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Original article:

Diagnostic role of the Bethesda system for reporting thyroid cytopathology in an academic institute of Central India: one year experience

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Abstract

Context: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has put an effort to overcome personalized usage of descriptive terminologies in thyroid aspiration smears.

Aims: The objective of this study was to interpret thyroid cytology by TBSRTC, to look for distribution of diagnostic categories and subcategories according to age and sex and to correlate the cytopathology with histopathology, whenever possible.

Methods and Material: This was a prospective study of 151 fine needle aspirations (FNA) of thyroid nodules. All fine needle aspiration cytology (FNAC) diagnoses were interpreted according to TBSRTC into nondiagnostic/unsatisfactory (ND/UNS), benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious of a follicular neoplasm (FN/SFN), suspicious for malignancy (SFM), and malignant. Histological correlation was done, when surgical material was available.

Key-words: Fine Needle Aspiration, Thyroid, Bethesda.

Introduction:

Fine needle aspiration cytology (FNAC) is considered as the first line investigation apart from other investigations like ultrasonography (USG), thyroid function tests, thyroid scan, and antibody levels for the primary evaluation of the patients [1]. It effectively distinguish thyroid lesions suitable for surgical resection with those that can be managed conservatively.[2] FNAC being minimally invasive and cost-effective is extremely useful in reducing unnecessary surgery for patients with benign disease. However, FNA interpretation suffers from personalized usage of descriptive terminologies.[3] In addition, there was never an effective linkage between the clinical management plans and thyroid FNA reporting, thus undermining the clinical utility of cytopathologic diagnoses. A confusion exist for the terms in FNA reporting like "atypical," "indeterminate," "suspicious," and "nondiagnostic" for which clinicians correlate and go for "negative FNAC/follow-up," "repeat FNAC," and "proceed to surgery."[4] In order to overcome the misinterpretation and to bridge this gap of communication National Cancer Institute (NCI) hosted "The NCI Thyroid Fine Needle Aspiration State of the Science Conference" at Bethesda, Maryland. The 2-day "live" conference in 2007 gave the committees an in-depth opportunity to present their conclusions and debate controversial areas.

One of the recommendations endorsed by this program was the establishment of a six-tiered diagnostic classification system based on a probabilistic approach, *"THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOLOGY"*[3].

TBSRTC has six distinct diagnostic categories (Table.1) and is constructed on the concept of the

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probability of finding malignancy in each diagnostic category. (Table. 2)[3] Each category has an implied risk of malignancy which ranges from 0% to 3% for the "benign" category to virtually 100% for the "malignant" category. Those aspirates that fall between benign and malignant were considered in AUS/FLUS, SFN/H¨urthle cell neoplasm, and SFM. As a function of these risk associations, individual category is linked to evidence based clinical management plans. The objective of the present prospective study, done in a tertiary care centre of central India, was to intrepret thyroid cytology smears by TBSRTC into various diagnostic categories,to determine distribution of diagnostic categories and subcategories according to age and sex, conveying brief management plan to the clinicians and its correlation with histopathology, whenever possible.

Table .1: The Bethesda System for Reporting Thyroid Cytopathology: Diagnostic categories.

I.	**Non diagnostic or Unsatisfactory** Cyst fluid only, Virtually acellular smear, Other (obscuring blood, clotting artefact etc)
II.	**Benign** Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule etc). Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context. Consistent with granulomatous (sub acute) thyroiditis and Others
III.	**Atypia of Undetermined significance/ Follicular lesion of Undetermined significance(AUS/FLUS)**
IV.	**Follicular neoplasm or suspicious for a follicular neoplasm (SFN)** Specify if Hürthle cell (oncocytic) type
V.	**Suspicious for malignancy (SFM)** Suspicious for papillary carcinoma. Suspicious for medullary carcinoma. Suspicious for metastatic carcinoma. Suspicious for lymphoma.
VI.	**Malignant** Papillary thyroid carcinoma. Poorly differentiated carcinoma. Medullary thyroid carcinoma. Undifferentiated (anaplastic) carcinoma. Squamous cell carcinoma. Metastatic carcinoma Non Hodgkin lymphoma and Others

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Table .2: TBSRTC: Implied risk of malignancy and recommended management

