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Original research

CLINICAL, SONOGRAPHIC, AND CYTOLOGICAL CORRELATES OF LARGE BENIGN THYROID NODULES: INSIGHTS FROM A HOSPITAL - BASED STUDY

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ABSTRACT

Background: *Large benign thyroid nodules (LBNs) frequently cause compressive or cosmetic symptoms despite their benignity. Accurate risk stratification combining sonographic and cytological criteria is crucial for appropriate management and selection for minimally invasive therapies such as radiofrequency ablation (RFA).*

Methods: *In this cross-sectional study, 150 patients with 174 thyroid nodules ≥ 20 mm, cytologically confirmed as benign (Bethesda II), were enrolled at the Center of Endocrinology and Diabetes, Family Hospital, Da Nang, Vietnam. Clinical, biochemical, and sonographic features were systematically assessed and categorized according to the ACR-TIRADS system. The study was part of the SS-RFAT trial (ClinicalTrials.gov Identifier: NCT07115576)*

Results: *The cohort was predominantly female (85.3%) with a mean age of 44.2 ± 14.8 years. The mean largest nodule diameter was 31.7 ± 10.3 mm. Most nodules were solid (75.8%) and isoechoic (47.7%), with smooth margins (98.3%) and wider-than-tall shape (99.4%). Suspicious sonographic features were rare (microcalcifications 2.3%, irregular margins 1.7%). All nodules were cytologically benign. Thyroid function was largely normal (TSH 1.27 ± 0.8 mIU/mL; FT4 1.28 ± 0.3 ng/dL).*

Conclusions: *Large thyroid nodules frequently exhibit benign sonographic and cytological characteristics. Integrating ACR-TIRADS and Bethesda classifications allows accurate exclusion of malignancy and supports the safe selection of patients for nonsurgical treatments such as RFA.*

Keywords: *Large benign thyroid nodule, ultrasonography, cytology, ACR-TIRADS, Bethesda system.*

I. INTRODUCTION

The detection of thyroid nodules has become an increasingly common phenomenon in clinical endocrinology and radiology, primarily attributable to the widespread use thyroid ultrasonography. Epidemiological data indicate that thyroid nodules are highly prevalent in the general population, with detection rates reaching up to 65% in autopsy and high-frequency ultrasound studies [1].

Despite this high prevalence, the vast majority of thyroid nodules (approximately 90-95%) are histologically and cytologically benign, presenting as asymptomatic findings. Consequently, the core objective of the clinical workup is to accurately identify and exclude the small proportion of nodules (5-10%) that harbor malignancy, thereby preventing unnecessary invasive procedures for benign lesions [2].

The management of benign thyroid nodules, particularly those of substantial size introduces a unique clinical challenge. In addition to conventional approaches such as surgery and thyroid hormone suppression therapy, radiofrequency ablation (RFA) has emerged as a promising therapeutic option for benign thyroid nodules [3]. Nevertheless, accurate

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characterization of large thyroid nodules remains a critical prerequisite for selecting the most appropriate treatment modality. While the overall risk of malignancy is not statistically associated with nodule size or volume , large nodules frequently induce mechanical or compressive symptoms, such as dysphagia, globus sensation, or dyspnoea due to tracheal deviation or compression. Furthermore, cosmetic concerns often necessitate intervention in the absence of malignant potential [4].

Current international guidelines, including those from the American Thyroid Association (ATA) and the Thyroid Imaging, Reporting and Data System (TI-RADS), utilize a risk stratification approach based on specific sonographic features [5, 6]. Characteristics such as microcalcifications, marked hypoechogenicity, and irregular margins are strongly associated with an increased likelihood of malignancy, while features like cystic or spongiform composition are highly predictive of benignity. Fine-Needle Aspiration Biopsy (FNAB), reported according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), remains the definitive diagnostic tool for confirming benignity (Bethesda II) [7].

The purpose of this study is to analyze the clinical presentation, sonographic characteristics, and cytological outcomes of patients presenting with thyroid nodules, with a specific emphasis on validating the diagnostic utility of modern risk stratification systems (ACR-TIRADS) in confirming the benign nature (Bethesda II) of large thyroid masses.

II. MATERIALS AND METHODS

2.1. Study design and patient selection

This cross-sectional, single-center study was conducted at the Centre of Endocrinology and Diabetes, Danang Family Hospital, Danang, Vietnam, and was approved by the Ethics Committee of the Institutional Review Board of the University of Medicine and Pharmacy, Hue University, Vietnam (Approval No. H2023/050). The study was part of the SS-RFAT trial (ClinicalTrials.gov Identifier: NCT07115576). Written informed consent was obtained from all participants prior to enrollment. The study population included patients who underwent one or two sessions of ultrasound-guided fine-needle aspiration biopsy (FNAB) to confirm the benign nature of thyroid nodules before undergoing radiofrequency ablation (RFA).

Patients were eligible for inclusion if they met the following criteria: (1) thyroid nodules with the largest diameter ≥ 20 mm; (2) presence of compressive symptoms or cosmetic concerns; (3) availability of thyroid function tests, including serum free thyroxine (FT4) and thyrotropin (TSH) levels; and (4) cytologically confirmed benign thyroid nodules based on one or two sessions of ultrasound-guided fine-needle aspiration (FNA). Prior to undergoing FNA, all patients received a comprehensive explanation of the procedure, including its potential benefits and risks, to ensure fully informed decision-making.

2.2. Clinical and biochemical assessment

Demographic data (age, gender, history of diseases, history of thyroid diseases and treatments), clinical examination (blood pressure, BMI, thyroid examination), presenting symptoms (e.g., dysphagia, dyspnoea, hoarseness) were recorded. The compressive symptom was evaluated by asking patients via a visual analog scale (from 0 to 10), and a cosmetic score was followed as clinical examination: 1, no palpable mass; 2, a palpable mass but no cosmetic problem; 3, cosmetic problem on swallowing only; 4, readily detected cosmetic problem.

Initial biochemical evaluation for all patients included the measurement of serum Thyroid-Stimulating Hormone (TSH) concentration and FT4. Additional laboratory test, such as thyroglobulin (Tg), was recorded where available.

2.3. Sonographic evaluation and risk stratification

All thyroid ultrasound examinations were performed by a single or a select group of experienced thyroid radiologists using real-time ultrasound system (Acuson NX2 or NX3, Siemens Medical Solutions, California, USA) equipped with an 8-12 MHz linear probe was used for all cases. Thyroid ultrasound variables included thyroid hyperperfusion (yes/no), number of nodules, large nodules location, nodule volume (calculated using the formula for an ellipsoid: $V = \pi abc/6$, where V is the volume and a, b, and c represent the three measured diameters).

Each nodule was systematically evaluated for the following sonographic features : echogenicity (hypoechoic, isoechoic, or hyperechoic - relative to the adjacent thyroid parenchyma), composition: (solid, mixed and cystic nodule), margins (regular/smooth or irregular/infiltrative), shape (taller-than-wide or wider-than-tall), calcifications (microcalcifications or macr calcification), vascularity (0 indicates no vascularity (no blood flow), 1 shows minimal perinodular (outer margin) vascularity, 2 denotes increased perinodular vascularity, 3 represents mild intranodular (inside the nodule) vascularity, and 4 signifies marked or extensive intranodular vascularity), extra-thyroidal extension [8].

Nodules were risk-stratified based on the ACR TI-RADS system. The decision for FNAB was based on the TI-RADS risk classification and the size cut-offs mandated by the respective guidelines (e.g., ≥2.0 cm for Very Low Suspicion nodules).

2.4. Fine-needle aspiration biopsy and cytopathology

FNAB was performed under real-time ultrasound guidance using a standardized technique (e.g., 27-gauge needle, trans-isthmic approach, 2-3 passes). Aspirated material was prepared using the 'classic' smear technique [9].

Cytological specimens were evaluated by a single dedicated cytopathologist. Cytological diagnoses were classified according to the 2023 Bethesda System for Reporting Thyroid Cytopathology: (i) nondiagnostic; (ii) benign; (iii) atypia of undetermined significance; (iv) follicular neoplasm; (v) suspicious for malignancy; and (vi) malignant. In this study, we focused on benign thyroid nodules (Bethesda II) [7].

2.5. Statistical analysis

Descriptive statistics were used to summarize the demographic, clinical, and sonographic characteristics of the cohort. Continuous variables were reported as mean (SD) or median (IQR), and categorical variables as frequencies and percentages. All analyses were performed using SPSS 20 window version.

III. RESULTS

The study cohort consisted of 150 patients, predominantly female (85.3% or 128 out of 150), with a mean age of 44.2 ± 14.8 years. The average BMI was 23.23±3.04. Notably, the vast majority of participants (96.0%) were treatment-naïve, having undergone no prior surgery, Radiofrequency Ablation (RFA), or hormone suppression therapy for their thyroid condition (Table 1).

