*ejpmr, 2017,4(1), 365-370*

**SJIF Impact Factor 3.628**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

# REPRODUCIBILITY OF "THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY" WITH IMPLICATION FOR RISK OF MALIGNANCY: AN EXPERIENCE AT A TERTIARY CARE CENTRE.

***[1]Dr. Deepika Gupta, [2]Dr. Namita Bhutani and [3]Dr. Saumya Bhagat**

[1]Former Junior Resident, Deptt of Pathology, Gsvm Medical College, Kanpur, India.
[2]Former Junior Resident, Deptt of Pathology, Pgims Rohtak, India.
[3]Former Junior Resident , Department of Pathology, Vijaynagar Institute of Medical Sciences, Bellary.

***Corresponding Author: Dr. Deepika Gupta**

Former Junior Resident, Deptt of Pathology, Gsvm Medical College, Kanpur, India.

**Article Received on 28/10/2016** **Article Revised on 18/11/2016** **Article Accepted on 08/12/2016**

## ABSTRACT

**Background**: The Bethesda system for reporting thyroid cytopathology represents a major step towards standardization, reproducibility, improved clinical significance and greater predictive value of thyroid fine needle aspirates (FNAs). **Aims**: The objective of this study was to analyze the thyroid cytology smears by TBSRTC, to determine the distribution of diagnostic categories and subcategories, to analyze cytological features and to correlate the cytopathology with histopathology, wherever surgery was done. **Materials and Methods:** This was a prospective study of 212 fine needle aspirations (FNA) of thyroid nodules. All fine needle aspiration cytology (FNAC) diagnoses were classified according to the features given in the monograph of TBSRTC into nondiagnostic/unsatisfactory (ND/UNS), benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FUS), follicular neoplasm/suspicious of a follicular neoplasm (FN/SFN), suspicious for malignancy (SFM) and malignant. Cytohistological correlation was done, when surgical material was available. **Results:** The distribution of various categories from 225 evaluated thyroid nodules was as follows: 3.7% ND/UNS, 87.2% benign, 1.4% AUS/FLUS, 1.4% FN, 1.4% SFM and 5.1% malignant. **Conclusion:** TBSRTC is an excellent reporting system for thyroid FNA. It also provides clear management guidelines to clinicians to go for follow-up FNA or surgery and also the extent of surgery.

**KEYWORDS:** follicular neoplasm/suspicious of a follicular neoplasm (FN/SFN).

## INTRODUCTION

Fine needle aspiration cytology (FNAC) is the firstline diagnostic test for evaluating thyroid nodules.[1] This simple, rapid, costeffective and minimally invasive technique is extremely useful in identifying a substantial proportion of thyroid nodules as benign and reducing unnecessary surgery for patients with benign disease. However, due to the lack of a standardized system of reporting, pathologists have been using different terminologies and diagnostic criteria, thereby creating confusion amongst referring clinicians in the interpretation of the cytopathology report, ultimately hindering a definitive clinical management.[2]

To overcome this issue and to address terminology and other issues related to thyroid FNACs, the "The Bethesda System for Reporting Thyroid Cytopathology" (TBSRTC) was described. It describes six diagnostic categories of lesions: Nondiagnostic/unsatisfactory, benign, atypical follicular lesion of undetermined significance (AUS), "suspicious" for follicular neoplasm (SFN), suspicious for malignancy (SM) and malignant.[3] Each category has an implied cancer risk, which ranges from 0% to 3% for the "benign" category to virtually 100% for the "malignant" category.

The objective of the present prospective study, done in our institute, was to report thyroid cytology smears by TBSRTC into various diagnostic categories, analyze their cytological features using TBSRTC monograph, conveying brief management plan to the clinicians and correlate with histology of surgical specimens received.

## MATERIALS AND METHODS

Ours was a prospective study of all patients with thyroid swelling referred to the Department of Pathology GSVM Medical college, Kanpur, for FNAC during the period from January 2015 to March 2015. We prospectively collected thyroid FNA smear from 212 patients and stained by HE and MGG and Leishman stain. Each case was categorized than as per current recommended bethesda nomenclature. Histological follow up was available in 30 cases.

