Original Research Article

Cytomorphological spectrum of thyroid lesions using Bethesda system of reporting with Histopathological correlation: A study of 87 cases

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Abstract

Introduction: The primary objective of evaluation of the thyroid lesions by FNAC is to distinguish the majority of benign from malignant lesions. To standardize the reporting system for thyroid FNA, NCI hosted a multidisciplinary Thyroid State of the Science Conference in Bethesda, in October 2007, providing a uniform and pertinent reporting nomenclature.

Aim and Objectives: To assess the effectiveness of FNAC by using Bethesda system of reporting in the evaluation of thyroid lesions.

Materials and Methods: This study included smears from all thyroid FNACs performed over a period of 6 months. FNA smears were reported according to the 6 diagnostic categories of TBSRTC. We could pursue follow up histology for 24 cases. The diagnosis offered in FNAC was compared with that observed on histopathology.

Results: We received 87 cases, out of which 9 were males and 78 were females with male to female ratio of 1:8.6. Benign lesions constituted 74.7% and malignant lesions 4.6%. Bethesda category I included 4.6% cases, category II 74.7% cases, category III 3.4% cases, category IV 10.3% cases, category V 2.3% cases and category VI 4.6% cases. Category I had no follow up cases, so the rate of malignancy could not be assigned. On histopathological examination, the rate of malignancy of category II was 6.6%, category III 50%, category IV 66.6%, category V 100% and category VI 100%.

Conclusion: The Bethesda System is a very useful and reproducible system of reporting thyroid cytopathology and also guides the clinicians for consistent management approach thereby preserving the credibility of reporting.

Introduction

Thyroid diseases are frequently encountered in India with a prevalence of a palpable thyroid nodule approximately 12.2%.[1] Consequently, fine needle aspiration cytology of the thyroid has proven to be an important and widely accepted cost effective, safe, simple and accurate method for triaging patients with thyroid nodules.[2] The primary objective of initial evaluation is to distinguish the majority of benign from those that are malignant and require removal so as to limit the morbidity and mortality.[3] However, FNA has limitations like sampling difficulties, which sometimes result in "non- diagnostic" aspirates and also there is significant overlap in morphologic features between various lesions, which can result in abnormal but non- conclusive results.[4,5]

In an attempt to standardize the reporting system for thyroid FNA, The National Cancer Institute (NCI) hosted a multidisciplinary Thyroid State of the Science Conference in Bethesda, Maryland, in October 2007.[6] The consensus from this conference suggested a 6 tier reporting system, with the use of Atypia of undetermined significance, Suspicious for follicular neoplasm/ suspicious for Hurthle cell neoplasm and Suspicious for malignancy- to report thyroid aspirates that fall between benign and malignant categories and thus, standardizing the cytology reporting for thyroid lesions, providing a uniform, explicit and clinically pertinent reporting nomenclature.[7]

Each category carries its own risk of malignancy ranging from 0-3% for benign category to 97-99% for malignant category.[8]

The present study was undertaken to assess the effectiveness of FNAC by using Bethesda system of reporting, in the evaluation of thyroid lesions on the basis of adequacy, cellularity and their cytomorphological features and also to compare the results with histopathological examination of the specimens that could be received.

Materials and Methods

This study included smears from all thyroid FNACs performed over a period of 6 months (January 2017 to July 2017). After taking consent, the patient was made to lie down in supine position with neck hyper-extended and was asked to refrain from swallowing during the procedure. The skin overlying the swelling was cleaned with alcohol and

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FNAC was done using 22-23 gauge disposable needle attached to a 20 ml plastic disposable syringe. Smears were prepared, air dried and fixed.MGG staining was done and FNA smears were studied for their adequacy, cellularity and cytomorphological features along with their relevant clinical and radiological details and were reported according to the 6 diagnostic categories of TBSRTC.[8] The 6 categories are-

1. Non diagnostic/ Unsatisfactory. (ND/UNS)
2. Benign
3. Atypia of Undetermined significance/ Follicular lesion of undetermined significance. (AUS/ FLUS)
4. Follicular Neoplasm/Suspicious for follicular neoplasm/ Follicular Neoplasm Hurthle cell type/ Suspicious for Follicular Neoplasm Hurthle cell type. (FN/ SFN/ FN HCT/ SFN HCT)
5. Suspicious for Malignancy. (SM)
6. Malignant

We could pursue follow up histology for 24 cases. The diagnosis offered in FNAC was compared with that observed on histopathological examination.

Results

We received 87 cases, out of which 9(10.3%) were males and 78(89.6%) were females with male to female ratio of 1:8.6.