Diagnostic Category	**Risk of malignancy (in %)**	**Management plan**[a]
I	1-4	Repeat FNA with ultrasound guidance
II	0-3	Clinical follow up
III	~5-15[b]	Repeat FNA
IV	15-30	Surgical lobectomy
V	60-75	Surgical lobectomy Or Near total thyroidectomy[c]
VI	97-99	Near total thyroidectomy[c]

a Actual management may depend on other factors (e.g., clinical and sonographic) besides the FNA interpretation.

b Estimate extrapolated from histopathologic data from patients with "repeated atypicals".

c In the case of "suspicious for metastatic tumour" or a "malignant" interpretation indicating metastatic tumour rather than a primary thyroid malignancy, surgery may not be indicated.

Material and methods:

The study had been conducted in patients referred to cytopathology section of pathology department in Mahatma Gandhi Medical College, Indore (M.P). The study design is prospective and spans duration from 1st October 2014 to 30th September 2015. Inclusion criteria considered were (i) Age 11 to 70 years (ii) Both genders (iii) Patients presenting with newly thyroid swelling or recurrence after a previous thyroid surgery. Patients presenting with any other neck swelling or bleeding disorder were excluded from the study. Patient's relevant history was taken and examination was done. Pre-FNAC requirements as recommended by Committee I of the NCI State of the Science Conference, Bethesda, were followed. The smears were prepared using conventional methods and stained with Papanicolaou stains. The cytological features were interpreted and reported according to TBSRTC. The risk of malignancy and recommended clinical management for each diagnostic category were communicated to the clinicians along with the report. Surgical specimens, wherever available, were processed and correlated with their FNA interpretations.

Statistics:

SPSS version:20 software was used in this study for Statistical analysis. *P*-value < 0.05 was conside-red significant while assessing correlation between two parameters. Considering histopathology as gold standard, sensitivity, specificity, positive predictive value and negative predictive value were calculated. While calculating statistical parameters, AUS/FLUS cases were excluded as non definitive diagnosis and categories "SFM" and "malignant" were considered as one unit. All the parameters were calculated either excluding FN/SFN or including it with either benign or malignant diagnosis to compare the effect on statistical values.

Results:

Study includes 151cases with majority being female (86.75%). Maximum cases were found in 21-40 yrs of age. Female: male ratio was 6.55. Long standing history of midline neck swelling, mainly diffuse and nodular in few cases, was the main presenting symptom. Less common

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complain were pain in the neck region, dysphagia and rarely hoarseness of voice and cough. There was no association of malignant lesion with gender (p value =0.448) but there was association of malignant lesion with higher age group (p value=0.038). The distribution of 151 cases is shown in Table 3.

Category I: The totals of 17 patients (11.26%) were diagnosed under nondiagnostic or unsatisfactory category. Some cases were subcategorized as haemorrhagic (6.62 %) and some as cyst fluid only (4.64 %) (Figure.1). No virtually acellular specimen was found.

Category II: It included most of the study cases with 116 cases (76.82% cases of total). It consist of cases consistent with benign follicular nodule (includes adenomatoid nodule, colloid nodule) with 98 cases (64.90%), lymphocytic thyroiditis with 8 cases (5.30%), granulomatous thyroiditis with 9 cases (5.96%) and one case of acute thyroiditis (0.66%).

Category III: It includes lesions which were indefinite for being benign or malignant. We have no case diagnosed in this category.

Category IV: It includes 14 cases (9.27%) of suspicious of follicular neoplasm (SFN).

Category V: It includes only 1 case (0.66%) which was further subcategorized in suspicious of papillary carcinoma.

Category VI: It included 3 cases (1.99%), each comprising of papillary thyroid carcinomas, poorly differentiated carcinoma and medullary carcinoma of thyroid.

Out of 151 cytologically studied cases, histopathological specimens of 16 (10.59 %) cases were followed up. (Table.4).