The cytological features were evaluated and the reporting was done according to TBSRTC (Table 1A). The clinicians were communicated implied risk of malignancy and recommended clinical management along with the report. (Table 1B) Histopathological specimens, wherever available, were processed as per standard methods.

**TABLE 1A**

| No. | Name of the category |
|---|---|
| I | **Nondiagnostic or unsatisfactory** |
| | Cystic fluid only |
| | Virtually acellular specimen |
| | Other (obscuring blood, collecting artifacts, 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 (subacute) thyroiditis |
| | Other |
| III | **Atypia of undetermined significance or follicular lesion of undetermined significance** |
| IV | **Follicular neoplasm or suspicious for a follicular neoplasm** |
| | Specify if Hurthle cell (oncocytic type) |
| V | **Suspicious for malignancy** |
| | Suspicious for papillary carcinoma |
| | Suspicious for medullary carcinoma |
| | Suspicious for metastatic carcinoma |
| | Suspicious for lymphoma |
| | Other |
| VI | **Malignant** |
| | Papillary thyroid carcinoma |
| | Poorly differentiated carcinoma |
| | Medullary thyroid carcinoma |
| | Undifferentiated (anaplastic) carcinoma |
| | Squamous cell carcinoma |
| | Carcinoma with mixed features (specify) |
| | Metastatic carcinoma |
| | Non-Hodgkin's lymphoma |
| | Other |

**TABLE 1 B**

| Diagnostic category | Risk of malignancy (%) | Usual management |
|---|---|---|
| Nondiagnostic or unsatisfactory | 1–4 | Repeat FNA with ultrasound guidance |
| Benign | 0–3 | Clinical follow-up |
| Atypia of undetermined significance or follicular lesion of undetermined significance | 5–15 | Repeat FNA |
| Follicular neoplasm or suspicious for follicular neoplasm | 15–30 | Surgical lobectomy |
| Suspicious for malignancy | 60–75 | Near-total thyroidectomy or surgical lobectomy |
| Malignant | 97–99 | Near-total thyroidectomy |

**RESULTS**

Of the 212 cases who underwent FNAC during the period from January 2015 to March 2015, initially, 8 cases(3.7%) turned out to be nondiagnostic, 185 (87.2%) benign, 9 (0.9%) AUS, 03 (1.4%) SFN,03 (1.4%) and 11 (5.1%) malignant. [Table 2].

**TABLE 2**

| S.No. | Diagnostic category | Number of cases in each category | % |
|---|---|---|---|
| 1 | Non diagnostic | 8 | 3.7 |
| 2 | Benign | 92 | (87.2) |

| | | | |
|---|---|---|---|
| | 1. Colloid goitre<br>2. Nodular goitre<br>3. Adenomatoid nodule<br>4. Hyperplastic nodule<br>5. Lymphocytic thyroiditis | 32<br>3<br>4<br>54 | 43.3<br>15.09<br>1.4<br>1.88<br>25.47 |
| 3 | AUS | 3 | 1.4 |
| 4 | SFN/FN<br>FN | 3 | 1.4 |
| 5 | Suspicious for malignancy(PCT) | 3 | 1.4 |
| 6 | Malignant<br>1. Papillary thyroid carcinoma<br>2. Medullary thyroid carcinoma<br>3. Poorly differentiated carcinoma<br>4. Anaplastic carcinoma<br>5. Squamous cell carcinoma | 6<br>1<br>1<br>2<br>1 | (5.1)<br>2.83<br>0.47<br>0.47<br>0.94<br>0.47 |

Distribution of cases in the Bethesda categories as per our study (*n*=212). Out of 212 cases, 30 cases were available for follow up histopathology. Out of these 30 cases, 3 cases had original FNA diagnoses as nondiagnostic, 12 cases as benign (Fig.1: benign cystic lesion and Fig.2 graves disease), 2 cases as AUS (Fig.3 Hurthle cell lesion), 3 cases as SFN (Fig.4 follicular neoplasm), 3 cases as SM and 5 cases as malignant (Fig.5. Papillary carcinoma). We compared the original FNA diagnoses of these 30 cases with the diagnoses obtained on HPE and calculated the malignancy risk for each category [Table 3].

