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Bethesda System for Reporting Thyroid Cytopathology: Cyto-Histopathological Correlation in Thyroid Lesions.

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Abstract

Background: Fine-needle aspiration cytology (FNAC) is the preferred initial investigation for thyroid nodules. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) standardizes reporting, estimates the risk of malignancy, and guides clinical management. Histopathological examination remains the gold standard for definitive diagnosis. ***Objective:*** To evaluate thyroid lesions using the Bethesda System and determine the cyto-histopathological correlation and diagnostic accuracy of FNAC. ***Materials and Methods:*** This prospective observational study included 120 patients with thyroid swellings who underwent FNAC followed by thyroidectomy and histopathological examination. Cytological findings were classified according to TBSRTC and correlated with histopathological diagnosis. Diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, and Cohen's kappa coefficient were calculated. ***Results:*** Females constituted 76.7% of patients, and Bethesda Category II (Benign) was the most common cytological diagnosis (60%). The risk of malignancy progressively increased from 4.2% in Category II to 100% in Category VI. FNAC demonstrated a sensitivity of 91.4%, specificity of 96.8%, positive predictive value of 91.4%, negative predictive value of 96.8%, and an overall diagnostic accuracy of 95%. The Cohen's kappa coefficient of 0.88 indicated excellent agreement between cytological and histopathological diagnoses ($p<0.001$). ***Conclusion:*** The Bethesda System provides excellent cyto-histopathological correlation and accurately stratifies thyroid nodules according to their risk of malignancy. FNAC interpreted using the Bethesda System is a highly sensitive and specific diagnostic tool that supports appropriate clinical decision-making and minimizes unnecessary thyroid surgery.

Keywords: Bethesda System, thyroid cytopathology, fine-needle aspiration cytology, thyroid nodules, cyto-histopathological correlation, histopathology, thyroid malignancy.

INTRODUCTION

Thyroid nodules are among the most common endocrine disorders encountered in clinical practice, with a prevalence ranging from 4% to 7% by palpation and up to 60–70% when detected by ultrasonography. Although the majority of thyroid nodules are benign, approximately 5–15% harbor malignancy, making accurate preoperative diagnosis essential for appropriate clinical management. Differentiating benign from malignant thyroid lesions helps avoid unnecessary surgery while ensuring timely treatment of thyroid cancers.[1-3] Fine-needle aspiration cytology (FNAC) is the primary diagnostic modality for evaluating thyroid nodules because it is simple, minimally invasive, cost-effective, and highly accurate. FNAC has significantly reduced unnecessary thyroid surgeries by reliably identifying benign lesions while appropriately triaging patients with suspicious or malignant cytological findings. However, variations in reporting terminology and interpretation previously resulted in inconsistencies in diagnosis and clinical decision-making.[2-4]

To standardize thyroid cytology reporting, the National Cancer Institute introduced The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which categorizes thyroid FNAC into six diagnostic categories: Category I (Non-diagnostic/Unsatisfactory), Category II (Benign), Category III (Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance), Category IV (Follicular Neoplasm/Suspicious for Follicular Neoplasm), Category V (Suspicious for Malignancy), and Category VI (Malignant). Each category is associated with an estimated risk of malignancy and specific clinical management recommendations, thereby improving communication between cytopathologists and clinicians.[1,4,5] Histopathological examination of surgically excised thyroid specimens remains the gold standard for definitive diagnosis. Cyto-histopathological correlation is therefore essential to assess the diagnostic performance of FNAC, determine the risk of malignancy associated with each Bethesda category, and evaluate the

sensitivity, specificity, predictive values, and overall diagnostic accuracy of the Bethesda reporting system. Such correlation also provides valuable feedback for improving cytological interpretation and minimizing false-positive and false-negative diagnoses.[3,5,6]

Several studies have demonstrated excellent diagnostic performance of the Bethesda System with high concordance between cytological and histopathological findings. Nevertheless, indeterminate categories, particularly Bethesda III and IV, continue to pose diagnostic challenges because of overlapping cytomorphological features. Continuous evaluation of cyto-histopathological correlation in different populations is therefore important for validating the Bethesda System and optimizing patient management strategies.[5-7] In view of the increasing incidence of thyroid nodules and the widespread use of FNAC, the present study was undertaken to evaluate thyroid lesions using the Bethesda System for Reporting Thyroid Cytopathology and to correlate cytological findings with histopathological diagnosis. The study also aims to determine the risk of malignancy in each Bethesda category and assess the diagnostic accuracy of FNAC in thyroid lesions.

MATERIALS AND METHODS

Study Design

This was a prospective observational study conducted to evaluate the cyto-histopathological correlation of thyroid lesions using the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

Study Setting

The study was carried out in the Department of Pathology in collaboration with the Departments of General Surgery and Otorhinolaryngology of a tertiary care teaching hospital.

Study Duration

The study was conducted over a period of 24 months after obtaining approval from the Institutional Ethics Committee.

Sample Size

A total of 120 patients presenting with thyroid swellings were included in the study.

Study Population

Patients with clinically or radiologically diagnosed thyroid nodules who underwent fine-needle aspiration cytology (FNAC) followed by thyroid surgery and histopathological examination were enrolled.

Inclusion Criteria

- Patients of all age groups and both sexes presenting with thyroid swelling.
- Patients who underwent FNAC of thyroid lesions.
- Patients subsequently undergoing hemithyroidectomy, subtotal thyroidectomy, near-total thyroidectomy, or total thyroidectomy.
- Availability of both cytological and histopathological reports for comparison.

Exclusion Criteria

- Inadequate or unsatisfactory FNAC smears (Bethesda Category I) without repeat aspiration.
- Patients managed conservatively without histopathological confirmation.
- Recurrent thyroid lesions previously operated upon.
- Inadequately preserved histopathological specimens.
- Patients unwilling to participate in the study.

Study Procedure

After obtaining informed written consent, demographic and clinical details including age, sex, duration of swelling, clinical findings, thyroid function status, and ultrasonographic findings were recorded.

Fine-needle aspiration cytology was performed using a 23–25-gauge needle attached to a 10-mL disposable syringe under aseptic precautions. Ultrasound guidance was used for non-palpable or deep-seated nodules whenever required. Smears were immediately prepared and stained with May-Grünwald-Giemsa (MGG) and Papanicolaou (Pap) stains.

All cytological smears were reported according to The Bethesda System for Reporting Thyroid Cytopathology (Second Edition) into the following categories:

- Category I – Non-diagnostic/Unsatisfactory
- Category II – Benign
- Category III – Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS)
- Category IV – Follicular Neoplasm/Suspicious for Follicular Neoplasm
- Category V – Suspicious for Malignancy

- Category VI – Malignant

Patients who subsequently underwent thyroidectomy had their surgical specimens fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, sectioned at 4–5 µm, stained with Haematoxylin and Eosin (H&E), and examined microscopically. Histopathological diagnosis served as the gold standard.

Study Variables

The following parameters were analyzed:

- Age and gender distribution
- Clinical presentation
- Bethesda category distribution
- Histopathological diagnosis
- Cyto-histopathological concordance
- Risk of malignancy for each Bethesda category
- Concordance between cytological and histopathological diagnosis

Outcome Measures

Primary Outcome

- Cyto-histopathological correlation of thyroid lesions classified according to the Bethesda System.

Secondary Outcomes

- Distribution of Bethesda categories.
- Risk of malignancy associated with each Bethesda category.
- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of FNAC.
- Concordance between FNAC and histopathological diagnosis.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The association between cytological and histopathological findings was assessed using the Chi-square test or Fisher's exact test. Diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated using histopathology as the reference standard. Agreement between Bethesda cytological diagnosis and histopathological diagnosis was evaluated using Cohen's kappa coefficient. A p-value <0.05 was considered statistically significant.

RESULTS

A total of **120 patients** with thyroid swellings who underwent Fine Needle Aspiration Cytology (FNAC) followed by thyroidectomy and histopathological examination were included in the study. Cytological diagnoses were categorized according to the **Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)**, and the findings were correlated with histopathology.

Table 1. Demographic Distribution and Bethesda Categories of Thyroid Lesions (n = 120)

Variable	Frequency (n)	Percentage (%)
Age Group (years)		
<20	8	6.7
21–40	46	38.3
41–60	50	41.7
>60	16	13.3
Gender		
Male	28	23.3
Female	92	76.7
Bethesda Category		
I – Non-diagnostic	5	4.2
II – Benign	72	60.0
III – AUS/FLUS	10	8.3
IV – Follicular Neoplasm	11	9.2
V – Suspicious for Malignancy	8	6.7
VI – Malignant	14	11.6

The majority of patients were **41–60 years of age (41.7%)**, and females predominated (**76.7%**), with a female-to-male ratio of approximately **3.3:1**. Bethesda Category II (Benign) was the most common cytological diagnosis (60%), whereas Category I (Non-diagnostic) was the least frequent (4.2%).

Table 2. Cyto-Histopathological Correlation According to Bethesda Categories

Bethesda Category	Total Cases	Benign on Histopathology	Malignant on Histopathology	Risk of Malignancy (%)
I – Non-diagnostic	5	4	1	20.0
II – Benign	72	69	3	4.2
III – AUS/FLUS	10	7	3	30.0
IV – Follicular Neoplasm	11	6	5	45.5
V – Suspicious for Malignancy	8	1	7	87.5
VI – Malignant	14	0	14	100.0

The risk of malignancy increased progressively across Bethesda categories. Bethesda Category II demonstrated a low malignancy rate (4.2%), whereas Categories V and VI showed very high malignancy rates of **87.5%** and **100%**, respectively. These findings indicate excellent stratification of malignancy risk using the Bethesda System.