Table.3: Distribution of cases according to the diagnostic categories of TBSRTC in various age groups and both the genders

Age	**Female**	**Male**	**I**	**II**	**III**	**IV**	**V**	**VI**	**Total cases**
11-20 yrs	10	3	1	12	0	0	0	0	13
21-30 yrs	40	2	4	34	0	4	0	0	42
31-40 yrs	38	4	3	30	0	8	0	1	42
41-50 yrs	23	5	4	21	0	1	0	2	28
51-60 yrs	14	4	3	14	0	0	1	0	18
61-70 yrs	6	2	2	5	0	1	0	0	8
Total cases	131	20	17	116	0	14	1	3	151
Percentage (%)	86.75	13.25	11.26	76.82	0.00	9.27	0.66	1.99	100

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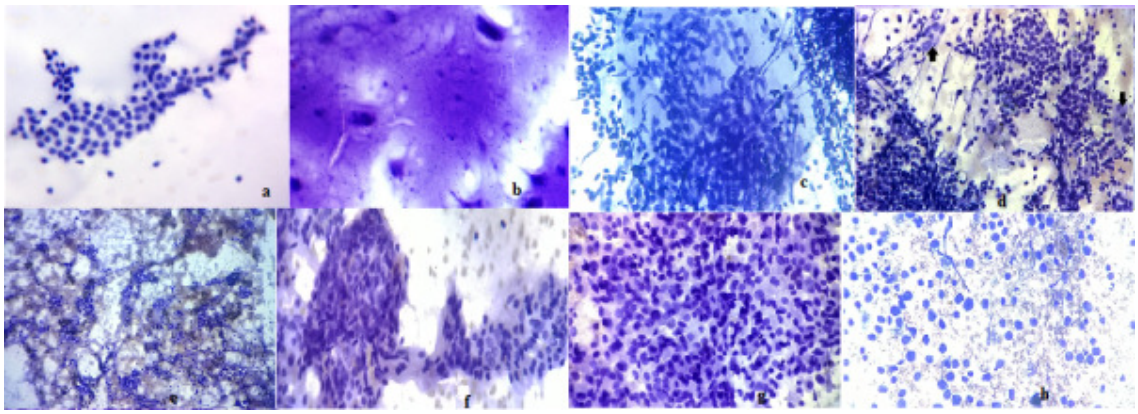

Figure1 shows Pap stained thyroid FNA smear: a: Benign follicular nodule; b: Colloid goiter; c: Granulomatous thyroiditis; d: Lymphocytic thyroiditis; e: Follicular Neoplasm; f: Papillary Carcinoma; g: Medullary Carcinoma; h: Poorly differentiated carcinoma.

Table.4: Cytological/Histological diagnosis correlation

Cytopathological correlation	No. of cases where surgical specimens where received (n=16)	% of the category	Histopathological diagnosis	No. of cases
ND/UNS (n=17)	1	5.88%	Colloid goiter	1
Benign (n=116)	9	7.76%	Colloid goiter	3
			Hashimotos thyroiditis	2
			Multinodular goiter	1
			Follicular adenoma	3
AUS/FLUS(n=0)	0	0	-	0
FN/SFN (n=14)	4	28.57%	Multinodular goiter	1
			Nodular goiter with adenomatous changes	1
			Follicular adenoma	1
			Undifferentiated carcinoma	1
SFM (n=1)	0	0	-	0
Malignant (n=3)	2	66.67%	Papillary carcinoma	1
			Non Hodgkins lymphoma	1

ND/UNS=non diagnostic/unsatisfactory; AUS/FLUS=atypia of undetermined significance/Follicular lesion of undetermined significance; FN/SFN= follicular neoplasm/suspected for a follicular neoplasm; and SFM= suspected for malignancy.

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Discussion:

This study shows the experience of one year in reporting thyroid aspirations by TBSRTC in a tertiary care centre of Central India. Practice guidelines set forth by the American Thyroid Association and National Comprehensive Cancer Network, state that FNA should be used as an initial diagnostic test because of its superior diagnostic reliability and cost- effectiveness, before both thyroid scintigraphy and ultrasonography. [5] Majority of the lesions are benign so interpretation in each case is very crucial for further management. TBSRTC recommend avoiding surgery and go for conservative management for ND/UNS, benign and AUS/FLUS categories and excision of nodules or partial/complete thyroidectomy in the FN/SFN, SFM and malignant categories [6].