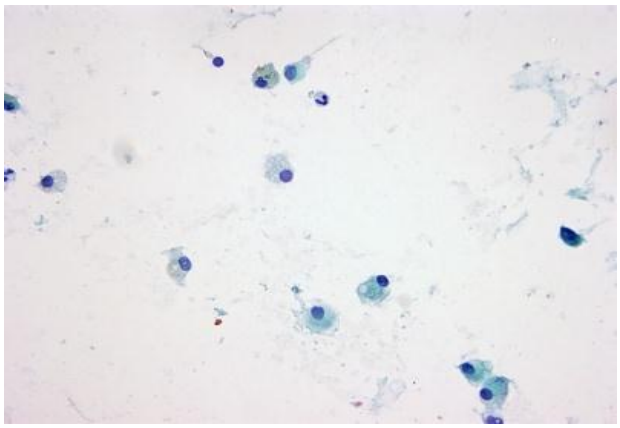

**FIGURE 1: BENIGN CYSTIC LESION**

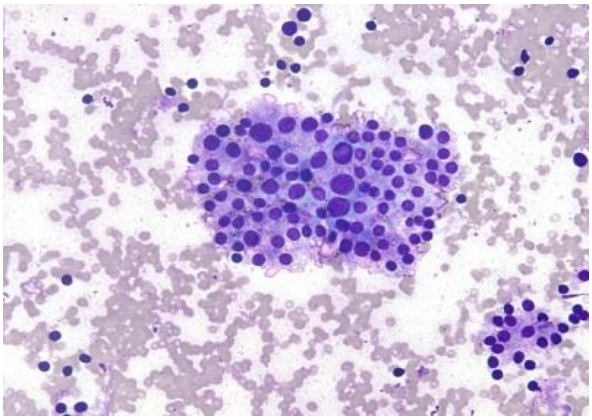

**FIGURE 2: Follicular epithelial cells arranged in groups and visible fire flares at periphery (graves disease)**

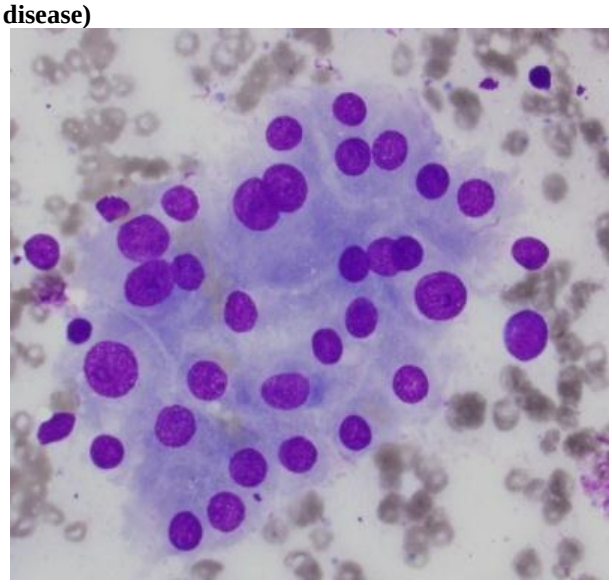

**FIGURE 3: Hurthle cell lesion**

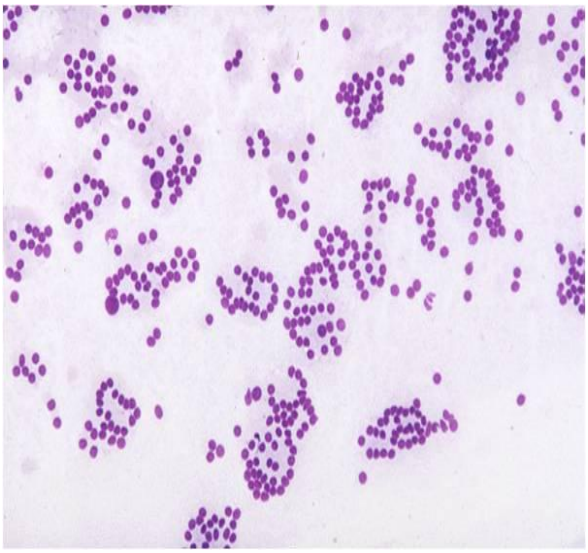

**FIGURE 4: Follicular epithelial cells arranged in microfollicles**

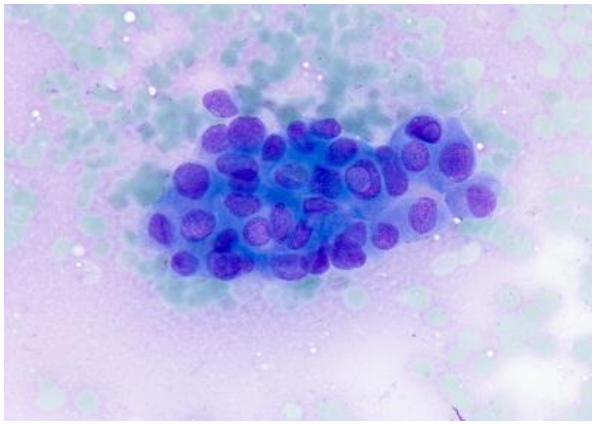

**FIGURE 5: Papillary carcinoma with intra nuclear inclusion**

**TABLE 3**

| S.No. | PREOPERATIVE FNAC Diagnosis as per TBSRTC | Diagnosis on HPE after surgical resection | Number of cases turned out to be malignant | Malignancy risk |
|---|---|---|---|---|
| 1. | Non diagnostic/unsatisfactory (n=5) | Colloid/Adenomatpoid Goitre-3, Lymphocytic Thyroiditis-1, PCT-1 | 1 | 20% |
| 2. | Benign (n=12) | Nodular goitre-8, Colloid goitre-2 Lymphocytic Thyroiditis-2, | 0 | 0 |
| 3. | AUS (n=2) | Adenomatoid Goitre-1, FA-1 | 0 | 0 |
| 4. | SFN/FN (n=3) | FC-1, Adenomatoid goitre-1, FA-1 | 1 | 33.3% |
| 5. | Suspicious for Malignancy (n=3) | PCT-2, Hashimoto thyroiditis-1 | 1 | 66.6% |
| 6. | Malignant (n=5) | PCT-5 | 5 | 100% |

Comparison of preoperative FNAC diagnoses with the diagnoses on HPE after surgical resection and calculation of malignancy risk for each Bethesda category.

## DISCUSSION

This paper shows the experience in reporting thyroid aspirations by TBSRTC in an Indian academic institution as well as response of clinicians to the brief management plan suggested. TBSRTC does not recommend surgery for ND/UNS, benign and AUS/FUS categories. In the FN/SFN, SFM and malignant categories, we expected excision of nodules or partial/complete thyroidectomy in all cases as per TBSRTC recommendations.

The present study had 8 (3.7%) cases in ND/UNS category. Other recent studies had 1.2% to 16.4% cases in this group.[4—11] The benign category had 185 cases (87.2%) with colloid goitre being the predominant group followed by lymphocytic thyroioditis. The "benign" category had a range of 34% to 87.5% in recent studies.[4-11] Twelve histopathological specimens from category diagnosed as "benign" were received. All of them were operated because of cosmetic reasons or pressure symptoms. 8 were colloid goiter, 2 nodular goitre and 2 lymphocytic thyroiditis.

