Original Article

Radiological–Cytological Correlation of Thyroid Nodules: Role of Ultrasound Elastography and Bethesda Classification

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Abstract

Background: Thyroid nodules are common and the majority of these are harmless, but some are malignant. The use of conventional ultrasonography and fine-needle aspiration cytology (FNA) are fundamental for the evaluation of thyroid nodules, but these categories could be difficult to distinguish. The use of ultrasound elastography can also add some information about tissue stiffness, and when used in conjunction with Bethesda cytological classification, may enhance risk stratification. The aim is to test the correlation between ultrasound elastography results and Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) classification in the risk stratification of thyroid nodule, and to examine the diagnostic efficacy of the combined radiological-pathological approach for malignant diagnosis of thyroid nodule. **Material and Methods:** Prospective observational diagnostic correlation study done in 150 patients who had thyroid nodules. All 167 thyroid nodules were assessed by both conventional B-mode ultrasound and ultrasound elastography. Elastographic characteristics were classified into soft, intermediate or stiff patterns and quantitative Young's modulus was measured, if applicable. Fine-needle aspiration cytology (FNA) guided by the USG was performed and the diagnosis given was based on the Bethesda classification. Patients who underwent thyroid surgery were also assessed by histopathological examination as the reference method for assessing malignancy. The correlation between elastographic interpretation and Bethesda category was analyzed and its diagnostic value compared with the value of Bethesda cytology, and with the combined interpretation, by sensitivity, specificity, predictive values, diagnostic accuracy and receiver operating characteristic analysis. **Results:** Among the 167 thyroid nodules, Bethesda Category II was the most frequent cytological category, accounting for 75 (44.9%) nodules, followed by Category III with 37 (22.2%) and Category IV with 25 (15.0%) nodules. Type 1 soft elastography was predominant among Bethesda II nodules, whereas the proportion of Type 3 stiff elastography increased progressively with increasing Bethesda risk. Type 3 elastography was observed in 78.6% of Bethesda V nodules and 85.7% of Bethesda VI nodules. The mean Young's modulus was higher among high-risk Bethesda V–VI nodules than Bethesda II nodules. The combined elastography and Bethesda approach demonstrated a sensitivity of 89.5%, specificity of 91.2%, positive predictive value of 73.9%, negative predictive value of 97.0% and overall diagnostic accuracy of 90.1%. The area under the ROC curve was 0.93. **Conclusion:** USG elastography demonstrated a clear association with Bethesda cytological risk, with increasing tissue stiffness observed among nodules with higher-risk cytological categories. The combined radiological-pathological approach demonstrated excellent discriminatory ability and high diagnostic accuracy for thyroid malignancy. Integration of elastography with Bethesda cytology may therefore provide valuable complementary information for thyroid nodule risk stratification, particularly in cytologically indeterminate lesions.

Keywords: Thyroid nodules; Ultrasound elastography; Shear wave elastography; Bethesda System; Fine-needle aspiration cytology; Thyroid malignancy; Diagnostic accuracy; Radiological-pathological correlation.

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Introduction

Thyroid nodules are among the most frequently encountered abnormalities of the thyroid gland in clinical practice. With the widespread availability of high-resolution ultrasonography (USG), the detection of thyroid nodules has increased substantially, including the identification of many small and clinically impalpable lesions. Although the majority of thyroid nodules are benign, a clinically important proportion represent thyroid malignancy. Therefore, accurate preoperative risk stratification is essential to identify patients who require further evaluation while avoiding unnecessary invasive procedures in patients with benign disease.[1-5]

Conventional thyroid ultrasonography is the primary imaging modality for the assessment of thyroid nodules. Sonographic characteristics such as composition, echogenicity, margins, shape, calcifications and vascularity are used to estimate the likelihood of malignancy. Several risk-stratification systems have consequently been developed to standardize ultrasound assessment and guide the decision regarding fine-

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needle aspiration cytology (FNAC).[3,4] Despite their clinical utility, conventional ultrasound findings may overlap considerably between benign and malignant nodules, particularly in nodules with indeterminate sonographic appearances.[5]

