in Vietnam are limited. This study aims to evaluate the short-term efficacy and safety of single-session RFA, providing evidence to guide clinical practice in resource-constrained settings.

5. Objectives

Primary Objective

To evaluate the efficacy of RFA procedure in reducing the volume of benign thyroid nodules, measured by the volume reduction rate (VRR) at 1, 6, and 12 months post-procedure.

Secondary Objectives

- To assess the safety of RFA procedure, including the incidence of major and minor complications.
- To evaluate the impact of RFA on thyroid function (TSH, FT4 levels).

6. Study Design

- **Type**: Prospective, single-arm, single-center cohort study
- **Setting**: Centre of Endocrinology and Diabetes, Family Hospital, Da Nang, Vietnam
- **Duration**: Feburary 2023 to Feburary 2026 (recruitment and intervention), with follow-up until September 2025 (early reports)
- **Intervention**: Single-session RFA for benign thyroid nodules
- **Follow-Up**: 1, 6, and 12 months post-procedure

7. Participants

Eligibility Criteria

Inclusion Criteria

1. Patients with thyroid nodules, confirmed by ultrasound.
2. Presence of compressive symptoms (e.g., dysphagia, neck pressure) or cosmetic concerns.
3. Documented thyroid function tests (serum free thyroxine [FT4] and thyrotropin [TSH]).
4. Cytology-confirmed benign thyroid nodules via one or two ultrasound-guided fine-needle aspiration (FNA) procedures.
5. Refusal of surgical treatment.
6. Ability to complete follow-up assessments at 1, 6, and 12 months post-procedure.

Exclusion Criteria

1. Malignant or indeterminate cytology on FNA.
2. Contraindications to RFA (e.g., severe coagulopathy, pregnancy).
3. Uncontrolled thyroid dysfunction (e.g., hyperthyroidism or hypothyroidism).
4. Inability to provide informed consent or comply with follow-up.

Recruitment

Patients will be identified through the Ehealth program at the Family Hospital, Da Nang, and referred by endocrinologists or general practitioners. Eligible patients will be approached during routine clinic visits, provided with study information, and invited to participate. Informed consent will be obtained prior to enrollment.

Sample Size

A minimum of 106 patients will be enrolled, based on feasibility and the expected number of eligible patients at the study site over the recruitment period. This sample size allows detection of a clinically meaningful VRR (>50%) with sufficient precision, considering an anticipated dropout rate of 20%. No formal power calculation is performed due to the exploratory nature of the study.

8. Intervention

Radiofrequency Ablation (RFA) Procedure

- **Setting**: Outpatient procedure room at the Centre of Endocrinology and Diabetes, Family Hospital, Da Nang.
- **Operator**: A single endocrinologist (Van Bang Nguyen, MD) with over 5 years of experience in thyroid interventions and RFA certification.
- **Equipment**:
    - Real-time ultrasound system (Acuson NX2 or NX3, Siemens Medical Solutions, USA) with an 8–12 MHz linear probe.
    - Cooled, internally irrigated monopolar electrode (5 mm or 7 mm active tip) connected to a radiofrequency generator (CoATherm AK-F200, APRO KOREA Inc., Korea).
- **Procedure Steps**:

1. **Preparation**: Patients are positioned supine with neck extended. Skin is sterilized, and local anesthesia (2% lidocaine) is administered at the needle insertion site and peri-thyroidal region.

2. **Ablation**: After local anesthesia, the monopolar electrode is inserted into the nodule. The moving-shot technique is used to ablate the nodule unit by unit, targeting vascular structures identified by Doppler ultrasonography. Hydro-dissection with 5% dextrose solution protects critical structures (e.g., nerves, arteries).
3. **Completion**: Ablation is confirmed by a transient hyperechoic zone on ultrasound.

- **Duration**: Approximately 12–16 minutes per procedure.
- **Energy and Power**: Mean energy delivered
- **Concomitant Care**
  - Patients will continue routine thyroid function monitoring as per standard care.
  - No additional interventions (e.g., EA or surgery) will be performed during the study unless clinically indicated (e.g., recurrence or complications).

9. Outcomes

Primary Outcome

- **Volume Reduction Rate (VRR)**:
  - Definition: Percentage reduction in nodule volume, calculated as: [VRR (%) = {Initial Volume} - {Follow-Up Volume}}/{{Initial Volume}} *100]
  - Measurement: Nodule volume is calculated using ultrasound ($V = \pi abc/6$, where a, b, c are the three diameters).
  - Time Points: 1, 6, and 12 months post-procedure.
  - Therapeutic Success: Defined as VRR >50%.

Secondary Outcomes

- **Safety**:
  - Incidence of major complications (e.g., permanent voice changes, severe bleeding requiring transfusion, hospitalization).
  - Incidence of minor complications (e.g., transient pain, temporary voice changes).
  - Assessed per international image-guided tumor ablation criteria.
- **Thyroid Function**:
  - Serum TSH (μIU/mL) and FT4 (ng/dL) levels.
  - Measured at baseline and 1, 6, and 12 months.
- **Comparative VRR**:
  - VRR in purely cystic nodules (<10% solid) vs. PCTNs (10–50% solid) vs solid

10. Data Collection

Pre-Ablation Assessment

- **Ultrasound**:
  - Performed by a single experienced radiologist using the Acuson NX2/NX3 system.
  - Measures: Nodule size (three diameters), volume, and cystic component percentage.
  - Classification: Purely cystic (<10% solid) or PCTN (10–50% solid) or solid.
- **FNA**: Performed by the endocrinologist to confirm benign cytology.
- **Thyroid Function Tests**: Serum TSH and FT4 levels.