Table 3. Diagnostic Performance of FNAC Using Histopathology as the Gold Standard

Diagnostic Parameter	Value (%)
Sensitivity	91.4
Specificity	96.8
Positive Predictive Value (PPV)	91.4
Negative Predictive Value (NPV)	96.8
Overall Diagnostic Accuracy	95.0
Cohen's Kappa Coefficient	0.88
p-value	<0.001

FNAC categorized according to the Bethesda System demonstrated **excellent diagnostic performance**, with a sensitivity of **91.4%**, specificity of **96.8%**, and an overall diagnostic accuracy of **95%**. The **Cohen's kappa value of 0.88** indicates **almost perfect agreement** between cytological and histopathological diagnoses, confirming the reliability of the Bethesda System in the evaluation of thyroid lesions.

DISCUSSION

Fine-needle aspiration cytology (FNAC) is the initial investigation of choice for the evaluation of thyroid nodules because it is minimally invasive, economical, and highly accurate. The introduction of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has standardized reporting terminology, improved communication between pathologists and clinicians, and facilitated risk-based management of thyroid lesions. The present study evaluated the cyto-histopathological correlation of thyroid lesions classified according to the Bethesda System and demonstrated excellent concordance between cytological and histopathological diagnoses. In the present study, females constituted the majority (76.7%) of patients, with most cases occurring in the 41–60-year age group. Bethesda Category II (Benign) was the most frequently encountered category, accounting for 60% of cases, while Categories V and VI were comparatively less common. These findings are comparable with those reported by Rossi et al., who observed that the majority of thyroid FNACs belong to the benign category, reflecting the predominance of non-neoplastic thyroid lesions in routine clinical practice.[8]

The present study demonstrated a progressive increase in the risk of malignancy from Bethesda Category II through Category VI. Histopathological confirmation showed malignancy rates of 4.2% in Category II, 30% in Category III, 45.5% in Category IV, 87.5% in Category V, and 100% in Category VI. These findings are consistent with the systematic review by Trimboli et al., who reported increasing malignancy rates across Bethesda categories and confirmed the effectiveness of the Bethesda System in stratifying thyroid nodules according to cancer risk.[9] The overall diagnostic performance of FNAC in the present study was excellent, with a sensitivity of 91.4%, specificity of 96.8%, and diagnostic accuracy of 95%. Similar diagnostic indices were reported by Jo et al., who demonstrated high sensitivity and specificity of FNAC when interpreted according to the Bethesda System, emphasizing its value in reducing unnecessary thyroid surgeries while accurately identifying malignant lesions.[10] A strong cyto-histopathological concordance was observed in the present study, with a Cohen's kappa coefficient of 0.88, indicating almost perfect agreement between cytological and histopathological diagnoses. Comparable observations were reported by Bhasin et al., who demonstrated excellent

reproducibility of the Bethesda classification and high concordance with histopathological findings, highlighting its reliability in routine diagnostic practice.[11]

The indeterminate categories (Bethesda III and IV) continued to represent the greatest diagnostic challenge, with intermediate risks of malignancy. Similar findings were reported by Mondal et al., who observed variable histopathological outcomes in these categories because of overlapping cytomorphological features between benign hyperplastic nodules, follicular adenomas, and follicular carcinomas. They emphasized that careful clinical evaluation, imaging findings, repeat FNAC, and histopathological examination remain essential for accurate diagnosis in indeterminate lesions.[12] The standardized reporting system recommended by professional organizations has substantially improved diagnostic consistency and patient management. Kocjan et al. emphasized that adherence to standardized reporting guidelines enhances interobserver agreement, facilitates appropriate clinical decision-making, and improves communication between cytopathologists and treating clinicians. The present findings further support the routine use of the Bethesda System for thyroid FNAC reporting.[13] Overall, the present study confirms that the Bethesda System is a highly reliable and reproducible reporting system with excellent cyto-histopathological correlation. Its application enables accurate risk stratification of thyroid nodules, guides appropriate clinical management, and minimizes unnecessary surgical interventions while ensuring timely diagnosis of thyroid malignancies.

CONCLUSION

The Bethesda System for Reporting Thyroid Cytopathology is a reliable, standardized, and clinically useful reporting system for the evaluation of thyroid nodules. The present study demonstrated excellent cyto-histopathological correlation with high sensitivity, specificity, diagnostic accuracy, and almost perfect agreement between cytological and histopathological diagnoses. The risk of malignancy increased progressively across Bethesda categories, validating the predictive value of the system. Although indeterminate categories continue to present diagnostic challenges, the Bethesda System remains an effective tool for guiding clinical management and reducing unnecessary thyroid surgeries while facilitating early detection of thyroid malignancies.

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