The classification of "indeterminate" lesions (those not clearly benign or malignant) in thyroid cytopathology has long been a source of confusion for both pathologists and clinicians. The general category AUS/FUS is reserved for specimens that contained cells (follicular, lymphoid, or other) with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm or suspicious for malignancy. We had 2 cases in group AUS/FUS. An AUS result has been reported in 3.2–29% of thyroid cases.[4-11] TBSRTC suggests that the frequency of AUS interpretations should be in the range of approximately 7% of all thyroid FNA interpretations. This is a category of last resort and should not be used indiscriminately. Not much data exists in the literature to support the recommendation that the category should not exceed 7% of all thyroid categories.[12] The incidence also varies with experience and training of cytopathologists. The recommended management for an initial AUS/FUS interpretation is the clinical correlation and, for most cases, a repeat FNA at an appropriate interval. A repeat FNA usually results in a more definitive interpretation; only about 20–25% of nodules are repeatedly AUS

Committee V of the NCI Thyroid Fine Needle Aspiration State of the Science Conference has provided guidelines for indications of ancillary studies, specific ancillary studies to be performed and sample preparation for each study. Immunohistochemistry panels have been suggested for suspicious malignancies which include medullary carcinoma (calcitonin, thyroglobulin, CEA and chromogranin), anaplastic carcinoma (pancytokeratin) and metastatic carcinoma (TTF-1). These are to be done on cell block from FNA, preferably

including at least one dedicated pass for the study. For suspicious lymphoma, flow cytometric immunophenotyping is suggested. Dedicated passes are also needed for studies to detect genetic alterations such as BRAF mutation or RET/PTC chromosomal rearrangements, which are very promising for the diagnosis of papillary carcinoma. Immunocytochemistry on cytospin, direct smear, or prefixed monolayer may also be utilized, but protocols should be carefully validated.[13]

The category malignant had a range of 2.9% to 11% in recent studies.[4-11] The present study had 11 (5.1%) cases in the malignant category. We received 5 specimens from the category diagnosed as "malignant" cytologically. All of them were diagnosed as papillary carcinoma both histopathologically and cytologically.

**Table 4 A and 4 B shows a comparison of statistical parameters of our study and other studies over the past years.**

**TABLE 4A Comparison of % of Distribution of FNA Diagnosis of Present Study with Previous Studies**

| | ND/US | BENIGN | AUS | SFN/FN | Suspicious for malignancy | malignant |
|---|---|---|---|---|---|---|
| Present study (2014) | 3.7 | 87.26 | 1.4 | 1.4 | 1.4 | 5.18 |
| Yassa et al (2007) | 7 | 66 | 4 | 9 | 9 | 5 |
| Yang et al (2007) | 10.4 | 64.6 | 3.2 | 11.6 | 2.6 | 7.6 |
| Theoharis et al (2009) | 11.1 | 73.8 | 3 | 5.5 | 1.4 | 5.2 |
| Jo at el (2010) | 18.6 | 59 | 3.7 | 9.7 | 2.3 | 7 |
| Renshaw et al (2011) | 24 | 54 | 7.7 | 8.6 | 1.9 | 4.2 |
| Juing wu et al (2012) | 20 | 39 | 27.2 | 8.4 | 2.6 | 2.7 |
| Santosh kumar mondel et al (2013) | 1.2 | 87.5 | 1 | 4.2 | 1.4 | 4.7 |

**TABLE 4B Comparison of the % of Malignancy Risk of Present Study with Previous Studies**

| | ND/US | BENIGN | AUS | SFN/FN | Suspicious for Malignancy | Malignant |
|---|---|---|---|---|---|---|
| Present study (2014) | 20 | 0 | 0 | 33.3 | 66.6 | 100 |
| Yassa et al (2007) | 10 | 0.3 | 19.2 | 32.2 | 64.8 | 98.4 |
| Yang et al (2007) | 10.7 | 0.7 | 19.2 | 32.2 | 64.8 | 98.4 |
| Theoharis et al (2009) | 9 | 2 | 6 | 14 | 53 | 97 |
| Jo at el (2010) | 8.9 | 1.1 | 17 | 25.4 | 70 | 98.1 |
| Renshaw et al (2011) | 20 | 2 | 25 | 30 | 97.3 | 100 |
| Juing wu et al (2012) | 14 | 9.5 | 22 | 27 | 67 | 100 |
| Santosh kumar mondel et al (2013) | 0 | 4.5 | 20 | 30.6 | 75 | 97.8 |