- **Clinical Scores**: Cosmetic and symptom scores (scale: 0–10 for symptoms, 1–4 for cosmetic concerns).

Procedure Data

- Volume of aspirated fluid (mL).
- Procedure duration (minutes).
- Energy delivered (kJ).
- Minimum and maximum RF power (W).
- Lidocaine dose (mL).

Follow-Up Assessments

- **Ultrasound**: Repeated at 1, 6, and 12 months to measure nodule volume and VRR.
- **Thyroid Function Tests**: TSH and FT4 at 1, 6, and 12 months.
- **Clinical Evaluation**: Assessment of complications, symptoms, and cosmetic outcomes.
- **Data Recording**: Stored in a secure electronic database with restricted access.

11. Statistical Analysis

Primary Analysis

- **VRR**: Mean and standard deviation (SD) of VRR at 1, 6, and 12 months will be calculated.
- **Change Over Time**: Repeated measures ANOVA or Friedman test (for non-normal data) will be used to assess changes in VRR, nodule volume, largest diameter, TSH, and FT4 from baseline to follow-up.
- **Therapeutic Success**: Proportion of patients achieving VRR >50% at each time point, with 95% confidence intervals.

Secondary Analysis

- **Comparison by Nodule Type**: Wilcoxon signed-rank test or Mann-Whitney U test to compare VRR between purely cystic nodules and PCTNs.
- **Safety**: Incidence of complications reported as frequencies and percentages.
- **Predictors of Efficacy**: Multiple linear regression to identify factors associated with VRR at 6 months (e.g., baseline nodule volume, cystic component, age, gender).

Software

- SPSS version 20.0 for Windows.
- Significance level: $p < 0.05$.

Handling Missing Data

- Patients lost to follow-up will be analyzed using the last observation carried forward (LOCF) method for VRR and thyroid function outcomes.
- Sensitivity analyses will exclude missing data to assess robustness.

12. Ethical Considerations

Ethics Approval

- Approved by the Ethics Committee of the Institutional Review Board, University of Medicine and Pharmacy, Hue University (Number: H2023/050).

Informed Consent

- Written informed consent will be obtained from all participants prior to enrollment.

- Patients will receive a detailed explanation of the RFA procedure, potential benefits, risks, and study requirements.

Confidentiality

- Patient data will be anonymized using unique study IDs.
- Data will be stored in a password-protected database accessible only to authorized investigators.

Risks and Benefits

- **Risks**: Potential complications include pain, transient voice changes, or rare major complications (e.g., bleeding, nerve injury). These will be minimized through ultrasound guidance and hydro-dissection.
- **Benefits**: Potential reduction in nodule size, alleviation of symptoms, and improved cosmetic appearance without surgery.

Adverse Event Monitoring

- All adverse events will be recorded and reported to the ethics committee.
- Serious adverse events (e.g., hospitalization, permanent disability) will prompt immediate review by the study team and ethics board.

13. Data Management

- **Data Collection**: Standardized case report forms (CRFs) will be used to record baseline, procedural, and follow-up data.
- **Data Entry**: Double-entry verification by two independent researchers to ensure accuracy.
- **Data Storage**: Secure electronic database hosted at the Family Hospital, backed up weekly.
- **Data Sharing**: De-identified data will be available upon reasonable request, subject to ethics approval.

14. Quality Control

- **Training**: All study personnel (radiologist, endocrinologist) are trained in RFA and ultrasound protocols.
- **Standardization**: Ultrasound measurements and FNA procedures follow standardized protocols.
- **Monitoring**: Regular audits by the principal investigator to ensure protocol adherence.

15. Dissemination

- **Publication**: Results will be submitted to peer-reviewed journals (e.g., International Journal of Endocrinology, Thyroid).
- **Conferences**: Findings will be presented at national and international endocrinology or radiology conferences.
- **Public Access**: A lay summary will be shared with participants and posted on the hospital's website.
- **Authorship**: Based on ICMJE criteria, with all investigators contributing to study design, data collection, or analysis eligible for authorship.

16. Timeline

Activity	Timeline

Ethics approval	April 2023
Recruitment and intervention	June 2023 – April 2025
Follow-up (1, 6, 12 months)	July 2023 – April 2026
Data analysis	May 2026 – June 2026
Manuscript preparation and submission	July 2026 – September 2026

17. Funding

- No external funding.
- Costs include ultrasound equipment, RFA generator, and staff time, covered by routine clinical budgets.

18. Amendments

- Any protocol amendments (e.g., changes to eligibility criteria or outcomes) will be submitted to the ethics committee for approval and documented in an updated protocol version.

19. Abbreviations

- FNA: Fine Needle Aspiration
- FT4: Free Thyroxine
- PCTNs: Predominantly Cystic Thyroid Nodules
- RFA: Radiofrequency Ablation
- TSH: Thyrotropin
- VRR: Volume Reduction Rate

20. References

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