The age of patients ranged from 10 years to 70 years with a mean age of 31.1 years. Maximum number of cases were seen in the age group of 11- 30 years.

Out of 87 cases, Bethesda category I included 4 cases (4.6%), out of which 3(75%) aspirates had only blood and in 1(25%) only fluid was aspirated. Category II included 65 cases (74.7%), out of which 32(49.2%) were of colloid goiter. These cases had scant cellularity comprising of flat monolayered sheets of benign follicular cells interspersed in colloid filled background. There was minimal nuclear crowding and overlapping with almost absent microfollicle formation. [Fig. 1] 27(41.5%) cases were that of lymphocytic thyroiditis comprising of cellular smears with mixed population of thyroid follicular epithelial cells, Hurthle cells and polymorphous lymphoid cells which were dispersed as isolated cells or interspersed within the follicular cell clusters. 6(9.2%) cases were of primary hyperplasia with smears showing benign follicular cells arranged in flat monolayered sheets, showing mild pleomorphism but without any atypia. Minimal crowding and overlapping were noted in 3 cases. All cases revealed fire flares. Category III included 3(3.4%) cases, out of which 2 were sparsely cellular smears having follicular cells in microfollicular arrangement without significant atypia [Fig. 2] and 1 had a cellular smear with macrofollicles and few microfollicles without significant atypia. Colloid was absent in all cases. Category IV included 9(10.3%) cases. Out of these 9 cases, 8 had moderate to marked cellularity composed of uniform follicular cells arranged in crowded clusters and repetitive pattern of microfollicles with significant overlapping and atypia devoid of colloid[Figure 3] and 1 case had markedly cellular aspirate comprising of predominantly Hurthle cells with dysplasia, colloid free

background and absent lymphocytes. Category V included 2(2.3%) cases both of which had sparse cellularity with follicular cells arranged in sheets or dispersed in small clusters having nuclear enlargement, pale chromatin, overlapping and moulding with presence of nuclear grooves in a few cells. Colloid was absent and papillary architecture, nuclear pseudo inclusions and psamomma bodies were not seen. They were reported as suspicious for papillary carcinoma. Category VI included 4(4.6%) cases, 3(75%) out of which were reported as papillary thyroid carcinoma. These cases had marked cellularity with papillary architecture, cells were having nuclear enlargement, pale powdery chromatin, overlapping and moulding with nuclear grooves and pseudo inclusions in a colloid free background. However there were no psamomma bodies in any of these cases [Fig. 4]. 1(25%) was reported as medullary thyroid carcinoma with smears showing marked cellularity comprising of plasmacytoid and spindle shaped cells with mild pleomorphism, few binucleate cells, granular cytoplasm and presence of amyloid, colloid was absent. [Fig. 5][Table 1]

We could receive only 24 cases for histopathological examination since benign lesions usually don't undergo surgical management unless suspicious clinically or radiologically.

Out of the 4 cases reported as ND/UNS, follow up histology was available for none, so the rate of malignancy couldn't be assigned. One patient came for follow up FNAC and was diagnosed colloid goiter subsequently. From the 65 cases reported as benign, follow up histology of 15 was available, from which 14 were benign and 1 turned out to be Follicular adenoma, so the rate of malignancy for this category came out to be 6.7%. Of the 4 cases reported as AUS/FLUS, we received follow up histology of only 2, out of which 1 was reported as colloid goitre and the other was reported as Follicular adenoma on histopathological examination, resulting in the rate of malignancy of 50% for this category. Out of 9 cases reported under the category FN/SFN/FN HCT/ SFN HCT, follow up histology of 3 were received, 1 out of which was reported as Adenomatoid hyperplasia, other was reported as follicular adenoma and the last one reported as follicular neoplasm- Hurthle cell type with indeterminate malignant potential, giving the malignancy rate for this category to be 66.6%. Of the 2 cases reported as suspicious for malignancy (papillary carcinoma), histology of only 1 case was received which turned out to be Follicular variant of papillary carcinoma, so the malignancy rate for this category was 100%. Out of 4 cases reported as malignant on FNAC, 3 were received for follow up histology. Out of these, 2 were papillary thyroid carcinoma and 1 was medullary thyroid carcinoma, giving a malignancy rate of 100% and cytohistologic concordance of 100%. [Table 2]

Discussion

Thyroid enlargement is a common occurrence in most of the regions of the world with sub Himalayan region comprising the world's biggest goitre belt.[9] FNAC is the first line of diagnostic test for evaluating thyroid nodules and can effectively triage patients with thyroid nodules as to who require surgery and who do not.[10] However a consistent and homogenous reporting terminology for the diagnosis of thyroid FNA was deficient which led to the introduction of TBSRTC in October 2007.[11]

In our study using 6 diagnostic categories of the Bethesda System, the reporting of thyroid FNAs seemed more simplified and systematic and thus, helped guiding the clinicians towards better management of the thyroid nodules. Out of the total 87 cases, 9(10.3%) were males and 78(89.6%) were females with the male to female ratio of 1:8.6 and the maximum number of cases were in the age group of 11- 40 years. These results being almost similar to studies done by Awasthi et al[12] and Reddy et al.[11] The distribution of the FNAC diagnosis of thyroid lesions by using Bethesda system in our institution was compared with the studies done by Yassa et al,[3] Yang et al,[13] Nayar et al,[7] Theoharis et al,[14] Jo et al,[15] Mufti et al,[16] Williams et al,[17] Mondal et al,[18] Arul et al,[10] Reddy et al.[11] [Table 3] Our results were in close approximation with that of Nayar R et al[7] However, our results showed slight to marked variations with other studies.[3,13-18,10,11] This could be because our sample size was smaller than the rest of the studies.

The malignancy rate of ND category could not be assessed because out of 4 cases of FNAC, none was available for histopathological follow up, rather there was 1 case which came for follow up FNAC after 5 months of its initial procedure and was diagnosed as colloid goitre subsequently. The rate of malignancy for benign category was observed to be 6.7% which is almost similar to the study of Theoharis et al.[14] The malignancy rate of AUS/FLUS category was 50%, compatible with the studies of Mufti et al,[14] Theoharis et al.[14] The malignancy rate of FN/SFN/FN HCT/ SFN HCT category was 66.5% which was higher in comparison to other studies and could be due to a low sample size and even less number of histopathological follow up in our study. The rate of malignancy of suspicious for malignant category was 100% which was slightly higher than that observed by Williams et al.[17] The malignancy rate of malignant category was observed to be 100% which is compatible with the studies of Theoharis et al,[14] Mufti et al,[16] Williams et al,[17] Jo et al.[15] [Table 4]

The rate of malignancy in our study was somewhat higher for a few categories as compared to other studies and can be well explained with the fact that in our study there was small sample size and further less number of histologic follow up, leading to a smaller denominator and thus the malignancy rate for ND, Benign and SFM could not be accurately compared.

However, despite a good reproducibility of The Bethesda system of reporting thyroid nodules, there are a few difficulties. Unlike categories benign and malignant, there are certain categories which have many inter observer variations and overlapping features leading to difficulty in assigning them a particular category. The AUS/FLUS categorization of a lesion in this regard is heterogeneous and very subjective. The other grey zone, is the distinction between follicular hyperplasia, follicular patterned neoplasm having overlapping cytomorphological features, sometimes leading in difficulty to confidently categorize them either as benign or FN/SFN, so we relied on the presence of good cellularity and repetitive microfollicular pattern to categorize them into category IV. Another controversial aspect deals with the follicular patterned neoplasm having good cellularity with predominance of Hurthle cells for which the differential is hyperplasia in the setting of an adenomatous or thyroiditis gland versus a Hurthle cell neoplasm, especially if the specimen is composed exclusively of Hurthle cells without atypia(dysplasia) and without colloid. Some cytopathologists categorize them as FNHCT/SFN HCT and others as benign.[7,19] Similarly the differentiation between SM and Malignant is not clearly demarcated and depends to some extent on the confidence and experience of the pathologist.[7]

In our study, however we had a case with predominant Hurthle cells having small and large cell dysplasia with colloid in the background and was diagnosed as FN HCT/ SFN HCT on FNAC. On follow up histopathological examination the same was diagnosed as Follicular neoplasm Hurthle cell type of undetermined malignant potential with questionable capsular invasion.

Our study had a few limitations:
1. Biochemical correlation could not be done as thyroid serology of most of the patients could not be done.
2. Our sample size was small and histology of all cases could not be done which led to a higher malignancy rate for most of the categories.

Table 1: Distribution of cases according to the Bethesda category of reporting thyroid cytopathology.

Category	Distribution of Cases
I. Unsatisfactory/ Non Diagnostic	4.6%
II. Benign	74.7%
Colloid goiter	49.2%
Lyphocytic thyroiditis	41.5%
Primary hyperplasia	9.2%
III. Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance	3.4%

IV. Follicular Neoplasm/ Suspicious For Follicular Neoplasm/ Follicular Neoplasm Hurthle Cell Type/ Susupicious For Follicular Neoplasm Hurthle Cell Type	10.3%
V. Suspicious for Malignancy	2.3%
VI. Malignant	4.6%
Papillary thyroid carcinoma	75%
Medullary thyroid carcinoma	25%

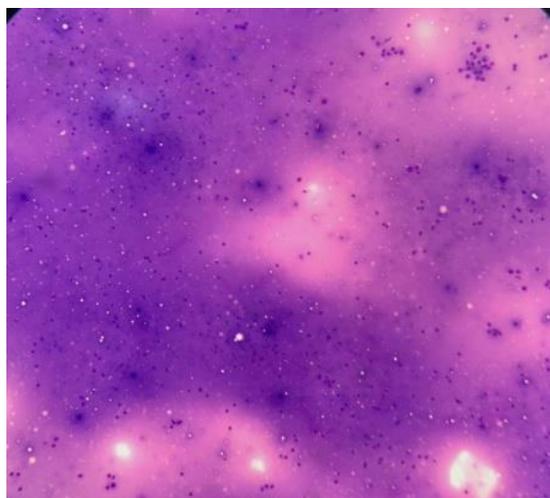**Table 2:** Table showing cytohistologic correlation and rate of malignancy for each category.

FNAC		Histopathological Diagnosis										Malignancy Rate (%)
Bathesda category	No. of cases	Histology received	Benign	Follicular adenoma	Hurthle cell adenoma	Follicular cracinoma	Hurthle cell carcinoma	Papillary carcinoma	Follicular variant of papillary carcinoma	Medullary carcinoma		
ND/UNS	04	00	-	-	-	-	-	-	-	-		-
BENIGN	65	15	14	01								6.6
AUS/FLUS	03	02	01	01								50
FN/SFN/FN HCT/SFN HCT	09	03	01	01	01							66.6
SM	02	01							01			100
MALIGNANT	04	03						02		01		100
Total	87											

Table 3: Comparison of the distribution of Bethesda diagnostic categories of the present study with published studies.

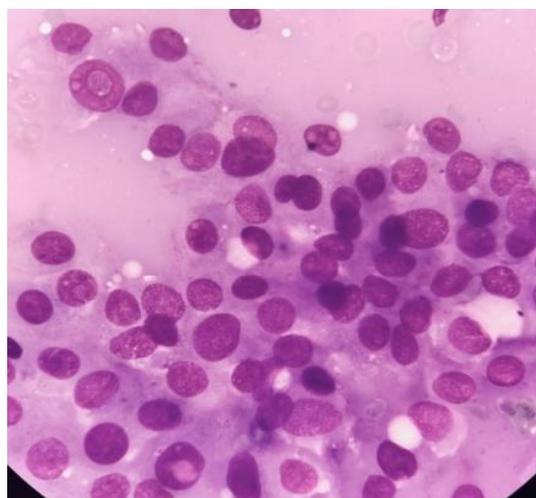| Study	Year	No. of cases	UNS/ ND (%)	BENIGN (%)	AUS/FLUS (%)	FN/SFN/FN HCT/SN HCT (%)	SM (%)	MALIGNANT (%)
Yassa et al[3]	2004	3589	7	66	4	9	9	5
Yang et al[13]	2005	4703	10.4	64.6	3.2	11.6	2.6	7.6
Nayar et al[7]	2006	5194	5	64	18	6	2	5
Theoharis et al[14]	2008	3207	11.1	73.8	3	5.5	1.4	5.2
Jo et al[15]	2009	3080	18.6	59	9.7	9.7	2.3	7
Mufti et al[16]	2010	250	11.6	77.6	4	4	2.4	3.6
Williams et al[17]	2010	1481	28.9	45.7	4.4	4.4	1.3	0.9
Mondal et al[18]	2012	1020	1.2	87.5	4.2	4.2	1.4	4.7
Arul et al[10]	2014	603	2.7	65.3	10.6	10.6	5.3	6.3
Reddy et al[11]	2017	484	3.7	89.2	0.002	2	0.6	4.1
Present study	2017	87	4.6	74.7	10.3	10.3	2.3	4.6

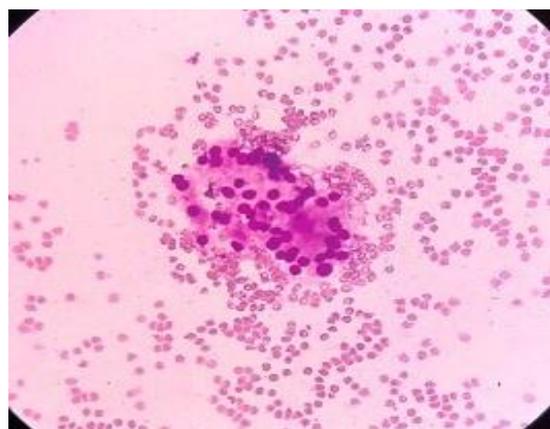**Table 4:** Comparison of the Rate of malignancy of each Bethesda category of our study with the previous studies.