Table 1: The demographic information of patients with thyroid nodules

Characteristics	Summary statistics
Number of patients	150
Age (years) [(mean ± SD) (range)]	44.2 ± 14.8 (14 - 77)
Male/Female	22/128
BMI	23.23 ± 3.04 (17.2 - 33.7)
Duration of thyroid nodules	1.94 ± 3.48
Previous treatment	
No	144 (96.0)
Surgery	4 (2.7)
RFA	1 (0.65)
Hormone suppression therapy	1 (0.65)
Cosmetic score	2.7 ± 0.95 (1 - 4)
Symptom score	3.5 ± 3.7 (0 - 10)

The analysis covered 174 total thyroid nodules, confirming the study's focus on large lesions with a mean largest diameter of 31.65 ± 10.29 mm (ranging from 20 to 73 mm). A high proportion of patients (72.0%) presented with Multinodular. The nodules were distributed almost equally between the right lobe (50.57%) and the left lobe (47.7%), with only a small fraction (1.7%) located in the isthmus (Table 2).

Table 2: The characteristic of large benign thyroid nodules

Characteristics	Summary statistics
Number of nodules	174
Single (n,%)	42 (28.0)
Multiple (n,%)	108 (72.0)
Nodule position (n,%)	

Characteristics	Summary statistics
Left	83 (47.7)
Isthmus	3 (1.7)
Right	88 (50.57)
Mean largest nodule diameter (mm) [(mean ± SD) (range)]	31.65 ± 10.29 (20-73)

Sonographic evaluation confirmed the benign nature of the nodules. The nodules were mainly Solid (75.8%) in composition and frequently Isoechoic (47.7%). Crucially, high-suspicion features were overwhelmingly absent: 98.28% had smooth margins, and 99.42% were Wider-than-tall, with only one nodule (0.58%) showing a Taller-than-wide shape. Microcalcifications were rare (2.29%), and 100% of the nodules showed no extrathyroidal extension (Table 3).

Table 3: Ultrasonographic classification of benign thyroid nodule

Feature	Categories / Definitions	N (%)
Echogenicity (n,%)	Hypoechoic	40 (23.0)
	Isoechoic	83 (47.7)
	Hyperechoic	34 (19.5)
	Anechoic	17 (9.8)
Composition (n,%)	Solid	132 (75.8)
	Mixed	28 (16.09)
	Cystic	14 (8.04)
Margins (n,%)	Regular/Smooth	171 (98.28)
	Irregular/Infiltrative	3 (1.72)
Shape (n,%)	- Taller-than-wide	1 (0.58)
	- Wider-than-tall	173 (99.42)
Calcifications (n,%)	Microcalcifications	4 (2.29)
	Macrocalcifications	15 (8.62)
	Eggshell calcification	1 (0.57)
	None	154 (88.52)
Vascularity (score) (n,%)	0	76 (43.7)
	1	58 (33.3)
	2	26 (14.9)
	3	11 (6.3)
	4	3 (1.8)
Extrathyroidal extension (n,%)	Present	0
	Absent	174 (100)

The biochemical profile confirmed that the cohort was predominantly euthyroid. The mean Thyroid-Stimulating Hormone (TSH) level was 1.27 ± 0.8 mIU/ml, and the mean Free Thyroxine (FT4) was 1.28 ± 0.3 ng/dL. Reflecting the large volume of thyroid tissue characteristic of the large nodules and Multinodular, the mean Thyroglobulin (Tg) level was significantly elevated at 138.14 ± 152.48 ng/ml (Table 4).

Table 4: Biochemical Assessment of benign thyroid nodule

Characteristics	Summary statistics
FT4 (ng/dL) [(mean ± SD) (range)] (n=171)	1.28 ± 0.3 (0.46 - 3.16)
TSH (mIU/ml) [(mean ± SD) (range)] (n=171)	1.27 ± 0.8 (0.01 - 4.17)
Thyroglobulin (ng/ml) [(mean ± SD) (range)] (n=134)	138.14 ± 152.48 (3.98 - 500)

IV. DISCUSSION

The advent of high-resolution ultrasonography has markedly increased the detection rate of thyroid nodules, creating a need for standardized risk stratification systems to manage the large number of patients with incidental or symptomatic findings [10]. Although 90 - 95% of thyroid nodules are benign, large benign nodules defined in this study as having a maximal diameter > 20 mm pose significant clinical challenges because of compressive symptoms (e.g., dysphagia, dyspnoea) and cosmetic concerns [4].

This cross-sectional study systematically evaluated 150 patients with 174 large benign nodules, all rigorously confirmed as benign (Bethesda II) by fine-needle aspiration biopsy (FNAB). A key contribution of this work is the reinforcement of the current clinical paradigm, which prioritizes feature-based risk assessment (e.g., ACR-TI-RADS) over nodule size alone when predicting malignancy. The mean largest diameter of the nodules was 31.65 ± 10.29 mm (range 20 - 73 mm). Importantly, the 100% benign cytology demonstrates that strict adherence to combined sonographic and cytological guidelines enables safe selection of patients for nonsurgical, volume-reducing therapies such as radiofrequency ablation (RFA), thus preventing unnecessary surgery in histologically innocuous but clinically significant lesions [11].

The cohort exhibited a strong female predominance (85.3%), consistent with global epidemiology of thyroid nodules. The mean age was 44.2 ± 14.8 years, somewhat younger than typical population-based reports, which often show the highest prevalence above 45 years. This suggests a selection effect, whereby younger patients with symptomatic or cosmetically bothersome nodules are more motivated to seek intervention before nodules reach extreme sizes or comorbidities develop.

Multinodularity was frequent, affecting 72.0% of patients, reflecting chronic goitrous disease as the underlying pathology. Although RFA typically targets the dominant symptomatic nodule, the multinodular context highlights the need for ongoing surveillance. Nodule distribution was nearly symmetrical between lobes (right: 50.6%, left: 47.7%), with minimal isthmic involvement (1.7%).

Ultrasound characterization was central in bridging the gap between large nodule size and low malignancy risk. Most nodules corresponded to low-suspicion ACR-TI-RADS categories (TR2-TR3). High-suspicion features were rare: only 1.72% exhibited irregular/infiltrative margins, 0.58% were taller-than-wide, and 2.29% contained microcalcifications; no extrathyroidal extension was observed. The overwhelming prevalence of smooth, regular margins (98.3%) reinforced the benign profile.

FNAB confirmed benign cytology in all nodules, underscoring the necessity of biopsy, particularly for nodules with mildly suspicious features. Regarding composition, 75.8% were solid and 47.7% were isoechoic - features consistent with adenomatous hyperplasia in multinodular goiter. Solid, low-risk nodules represent ideal RFA targets due to their stable ablation response and long-term symptom relief.

The cohort was euthyroid, with mean TSH 1.27 ± 0.8 mIU/mL and FT4 1.28 ± 0.3 ng/dL, indicating predominantly non-toxic nodules. Notably, mean thyroglobulin (Tg) levels were markedly elevated

(138.14 ± 152.48 ng/mL), reflecting increased thyroid mass rather than malignancy. Tg thus served as a surrogate marker for disease burden and will be valuable for monitoring treatment response, given that Tg decline is expected to correlate with RFA-induced volume reduction.

The definitive benign diagnosis, coupled with large nodule size, establishes RFA as an optimal treatment for symptomatic or cosmetically distressing large benign nodules, particularly when surgery is contraindicated or undesired. RFA consistently achieves durable volume reduction rates of 50 - 80% within 6 - 12 months, translating into marked improvement in both compressive symptoms and cosmetic outcomes. Solid nodule predominance in this cohort suggests favorable long-term results [12].

Compared with thyroidectomy, RFA carries a lower risk profile: meta-analyses report overall complication rates around 2.4%, with major complications < 1.5% and minimal risk of permanent hypothyroidism (0.07%) or recurrent laryngeal nerve injury. This supports its role as a minimally invasive, first-line alternative for large benign nodules [13, 14].

Strengths of this study include rigorous selection criteria (FNAB Bethesda II confirmation in all cases) and standardized diagnostic assessments by an experienced single-center team, ensuring high internal validity. However, limitations include selection bias toward intervention-seeking patients, limiting generalizability to asymptomatic LBN populations. As a baseline characterization, this analysis cannot yet address outcomes such as volume reduction, symptom improvement, or recurrence.

An administrative clarification is required: the clinical trial identifier listed (NCT07115576) does not correspond to a thyroid study and should be corrected in future publications to ensure protocol transparency.

This baseline characterization provides a solid foundation for the ongoing SS-RFAT trial. Future multi-center, prospective studies are essential to validate these findings across broader populations and to establish RFA as a standard non-surgical therapy for large benign thyroid nodules.

V. CONCLUSION

Most large (≥ 20 mm) benign thyroid nodules in this study showed typical benign ultrasound features - smooth margins, wider-than-tall shape, and absence of microcalcifications or extrathyroidal extension - with Bethesda II cytology and normal thyroid function. These results confirm that nodule size alone does not indicate malignancy, and management should be based on combined sonographic and cytological assessment. Radiofrequency ablation may be a safe, effective alternative for appropriately selected benign large nodules.

Declarations

Ethics approval and consent to participate: Written informed consent form was given to patients this report is a part of PhD thesis

Competing interests

Conflict of interest relevant to this article was not reported.

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