

# ULTRASOUND CHARACTERISTICS OF THYROID NODULES: DIFFERENTIATING BENIGN FROM MALIGNANT NODULES USING HISTOPATHOLOGY AS THE GOLD STANDARD.



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## ABSTRACT

**Background:** Thyroid nodules represent a prevalent observation in clinical practice. The precise distinction between benign and malignant nodules is essential for establishing suitable management and therapeutic interventions. Ultrasound represents the principal imaging technique employed in the characterization of thyroid nodules, providing valuable information on characteristics such as echogenicity, size, and vascularity. Despite its widespread use, the diagnostic accuracy of ultrasound in distinguishing benign from malignant nodules varies, necessitating further research to establish reliable ultrasound markers. Therefore, this study aimed to evaluate ultrasound characteristics of thyroid nodules to differentiate benign from malignant nodules using histopathology as the gold standard.

**Materials and Methods:** This retrospective investigation examined 175 thyroid nodules obtained from 155 individuals who underwent thyroid ultrasonography followed by fine-needle aspiration (FNA) or core-needle biopsy (CNB) at King Fahad Hospital, Saudi Arabia, between 2021 and 2024. Ultrasound features, including echogenicity, size, and vascularity, were recorded and analyzed. The Chi-square method of statistics was used to analyze categorical data, and the Mann-Whitney U test was employed to evaluate nodule size measurements.

**Results:** Among the total of 175 nodules examined, 154 were classified as benign, whereas 21 were identified as malignant. A correlation of statistical significance was found regarding gender and the diagnosis of nodules ( $p=0.05$ ), with overall and malignant thyroid nodules more frequently observed in females than in males. Malignant nodules tended to show a greater likelihood of being hypoechoic in relation to the adjacent normal thyroid parenchyma, than benign nodules ( $p=0.002$ ). No significant differences were observed regarding hyperechoic, isoechoic, mixed echogenicity, or vascularity characteristics, nor in the sizes of nodules between benign and malignant thyroid nodules.

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**Conclusion:** This research emphasizes the significance of thyroid nodules' echogenicity in malignancy prediction, while other ultrasound features, such as size and vascularity, did not significantly correlate with malignancy. Further prospective, multi-center research is needed to validate these findings and improve diagnostic accuracy in thyroid nodule management.

**Keywords:** Thyroid nodules, Cancer, Ultrasound, Histopathology

## 1. INTRODUCTION

Thyroid nodules are characterized as discrete lesions located within the thyroid gland, are a frequent incidental finding during clinical evaluations. Research indicates that these nodules can be detected in about 50% of the adult population, emphasizing their prevalence [1], With under 15% of thyroid nodules being of clinical importance, the potential risk of thyroid cancer is relatively minimal [2, 3], Although most thyroid nodules do not cause symptoms, they are usually benign and lack clinical significance [4], Malignant nodules exhibit an annual growth rate of approximately 15% globally, participating to the rising burden of thyroid cancer, which ranks among the most prevalent endocrine malignancies and stands as the seventh most common cancer in women and the fifteenth in men [5, 6]. Therefore, employing a non-invasive method to distinguish benign from malignant thyroid nodules is important. Assessing the neck through diagnostic imaging can incidentally detect thyroid nodules. Ultrasound is the primary imaging technique for detecting these nodules [7], and has enhanced the evaluation of malignancy risk via sonographic characteristics such as echogenicity, composition, calcification, and border regularity [5, 8]. Additionally, age and gender are significant factors linked to an elevated risk of thyroid cancer. This malignancy predominantly impacts females, yet males may exhibit greater mortality rates, with aging correlating with less favorable outcomes [2].

The procedures of ultrasound-guided fine-needle aspiration cytology (FNA) and core-needle biopsy (CNB) are deemed the most proficient [9]. However, these procedures are redundant for non-cancerous thyroid nodules and must be allocated to individuals with heightened malignancy susceptibility. Thus, with the aim to avoid overdiagnosis benign cases, this study is aimed at identifying the ultrasonographic characteristics of thyroid nodules in order to identify individuals at malignancy risk who might benefit from FNA and/or CNB.

