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Original Article

A study of malignancy rates in different diagnostic categories of the Bethesda system for reporting thyroid cytopathology: An institutional experience



P. Arul*, C. Akshatha, Suresh Masilamani

Department of Pathology, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur, Tamil Nadu, India

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ABSTRACT

Background: The Bethesda system for reporting thyroid cytopathology (TBSRTC) was introduced to standardize the communication of fine-needle aspiration cytology (FNAC) interpretation between clinicians and pathologists. This study was undertaken to evaluate the diagnostic utility of TBSRTC for reporting thyroid FNACs and rate of malignancy in each diagnostic category of TBSRTC.

Methods: A total of 603 thyroid FNAC results were retrieved retrospectively between July 2012 and January 2015 and reclassified according to TBSRTC. Of these, 392 cases had a histopathological follow-up. The FNACs results were compared to the histopathological diagnoses and the malignancy rates of each diagnostic categories of TBSRTC were calculated.

Results: Of the 603 FNACs, nondiagnostic were 16 (2.7%), benign were 393 (65.2%), atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) were 60 (10%), follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN) were 64 (10.6%), suspicious for malignancy (SM) were 32 (5.3%), and malignant were 38 (6.3%). In 392 cases, there was follow-up histopathology. The malignancy rate for nondiagnostic, benign, AUS/FLUS, FN/SFN, SM, and malignant categories were 0%, 0.8%, 24.4%, 28.9%, 70.8%, and 100%, respectively.

Conclusion: Our study validated the efficacy of TBSRTC. In conclusion, the malignancy rate of AUS/FLUS in this study was higher than the risk mentioned in TBSRTC and other published studies. Hence, AUS/FLUS category patients in our setup warrant further workup including ultrasound and/or thyroid scan in addition to immediate repeat FNAC.

* Corresponding author. Department of Pathology, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur, 621 113, Tamil Nadu, India. Tel.: +91 9500474972 (mobile); fax: +91 04328 224252.

E-mail address: drarul3@gmail.com (P. Arul).

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At a glance commentary

Scientific background on the subject

There is some lack of uniformity with regards to the reporting terminology for thyroid cytology used by pathologists worldwide, resulting in the miscommunication of results among healthcare providers. We evaluated the diagnostic utility of Bethesda system for reporting thyroid cytopathology and the rate of malignancy in each diagnostic category of Bethesda system.

What this study adds to the field

Using Bethesda reporting system is likely to result in the better communication of pathological data to clinicians and allows easy and reliable sharing of information among healthcare providers. Usage of atypia of undetermined significance/follicular lesion of undetermined significance category seems to be disproportionately high and this needs to be further evaluated using inter-observer correlation studies.

Fine-needle aspiration cytology (FNAC) is considered a useful simple preoperative technique for triaging patients with thyroid nodules [1]. Most of the thyroid nodules are benign and approximately 5–10% are malignant requiring operative and medical management. Hence, it is important to differentiate benign nodules from malignant nodules to avoid unnecessary surgery [2,3]. Reporting of FNAC of the thyroid using a standard terminology is not yet widely implemented. The diagnostic terminology varies between pathologists and even institutions creating confusion in the sharing of data between pathologists and clinicians [4]. In an attempt to address this problem, multiple organizations have proposed diagnostic guidelines for reporting thyroid FNAC results including the Papanicolaou Society of Cytopathology Task Force and the American Thyroid Association, however, none have been universally accepted [5,6]. To achieve the standardization of morphological criteria and diagnostic terminology for the reporting of thyroid FNAC, in 2007, the National Cancer Institute (NCI) organized the NCI thyroid fine-needle aspiration state of the science conference which proposed a 6 tier system named The Bethesda system for reporting thyroid cytopathology (TBSRTC) [7,8]. The six diagnostic categories namely nondiagnostic or unsatisfactory, benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN), suspicious for malignancy (SM), and malignant [7,8]. This system also describes the malignancy risk in each category and their recommended clinical management. The risks of malignancy in nondiagnostic or unsatisfactory, benign, AUS/FLUS, FN/SFN, SM, and malignant were 1–4%, 0–3%, 5–15%, 15–30%, 60–75%, and 97–99%, respectively [8]. This study was undertaken to evaluate the diagnostic utility of TBSRTC

for reporting thyroid FNACs and the rate of malignancy in each diagnostic category of TBSRTC.

Materials and methods

After obtaining approval from the Institutional Ethical Committee, all the FNACs of thyroid lesions between July 2012 and January 2015 were retrieved retrospectively. The slides were stained by hematoxylin and eosin (H and E) and May-Grunwald Giemsa. A total of 603 cases of FNACs were included in this study. The FNACs were reclassified according to the 6 tier diagnostic categories of TBSRTC [8].

Satisfactory for evaluation

The specimen was considered satisfactory for evaluation if it contains at least six groups of benign follicular cells, each group composed of at least 10 cells.

Nondiagnostic or unsatisfactory

The specimen was considered nondiagnostic when it contains predominantly blood or overly thick smears or absence of colloid or an insufficient number or fixation quality of follicular cells. Aspirates diagnosed as cyst fluid containing macrophages only also categorized as nondiagnostic.

Benign

The cases were categorized as benign if they showed the cytomorphological features of nodular colloid goiter, chronic lymphocytic thyroiditis, hyperplastic or adenomatoid nodule [Fig. 1], thyrotoxicosis, and de Quervain's thyroiditis or granulomatous thyroiditis.

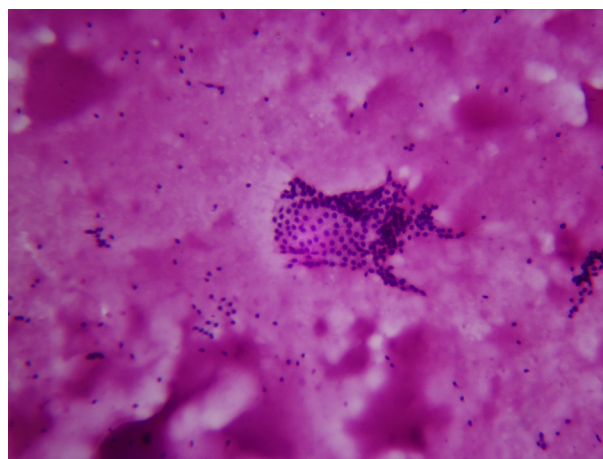


Fig. 1 – Fine-needle aspiration cytology of adenomatoid nodule in nodular colloid goiter is showing clusters and singly scattered follicular epithelial cells in the background of colloid (H and E, $\times 100$).

Atypia of undetermined significance/follicular lesion of undetermined significance

This category was diagnosed when cases that cannot be classified into any of the diagnostic categories of Bethesda system and showing nuclear or architectural atypia [Fig. 2].

Follicular neoplasm/suspicious for a follicular neoplasm

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/SFN. The cases showing morphological features of hurthle cell neoplasm were also included in this category.

Suspicious for malignancy

The cases showing cytomorphological features suggestive of papillary carcinoma, medullary carcinoma, lymphoma, or metastatic carcinoma were categorized as SM.

Malignant category

The aspirate revealing cytomorphological features of the conclusive evidence of malignancy were placed in this category. The malignancies included in this category were a papillary carcinoma, medullary carcinoma, anaplastic carcinoma, lymphoma, and metastatic carcinoma.

Follow-up cytology and histopathology

Of the 603 FNAC cases, 392 cases subsequently underwent surgical intervention. The tissue specimens processed routinely and 4 μ m sections were cut and stained with H and E. The results of final histopathological diagnoses [Fig. 3] were compared to FNAC diagnoses and to find out malignancy rate of each categories of TBSRTC. Papillary microcarcinoma (<1 cm) on resection were not considered malignant except

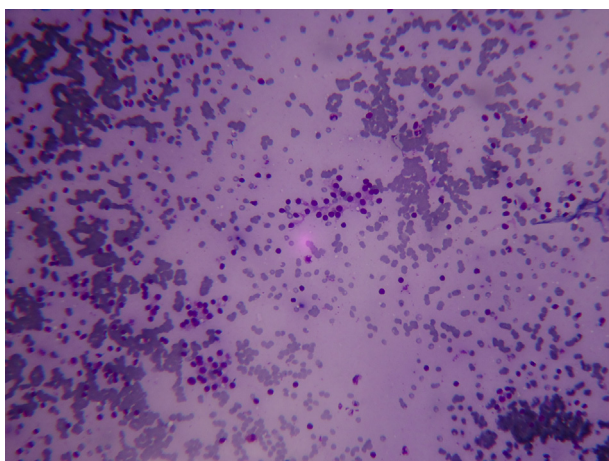


Fig. 2 – Fine-needle aspiration cytology of atypia of undetermined significance/follicular lesion of undetermined significance showing follicular epithelial cells with nuclear atypia (MGG, $\times 100$).

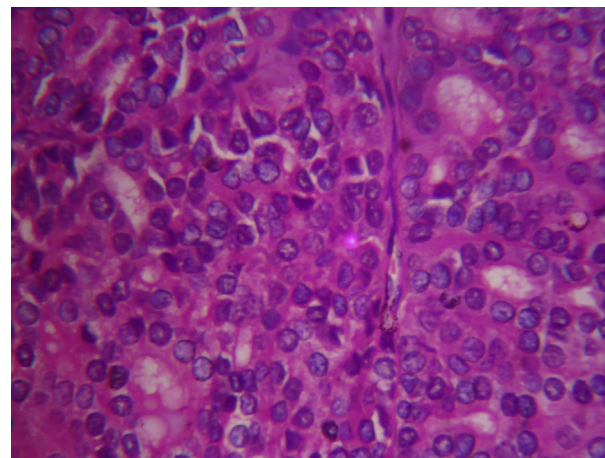


Fig. 3 – Histopathological section of papillary carcinoma of thyroid showing fibrovascular core and tumor cells with ground glass nuclei (H and E, $\times 400$).

when the prior cytologic interpretation was SM or malignant, because the subcentimeter foci would not be targeted by the needle. In calculating, the malignancy follow-up rate for the benign category, the total number of original FNAC diagnoses was used as the denominator, as similarly performed in other studies [9–12].

Frequency, percentage and malignancy rate were calculated using IBM SPSS 20. The results were compared to the TBSRTC and published studies.

Results

In total, 603 FNAC cases between July 2012 and January 2015 were reviewed and analyzed by Bethesda system. Of these, nondiagnostic were 16 (2.7%), benign were 393 (65.2%), AUS/FLUS were 60 (10%), FN/SFN were 64 (10.6%), SM were 32 (5.3%), and malignant were 38 (6.3%) are shown in Table 1. Among the

Table 1 – Distribution of FNAC diagnoses according to Bethesda system (n = 603).

Diagnostic category	Number of cases (%)
Nondiagnostic	16 (2.7)
Benign	393 (65.2)
Nodular colloid goiter	185 (30.7)
Hashimoto's thyroiditis	174 (28.9)
Adenomatoid nodule/nodular hyperplasia	34 (5.6)
AUS/FLUS	60 (10)
FN/SFN	64 (10.6)
FN	64 (10.6)
SM	32 (5.3)
Suspicious for papillary carcinoma	32 (5.3)
Malignant	38 (6.3)
Papillary carcinoma	34 (5.6)
Follicular variant of papillary carcinoma	3 (0.5)
Medullary carcinoma	1 (0.2)

Abbreviations: AUS/FLUS: Atypia of undetermined significance/follicular lesions of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; SM: Suspicious for malignancy; FNAC: Fine-needle aspiration cytology.

603 FNAC cases, 392 cases underwent surgery and corresponding final histopathological diagnoses were available. The distribution of 392 FNAC cases is shown in Table 2. The correlation of 392 cases of FNAC diagnoses with corresponding histopathological diagnoses was done. The malignancy rates of 6 tier Bethesda categories are shown in Table 3.

Of the total FNAC (603) cases, 16 were nondiagnostic. Of these, 10 had subsequent surgical resection specimens. None of them showed malignancy on HPE; the malignancy rate for the nondiagnostic category was 0%.

Of the cases, 393 were classified as a benign category. Among these, 256 had follow-up histopathology and three cases were turned out to be follicular carcinoma. The overall malignancy rate for the benign category was 0.8%.

Of the 60 cases of AUS/FLUS, 41 had follow-up histopathology. Of these, 10 cases were diagnosed as follicular carcinoma; thus malignancy rate for AUS/FLUS category was 24.4%.

We classified 64 cases as FN/SFN among 603 FNACs. Of these, 45 had follow-up histopathology. Of these 45 cases, 13

were turned out to be follicular carcinoma; thus malignancy rate for FN/SFN category was 28.9%.

Twenty-four out of 32 cases of SM were available for HPE. Of these, 16 cases were found to be papillary carcinoma, and 1 case was diagnosed as follicular carcinoma; thus malignancy rate for SM category was 70.8%.

We categorized 38 cases as malignant among 603 cases. Of these, 16 had follow-up histopathology. All 16 cases were found to be malignant with 14 cases of papillary carcinoma, 1 case of follicular variant of papillary carcinoma, and 1 case of medullary carcinoma; thus the malignancy rate for malignant category was 100%.

Table 2 – Distribution of FNAC diagnoses who undergone surgical intervention (n = 392).

Diagnostic category	Number of cases (%)
Nondiagnostic	10 (2.6)
Benign	256 (65.3)
Nodular colloid goiter	118 (30.1)
Hashimoto's thyroiditis	117 (29.8)
Adenomatoid nodule/nodular hyperplasia	21 (5.4)
AUS/FLUS	41 (10.5)
FN/SFN	45 (11.5)
FN	45 (11.5)
SM	24 (6.1)
Suspicious for papillary carcinoma	24 (6.1)
Malignant	16 (4.1)
Papillary carcinoma	14 (3.5)
Follicular variant of papillary carcinoma	1 (0.3)
Medullary carcinoma	1 (0.3)

Abbreviations: AUS/FLUS: Atypia of undetermined significance/follicular lesions of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; SM: Suspicious for malignancy; FNAC: Fine needle aspiration cytology.

Discussion

Thyroid enlargement is a common occurrence in the most regions of the world. In India, the sub-Himalayan region has the world's biggest goiter belt [13]. Thyroid enlargement regardless of being diffuse or nodular should be investigated mainly to rule out the possibility of a neoplasm or thyroiditis. FNAC is usually the first line of investigation and other investigations such as ultrasound, thyroid profile, thyroid scan, and serology are done subsequently with an aim to select the patients who require surgical management and those require medical management [14,15].

Reviewing of the FNAC slides in our study using 6 tier diagnostic categories of Bethesda system, it seemed more simplified, systematic, with great clarity; thus, it would be more useful in guiding clinicians toward the management of thyroid nodules [16]. We recognized that distribution of the FNAC diagnoses of thyroid lesions using Bethesda system in our institution showed slightly different statistical values when compared with published studies [9–11,17–23], that are shown in Table 4. The benign, SM, and malignant categories of our study were comparable to frequencies found by the most of the published studies. However, the percentages of AUS/FLUS, and FN/SFN categories were significantly higher than other studies with a low percentage of a nondiagnostic category [Table 4]. The heterogeneity and subjectivity could be the reason for the higher percentage of AUS/FLUS category. Our institute is a tertiary care center and we have a high number of referral patients who had been given an inconclusive

Table 3 – Correlation of FNAC and histopathological diagnoses and malignancy rate on surgically resected specimen for Bethesda categories (n = 392).

FNAC	Diagnostic category	Number of cases	Histopathological diagnoses					Malignancy rate (%)	
			Benign	Follicular adenoma	Hurthle cell adenoma	Follicular carcinoma	PCT		Follicular variant of PCT
Nondiagnostic	10	9	1	–	–	–	–	–	0
Benign	256	237	16	–	3	–	–	–	0.8
AUS/FLUS	41	7	24	–	10	–	–	–	24.4
FN/SFN	45	1	30	1	13	–	–	–	28.9
SM	24	7	–	–	1	16	–	–	70.8
Malignant	16	–	–	–	–	14	1	1	100
Total	392	261	71	1	27	30	1	1	

Abbreviations: FNAC: Fine-needle aspiration cytology; AUS/FLUS: Atypia of undetermined significance/follicular lesions of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; SM: Suspicious for malignancy; PCT: Papillary carcinoma of thyroid.

Table 4 – Comparison of the distribution of Bethesda diagnostic categories of the present study with published studies.

Study	Year	Number of cases	Nondiagnostic (%)	Benign (%)	AUS/FLUS (%)	FN/SFN (%)	SM (%)	Malignant (%)
Jo et al. [9]	2009	3080	18.6	59	3.4	9.7	2.3	7
Mondal et al. [10]	2012	1020	1.2	87.5	1	4.2	1.4	4.7
Mufti and Molah [11]	2010	250	11.6	77.6	0.8	4	2.4	3.6
Park et al. [17]	2011	1730	13.3	40.6	9.1	0.4	19.3	17.3
Williams et al. [18]	2010	1481	28.9	45.7	18.8	4.4	1.3	0.9
Theoharis et al. [19]	2008	3207	11.1	73.8	3	5.5	1.4	5.2
Al-shraim et al. [20]	2007	323	6.2	57.3	13.6	16.1	1.5	5.3
Nayar and Ivanovic [4]	2006	5194	5	64	18	6	2	5
Yang et al. [21]	2005	4703	10.4	64.6	3.2	11.6	2.6	7.6
Yassa et al. [22]	2004	3589	7	66	4	9	9	5
Present study	2014	603	2.7	65.3	10	10.6	5.3	6.3

Abbreviations: AUS/FLUS: Atypia of undetermined significance/follicular lesions of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; SM: Suspicious for malignancy.

diagnosis in other hospitals. This could have been resulting in a high number of FN/SFN cases in our study. The reason for the low frequency of nondiagnostic category can be attributed to the fact that, in our institute, ultrasound-guided FNAC was performed for small nodules and it was done by well trained and experienced pathologists.

We found malignancy rates of thyroid lesions in our study were comparable with those mentioned in the Bethesda system and also with published studies in most categories. The malignancy rate of the nondiagnostic category of our study was 0% similar to Mondal et al. study [10] and it was the higher in most of the previous studies [17,18,21]. The malignancy rate of the benign category was 0.8% similar to Bethesda system, Jo et al., Yang et al., and Yassa et al. studies [8,9,21,22]. The malignancy rate of AUS/FLUS category (24.4%) was the higher than those reported in the TBSRTC guidelines and few other studies [4,8]. A study done by Layfield et al. [23] found that there is a wide variation in the malignancy rate for AUS/FLUS category diagnoses between the different institution and among cytopathologists within the same institution, depending on whether they had received cytopathology fellowship training. Cibas et al. [8] stated that AUS/FLUS category may never have good inter-observer reproducibility, even after pathologists familiarize themselves with the criteria. We had a histopathological specimens of 41 out of 60

FNAC cases, thus the malignancy rate of AUS/FLUS in our study may approximate the true malignancy risk for AUS/FLUS. Some studies observed that the use of liquid-based cytology can improve the diagnostic accuracy of AUS/FLUS. The ultrasonographic findings such as hyper-echogenicity, irregular nodule borders, calcifications, and vascular abnormalities are the features of malignancy [23]. Hence, AUS/FLUS category patients in our setup warrant further workup including ultrasound and/or thyroid scan in addition to immediate repeat FNAC.

The malignancy rate of FN/SFN, SM, and malignant categories (28.9%, 70.8%, and 100% respectively) was similar to most published studies [8–11,17–22], [Table 5]. The most of the follicular carcinoma diagnosed in our study were classified as AUS/FLUS and FN/SFN. Hence, this study reinforces the follicular neoplasm fall into AUS/FLUS or FN/SFN group since cytology cannot detect capsular or vascular invasion to differentiate follicular adenoma from carcinoma.

Even though this study provides useful information, there are few limitations.

1. Clinico-radiological and biochemical correlation were not available as it is a retrospective study.
2. The quality of staining was not good in some slides; hence, we felt some difficulty in reporting of FNACs.

Table 5 – Comparison of the malignancy rates by FNAC category of present study, Bethesda system and published studies.

Study	Year	Number of cases	Nondiagnostic (%)	Benign (%)	AUS/FLUS (%)	FN/SFN (%)	SM (%)	Malignant (%)
Bethesda system [8]	–	–	1–4	0–3	5–15	15–30	60–75	97–99
Jo et al. [9]	2009	892	8.9	1.1	17	25.4	70	98.1
Mondal et al. [10]	2012	323	0	4.5	20	30.6	75	97.8
Mufti and Molah [11]	2010	84	20	3.1	50	20	80	100
Park et al. [17]	2011	1547	35.3	5.6	69	50	98.7	98.9
Williams et al. [18]	2010	388	18.2	16	24.7	32.6	94.1	100
Theoharis et al. [19]	2008	378	–	9.8	48	34	87	100
Al-shraim et al. [20]	2007	323	35	10.3	15.9	32.7	60	94
Nayar and Ivanovic [4]	2006	1413	9	2	6	14	53	97
Yang et al. [21]	2005	1052	10.7	0.7	19.2	32.2	64.8	98.4
Yassa et al. [22]	2004	1242	10	0.3	24	28	60	97
Present study	2014	392	0	0.8	24.4	28.9	70.8	100

Abbreviations: AUS/FLUS: Atypia of undetermined significance/follicular lesions of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; SM: Suspicious for malignancy; FNAC: Fine-needle aspiration cytology.

Conclusion

Our study validated the efficacy of TBSRTC. In conclusion, the malignancy rate of AUS/FLUS in this study was the higher than the risk mentioned in TBSRTC and other published studies. Hence, AUS/FLUS category patients in our setup warrant further workup including ultrasound and/or thyroid scan in addition to immediate repeat FNAC. Using this reporting system can improve the communication between the pathologists and clinicians and allows easy and reliable sharing of data between institutions and laboratories.

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