TBSRTC is a relatively recent six-category scheme to classify thyroid cytology smears. It needs to be validated by more prospective studies on larger number of cases with histopathological correlation. There is need for consensus amongst institutions in various countries to utilize TBSRTC to facilitate easy sharing of data across the world for surveys and research.

## CONCLUSION

This study is a prospective analysis of reporting of thyroid aspiration smears by TBSRTC using the Bethesda monograph. The Bethesda system is very useful for a standardized system of reporting thyroid cytopathology, improving communication between cytopathologists and clinicians and interlaboratory agreement, leading to more consistent management approaches.

## REFERENCES

1. Cibas ES. Fine needle aspiration in the workup of thyroid nodules. Otolaryngol Clin North Am. 2010; 43: 257–71.
2. Lewis CM, Chang KP, Pitman M, Faquin WC, Randolph GW. Thyroid fine needle aspiration biopsy: Variability in reporting. Thyroid. 2009; 19: 717–23.
3. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2009; 132: 658–65.
4. J. Yang, V. Schnadig, R. Logrono and P. G. Wasserman, "Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations," Cancer, 2007; 111(5): 306–15.
5. R. Nayar and M. Ivanovic, "The indeterminate thyroid fine-needle aspiration: Experience from an academic center using terminology similar to that proposed in the 2007 national cancer institute thyroid fine needle aspiration state of the science conference," Cancer Cytopathology, 2009; 117(3): 195–202.
6. C. G. A. Theoharis, K. M. Schofield, L. Hammers, R. Udelsman and D. C. Chhieng, "The bethesda thyroid fine-needle aspiration classification system:

year 1 at an academic institution," Thyroid, 2009; 19(11): 1215–23.
7. V. Y. Jo, E. B. Stelow, S. M. Dustin, and K. Z. Hanley, "Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda system for reporting thyroid cytopathology," The American Journal of Clinical Pathology, 2010; 134(3): 450–56.
8. M. Bonzanini, P. Amadori, L. Morelli et al., "Subclassification of the 'grey zone' of thyroid cytology; a retrospective descriptive study with clinical, cytological, and histological correlation," Journal of Thyroid Research, 2011; 11, Article ID 251680.
9. J. T. Broome and C. C. Solorzano, "The impact of atypia/follicular lesion of undetermined significance on the rate of malignancy in thyroid fine-needle aspiration: evaluation of the Bethesda system for reporting thyroid cytopathology," Surgery, 2011; 150(6): 1234–41.
10. M. M. Al-Shraim, O. M. Kaood, M. R. Hussein et al., "Assessment of malignancy rate in thyroid nodules according to the Bethesda system of fine-needle aspiration: report from a tertiary center in the Southwestern region of Saudi Arabia," Saudi Medical Journal, 2012; 33(2): 167–71.
11. S. K. Mondal, S. Sinha, B. Basak, D. N. Roy and S. K. Sinha, "The Bethesda system for reporting thyroid fine needle aspirates: a cytologic study with histologic follow-up," Journal of Cytology, 2013; 30(2): 94–9.
12. L. J. Layfield, M. J. Morton, H. M. Cramer and S. Hirschowitz, "Implications of the proposed thyroid fine-needle aspiration category of follicular lesion of undetermined significance: a five-year multi-institutional analysis," Diagnostic Cytopathology, 2009; 37(10): 710–4.
13. C. Filie, S. L. Asa, K. R. Geisinger et al., "Utilization of ancillary studies in thyroid fine needle aspirates: a synopsis of the national cancer institute thyroid fine needle aspiration state of the science conference," