

Reproducibility of Cytomorphological Diagnosis and Assessment of Risk of Malignancy of Thyroid Nodules Based on the Bethesda System for Reporting Thyroid Cytopathology: A Tertiary Cancer Center Perspective

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Abstract

Introduction: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was introduced for unifying the terminology and morphologic criteria along with the corresponding risk of malignancy, leading to more consistent management approaches. The aim of this study was to study the utility and reproducibility of TBSRTC in reporting thyroid cytology in a referral cancer center. **Methods:** The fine-needle aspiration (FNA) of all thyroid nodules were included for a period of 5 years, from January 2016 to December 2021, in this cancer center. They were retrospectively reviewed and recategorized according to TBSRTC by two experienced pathologists. Cytohistopathological correlation was done for the cases which underwent surgical resection. **Results:** 522 fine-needle aspiration cytology (FNAC) of thyroid swellings were evaluated and categorized according to TBSRTC. There was agreement in the cytological diagnosis of 512 cases, of which 260 (50.78%) were benign lesions, 189 (36.91%) were malignant, 5 (0.97%) were unsatisfactory/nondiagnostic, 41 (8.01%) were follicular neoplasm/suspicious for neoplasm, 13 (2.53%) were suspicious for malignancy, and 4 (0.78%) cases were reported as atypia of undetermined significance. Two cytopathologists were in agreement in 512 cases (98%) of cases. Almost complete concordance was noted in the malignant (99%) and benign categories (98%). Disagreement was seen in 10 cases. Histological follow-up was available in 201 cases with an overall malignancy rate of 62.68% (126/201). **Conclusion:** TBSRTC proved to be a very simple and effective reporting system for thyroid FNAC, especially in the setting of a cancer center. This enables proper triaging of cases with thyroid masses into those who require surgical intervention and those who can avoid it, thereby preventing unnecessary morbidity.

Keywords: Fine-needle aspiration cytology, malignancy, The Bethesda System for Reporting Thyroid Cytopathology, thyroid

INTRODUCTION

Thyroid nodules are frequent presentation of underlying thyroid diseases in Indian community. Palpable thyroid nodules are prevalent in approximately 12.2% of the population. Malignant thyroid neoplasms, especially in the perspective of thyroid cancer, constitute a minor part, the incident cases of which are around 8.7 cases/1 lakh population per year.^[1] Fine-needle aspiration cytology (FNAC) of thyroid nodules is a crucial and extensively accepted first-line diagnostic method for categorizing thyroid nodules into benign or malignant.^[1] Utmost of them are benign, while a paltry 5% to 10% are

cancerous requiring some sort of surgical and medical intervention.^[2,3]

There were different reporting systems with varied terminologies and different categories. However, none of these were advocated internationally. The diverse appellations constantly created confusion in reporting and limited interpretation

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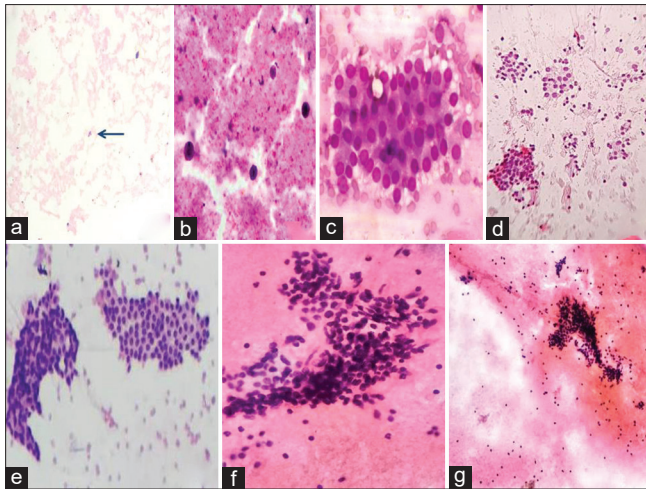


Figure 1: (a) Cat I – Single cluster of follicular cells in backdrop of abundant colloid (PAP, $\times 100$). (b) Cat II-Colloid goiter with cystic changes (PAP, $\times 400$). (c) Cat II – Hyperplastic goiter showing fire-flare appearance (PAP, $\times 400$). (d) Cat III – Macrofollicular and microfollicular pattern with colloid-FLUS (PAP, $\times 100$). (e) Cat III – papillary configuration lacking nuclear features in a background of lymphocytic thyroiditis (PAP, $\times 100$). (f) Cat III – Paucicellular smear with papillary as well as follicular arrangement lacking nuclear features of papillary carcinoma (PAP, $\times 400$). (g) Cat III – Papillary arrangement with cyst macrophages mimicking papillary hyperplasia (PAP, $\times 100$)

by clinicians. The National Cancer Institute proposed. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). By following this system for reporting thyroid FNA, the cytopathological diagnosis could be suitably tiered into 6 categories. Each category has its corresponding implied risk of malignancy along with recommendations for proposed clinical and surgical management.^[4,5]

The current study was to assess the utility of the applicability of TBSRTC in a tertiary oncology center and to analyze the usefulness of ultrasound-guided fine-needle aspiration (FNA) and cellblock preparation in atypia of undetermined significance category cases. As in a cancer center scenario, malignant cases constitute a substantial proportion; the aim was to evaluate the practicality of the use of TBSRTC in sorting the benign from malignant nodules by which gratuitous surgeries can be avoided.

METHODS

This was a retrospective study undertaken, with necessary approval from the Institutional Ethics Committee approval. Smears of all FNAs of thyroid nodules from January 2016 to December 2020 (5 years) were retrieved and analyzed. IRB board name:IEC,AHPGIC,CUTTACK. Approval number:031-IEC-AHPGIC. Approved date:28.06.21.

Inclusion criteria

Inclusion criteria are FNA cases of thyroid nodules at our center.

Exclusion criteria

Exclusion criteria are patients who had the presence of neck swellings other than thyroid lesions.

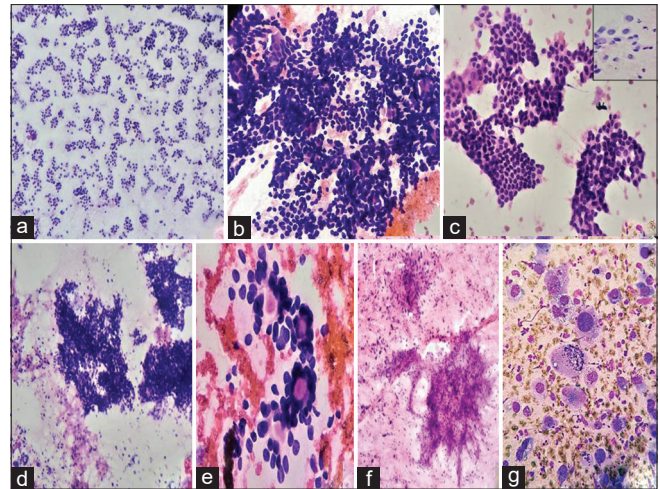


Figure 2: (a) Cat IV – Cellular smear with microfollicular arrangement (May–Grunwald–Giemsa, $\times 100$), (b) Cat IV – Follicles with some of the nuclei showing intranuclear inclusions and nuclear grooves (PAP, $\times 400$), (c) Cat VI – Papillary carcinoma (PAP, $\times 100$), Inset-intranuclear cytoplasmic inclusion and nuclear grooves, (d) Cat VI – Medullary carcinoma thyroid (spindle cells with amorphous eosinophilic material) (PAP, $\times 100$), (e) Cat V – suspicious of medullary carcinoma (plasmacytoid cells with eosinophilic amorphous material in lumen) (PAP, $\times 400$), (f) Cat VI – Anaplastic carcinoma showing spindle cells with marked pleomorphism admixed with necrotic debris (PAP, $\times 100$), (g) Cat VI – Anaplastic carcinoma showing pleomorphic, bizarre cells (May–Grunwald–Giemsa, $\times 400$)

All the slides were stained with May–Grunwald–Giemsa and Papanicolaou stain in accordance with the standard protocol. The cytological features of the smears were evaluated, and reporting was done based on the criteria laid down by the TBSRTC and was categorized into six categories by two experienced pathologists. The six categories are (I) nondiagnostic/unsatisfactory (ND/UNS), (II) benign, (III) atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), (IV) follicular neoplasm (FN) or suspicious for FN (SFN), (V) suspicious for malignancy (SFM), and (VI) malignant. The results of the two pathologists were observed for interobserver variability by calculating the percentage of agreement. In cases available, histopathological (HP) and clinical follow-up information was accessed from the records. In these cases, the cytohistological correlation was done, and the malignancy rate was calculated. Descriptive statistics such as mean and ratio are used for the interpretation of the study.

RESULTS

A total of 522 FNAs of thyroid nodules done in 5 years were evaluated. Age and gender-wise distribution of cases has been tabulated in Table 1. Maximum cases were between 3rd and 6th decade. Age ranged from as young as 8 years to as elderly as 87 years. Females were predominantly affected, accounting for 76.4% (399 cases).

In this study, the cytological diagnosis was concordant in 512 cases (98%), whereas in 10 (2%) cases, the cytological

diagnosis was not in agreement. The incidence of The Bethesda category in concordant cases is enumerated in Table 2.

Cytological diagnosis was reproducible in almost all categories, Cat I: ND/US (100%) [Figure 1a], Cat II: Benign (98.83%) [Figure 1b,c] Cat III: AUS/FLUS (100% agreement) [Figure 1d-g], Cat IV : FN/SFN (93.33%) [Figure 2a,b], Cat V: SFM (93.33%) [Figure 2e], Cat VI: malignant (99.47%) [Figure 2c,d,f,g].

The cytological discordant cases are shown in Table 3. It was observed that two cases categorized as Cat I were recategorized as Cat II (colloid goiter with cystic changes). HP diagnosis was available in one case, which showed the features of colloid goiter. Further, three discrepant cases were

categorized in the benign category by one of the observers, whereas according to corresponding other observers, two of them were recategorized into FN/SFN and one case as AUS. HP of the corresponding cases was follicular adenoma, adenomatoid goiter, and papillary carcinoma, respectively. Considering the AUS category, disagreement was in 2 cases, there was a case where the fina findings led one pathologist to put it under CAT IV(FN/SFN), however the second pathologist categorised it as CAT V(suspicious for malignant). Finally histopathological diagnosis came out to be follicular variant of papillary carcinoma. A case diagnosed as suspicious for malignant (sus for medullary carcinoma) by one observer was diagnosed as Cat 6 malignant (medullary carcinoma). Histology confirmed the diagnosis of medullary carcinoma. In this study, agreement in cytological diagnosis was seen in 98% of the cases.

In this study 522 FNA cases were included. Of these histopathological diagnosis was available in 201 cases. Figure 3a-f displays the histopathology of different thyroid lesions. Table 4 highlights the cytological diagnosis, histopathological followup and malignancy rate of the available cases. From this cytohistological correlation it was evident that malignant cases comprised 62.68% (126 of 201 cases). Two cases of the nondiagnostic category (Cat I) were available for histopathology follow-up, both being benign nodules (adenomatoid goiter and follicular adenoma).

A total of 56 (Cat II) cases underwent surgery. Histopathology evaluation yielded a null malignancy rate, with 48 cases

Table 1: Age- and gender-wise distribution of cases (total: 522 cases)

Age (years)	Female	Male	Total	Percentage
1-10	2	1	3	0.57
11-20	12	4	16	3.06
21-30	63	11	74	14.17
31-40	82	16	98	18.77
41-50	92	27	119	22.79
51-60	89	28	117	22.41
61-70	52	23	75	14.36
71-80	6	12	18	3.44
81-90	1	1	2	0.38
Total	399	123	522	100.00

Table 2: Summarization of the Bethesda category in 512 cases (concordant diagnosis)

The Bethesda category	Diagnostic category	Number of cases (total - 512 cases)	Percentage of cases
CAT I	ND or unsatisfactory	4	0.78
CAT II	Benign	261	50.97
CAT III	AUS or follicular lesion	4	0.78
CAT IV	FN or SFN	41	8.01
CAT V	SUS for malignancy	13	2.53
CAT VI	Malignant	189	36.91

ND: Nondiagnostic, AUS: Atypia of undetermined significance, FN/SFN: Follicular neoplasm/suspicious for FN, SUS: Suspicious

Table 3: Details of discordant cases (n=10 cases)

Case serial number	Observer 1		Observer 2		HP diagnosis
1	CAT I	Cyst fluid	CAT I	CG	-
2	CAT II	CG	CAT I	Cyst macrophages	CG
3	CAT II	LT	CAT III	AUS	PCT
4	CAT II	AN	CAT IV	FN/SFN	FA
5	CAT V	SUS for PCT	CAT III	AUS	PCT
6	CAT III	AUS	CAT IV	FN/SFN	FV PCT
7	CAT III	AUS	CAT IV	FN/SFN	FA
8	CAT II	AN	CAT IV	FN/SFN	AN
9	CAT IV	FN/SFN	CAT V	SUS PCT	FV PCT
10	CAT V	SUS for MCT	CAT VI	MCT	MCT

LT: Lymphocytic thyroiditis, CG: Colloid goiter, FA: Follicular adenoma, AUS: Atypia of undetermined significance, FN/SFN: Follicular neoplasm/suspicious for FN, SUS: Suspicious, PCT: Papillary carcinoma thyroid, FV PCT: Follicular variant of PCT, AN: Adenomatoid nodule, MCT: Medullary carcinoma thyroid

Table 4: Histopathological follow-up of and malignancy rate of the available fine needle aspiration cytology cases (n=201)

FNAC (TBSRTC CAT) Cytological diagnosis	Number of cases	HP diagnosis						Malignancy rate
		Benign	FA	HA	FC	FV PCT	Other malignant (PCT, MCT, lymphoma, metastatic)	
ND (CAT I)	2	2						0
Benign (CAT II)	56	48	6	2				0
AUS/FLUS (CAT III)	6		2		1	1	2	66.66
FN/SFN (CAT IV)	35	1	10	4	18	2		57.14
SM (CAT V)	12				1		11	100
Malignant (CAT VI)	90						90	100
Total	201	51	24		20	3	103	

ND: Nondiagnostic, AUS/FLUS: Atypia of undetermined significance/follicular lesion of undetermined significance, FN/SFN: Follicular neoplasm/suspicious for FN, SM: Suspicious for malignant, FA: Follicular adenoma, HA: Hurthle cell adenoma, FC: Follicular carcinoma, PCT: Papillary carcinoma thyroid, FV PCT: Follicular variant of PCT, MCT: Medullary carcinoma thyroid, FNAC: Fine-needle aspiration cytology cases, TBSRTC: The Bethesda System for Reporting Thyroid Cytology, HP: Histopathological

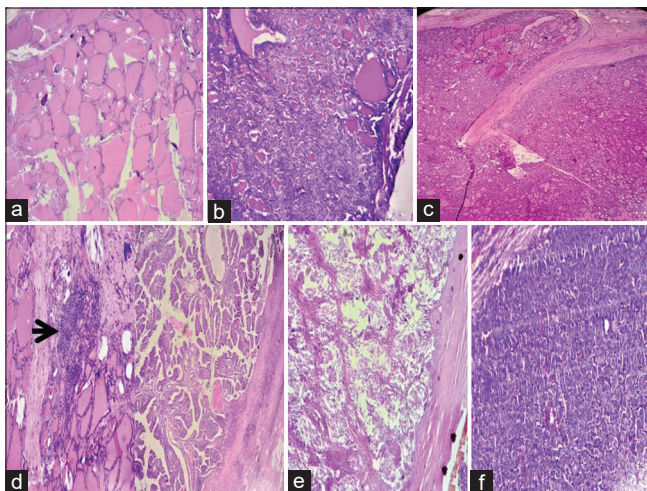


Figure 3: (a) Colloid goiter (H and E, ×100), (b) Hyperplastic nodule (H and E, ×100), (c) Follicular carcinoma (with capsular invasion) (H and E, ×100), (d) Papillary carcinoma with lymphocytic thyroiditis (H and E, ×100), (e) Papillary carcinoma (H and E, ×100), (f) Medullary carcinoma (H and E, ×100), (g) Follicular variant of papillary carcinoma thyroid (H and E, ×100)

being benign and 08 cases with the diagnosis of follicular adenoma (six) and Hurthle cell adenoma (two cases).

All the six cases with AUS/FLUS were subjected to ultrasound-guided FNAC, and cellblock was done in all these cases. By applying this method, two of these cases could be recategorized as papillary carcinoma and a single case as a follicular variant of papillary carcinoma. Histological examination also confirmed the same, and the other three cases included two cases of follicular adenoma and follicular carcinoma. Hence, it was analyzed that USG-guided aspiration and cellblock increased the diagnostic yield in Cat III cases. The overall malignancy rate of Cat III lesions was 66.66%. There were 35 surgically resected Cat IV nodules, of which 20 cases were malignant (57.14% malignancy rate), comprising of 18 cases of follicular carcinoma and 2 cases of follicular variant of papillary carcinoma. Twelve cases of Cat V nodules and 90 cases of Cat VI nodules underwent surgery in this institution, and all were confirmed to be malignant (malignancy rate being 100%).

DISCUSSION

The initiation of the FNA of the thyroid gland dates back to 1952, with utmost acknowledgment to Soderstrom.^[6] Thyroid cytopathology practice requires precise, concise, reproducible diagnosis, and appropriate interdisciplinary communication. In fact, the use of FNA has significantly minimized the number of unwanted surgeries for noncancerous nodules.^[5,6] Diagnosis between benign and malignant lesions is crucial, especially in our cancer center setting. Diagnostic difficulties arise in paucicellular smears, smears with overlapping cytological features, aspirate samples are suboptimal to reliably exclude malignant lesions, lack of radiological details. There were many systems of reporting such as the Papanicolaou Society of Cytopathology, the Italian society for anatomic pathology and cytopathology, and the American Thyroid Association.^[7,8] The lack of any universal terminology created confusion and complications in the management of these types of lesions.^[2,3]

To accomplish an evenness of the diagnostic terms and cytomorphological features for the reporting of thyroid FNAC, the National Cancer Institute suggested TBSRTC. This embodied six categories of lesions with inferred risks of malignancy and evidence-based concise management recommendations.^[9,10]

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is tiered into:^[9]

- I. ND/UNS
- II. Benign
- III. AUS/FLUS
- IV. FN/Hurthle cell neoplasm or suspicious for a FN/Hurthle neoplasm
- V. SFM
- VI. Malignant

In our study, the interobserver agreement was in 98% of the cases. There were ten cytologically discordant cases. Of this, in two cases, either of the observers put one case in Cat 1 due to the presence of only cyst macrophages in one case and the presence of abundant thin colloid without any cellular elements in the other case. However, in the former case correlating the clinical history, ultrasonographic findings, and revisiting the slides, there was a

very thin colloid prompting the other observer to put it in the Cat II. In the second case scenario, there was only a thin colloid devoid of any cellular elements, thereby being put under Cat I by one observer, whereas the second observer found a single small group of follicular cells falling short of adequacy along with the presence of abundant colloid, hence put it in Cat II.

One of the three discordant tagged in Cat II was categorized as Cat III and the rest as FN/SFN (Cat IV). In the first case, one of the observers found only the features of lymphocytic thyroiditis with occasional cells showing feature of nuclear groove whereas, with these features, the other observer put it in Cat III (AUS), which on histological examination revealed a small focus of papillary carcinoma amidst background of lymphocytic thyroiditis.

Considering the other two Ccat II discrepant cases, one of the cases had both microfollicles and macrofollicles, in the presence of very scant colloid, and another case displayed clot causing an artefactual increase in cellularity and presence of a microfollicular pattern in the presence of scant colloid leading to escalation of cytological diagnosis to Cat IV (FN/SFN) category by the other observers, both cases proved to be adenomatoid nodule on histopathology. There were two discordant Cat III cases, in one case, smears had both macro follicles and few microfollicles, but with papillary nuclear features; hence, a specific diagnosis could not be put forth, but histological features revealed to be a follicular variant of papillary carcinoma. In the second scenario, paucicellularity with occasional microfollicles led it to be in Cat IV which was follicular adenoma histomorphologically.

From these findings, it was evident that distinguishing hyperplastic nodules from follicular adenoma cytologically are not an easy task. This interpretation is also in agreement with the findings of Bhasin *et al.* and Awasthi *et al.*^[4,9,11] Earlier studies done by Awasthi *et al.*, and Alshaikh *et al.* suggest that AUS/FLUS is a heterogeneous category, subjected to wide interobserver subjective variability.^[11,12] In the current analysis, AUS/FLUS constituted only 0.78% of the concordant cases. The Cat III cases were subjected to ultrasound-guided FNA, and cellblock was prepared in these cases. The advocacy of this method aided in the reclassification of some of these lesions into malignant or benign. This may be due to better localization of lesions radiologically, especially in the perspective of the small size of suspicious nodules. Further cell block increased the cytologic diagnostic accuracy of these lesions. Almost all of the cases turned up for USG-guided FNAC may be due to the fact that they are all referral cases and this being a tertiary cancer center.

There were dual cases of disagreement of suspicious for malignant (SUS) and malignant category. One case was due to the only plasmacytoid appearance of cells and lack of availability of serum calcitonin level, hence, diagnosed as Cat V (suspicious of medullary carcinoma) by one observer and as Cat VI (medullary carcinoma) by other pathologists. The second case was suspicious for papillary carcinoma

versus papillary carcinoma. Both cases were malignant on HP evaluation. Even though the risk of malignancy in Cat V is <Cat VI, the favored surgical intervention is near-total thyroidectomy. Hence, the distinction may not be of much value in deciding treatment.^[9,11]

Taking into account the cytohistological correlation of all the available cases, (201) overall malignancy rate was 62.68%. In comparison to TBSRTC, the risk for malignancy in Cat I was nil (vs. 1%–4% in TBSRTC), Cat II was null (TBSRTC was 0%–3%), Cat III was 66.66% (compared to 5%–15% TBSRTC), Cat IV was 57.14% (15%–30% suggested in TBSRTC), and Cat V and Cat VI were 100% compared to 60%–75% and 97%–99%, respectively, in TBSRTC. The malignancy rate was comparable in Cat I and Cat II cases in reference to TBSRTC. The high risk of malignancy in Cat III as compared to TBSRTC may be owing to the fact that this is a tertiary cancer center and most of the cases are referred cases. However, the malignancy rate is comparable to the range reported in the literature.^[13–15] Cat V and Cat VI cases had a 100% risk of malignancy at par with the TBSRTC and in other cohorts.^[5,13,15] Even though the risk of malignancy is lower in Cat V than Cat VI, a near-total thyroidectomy is a preferred management option in a greater proportion of these cases, hence taking painstaking effort to put in malignant category carries little value.

Limitations of this study are its retrospective nature, lack of sonographic, biochemical, and clinical details in all the cases. The changes made in the revised 2017 TBSRTC were not taken into account. TBSRTC 2017 includes an introduction of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTPs) thyroid carcinoma and the inclusion of molecular testing for Cat III and Cat IV nodules. The commencement of this new entity led to the categorization of the risk of malignancy in two ways: when NIFTP is not regarded as malignant and when NIFTP is under the umbrella of malignant nodules.^[16]

CONCLUSION

In a referral oncology institution like ours, TBSRTC proved to be a practical, standardized system of reporting thyroid FNA with greater reproducibility. It was also evident that Cat III cases when subjected to USG-guided FNAC and cellblock preparation increased the diagnostic yield, thereby categorizing them into malignant or benign cytologically. This will enhance in better interdepartmental communication and thus prevent unnecessary surgical interventions. The high malignancy rates in The Bethesda categories in the setting of cancer center may be hinting at the fact that the treating physicians should be aware about the incidence of malignant nodules in their respective hospitals, referral centers, or cancer centers, which will aid in deciding their treatment paradigms. TBSRTC should be advocated in all cancer centers to bring about the uniformity of terminologies and efficient clinical management.

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Conflicts of interest

There are no conflicts of interest.

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