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Evaluation of thyroid cytology using the Bethesda system for reporting thyroid cytopathology: An institutional experience

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Abstract

Introduction: Fine-needle aspiration cytology (FNAC) is a rapid, cost-effective and safe to evaluate thyroid nodules. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) offers a standardized reporting system for FNAC. This study aimed to categories thyroid FNAC according to TBSRTC and evaluate its accuracy with histopathology examination (HPE) report.

Method: This was a cross-sectional study of retrospectively collected data of thyroid FNAC and HPE during Jul 2022 to Aug 2024 in the Department of Pathology at Dhulikhel Hospital, Kathmandu University Hospital, Nepal. All FNAC specimens of thyroid received were included, categorized as per TBSRTC and compared with the available HPE report for accuracy (true positive + true negative/total number of cases). The study was approved by the institutional review board. Data analysis was performed using IBM SPSS.

Result: Out of 152 thyroid FNAC non-diagnostic were 14(9.2%), benign 86(56.6%), atypia of undetermined significance (AUS) 7(4.6%), follicular 4(2.6%), suspicious for malignancy 13(8.6%), and malignant were 28(18.4%). Sensitivity was 100% and specificity 90.9%. The positive predictive value and negative predictive value were 93.3%% and 100% respectively. The accuracy of FNAC in differentiating benign from malignant was 96%. The malignancy rate for benign, atypia of undetermined significance, follicular neoplasm, suspicious for malignancy, and malignant categories were 0%, 33.3%, 33.3%, 75%, and 93.3%, respectively.

Conclusion: Our study affirms accuracy of TBSRTC with gold standard histopathology. However, the malignancy rate of AUS was higher than the risk mentioned in TBSRTC, and warrants further workup including ultrasound or thyroid scan in addition to repeat FNAC.

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Introduction

Thyroid nodules are commonly encountered in clinical practice. They can be detected by clinical examination in 4-8% of adults, which can increase to 50-60 % by high-resolution ultrasonography.[1-3] Thyroid nodules are more common in females due to the high prevalence of endocrine disorders.[3] Benign thyroid lesions are more common than malignant ones, and the incidence of malignancy in thyroid nodules is 5-10%; therefore, surgical removal of every thyroid nodule is unnecessary, expensive, and potentially risky.[2,4]

Fine-needle aspiration cytology (FNAC) is a rapid, cost-effective and safe method to diagnose thyroid carcinoma and to stratify thyroid nodules for surgical management.[5] It has higher sensitivity and predictive value for diagnosis than any other single diagnostic method.[5]

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) offers a standardised reporting system for fine-needle aspiration (FNA) cytology results, providing a common language for communication between pathologists and clinicians.[6] The six diagnostic categories suggested by TBSRTC, 2023 are: I) Non-diagnostic (ND); II) Benign; III) Atypia of Undetermined Significance (AUS); IV) Follicular Neoplasm(FN); V) Suspicious for Malignancy (SFM); and VI) Malignant.[7]

These categories have a specific link to the risk for malignancy and clinical management. The aim of the study was to evaluate the diagnostic performance (sensitivity and specificity) of FNAC categorised by (TBSRTC) against histopathology report as the gold standard in thyroid lesion diagnosis.

Method

A retrospective, analytical cross-sectional study was conducted in the Department of Pathology, Dhulikhel Hospital-Kathmandu University Hospital (DH-KUH) from July 2022 to August 2024. Ethical approval was taken from the Institutional Review Committee of Dhulikhel Hospital-Kathmandu University Hospital (Reference no: 305/24). Thyroid nodules FNAC and HPE slides were analysed together with patient's clinico-demographic information. Samples with incomplete records were excluded from the study.

Thyroid FNAC and paired HPE slides (May Grunwald Giemsa (MGG) and Papanicolaou (PAP) stain) were reviewed under light microscope and categorised as per TBSRTC.[2]

The TBSRTC includes 6 categories. It considers a thyroid FNAC specimen satisfactory for evaluation when it contains at least six groups of benign-appearing follicular cells, with each group consisting of at least 10 cells.