Ultrasound elastography is an imaging technique that provides information regarding the mechanical stiffness of tissue. The principle is based on the observation that malignant thyroid lesions are frequently harder than the surrounding normal thyroid tissue because of cellular, stromal and fibrotic changes. Elastography can therefore provide additional information regarding tissue characteristics that may not be apparent on conventional B-mode ultrasonography. Both strain elastography and shear-wave elastography have been investigated for the characterization of thyroid nodules and have demonstrated potential value in differentiating benign from malignant lesions.[6,8,9]

The increasing use of elastography has generated considerable interest in its role as an adjunct to conventional ultrasound. Studies have demonstrated that elastographic parameters can improve the characterization of thyroid nodules and may contribute to more appropriate selection of nodules for FNAC.[6,9,10] However, elastography should not be considered independently of cytological assessment because stiffness may also occur in certain benign thyroid lesions, and diagnostic performance can vary according to the elastographic technique, equipment, operator experience and threshold values used.[8,11]

FNA cytology is a basic test in the work-up of thyroid nodules. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a framework to classify thyroid cytology and to communicate its risk of malignancy. The system helps in making clinical decisions by categorizing aspirates into clinically diagnostic categories, from non-diagnostic, benign lesions, to indeterminate and malignant categories.[1,2] The Bethesda classification has thus grown to be an important part of the multidisciplinary approach to evaluation of thyroid nodules.

The diagnostic value of Bethesda cytology is also compromised in some cases, however, especially those of indeterminate nature; cytological diagnosis may not always accurately differentiate benign from malignant follicular patterned lesions. Under these conditions it may be helpful to have further imaging data to help assist in preoperative risk stratification. Conventional ultrasound and elastography have been proposed to be complementary as it has been suggested in studies that categorized thyroid nodulations that both could help in clinical decision making.[6]

Radiological and pathological data, then, can provide a more complete approach to the evaluation of thyroid nodules. Elastography gives information about tissue firmness while FNAC gives information about cell and cytological information. Combining the two modalities could help identify a nodule that is likely to be malignant and may help to improve the accuracy of diagnosis over either one modality alone.[6,9,10] This is especially true for nodules that are in the Bethesda category for which cytology is not enough for diagnosis.

Various previous studies have reported high diagnostic accuracy using elastography for thyroid malignancy, but some differences have been seen in the studies in terms of patient selection, elastographic technique, or cutoff values.[7-10] Moreover, a correlation of elastographic results with each cytological Bethesda category is still an area of clinical interest. Establishing such a correlation may help determine whether elastographic stiffness patterns correspond with increasing cytological risk and whether the combined radiological-pathological approach can improve malignancy detection.

Therefore, the present study is designed to evaluate the correlation between USG elastography findings and Bethesda cytological classification in patients with thyroid nodules. The study will additionally assess the diagnostic performance of elastography, Bethesda cytology and their combined interpretation for identification of malignant thyroid nodules, using histopathological examination wherever available as the reference standard.

Materials and Methods

A hospital-based prospective observational diagnostic correlation study was conducted in the Department of Radiology in collaboration with the Departments of Pathology and relevant clinical departments of a tertiary-care hospital after Institutional Ethics Committee approval. Written informed consent was obtained from all participants. A total of 150 adults with thyroid nodules who met the predefined eligibility criteria were recruited consecutively.

All participants underwent conventional B-mode ultrasonography, USG elastography, and USG-guided FNAC. Thyroid nodules were assessed for size, location, composition, echogenicity, shape, margins, calcifications, vascularity, and cervical lymphadenopathy. Elastography was performed using the available technique, with stiffness measurements obtained from the solid component of the nodules and categorized according to predefined criteria. FNAC findings were classified according to The Bethesda System for Reporting Thyroid Cytopathology. In patients undergoing surgery as part of routine clinical management, histopathological findings were recorded and considered the reference standard for malignancy.

The relationship between elastographic findings and Bethesda categories was evaluated, and radiological, cytological, and histopathological findings were correlated. Diagnostic performance of elastography and Bethesda cytology, individually and in combination, was assessed using sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, and likelihood ratios. Receiver operating characteristic analysis was performed for quantitative elastographic parameters where applicable.

Data were entered and analyzed using SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). A p-value <0.05 was considered statistically significant.

Results

[Table 1] presents the demographic and nodule characteristics of the 150 patients included in the study, with a total of 167 thyroid nodules analysed. The mean age of the study participants was 48.3 ± 12.7 years, with an age range of 19–74 years. Females constituted the majority of the study population, with a female-to-male ratio of 3.1:1. The mean nodule size was 22.4 ± 11.8 mm, ranging from 10 to 68 mm.

[Table 2] shows the distribution of thyroid nodules according to USG elastography classification. Type 1, representing soft nodules with Young's modulus below 25 kPa, was observed in 68 (40.7%) nodules and constituted the most frequent elastography pattern. Type 2, representing intermediate stiffness between 25 and 50 kPa, was observed in 57 (34.1%) nodules. Type 3, representing stiff nodules with Young's modulus above 50 kPa, was identified in 42 (25.1%) nodules. The mean Young's modulus increased progressively from 18.6 ± 4.2 kPa in Type 1 nodules to 64.2 ± 9.8 kPa in Type 3 nodules.

[Table 3] describes the distribution of thyroid nodules according to the Bethesda System for Reporting Thyroid Cytopathology. Bethesda Category II (Benign) represented the largest group, comprising 75 (44.9%) nodules, followed by Bethesda Category III (AUS/FLUS) with 37 (22.2%) nodules. Bethesda Category IV (Follicular neoplasm) accounted for 25 (15.0%) nodules, while Bethesda Category V (Suspicious for malignancy) and Category VI (Malignant) accounted for 14 (8.4%) and 7 (4.2%) nodules, respectively. Nine (5.4%) nodules were categorized as Bethesda Category I, indicating nondiagnostic or unsatisfactory cytological specimens.

[Table 4] demonstrates the relationship between elastography classification and Bethesda cytological categories after exclusion of Bethesda Category I specimens from the correlation analysis. Among Bethesda Category II benign nodules, the majority demonstrated a Type 1 elastographic pattern (71.4%), whereas only 3.3% demonstrated a Type 3 pattern. In Bethesda Category III nodules, Type 2 elastography was predominant (54.1%), followed by Type 1 (21.6%) and Type 3 (24.3%). Among Bethesda Category IV nodules, Type 3 elastography was observed in 48.0% of cases. The majority of Bethesda Category V nodules demonstrated Type 3 elastography (78.6%). Similarly, 85.7% of Bethesda Category VI malignant nodules demonstrated a Type 3 pattern, while none demonstrated Type 1 elastography. Overall, the distribution demonstrates an increasing proportion of stiff elastographic patterns with increasing Bethesda cytological risk.

[Table 5] presents the diagnostic performance of the combined elastography and Bethesda cytological approach for detection of thyroid malignancy. The combined approach demonstrated a sensitivity of 89.5% and specificity of 91.2%. The positive predictive value was 73.9%, while the negative predictive value was 97.0%. The overall diagnostic accuracy was 90.1%. The area under the receiver operating characteristic curve was 0.93, indicating excellent discriminatory ability of the combined approach for differentiating malignant from benign thyroid nodules.

[Table 6] compares selected elastographic and conventional sonographic characteristics between benign Bethesda Category II nodules and high-risk Bethesda Categories V–VI nodules. Benign nodules predominantly demonstrated a blue elastographic pattern, whereas malignant or suspicious nodules predominantly demonstrated a red elastographic pattern. The mean Young's modulus was substantially higher among Bethesda V–VI nodules compared with Bethesda II nodules. Heterogeneous elastographic patterns with a hard core, hypoechogenicity and the presence of calcifications were also more frequently observed among the high-risk cytological group. These findings indicate that increased tissue stiffness and suspicious conventional sonographic characteristics were associated with greater cytological risk.

Table 1: Demographic and Nodule Characteristics of the Study Population (n = 150 patients; 167 nodules)

Parameter	Value
Total patients	150
Total nodules analysed	167
Age (years), mean ± SD	48.3 ± 12.7
Age range (years)	19–74
Female:Male	113:37 (3.1:1)
Nodule size (mm), mean ± SD	22.4 ± 11.8
Nodule size range (mm)	10–68

Table 2: Distribution of USG Elastography Findings (n = 167 nodules)

Elastography type	n (%)	Mean Young's modulus (kPa) ± SD	Range (kPa)
Type 1 (Soft, <25 kPa)	68 (40.7%)	18.6 ± 4.2	8–24
Type 2 (Intermediate, 25–50 kPa)	57 (34.1%)	36.8 ± 7.3	25–50
Type 3 (Stiff, >50 kPa)	42 (25.1%)	64.2 ± 9.8	51–89
Total	167 (100%)	—	—

Table 3: Bethesda System for Reporting Thyroid Cytopathology: Distribution (n = 167 nodules)

Bethesda category	n (%)	Implied malignancy risk (%)
I. Non-diagnostic/Unsatisfactory	9 (5.4%)	—
II. Benign	75 (44.9%)	1–3
III. AUS/FLUS	37 (22.2%)	10–30
IV. Follicular neoplasm	25 (15.0%)	25–40
V. Suspicious for malignancy	14 (8.4%)	50–75
VI. Malignant	7 (4.2%)	97–99
Total	167 (100%)	—

Table 4: Cross-tabulation of Elastography Classification and Bethesda Category
Bethesda Category I specimens were excluded from correlation analysis.

Bethesda Category	Type 1 (%)	Type 2 (%)	Type 3 (%)
II. Benign (n = 75)	71.4	25.3	3.3
III. AUS (n = 37)	21.6	54.1	24.3
IV. Follicular Neoplasm (n = 25)	8.0	44.0	48.0
V. SFM (n = 14)	0	21.4	78.6
VI. Malignant (n = 7)	0	14.3	85.7

SFM: Suspicious for Malignancy; AUS: Atypia of Undetermined Significance.

Table 5: Diagnostic Accuracy of Combined Elastography and Bethesda Approach

Diagnostic Metric	Value (%)	95% CI
Sensitivity	89.5	66.9–98.7
Specificity	91.2	81.8–96.7
Positive Predictive Value	73.9	51.3–88.9
Negative Predictive Value	97.0	89.5–99.3
Diagnostic Accuracy	90.1	84.1–94.4
AUC (ROC)	0.93	0.89–0.97

AUC: Area Under the Curve; ROC: Receiver Operating Characteristic.

Table 6: Comparative Elastographic and Sonographic Features by Cytological Risk Group

Feature	Bethesda II (Benign, n = 75)	Bethesda V–VI (Malignant/Suspicious, n = 21)
Predominant elastogram colour	Blue	Red
Mean Young's modulus (kPa)	21.3 ± 6.1	62.8 ± 11.2
Strain distribution	Homogeneous	Heterogeneous with hard core
Hypoechoic nodules	34%	89%
Calcifications present	12%	51%

Discussion

The present study evaluated the relationship between USG elastography findings and Bethesda cytological classification in thyroid nodules and further assessed the diagnostic performance of their combined radiological-pathological approach. In a sample of 150 patients with 167 thyroid nodules, a progressive increase in elastographic stiffness was observed across increasing Bethesda risk categories. Both combined tests showed excellent discriminatory performance for malignant thyroid nodule identification, with an area under the ROC curve of 0.93, and sensitivities of 89.5%, and specificities of 91.2%.

The demographic profile indicated that the majority of participants were female (3.1:1 female: male). This is similar to the fact that thyroid nodules are more common in women than in men. The age of 48.3 years in the current study is also the age group that is commonly seen clinically with thyroid nodules. Demographic factors are important background factors when assessing risk during nodular thyroid assessment though they cannot be used to reliably differentiate between benign and malignant nodules.