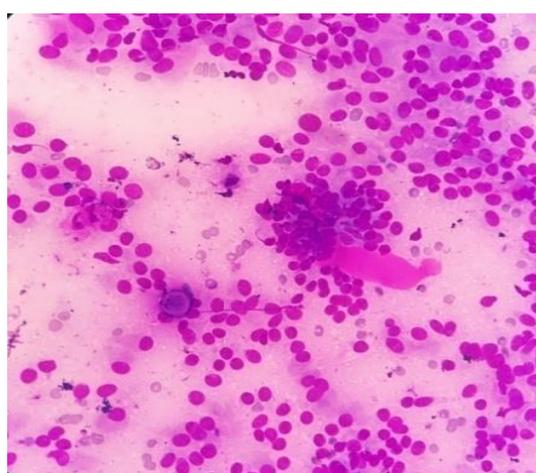| Study	Year	No. of cases	UNS/ND (%)	BENIGN (%)	AUS/FLUS (%)	FN/SFN/FN HCT/SF HCT (%)	SM (%)	MALIGNANT (%)
Yassa et al[3]	2004	1242	10	0.3	24	28	60	97
Yang et al[13]	2005	1052	10.7	0.7	19.2	32.2	64.8	98.4
Nayar et al[7]	2006	1413	9	2	6	14	53	97
Theoharis et al[14]	2008	378	-	9.8	48	34	87	100
Jo et al[15]	2009	892	8.9	1.1	17	25.4	70	98.1
Mufti et al[16]	2010	84	20	3.1	50	20	80	100
Williams et al[17]	2010	388	18.2	16	24.7	32.6	94.1	100
Mondal et al[18]	2012	323	0	4.5	20	30.6	75	97.8
Arul et al[10]	2014	392	0	0.8	24.4	28.9	70.8	100
Present study	2017	24	-	6.6	50	66.5	100	100

Fig. 1: Colloid goiter, smear having scant cellularity of benign follicular cells interspersed in colloid filled background. (MGG stain, 10X)
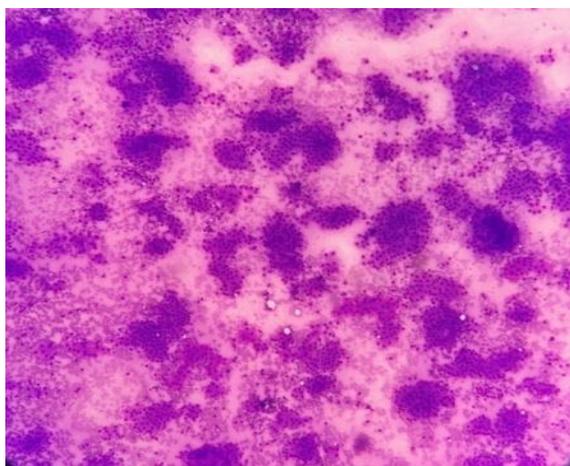

Fig. 2: Atypia of undetermined significance, smear having scant cellularity with thyroid follicular cells in microfollicular arrangement showing nuclear overlapping, crowding. (MGG stain,40X)

Fig. 3: Suspicious for follicular neoplasm, smear having high cellularity containing uniform follicular cells in clusters with predominance of microfollicles. (MGG stain,10X)

Fig. 4: Papillary thyroid carcinoma, smear showing thyroid follicular cells with intranuclear peseudoinclusions, nuclear grooves and nuclear moulding. (MGG stain,100X)

Fig. 5: Medullary thyroid carcinoma, smear with moderate cellularity showing spindle cells, mild pleomorphism and amyloid. (MGG stain,40X)

Conclusion

The Bethesda System is a very useful and reproducible system of reporting thyroid cytopathology and also guides the clinicians for consistent management approach thereby preserving the credibility of reporting. Further each category carries its own risk of malignancy, reflecting the importance of categorization to ensure proper follow up and management. Thus, we strongly recommend its application in day to day reporting of thyroid lesions.

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