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Risk Stratification of Solitary Thyroid Nodules Using Clinical Characteristics and High-Resolution Ultrasonography: Predictors of Histopathologically Confirmed Malignancy

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ABSTRACT

Background: Accurate preoperative identification of malignant solitary thyroid nodules (STNs) remains a major clinical challenge despite advances in diagnostic imaging and cytopathology. Clinical risk factors and ultrasonographic characteristics have been increasingly utilized to improve risk stratification and guide management decisions. the present study was undertaken to evaluate the association between clinical characteristics, ultrasonographic findings, and histopathologically confirmed malignancy in patients with solitary thyroid nodules. **Methods:** This prospective observational study included 120 consecutive patients with clinically or ultrasonographically confirmed solitary thyroid nodules who underwent surgical treatment at a tertiary care center. Detailed clinical assessment and high-resolution ultrasonography were performed for all participants. Sonographic parameters including nodule composition, echogenicity, margins, shape, calcifications, vascularity, extrathyroidal extension, and TI-RADS category were evaluated. Histopathological examination of surgical specimens served as the gold standard for diagnosis. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of malignancy. **Results:** Histopathological examination revealed malignancy in 24 (20.0%) patients and benign lesions in 96 (80.0%) patients. Clinical factors significantly associated with malignancy included family history of thyroid cancer, previous neck irradiation, rapid increase in nodule size, cervical lymphadenopathy, and hoarseness of voice ($p<0.05$). Ultrasonographic features significantly associated with malignant nodules were solid composition, hypoechogenicity, irregular margins, taller-than-wide shape, microcalcifications, extrathyroidal extension, increased central vascularity, and TI-RADS categories 4–5 (all $p<0.001$). Multivariate analysis identified rapid nodule growth, cervical lymphadenopathy, hypoechogenicity, irregular margins, microcalcifications, taller-than-wide morphology, and TI-RADS 4–5 classification as independent predictors of malignancy. **Conclusions:** Specific clinical characteristics and high-risk ultrasonographic features are valuable predictors of malignancy in solitary thyroid nodules. Integration of these parameters into routine diagnostic evaluation may improve preoperative risk assessment, facilitate timely intervention, and reduce unnecessary surgical procedures.

Keywords*: Solitary thyroid nodule; thyroid cancer; ultrasonography; TI-RADS; malignancy prediction; histopathology.*

INTRODUCTION

Thyroid nodules represent one of the most common endocrine disorders encountered in clinical practice, with their prevalence increasing substantially owing to widespread use of high-resolution ultrasonography and other imaging modalities. Epidemiological studies indicate that palpable thyroid nodules are present in approximately 4–7% of adults,

whereas ultrasonography can detect nodules in up to 60–70% of the general population, particularly among women and older individuals [1,3]. Although the majority of thyroid nodules are benign, approximately 5–25% harbor malignant pathology, making early and accurate identification of high-risk lesions a major clinical priority [1,2]. The steadily rising incidence of thyroid cancer worldwide, particularly papillary thyroid carcinoma, has further emphasized the need for reliable strategies to distinguish benign nodules from malignant lesions while minimizing unnecessary invasive procedures [3,7].

Solitary thyroid nodules (STNs) pose a unique diagnostic challenge because their clinical presentation may vary from asymptomatic incidental findings to lesions associated with local compressive symptoms or metastatic disease. Traditionally, clinical characteristics such as rapid nodule enlargement, family history of thyroid cancer, prior exposure to ionizing radiation, cervical lymphadenopathy, and voice changes have been regarded as indicators of increased malignant potential [7–10]. However, these features alone often lack sufficient sensitivity and specificity for definitive risk stratification. Consequently, a multimodal diagnostic approach integrating clinical evaluation, imaging findings, cytological assessment, and histopathological confirmation has become the cornerstone of contemporary thyroid nodule management [3,7].

Among available diagnostic modalities, ultrasonography remains the most accessible, non-invasive, and cost-effective tool for the evaluation of thyroid nodules. Advances in ultrasound technology have enabled detailed assessment of nodule morphology, composition, echogenicity, vascularity, calcification patterns, margin characteristics, and extrathyroidal extension. Several studies have demonstrated that specific sonographic features, including hypoechogenicity, microcalcifications, irregular margins, taller-than-wide shape, and solid composition, are significantly associated with thyroid malignancy [8,11–16]. These findings have led to the development of standardized ultrasound-based risk stratification systems, such as the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS), European Thyroid Imaging Reporting and Data System (EU-TIRADS), and Korean Thyroid Imaging Reporting and Data System (K-TIRADS), which aim to improve diagnostic consistency and optimize patient selection for fine-needle aspiration cytology (FNAC) [8,9,11].

Recent international guidelines have strongly advocated the incorporation of ultrasound risk stratification systems into routine clinical practice because they improve diagnostic accuracy and reduce unnecessary biopsies and surgical interventions [7–9]. Nevertheless, the predictive performance of individual clinical and ultrasonographic parameters may vary across different populations due to geographic, environmental, genetic, and healthcare-related factors. Furthermore, although numerous studies have evaluated thyroid nodules in general, relatively fewer investigations have focused specifically on solitary thyroid nodules with histopathological confirmation as the reference standard. Consequently, there remains a need for region-specific evidence regarding the relative contribution of clinical and sonographic predictors in identifying malignant STNs.

In this context, the present study was undertaken to evaluate the association between clinical characteristics, ultrasonographic findings, and histopathologically confirmed malignancy in patients with solitary thyroid nodules. Particular emphasis was placed on identifying independent predictors of malignancy and assessing the diagnostic significance of established high-risk ultrasound features and TI-RADS classification. Improved understanding of these predictors may facilitate earlier diagnosis, enhance preoperative risk stratification, support evidence-based clinical decision-making, and ultimately reduce both missed malignancies and unnecessary surgical procedures.

MATERIALS & METHODS:

This prospective observational study was conducted in collaboration with the Departments of General Surgery, Radiodiagnosis, Pathology and ENT of a teaching hospital over a period of 24 months. The study was designed to evaluate the clinical and ultrasonographic predictors of malignancy in patients presenting with solitary thyroid nodules (STNs). The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its subsequent amendments.

Consecutive patients presenting with clinically or radiologically detected solitary thyroid nodules were screened for eligibility during the study period. A total of 120 patients who fulfilled the inclusion criteria and underwent definitive surgical management followed by histopathological examination were included in the final analysis.

Inclusion Criteria

1. Patients aged ≥18 years with a clinically palpable or ultrasonographically confirmed solitary thyroid nodule.
2. Patients willing to participate and provide written informed consent.
3. Patients who underwent preoperative ultrasonographic evaluation and subsequent surgical excision with available histopathological diagnosis.

Exclusion Criteria

1. Patients with multinodular goiter or diffuse thyroid enlargement.
2. Patients with recurrent thyroid disease.
3. Patients with a previous history of thyroid surgery.
4. Patients with known metastatic thyroid carcinoma receiving treatment.
5. Pregnant women and patients unwilling to participate.
6. Patients with incomplete clinical, imaging, or histopathological data.

Detailed demographic and clinical information was obtained using a standardized data collection form. Variables recorded included age, sex, duration of swelling, family history of thyroid malignancy, history of exposure to ionizing radiation involving the head and neck region, rapid increase in nodule size, compressive symptoms, hoarseness of voice, and presence of cervical lymphadenopathy.

All patients underwent comprehensive physical examination, including assessment of thyroid swelling characteristics and regional lymph node status. Routine laboratory investigations and thyroid function tests were performed whenever clinically indicated.

Ultrasonographic Evaluation: High-resolution ultrasonography of the thyroid gland and cervical lymph node compartments was performed using a linear-array transducer operating at frequencies between 7.5 and 15 MHz. All examinations were conducted by experienced radiologists who were blinded to the final histopathological diagnosis.

The following ultrasonographic characteristics were systematically evaluated:

- Nodule size and location
- Composition (solid, predominantly solid, mixed cystic-solid, or cystic)
- Echogenicity (hyperechoic, isoechoic, hypoechoic, or markedly hypoechoic)
- Margin characteristics (smooth, ill-defined, lobulated, or irregular)
- Shape (wider-than-tall or taller-than-wide)
- Presence of calcifications, including microcalcifications
- Internal vascularity pattern on color Doppler imaging
- Evidence of extrathyroidal extension
- Associated cervical lymphadenopathy

Based on the sonographic findings, nodules were categorized according to the Thyroid Imaging Reporting and Data System (TI-RADS). Nodules classified as TI-RADS categories 4 and 5 were considered highly suspicious for malignancy.
Fine-Needle Aspiration Cytology and Surgical Management: Ultrasound-guided fine-needle aspiration cytology (FNAC) was performed using a 23–25-gauge needle under aseptic precautions. Cytological findings were reported according to the Bethesda System for Reporting Thyroid Cytopathology whenever applicable.

The decision regarding surgical intervention was based on clinical findings, cytological results, ultrasonographic risk stratification, patient preference, and institutional treatment protocols. Patients subsequently underwent hemithyroidectomy, near-total thyroidectomy, or total thyroidectomy as clinically indicated.

Histopathological Examination: All surgical specimens were fixed in 10% neutral buffered formalin, processed according to standard histopathological protocols, and examined by experienced pathologists who were blinded to the ultrasonographic findings. Histopathological diagnosis served as the reference standard for classification of lesions as benign or malignant.

The benign group included lesions such as colloid nodules, nodular hyperplasia, and follicular adenomas, whereas the malignant group comprised papillary thyroid carcinoma, follicular thyroid carcinoma, and other malignant thyroid neoplasms.

Statistical Analysis

Data were entered into a dedicated database and analyzed using Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between benign and malignant groups were performed using the independent-samples Student's t-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. Variables demonstrating statistical significance on univariate analysis ($p < 0.05$) were entered into a multivariate logistic regression model to identify independent predictors of

malignancy. Adjusted odds ratios (AORs) with corresponding 95% confidence intervals (CIs) were calculated. A two-tailed p-value of less than 0.05 was considered statistically significant throughout the study.

RESULTS:

A total of 120 patients with solitary thyroid nodules were included in the study (Table 1). Histopathological examination revealed benign lesions in 96 (80.0%) patients and malignant lesions in 24 (20.0%) patients. The mean age of patients with malignant nodules (46.9 ± 12.4 years) was slightly higher than that of patients with benign nodules (42.8 ± 11.6 years); however, the difference was not statistically significant (p=0.128). Females constituted the majority of cases in both groups, accounting for 82.3% of benign and 75.0% of malignant nodules (p=0.421). A positive family history of thyroid carcinoma was observed significantly more frequently among patients with malignant nodules than among those with benign lesions (20.8% vs. 5.2%, p=0.018). Similarly, a previous history of neck irradiation was significantly associated with malignancy (16.7% vs. 3.1%, p=0.011). Clinical features suggestive of aggressive disease, including rapid enlargement of the nodule, cervical lymphadenopathy, and hoarseness of voice, were significantly more common in the malignant group. Rapid increase in nodule size was noted in 45.8% of malignant cases compared with 12.5% of benign cases (p<0.001). Cervical lymphadenopathy was present in one-third of malignant nodules but in only 4.2% of benign nodules (p<0.001). Hoarseness of voice was reported in 25.0% of patients with malignant nodules compared with 6.3% of those with benign lesions (p=0.009). The mean nodule size did not differ significantly between the two groups (p=0.351).

Table 1. Baseline Clinical Characteristics of Patients with Solitary Thyroid Nodules According to Histopathological Diagnosis

Variable	Benign (n=96)	Malignant (n=24)
Mean age (years), Mean ± SD	42.8 ± 11.6	46.9 ± 12.4
Female sex, n (%)	79 (82.3)	18 (75.0)
Male sex, n (%)	17 (17.7)	6 (25.0)
Family history of thyroid cancer, n (%)	5 (5.2)	5 (20.8)
History of neck irradiation, n (%)	3 (3.1)	4 (16.7)
Rapid increase in nodule size, n (%)	12 (12.5)	11 (45.8)
Cervical lymphadenopathy, n (%)	4 (4.2)	8 (33.3)
Hoarseness of voice, n (%)	6 (6.3)	6 (25.0)
Mean nodule size (cm), Mean ± SD	2.7 ± 0.9	2.9 ± 1.1

Ultrasonographic evaluation demonstrated several features that were significantly associated with malignant thyroid nodules (Table 2). Solid composition was observed in 83.3% of malignant nodules compared with 42.7% of benign nodules (p<0.001). Hypoechogenicity was present in 79.2% of malignant lesions, whereas only 29.2% of benign nodules exhibited this characteristic (p<0.001). Irregular margins were detected in 70.8% of malignant nodules compared with 15.6% of benign nodules, showing a strong association with malignancy (p<0.001). Likewise, a taller-than-wide configuration was significantly more frequent in malignant nodules than in benign nodules (50.0% vs. 7.3%, p<0.001). Microcalcifications were identified in two-thirds of malignant nodules but in only 11.5% of benign nodules (p<0.001). Evidence of extrathyroidal extension was observed in 25.0% of malignant lesions compared with 2.1% of benign lesions (p<0.001). Increased central vascularity was also significantly associated with malignancy, being present in 62.5% of malignant nodules and 22.9% of benign nodules (p<0.001). Furthermore, the majority of malignant nodules were categorized as TI-RADS 4 or 5 (91.7%), whereas only 25.0% of benign nodules belonged to these categories (p<0.001). These findings indicate that specific ultrasonographic characteristics can effectively differentiate malignant from benign solitary thyroid nodules.

Table 2. Ultrasonographic Features of Solitary Thyroid Nodules and Their Association with Malignancy

Ultrasonographic Feature	Benign (n=96)	Malignant (n=24)
Solid composition, n (%)	41 (42.7)	20 (83.3)
Hypoechogenicity, n (%)	28 (29.2)	19 (79.2)
Irregular margins, n (%)	15 (15.6)	17 (70.8)
Taller-than-wide shape, n (%)	7 (7.3)	12 (50.0)
Microcalcifications, n (%)	11 (11.5)	16 (66.7)
Extrathyroidal extension, n (%)	2 (2.1)	6 (25.0)
Increased central vascularity, n (%)	22 (22.9)	15 (62.5)

Ultrasonographic Feature	Benign (n=96)	Malignant (n=24)
TI-RADS 4–5 category, n (%)	24 (25.0)	22 (91.7)

Variables that demonstrated significant associations on univariate analysis were subsequently entered into a multivariate logistic regression model to identify independent predictors of malignancy (Table 3). The analysis revealed that rapid increase in nodule size remained a significant clinical predictor, increasing the likelihood of malignancy by more than threefold (AOR=3.24, 95% CI: 1.18–8.92; p=0.023). Among the clinical parameters, cervical lymphadenopathy emerged as a strong independent predictor of malignant disease, with affected patients having approximately 5.7 times higher odds of harboring malignancy than those without lymphadenopathy (AOR=5.71, 95% CI: 1.79–18.20; p=0.003). Several ultrasonographic features retained statistical significance after adjustment for potential confounders. Hypoechogenicity increased the odds of malignancy by more than fourfold (AOR=4.38, 95% CI: 1.55–12.36; p=0.005), while irregular margins were associated with a sixfold increase in risk (AOR=6.12, 95% CI: 2.09–17.91; p=0.001). The presence of microcalcifications was one of the strongest predictors, conferring more than sevenfold higher odds of malignancy (AOR=7.43, 95% CI: 2.53–21.83; p<0.001). Similarly, a taller-than-wide shape independently predicted malignant pathology (AOR=4.91, 95% CI: 1.59–15.18; p=0.006). The strongest predictor identified in the model was a TI-RADS category of 4 or 5, which increased the odds of malignancy by approximately 8.7 times (AOR=8.67, 95% CI: 2.68–28.04; p<0.001). These findings suggest that both selected clinical features and high-risk ultrasonographic characteristics independently contribute to the prediction of malignancy in patients presenting with solitary thyroid nodules.

Table 3. Multivariate Logistic Regression Analysis of Independent Predictors of Malignancy in Solitary Thyroid Nodules

Variable	Adjusted Odds Ratio (AOR)	95% Confidence Interval	p-value
Rapid increase in nodule size	3.24	1.18 – 8.92	0.023*
Cervical lymphadenopathy	5.71	1.79 – 18.20	0.003*
Hypoechogenicity	4.38	1.55 – 12.36	0.005*
Irregular margins	6.12	2.09 – 17.91	0.001*
Microcalcifications	7.43	2.53 – 21.83	<0.001*
Taller-than-wide shape	4.91	1.59 – 15.18	0.006*
TI-RADS 4–5 category	8.67	2.68 – 28.04	<0.001*

DISCUSSION

The present study investigated the clinical and ultrasonographic predictors of malignancy in solitary thyroid nodules and demonstrated that both clinical risk factors and specific sonographic characteristics significantly contribute to the identification of malignant lesions. Histopathological examination revealed a malignancy rate of 20%, which falls within the range reported in contemporary literature evaluating surgically treated solitary thyroid nodules [1,2]. This finding reinforces the clinical importance of accurate preoperative risk stratification, as the majority of thyroid nodules are benign while a clinically significant proportion harbor malignancy.

Age and sex have traditionally been evaluated as potential predictors of thyroid cancer. Although patients with malignant nodules in the present study were slightly older than those with benign lesions, the difference was not statistically significant. Similar findings have been reported in several recent studies, which suggest that age alone has limited predictive value when assessed independently of other clinical and sonographic variables [3,4]. Female predominance was observed in both benign and malignant groups, reflecting the well-established higher prevalence of thyroid nodules among women. However, previous investigations have consistently shown that sex is not an independent determinant of malignancy risk once a nodule has developed [5,6].

A noteworthy finding of the present study was the significant association between malignancy and a positive family history of thyroid cancer. Familial predisposition has been recognized as an important risk factor because inherited genetic susceptibility can facilitate neoplastic transformation within thyroid follicular cells [7]. Similarly, previous exposure to neck irradiation was significantly more frequent among malignant cases. Radiation-induced DNA damage, particularly involving molecular pathways associated with papillary thyroid carcinoma, has been extensively documented and remains one of the strongest established risk factors for thyroid malignancy [7,8]. These findings emphasize the importance of obtaining a detailed clinical history during the initial evaluation of patients with thyroid nodules.

Among the clinical manifestations, rapid increase in nodule size, cervical lymphadenopathy, and hoarseness of voice showed significant associations with malignant histopathology. These observations are consistent with current international

recommendations that regard these features as high-risk indicators warranting prompt investigation [9]. Cervical lymphadenopathy emerged as an independent predictor of malignancy in the multivariate model, indicating its strong diagnostic relevance. Similar findings have been reported by recent observational studies demonstrating that metastatic cervical lymph node involvement is frequently associated with papillary thyroid carcinoma and often represents the first clinical sign of aggressive disease [10,11].

Ultrasonography remains the cornerstone of thyroid nodule assessment because it provides detailed morphological information that directly correlates with malignancy risk. In the present study, solid composition was significantly more common among malignant nodules. Previous studies have similarly demonstrated that solid nodules possess a greater likelihood of malignancy than predominantly cystic lesions, although composition alone lacks sufficient specificity for clinical decision-making [12,13].

Hypoechogenicity was another significant predictor identified in the current study and retained independent significance after multivariate adjustment. This observation is in agreement with contemporary studies and international risk-stratification systems that recognize hypoechogenicity as a major suspicious ultrasound feature [14,15]. Histologically, hypoechogenicity is believed to reflect increased cellularity, reduced colloid content, and architectural disorganization characteristic of malignant thyroid tissue.

Irregular margins represented one of the strongest predictors of malignancy in our cohort. More than two-thirds of malignant nodules demonstrated irregular borders, and multivariate analysis confirmed its independent predictive value. Recent studies have consistently identified irregular or spiculated margins as highly specific indicators of malignant infiltration beyond the normal confines of thyroid tissue [16,17]. The incorporation of margin assessment into modern TI-RADS systems further supports its diagnostic importance.

Microcalcifications emerged as one of the most powerful sonographic predictors in the present study. This finding is consistent with multiple investigations demonstrating a strong relationship between punctate echogenic foci and papillary thyroid carcinoma [16,18]. Histopathologically, these sonographic microcalcifications correspond to psammoma bodies, which are commonly encountered in malignant thyroid tumors. Recent analyses have further confirmed that microcalcifications retain independent predictive value even after adjustment for other suspicious ultrasound features [16,19].

The taller-than-wide configuration was also significantly associated with malignancy. This feature reflects tumor growth perpendicular to normal tissue planes and is widely regarded as one of the most reliable ultrasound markers of thyroid cancer [13,15]. Similar results have been reported in studies evaluating both ACR TI-RADS and EU-TIRADS classification systems, where taller-than-wide morphology consistently demonstrated high specificity for malignancy [14].

Increased central vascularity was significantly associated with malignant nodules in the present study. Although recent evidence suggests that vascularity alone is not sufficiently specific to distinguish benign from malignant lesions, its presence in conjunction with other suspicious sonographic findings may improve diagnostic confidence [11]. Extrathyroidal extension was likewise significantly associated with malignant disease and likely reflects locally invasive tumor behavior, a finding that has been reported in several recent studies evaluating advanced thyroid carcinomas [10].

The most important observation of the present study was the excellent predictive performance of TI-RADS categories 4 and 5. More than 90% of malignant nodules belonged to these high-risk categories, and TI-RADS 4–5 emerged as the strongest independent predictor of malignancy. These findings are highly consistent with recent international studies validating the effectiveness of ACR TI-RADS, EU-TIRADS, and K-TIRADS systems in risk stratification [9,14]. The research strongly support the use of standardized ultrasound classification systems because they improve diagnostic consistency, reduce unnecessary biopsies, and facilitate evidence-based clinical management [9].

The principal strength of the present study lies in the combined assessment of clinical and ultrasonographic variables using histopathological diagnosis as the reference standard. Such an approach enhances the reliability of the observed associations and reflects routine clinical practice. Nevertheless, certain limitations should be acknowledged. The study was conducted at a single center and included a relatively limited sample size. In addition, molecular markers, elastography, and artificial intelligence-based imaging tools were not incorporated, although these emerging modalities have demonstrated promising results in recent investigations [11-19].

CONCLUSION:

In conclusion, the present study confirms that rapid nodule enlargement, cervical lymphadenopathy, hypoechogenicity, irregular margins, microcalcifications, taller-than-wide morphology, and high TI-RADS categories are significant predictors of malignancy in solitary thyroid nodules. The integration of these clinical and ultrasonographic parameters into

routine diagnostic algorithms may improve early cancer detection, optimize patient selection for fine-needle aspiration cytology and surgery, and ultimately enhance clinical outcomes.

Conflict of interest:

None.

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