Non-aspiration technique was mainly practiced as aspiration technique is associated with low cellularity and more blood. Similar suggestions by different studies like Maurya et al [7] also recommend the non-aspiration technique better for thyroid lesion evaluation by FNAC.Cases failed to meet the adequacy criteria were included in ND/UNS category. A thyroid aspirate is said to be adequate if it contains a 'minimum of six groups with at least ten well-visualized follicular cells preferably on a single slide. Non malignant other cellular components are not included in the adequacy criteria [8]. Exceptions to this requirement include cytological atypia, inflammatory condition and colloid nodules. Samples which are poorly prepared, poorly stained, having obscured follicular cells or containing cyst fluid, with or without histiocytes are included in this category. [6] Cyst fluid may yield only macrophages, but the risk of malignancy is low for these lesions if they are simple and under 3 cm [9].For this category, it is advised to re-aspirate after a minimum period of three months to prevent false positive results due to reactive or reparative changes, as recommended by Committee VI (Post-FNA Technique and Treatment Options) [10].Cases in the non diagnostic category can be reduced by an ultrasound guided FNAC performed for small nodules or nodules that appear heterogeneous on palpation [11].There are recommendations put down by Committee I on indications of thyroid FNA and Committee II on training and credentialing which are likely to reduce the number in this category[12].

Most nodules with an ND/UNS interpretation were proved to be benign[13]. Taking sign and symptoms of the patient into consideration, some clinicians preferred to go for surgery rather than waiting for 3 months for repeat FNA. Benign category comprises the bulk of about 76.82% cases in the present study. Similarly majority of cases were classified in this category by Anand K Verma et al [14] (80.0% cases), Mondal et al [15] (87.5% cases),Vasudha M Bhagat et al [16] (87.5% cases) and Kyungii Lee et al [17] (67.7% cases)In benign follicular nodule, follicular cells were arranged in diffuse evenly spaced sheet with rare microfollicles formation.(Figure.1) Colloid can be thin forming "thin membrane/cellophane" coating (Figure.1) or impart a "crazy pavement," "chicken wire," or mosaic like appearance and when dense often shows cracks. [6]The presence of abundant colloid reliably identifies most benign processes despite scant follicular cells [18]. The subcategory consistent with lymphocytic thyroiditis (LT) had polymorphic lymphoid cells, Hürthle cells (oncocytes) with no intact lymphoid follicles. (Figure.1) The subcategory consistent with granulomatous thyroiditis (GT) had clusters of epithelioid histiocytes with no granulomas formation or multinucleated giant cells (Figure.1) were seen in most of the cases. The subcategory "other" included a case of acute thyroiditis (0.66%). In the

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present study no case was diagnosed as category AUS. AUS is a category of last resort and should not be used indiscriminately [19]. Not much data exists in the literature to support the recommendation that this category should not exceed 7% of all thyroid categories [20]. The incidence also varies with experience and training of cytopathologists. There were 9.27% cases in category FN/SFN (Figure.1) with no case diagnosed as FN, Hürthle cell type. Similar findings were of Jo et al (9.7%) [21]. The term SFN is preferred over FN for this category because a significant proportion of cases in various studies prove not to be neoplasm but rather hyperplastic proliferations of follicular cells, most commonly those seen in multinodular goitre. The cytology of nodular goitre can overlap with those of follicular adenoma and cytological criteria alone cannot reliably distinguish between the two in certain cases [22].FNAs sometimes do not reflect the histology of the entire nodule [23]. This could be due to wrong site selection, inaccurate sampling, artefacts in smear preparation and interpretation of cytopathologists. In the category SFM, only one case (0.66% of total cases) was classified and was under the subcategory of suspicious for papillary carcinoma (Figure.16). Vasudha M Bhagat et al [16] found 0.63% and Mondal et al [15] found 1.4% in this category. Suspicious of malignancy and AUS results prove to be an area of uncertainty and are often resolved by diagnostic surgical resection.[24]