## 2. METHODS

Validation for this retrospective research was obtained from the Institutional Review Board at the General Directorate of Health Affairs in Madinah, Saudi Arabia (reference no: H-03-M84), and performed on data collected from the archive of King Fahad Hospital on subjects who underwent thyroid ultrasound procedure and ultrasound-guided fine-needle aspiration or core-needle biopsy at the Department of Radiology. In this retrospective study, we reviewed a dataset of 404 patients between 2021 and 2024. In this study, radiologists used the Thyroid Imaging Reporting and Data System to evaluate B-mode ultrasound images and provide detailed annotations and thyroid nodule diagnoses. FNA and CNB of each patient was also obtained. Data from subjects included age, gender, and detailed diagnostic characteristics of thyroid nodules. These features encompassed nodule morphology and composition, such as (sponge-like, solid, cystic, and microcalcifications). Additionally, echogenicity was assessed relative to normal thyroid parenchyma, categorized as (hypoechoic, isoechoic, hyperechoic, or mixed). The nodules were also classified by shape (round, oval, irregular), margin of the nodule (well-defined, ill-defined) and vascularity (non-hyper vascular and hyper-vascular) were extracted. Patients with no available records or ultrasound examinations were excluded.

### 2.1 Statistical analysis

This research utilized statistical analysis through the Chi-square test to assess categorical variables such as gender, the echogenicity of thyroid nodules, and their vascularity patterns observed in ultrasound images, correlating these factors with the nodules' diagnosis, which was categorized as either benign or malignant based on histopathological findings. To compare the size of thyroid nodules (length, width, and thickness) of benign versus malignant nodules, Mann-Whitney U test for independent samples was utilized. Blinded data analysis was performed using IBM SPSS Statistics (Version 21.0, Armonk, NY: IBM Corp). Statistical significance was established at  $p \leq 0.05$ .

## 3. RESULTS

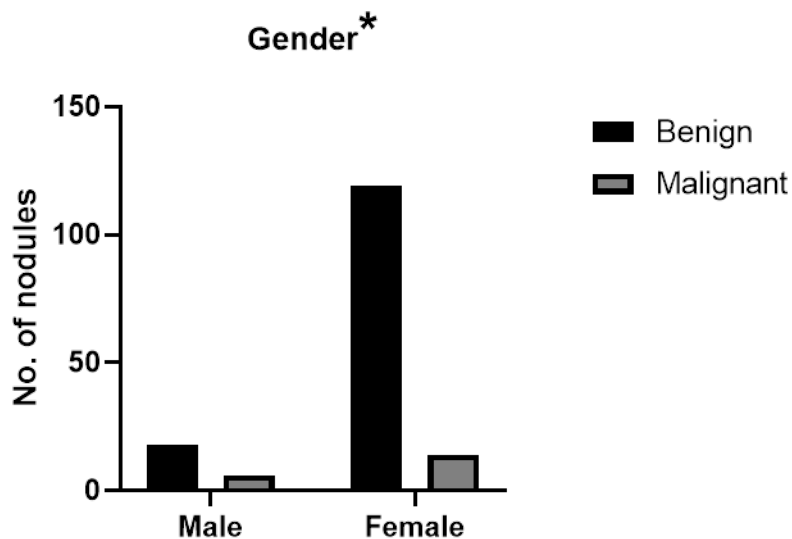
In this research, 175 thyroid nodules from a sample of 155 participants were analyzed, comprising 154 benign thyroid nodules and 21 malignant nodules. Participant characteristics are shown in Table 1, revealing that the research study comprised 24 male patients and 131 female patients with a mean age of  $48.2 \pm 12.7$  years. In total, 26 patients had hypertension and 30 patients had diabetes.

**Table 1** Patients characteristics.

| Characteristics       | Descriptive statistics |
|-----------------------|------------------------|
| Age, years [mean±SD]  | 48.2±12.7              |
| Female, n [%]         | 131, [84.5]            |
| Hypertension, n [%]   | 26, [16.7]             |
| Diabetes, n [%]       | 30, [19.3]             |
| TSH, mIU/mL [mean±SD] | 2.5±1.9                |
| T3, ng/dL [mean±SD]   | 4.9±1.9                |
| T4, µg/dL [mean±SD]   | 12.4±4.1               |

### 3.1 Gender vs Thyroid nodules

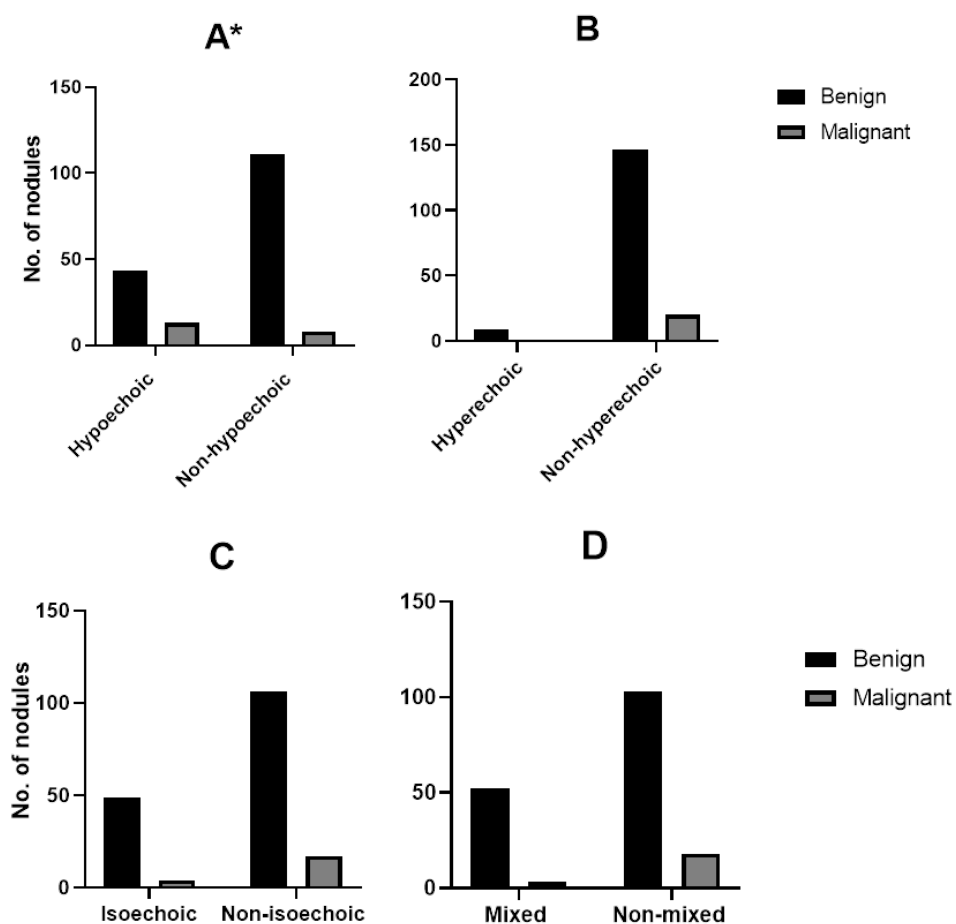
A significant correlation is observed between gender and the diagnosis of thyroid nodules (Pearson Chi-Square 3.8, p=0.05, Figure 1), with thyroid nodules more frequently observed in females than in males. Among the malignant nodules, 70% were found in females and 30% in males, while benign nodules were observed in 86.9% of females and 13.3% of males.



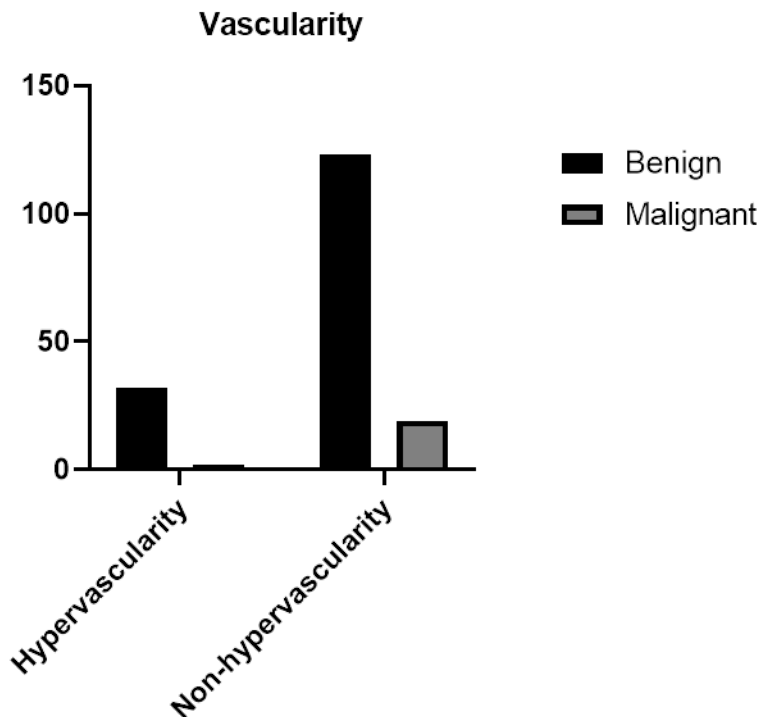
**Figure 1** Distribution of Thyroid Nodules by Gender. \* p<0.05 using chi-square test.

### 3.2 Ultrasound features of Thyroid nodules

Predominantly hypoechoic thyroid nodules (Pearson Chi-Square 9.4,  $p=0.002$ , Figure 2A) had an elevated probability of malignancy, with 61.9% of malignant nodules being hypoechoic compared to 38.1% of benign nodules. However, no statistically significant difference was observed between malignant and benign nodules regarding predominantly hyperechoic ( $p=0.84$ , Figure 2B), isoechoic ( $p=0.23$ , Figure 2C), mixed echogenicity nodules ( $p=0.07$ , Figure 2D), and nodules with vascularity ( $p=0.22$ , Figure 3).



**Figure 2** Echogenicity of benign and malignant thyroid nodules. Hypoechoicvs non-hypoechoic (A), hyperechoic vs non-hyperechoic (B), isoechoicvs non-isoechoic (C), and mixechogenicity vs non-mixechogenicity (D).\* $p<0.05$  using chi-square test.



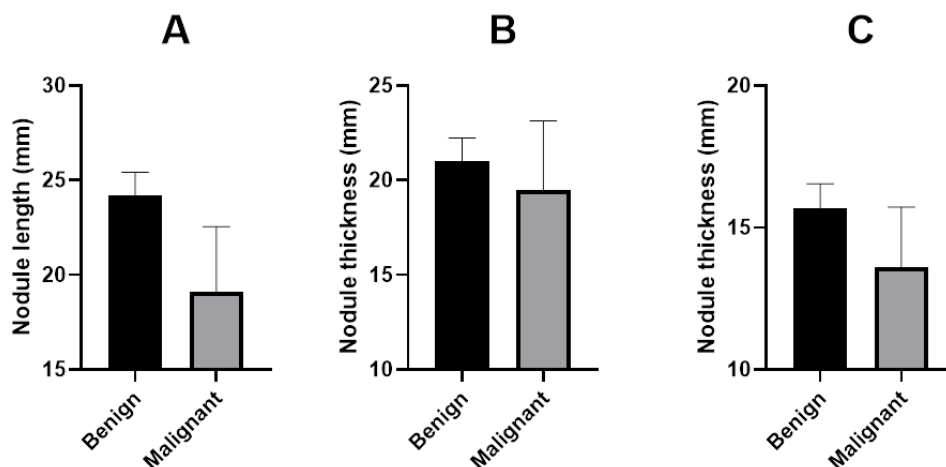
**Figure 3** Vascularity of benign vs malignant thyroid nodules.

### 3.3 Thyroid nodules size

There was an absence of statistically significant variation in the dimensions of nodules when comparing malignant and benign thyroid nodules in relation to length ( $p=0.07$ , Figure 4A), width ( $p=0.35$ , Figure 4B), and thickness ( $p=0.20$ , Figure 4C).

## 4. DISCUSSION

Ultrasonography serves as a vital imaging technique for assessing the features of thyroid nodules. [10, 11]. This imaging technique provides clear and detailed images of the thyroid, allowing for the examination of nodule size, structure, and echogenicity [12]. It also aids in assessing additional factors like calcifications and vascularity [10]. Therefore, this study aimed to determine the ability of ultrasound to differentiate between the features of thyroid nodules to identify individuals at risk for malignancy who would gain benefits from fine needle aspiration (FNA) and/or core needle biopsy (CNB), thus reducing the likelihood of incorrect diagnosis of benign nodules. The analysis showed that predominantly hypoechoic thyroid nodules exhibit a higher malignancy risk than non-hypoechoic



**Figure 4** Benign vs malignant Thyroid nodule size. Thyroid nodule length(A), width (B) and thickness (C).

nodules. This suggests that ultrasound evaluation of nodule echogenicity may effectively assess malignancy risk.

Factors relating to patient demographics, including age and gender, are linked to a higher likelihood of malignancy [2]. In the current study, the mean demographic age was assessed to be 48.2 years, ranging from 15 to 77 years, which is consistent with outcomes reported in previous literature [13, 14]. The data set was predominantly composed of female subjects in comparison to male subjects (84.5% vs. 15.5%), consistent with the existing literature, which documents the prevalence of females within a range of 71-86% [15, 16]. These findings suggest that, in addition to sonographic features of thyroid nodules, a comprehensive evaluation of the patient’s clinical characteristics is essential for achieving an optimal diagnosis.

Thyroid nodule echogenicity, which relates to the ultrasound signal intensity emitted by thyroid nodule, serve as a significant prognostic indicator of the likelihood of malignancy. Consistent with our findings, previous reports have indicated that thyroid nodules with hypoechoic echotexture on ultrasound are correlated with heightened malignancy risk. [17, 18]. Additionally, 5-10% of hyperechoic thyroid nodules are indicative of potential malignancy [19]. In the current investigation, no relationship was observed between the echogenicity of thyroid nodules whether hyperechoic, isoechoic, or mixed-echogenicity and their intrinsic nature.

Ultrasound color Doppler imaging has become an important tool in predicting the malignancy of thyroid nodules. By evaluating vascularity patterns within the nod-

ule, color Doppler provides critical information regarding the potential for malignancy [20, 21]. Malignant thyroid nodules frequently demonstrate increased internal vascularity, particularly central blood flow, which is indicative of the angiogenesis associated with tumor development. This vascular pattern contrasts with benign nodules, which typically exhibit peripheral or minimal blood flow [22, 23]. It has been reported that the combination of grayscale ultrasound features with color Doppler imaging serves as a valuable approach for evaluating thyroid nodules. These imaging modalities can be effectively employed as first-line diagnostic tools to evaluate malignancy risk in thyroid nodule patients [24, 25]. Although the findings of our current investigation do not align with the reported findings, it is important to emphasize that incorporating color Doppler imaging with other sonographic criteria enhances the accuracy of diagnosis for thyroid nodules.

The association between the dimensions of thyroid nodules and the likelihood of malignancy, as evaluated through ultrasonography, continues to be a prominent area of research inquiry [26]. Thyroid nodules of larger size are linked to a higher likelihood of malignancy, particularly those that exceed 4 cm in diameter [27, 28]. It has been indicated that nodules exceeding 2 cm in size exhibit a threshold effect, wherein the risk of malignancy does not significantly escalate beyond this measurement [26, 29, 30]. Despite this, the malignancy rates in smaller nodules (under 2 cm) can still be notable, and FNA tend to be challenging to diagnose these smaller nodules [31]. It is noteworthy that our study found no significant correlation between thyroid nodule size and malignancy risk. However, the size of the nodule could potentially serve as a significant predictor of malignancy, underscoring the need for its assessment alongside additional sonographic features and clinical findings when deciding the most effective management approach.

## 5. LIMITATIONS

This retrospective study has several limitations. Being a single-center retrospective study, the findings may have limited generalizability to other populations or clinical settings. To enhance the reliability and accuracy of the correlations between ultrasound features and diagnostic outcomes, further prospective, multicenter studies are needed.

## 6. CONCLUSION

In conclusion, this study reinforces the value of ultrasonography in assessing thyroid nodules, with hypochoic echogenicity being a significant predictor of malignancy. Furthermore, the incidence of thyroid nodules is markedly higher in female patients compared to

their male counterparts. However, additional prospective, multi-center studies are essential to enhance the effectiveness of ultrasound in differentiating between benign and malignant thyroid nodules.

## **7. CONFLICTS OF INTEREST**

All authors declare no conflict of interest.

## **8. ETHICAL APPROVAL**

This study was approved by Institutional Review Board, General Directorate of Health Affairs in Madinah, Saudi Arabia (reference no: H-03-M84)

## **9. FUNDING**

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