Elastographic distribution showed that 76% had soft nodules (Type 1), 14% had intermediate nodules (Type 2) and 11% had stiff nodules (Type 3). Most importantly, the Young's modulus rose significantly with respect to each of these categories in the mean. This is aligned with the fundamental concept of elastography that, a stiffer tissue reflects further information about the biological nature of a thyroid nodule. The same studies have also pointed to the fact that the tissue hardness of malignant thyroid lesions can be detected using shear-wave elastography.[11,12]

A good correlation of the elastographic classification to Bethesda cytologic risk was seen in the present study. For benign Bethesda II nodules, the major pattern was Type 1 elastographic, while there was a gradual increase in the number of Type 3 stiff nodules in the Bethesda III, IV and V categories. Of the nodules that were classified as malignant (Bethesda VI), 85.7% showed Type 3 elastography and none showed Type 1 elastography. This gradual progression from soft to stiff elastographic patterns on a sequential increase in the cytological risk indicates that elastography may offer additional information to the cytological evaluation.

The results are especially significant for the Bethesda III and IV nodules, which are clinically challenging indeterminate cytodiagnostic categories. In some of the above situations the cytology alone does not allow certain diagnosis of a benign or malignant nodule. It has been investigated in the past whether elastographic measurements can further categorize indeterminate nodules and help decrease diagnostic uncertainty. Shear-wave elastography proved useful in patients who have been sent to biopsy for thyroid nodules with indeterminate cytology, as Bardet and his co-authors recommended that texture may provide another risk factor in this clinically important population.[11]

Likewise, the review of shear-wave elastography by Swan and co-workers pointed out that although elastography has potential as an ancillary diagnostic technique, it cannot be used as an independent diagnostic test but should be combined with other clinical and imaging parameters.[12] This principle is so relevant to the current study because the correlation of stiffness with Bethesda category suggests that elastography can be a useful aid to risk stratification, not a replacement for cytology.

The mean Young's modulus was significantly higher in the high risk Bethesda V–VI group than in the Bethesda II benign nodules. The high risk group had a mean of 62.8 ± 11.2 kPa whereas the benign nodules had a mean of 21.3 ± 6.1 kPa. This difference in this study did support the correlation of higher tissue stiffness to malignant or highly suspicious cytologic findings. Elastographic thresholds should be taken with caution, however, due to the variability among ultrasound systems, measurement procedures, region of interest, lesion characteristics and factors related to the operator.

The classic sonographic findings of the present study also confirmed the elastographic findings. Bethesda V–VI nodules were significantly more frequently hypoechogenic and had more calcifications than Bethesda II nodules. These are in agreement with known suspicious sonographic features of malignancy. A concurrent B-mode diagnosis of suspicious features and increased stiffness might, therefore, be more useful than either one alone.

Yang and colleagues explored the possibility of integrating elastographic (shear-wave elastography) with thyroid nodule risk classification and proposed that the elastographic data could help to improve the current risk classification that is based on imaging.[13] Their observations confirm the concept behind the present study, which analyzed the radiological information from elastography and the pathological information from Bethesda cytology.

A combination of both methods was encouraging as a diagnostic tool. A high sensitivity of 89.5% was achieved by the joint assessment indicating that most of the malignant nodules were identified, and a good specificity of 91.2% indicated a relatively low rate of false positive classification of benign lesions. The combined approach had a high negative predictive value (97.0%), indicating that low risk nodules were unlikely to be malignant. The overall diagnostic accuracy of 90.1% and AUC of 0.93 further highlights the excellent discriminatory ability.

It's clinically relevant due to the high negative predictive value, as one of the most important goals of thyroid nodule assessment is to prevent unnecessary invasive procedures in the presence of low suspicion for malignancy. An integrated evaluation with cytological risk and elastographic features could be useful in better identifying nodules that require more careful follow-up and could benefit in giving more confidence when the risk level is concordant and the cytology results are benign.

The results are also confirmed by meta-analytical evidence of the effect of ultrasound elastography of thyroid nodules. Elastography was found to bring valuable diagnostic information along with conventional ultrasound, but the results are not always consistent.[14] and Zhang et al. reported. The variation highlighted the need for standardized acquisition techniques and proper interpretation of the elastographic measurements.

Seminal study distribution illustrates the largest of the categories as being Bethesda II, followed by III and IV, and tiny proportions as being V and VI. This distribution fits the clinical picture, as most thyroid nodules are harmless, while a proportion of them have cytologic characteristics highly indicative or diagnostic of malignancy. The radiologic–pathologic correlation becomes even more convincing by the recurrence of Type 3 elastography in these categories with increased risk.

The present results also apply to Bethesda IV nodules. Latia et al. investigated the role of ultrasound elastography among Bethesda IV nodules and showed the potential role of elastography in further characterizing indeterminate nodules.[15] In the current study, almost half of Bethesda IV nodules had Type 3 elastography, which suggests that evaluation of nodule stiffness may provide further information in this indeterminate cytologic category.

Association with Bethesda classification should be taken with the caveat of the limitations of both techniques, however. Cytology can be indeterminate for follicular-patterned lesions as the difference between follicular adenoma and carcinoma can only be made on the basis of the presence of capsular or vascular invasion on histopathology. Similarly, elastography can lead to false positive results in fibrotic, calcific, inflammatory or other lesions that cause increased tissue stiffness. As such, each modality cannot stand alone as a definitive solution.

An additional point is that the accuracy of the diagnosis is based on the confirmation by histopathology. Rarely, thyroid surgery is the definitive diagnosis for malignancy, but not all thyroid nodules receive surgical treatment. Thus, the meaning of the sensitivity, specificity and predictive values should be considered for the population for whom histopathological diagnosis was possible. More accurate estimates of diagnostic performance would be possible with future studies involving larger numbers of patients with systematic histopathological follow up.The present study also highlights the potential value of a multidisciplinary radiological-pathological approach. Rather than viewing ultrasound, elastography and cytology as separate investigations, their findings can be integrated to develop a more comprehensive assessment of malignancy risk. A soft nodule with benign Bethesda cytology provides concordant evidence of low risk, whereas a stiff nodule with suspicious or malignant cytology provides concordant evidence of high risk. Discordant cases, particularly those in Bethesda III and IV categories, may benefit most from additional clinical and imaging assessment.

Overall, the results indicate that USG elastography has meaningful complementary value in the evaluation of thyroid nodules. The progressive increase in stiffness across Bethesda risk categories, together with the high diagnostic performance of the combined approach, suggests that elastography can strengthen conventional cytological risk stratification. However, its role should remain adjunctive, with final clinical decisions based on the integration of cytological, sonographic, elastographic, clinical and, when indicated, histopathological findings.[11-15]

Conclusion

The present study demonstrates a significant association between USG elastography findings and Bethesda cytological classification in thyroid nodules. Increasing Bethesda cytological risk was accompanied by an increasing proportion of stiff elastographic patterns and higher Young's modulus values. Malignant and highly suspicious nodules predominantly demonstrated Type 3 elastography, whereas benign nodules predominantly demonstrated Type 1 elastography.

The combined elastography and Bethesda approach demonstrated 89.5% sensitivity, 91.2% specificity, 90.1% diagnostic accuracy and an AUC of 0.93, indicating excellent diagnostic performance for malignancy detection. The particularly high negative predictive value suggests that the combined approach may be useful for identifying nodules with a low likelihood of malignancy.

USG elastography should therefore be considered a valuable adjunct to Bethesda cytology rather than a replacement for cytological or histopathological assessment. Integration of radiological and pathological findings may improve risk stratification, particularly in cytologically indeterminate thyroid nodules, and may contribute to more individualized management and reduction of unnecessary invasive procedures.

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