Malignant category includes 1.99 % of total cases. Anand K Verma et al [14] found 2.2% of cases in this category. Aspirate classified as medullary carcinoma thyroid show numerous plasmacytoid isolated cells alternating with syncytial-like clusters (Figure.). Two surgical specimens were received from the malignant category. Sample classified as papillary carcinoma on FNAC (Figure.) show numerous true papillae (as per the name suggest) with ground glass nuclei (the classical feature) in histopathological examination (Figure.). The case diagnosed as poorly differentiated carcinoma on FNA (Figure.) was proven to be Non Hodgkin Lymphoma on histopathological examination (Figure.). According to the authors of the WHO volume on Pathology and Genetics of Tumours of Endocrine Organs, "a definitive diagnosis of poorly differentiated carcinoma can be made only at the histological level."[25]The correlation of cytological and histopathological diagnoses is an important quality assurance method, as it allows cytopathologists to calculate their false positive and false negative results [26].The false negative rate (FNR) is defined as the percentage of cases with benign cytology but proven to be malignant after histopathological examination. It may occur because of sampling error or misinterpretation of cytology and are of great concern because they indicate the potential to miss a malignant lesion. [27] Unfortunately, it is difficult to calculate the true frequency of false negative results as only a small percentage of patients with benign cytological findings undergo surgery. Most authorities are of the opinion that the true false negative rate is below 5%, even if all patients with thyroid FNAC have a histopathological examination. [28] The false positive rate (FPR) is defined as percentage of cases with a malignant FNA proven to be benign on histological examination.Ten cases were benign and two cases were malignant both by FNA and histopathological examination. None of the cases with a malignant diagnosis on cytology were proved to be benign on biopsy. Only one case which was suspicious of follicular neoplasm proved to be malignant lesion on examination of tissue specimen.

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Table.5: Cytological/histopathological correlation with benign and malignant cases.

Cytodiagnosis	Benign Histodiagnosis	Malignant Histodiagnosis
ND/UNS (n=1)	1	0
Benign(n=9)	9	0
AUS/FLUS(n=0)	0	0
FN/SFN(n=4)	3	1
SFM(n=0)	0	0
Malignant(n=2)	0	2

ND/UNS = nondiagnostic/unsatisfactory, AUS/FLUS = atypia of undetermined significance/follicular lesion of undetermined significance, FN/SFN = follicular neoplasm/suspected for a follicular neoplasm, and SFM = suspected for malignancy. n = total number of surgical specimen received from the given category.Risk of malignancy calculated in this study was found to be 0.0% in ND, Benign, AUS and SFM categories due to certain limitations like less number of cases involved in this short These findings were similar to those of Anand K Verma et al [14]. (Table.6)False positive rates were increased by 50% (from 0.0% to 50.0%) and false negative rates were increased by 2.9% (from 7.1% to 10%) in the present study when SFN category was considered as malignant. FPR results were uncommon and it was 0%in our study (when SFN category was excluded), which was consistent with other reports that cite FPR results ranging from 0 - 9%. [29]Non diagnostic category could be benign or malignant. When excluded for statistical purpose, false negative rates were increased.

duration of study. Also close follow up of each and every patients were not possible as not all the patients were operated in the same institute and many of them were treated by conservative managements. Risk of malignancy for SFN was found to be 7.14% and it was 100% in case of malignant lesion. If FN/SFN is included in malignant group, the sensitivity increases but the specificity decreases with marked decrement in positive predictive value.

Conclusion:

The six diagnostic categories are well defined, morphologically distinct and ensure a uniform reporting system for thyroid FNA. This facilitates effective communication among cytopathologists, endocrinologist, surgeons, radiologist and other health care providers. It also facilitates cytological – histological correlation for thyroid diseases and allows easy and reliable sharing of data from different laboratories for national and international collaborative studies.[30]

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Study with number of cases histologically correlated	Criteria	Sensitivity	Specificity	PPV	NPV
Present study (n=16)	FN/SFN cases Excluded	100% {19.8-100%}	100% {65.5-100%}	100% {19.8-100%}	100% {65.5-100%}
	FN/SFN cases included as benign	66.7% {12.5-98.2%}	100% {71.7-100%}	100% {19.8-100%}	92.9% {64.2-99.6%}
	FN/SFN cases included with malignant cases	75.0% {21.9-98.7%}	75.0% {42.8-93.3%}	50.0% {13.9-86.0%}	90.0% {54.1-99.4%}
Anand K Verma et al[14] (n=40)	FN/SFN cases excluded	76.92%	88.46%	76.92%	88.46%
	FN/SFN cases included with benign cases	73.33%	89.66%	78.57%	86.67%
	FN/SFN cases included with malignant cases	78.57%	81.25%	64.71%	89.66%

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