I. **Non-diagnostic (ND):** The specimen containing predominantly blood or overly thick smears or absence of colloid or an insufficient number or fixation quality of follicular cells, and cyst fluid aspirate containing macrophages only was considered nondiagnostic.
II. **Benign:** The smears with cytomorphological features of nodular colloid goitre, chronic lymphocytic thyroiditis, hyperplastic or adenomatoid nodule, thyrotoxicosis, and de Quervain's thyroiditis or granulomatous thyroiditis were categorised as benign.
III. **Atypia of undetermined significance (AUS):** The cases that cannot be classified into any of the diagnostic categories of Bethesda system and show nuclear or architectural atypia were grouped in this category.
IV. **Follicular neoplasm (FN):** Smears consisting of follicular cells of moderate to high cellularity, scant to the absent colloid, and predominantly repetitive microfollicular or trabecular configuration were interpreted as FN. Also, morphological features of Hurthle cell neoplasm were included in this category.
V. **Suspicious for malignancy (SFM):** The cases showing cytomorphological features suggestive of papillary carcinoma, medullary carcinoma, lymphoma, or metastatic carcinoma were categorized as SFM.

VI. **Malignant category:** Smears showing cytomorphological features conclusive of malignancy were placed in this category. The malignancies included were a papillary carcinoma, medullary carcinoma, anaplastic carcinoma, lymphoma, and metastatic carcinoma.

Patient's history, clinical diagnosis was obtained from the patient's record file and histopathological forms. Histopathological diagnosis was categorised as benign and malignant.

Patient's data was entered in Microsoft Excel, and data analysis was done using IBM SPSS 16. Frequency and percentage were calculated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using a 2×2 contingency table (FNAC vs. biopsy). Accuracy of FNAC for malignancy rate was calculated.

Result

In total, 152 thyroid FNACs were performed over a period of 2 years from Jul 2022 to Aug 2024. The age of patients ranged from 15 years to 85 years, and the maximum number of patients was in the age group of 41-50 years, Figure 1. The female to male ratio was 6.2:1.

The thyroid FNAC were reviewed and categorised according to TBSRTC. Of these, ND were 14(9.2%), benign 86(57.2%), AUS 7(4.6%), FN 4(2.6%), SFM 13(8.6%), and malignant 28(18.4%), Table 1.

Among 152 FNAC cases, 35 underwent surgery and had histopathological final diagnoses. The 35 FNAC cases included 10 benign, 15 malignant and 10 others, Table 2. The risk was nil for malignancy in FNAC diagnosis of benign cases.

None of the 14 ND cases on FNAC had subsequent surgical resection specimens, and we could not do further analysis of these 14 cases.

Of the 10 benign cases (out of 86) who had surgery and follow-up histopathology revealed all were benign (7 colloid nodules, 2 Hashimoto's thyroiditis and 1 Nodular hyperplasia). The overall malignancy risk for the benign category was 0%.

Out of 7 cases of AUS, 3 had had surgery and follow-up histopathology revealed 1 papillary carcinoma.

Among 4 FN, 3 had surgery and follow-up histopathology revealed 1 follicular carcinoma.
Of 13 cases of SFM, 4 had surgery and follow-up histopathology revealed 3 papillary carcinomas, a 75% malignancy rate for SFM category.

Among the 28 cytologically malignant categories, 15 had surgery (in 13, no data available). Out of 15 who had surgery, the follow-up histopathology revealed papillary carcinoma in 14 and Hashimoto thyroiditis with squamous metaplasia in one case.

Statistical analyses were done to find out accuracy of FNAC in detecting malignancy in thyroid swelling, which are as follows:

Sensitivity = True positive / (True positive + False negative) = 14/ (14+0) = 100%

Specificity = True negative / (True negative + False positive) = 10 / (10+1) = 90.9%

Positive predictive value (PPV) = True positive / (True positive + False positive) = 14/ (14+ 1) = 93.3%

Negative predictive value (NPV) = True negative / (True negative + False negative) = 10 / (10+ 0) = 100%

Accuracy = True positive + True negative / total number of cases = 14+10 /25 = 96%.

The overall malignancy risk (FNAC vs final histopathology report) for the benign category was 0% (all 10 benign FNAC were also benign on HPE), for AUS and FN 33.3%, for SFM 75% and malignant category 93.3% (14 out of 15), Table 2.

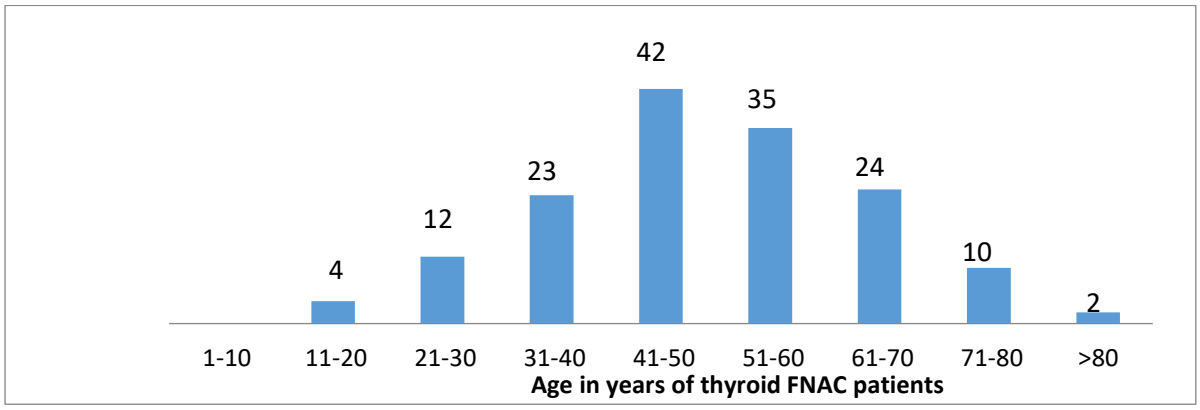

Figure 1. Age distribution of patients with thyroid fine needle aspiration cytology (FNAC), n=152

Table 1. Thyroid FNAC categories according to Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), n=152

Cytological categories		Subcategories		n	n(%)
I.	**Non diagnostic (ND)**	–	Cyst fluid only	4	14(9.2)
		–	Virtually acellular specimen	3	
		–	Other (obscuring blood, clotting artefact etc.)	7	
II.	**Benign**	–	Consistent with benign follicular nodule (includes colloid nodule and adenomatoid nodule)	78	86(56.6)
		–	Consistent with lymphocytic (Hashimoto) thyroiditis	8	
III.	**Atypia of undetermined significance (AUS)**	–		7	7(4.6)
IV.	**Follicular Neoplasm (FN)**	–		4	4(2.6)
V.	**Suspicious for Malignancy (SFM)**	–	Suspicious of papillary carcinoma	12	13(8.6)
		–	Suspicious of Medullary carcinoma	1	
VI.	**Malignant**	–	Papillary thyroid carcinoma	27	28(18.4)
		–	Squamous cell carcinoma	1	

Table 2. Malignancy risk of different categories of FNAC report and surgical specimen histopathology examination (HPE) report, n=35

FNAC (n)	Surgery and subsequent HPE (n)		Malignancy risk (%)
	Benign	Malignant	
Benign (86; 10 had surgery)	10	0	0
AUS (7; 3 had surgery)	2	1	33.3
FN (3)	2	1	33.3
SFM (3)	1	3	75
Malignant (15)	1	14	93.3

Discussion

Thyroid gland is the largest of all endocrine glands and lies in the anterior neck. Enlargement of thyroid is a common occurrence, with the sub-Himalayan region being the world's biggest goitre belt.[2] The causes of enlargement is variable. The difference in the management of

the benign and malignant thyroid nodules is important in order to avoid unnecessary, expensive, and potentially risky surgical procedures. The FNAC is a simple, minimally invasive, and cost-effective tool to distinguish between a malignant and benign lesion.[5]

The maximum number of cases that underwent thyroid FNAC was in the age group of 41-50 years of age. Similar findings were observed in other studies.[9-11] Thyroid nodules are more common in females due to the high prevalence of endocrine disorders.[4] In present study, thyroid lesions were more common in females with a female:male ratio of 6.2:1. Similar female predominance was noted in various studies.[10-12]

Among the six categories of TBSRTC, most cases belonged to category II, i.e. benign, reported in 55.3%. The benign cases are the commonest category in many studies.[2,5,10-13]

Malignant cases were the second most common category in our study, comprising 28(18.4%) cases. Similar findings were observed in other studies.[13,14] The reason for the malignant category having a higher number of cases could be attributed to the fact that tertiary care centres get more referral cases besides general population.

Category I, non-diagnostic smears were devoid of follicular cells, obscured with blood or clotting artefact or showed cystic fluid and cyst macrophages only. Repeat aspiration under ultrasonography guidance was advised for such smears. Cystic degeneration or necrosis or sclerotic, or calcified lesions lead to non-diagnostic aspirates.[15] The percentage of ND was 9.2% in our study, which is comparable to the findings of other studies.[5,14]

Follicular neoplasm comprised 2.6% cases in present study, which is comparable with reported studies.[5,10] The cases showing cytomorphological features suggestive of papillary carcinoma, medullary carcinoma, lymphoma, or metastatic carcinoma were categorized as SFM. The percentage of SFM is 8.6% in our study, which is comparable to the other studies.[15] Category III reported as AUS includes lesions with morphological abnormalities of the follicular cells with or without presence of nuclear atypia, which cannot be classified into benign, suspicious, or malignant categories. Repeat FNAC, molecular testing, diagnostic lobectomy or surveillance are options for clinical management.[5] The AUS accounted for 4.6% in our study, Table 3.

Among 152 FNAC cases, 35 underwent surgery, of which 10 were for benign (out of a total of 86 benign FNAC). Since the clinical option for benign cases is clinical and ultrasound follow-up, only 10 cases had thyroidectomy. On histopathology, all cases were benign (7 colloid nodules, 2 Hashimoto's thyroiditis and 1 Nodular hyperplasia). The overall malignancy rate for the benign category was nil. This is comparable to the implied risk of TBSRTC and other studies, Table 2 and Table 4.

Among the 28 cytologically malignant, 15 had histopathology available (13 patients possibly lost to follow-up). Only 1 case turned out benign (Hashimoto thyroiditis with squamoid metaplasia), and remaining 14 were papillary carcinoma, giving a malignancy rate for malignant category FNAC of 93.3%, which is less compared to other studies, Table 4. This discrepancy may be due to a smaller number of histopathology cases in present study, and also highlights the limitations of diagnostic tests.

Table 3. Comparison of the distribution of the FNAC diagnostic categories with other studies in the literature

Cytological category		Present n(%)	Alshaikh[5] n(%)	Naz[10] n(%)	Park[11] n(%)	Mondal[13] n(%)	Lee[14] n(%)	Yassa[16] n(%)
I.	ND	14(9.2)	69(10.1)	25(4.7)	(13.3)	12(1.2)	497(10.0)	269(7.4)
II.	Benign	87(57.2)	469(68.8)	403(76.3)	(40.6)	893 (87.5)	3362(67.7)	2361(65.7)
III.	AUS	7(4.6)	85(12.4)	67(12.7)	(9.1)	10 (1.0)	154(3.1)	144(4.0)
IV.	FN	4(2.6)	20(2.9)	11(2.1)	(0.4)	43 (4.2)	44(1.1)	328(9.0)
V.	SFM	13(8.6)	18(2.6)	18(3.4)	(19.3)	14(1.4)	253(5.1)	314(9.1)
VI.	Malignant	28(18.4)	28(4.1)	4(0.8)	(17.3)	48 (4.7)	645(13.0)	173(4.8)

Table 4. Comparison of malignancy risk of various FNAC categories in present study compared with other studies in the literature

Malignant risk		Present	Alshaikh[5]	Naz[10]	Park[11]	Jo[12]	Mondal[13]	Range of estimated ROM[7]
I.	ND	-	6.67	-	35.3	8.9	-	5-20
II.	Benign	0	15.0	11.1	5.6	11.0	4.5	2-7
III.	AUS	33.3	28.0	33.3	69.0	17.0	20.0	13-30
IV.	FN	33.3	22.0	25.0	50.0	25.4	30.6	23-34
V.	SFM	75	72.7	100	98.7	70.0	75.0	67-83
VI.	Malignant	93.3	100	100	98.9	98.1	97.8	97-100

The comparison of the statistical performance of the present study with other published studies in terms of key diagnostic metrics: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, shows our findings are comparable with published literature, Table 5.

These metrics are critical for evaluating effectiveness of diagnostic tests.

Sensitivity: In our study, the sensitivity is 100%, which reflects the ability of the diagnostic test to correctly identify true positives (malignant cases). It is comparable to the studies reporting 96.2%[16] and 98.9%[17] and higher than 64.3%[10] and 79.5%[11] in literature. The sensitivity in our study suggests a strong ability to detect malignancy.

Specificity: The specificity in our study is 90.9%, which is the ability to correctly identify true negatives (non-malignant cases). This value is comparable with studies[1,10,11,16,17] reporting 90.9%, 85.1%, 98%, 99.5%, 99.8%, 84.4% respectively, Table 5. High specificity values indicate few false-positive diagnoses, which is important to minimise unnecessary treatment or surgeries. Our specificity value of 90.9%, though strong, suggests that there may still be some false positives, potentially leading to overtreatment in non-malignant cases.

Positive Predictive Value (PPV): The PPV in our study is 93.3%, which indicates the likelihood that patients diagnosed as positive actually have malignancy. This value is quite high and comparable to other studies[10,11,13,16] reporting 100%, 97.8%, 97.7%, 97.4% PPV, respectively. Notably, the 100%[10] reflects that all patients diagnosed as positive were truly malignant, highlighting the usefulness of TBSRTC.

Negative Predictive Value (NPV): Our study's NPV is 100%, which represents the likelihood that patients diagnosed as negative do not have malignancy, compared to studies[1,10,11,16,17] to 80.9% to 99.7%, Table5.

Accuracy: The overall accuracy of our study is 96%, which reflects the proportion of true results (both true positives and true negatives) in the population tested. This is comparable to other studies, Table 5.

Table 5: Statistical analysis for comparison of FNAC accuracy of present study with others in the literature

Statistical analysis	Present	Naz[10]	Park[11]	Mondal[13]	Yassa[16]	Mora-Guzma[17]
Sensitivity	100	64.3	79.5	81.4	96.2	98.9
Specificity	90.9	85.1	98.0	99.5	99.8	84.4
Positive predictive value	93.3	100	97.8	97.7	97.4	69.6
Negative predictive value	100	88.8	80.9	95.4	99.7	99.5
Accuracy	96	80.3	95.8	95.8	99.6	97.9

In general, our study performs well in terms of sensitivity and PPV, indicating that when a malignancy is present, our methods are quite good at detecting it, and patients diagnosed as positive are likely to have true malignancies. The specificity and NPV, while strong, are not as high as those in some other studies, particularly those reporting near-perfect specificity and NPV values. This suggests a higher rate of false positives and false negatives in our study, which

could lead to overtreatment or missed malignancies. The accuracy of our study, while reasonable at 88%, is lower than the near-perfect values reported by studies like Yassa et al. (99.6%). This reflects the need to refine diagnostic criteria or techniques to minimise diagnostic errors and enhance the overall effectiveness of the tests.

The limitations of our study are a smaller sample size for cytology, a smaller number of histopathology cases for cytohistological correlation and clinico-radiological and biochemical correlations were not available for each case and thus were not evaluated. To overcome these limitations, studies with a larger sample size of cytology and histology with clinical, biochemical and radiological data is recommended.

Conclusion

The Bethesda system for thyroid cytology provides a standardised method for reporting thyroid cytopathology, enhancing communication between cytopathologists and clinicians, and promoting uniformity in reporting and management strategies. Our result with 96% accuracy of FNAC is consistent with reported literature. The malignancy rate of AUS in this study was higher than the risk mentioned in TBSRTC, and these patients may require further workup, including ultrasound or thyroid scan, in addition to repeat FNAC.

Author contribution

Concept and Design: DB, RM, AB; Literature search: DB, NG, BS; Data acquisition and compilation: DB, SJ; Statistical analysis and manuscript preparation: DB, RM; Manuscript editing and review: NG, AB; Accountability: All authors.

Conflict of Interest

None

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Supplementary material

The data and supplementary material that support the findings of this study are available from the corresponding author upon reasonable request.

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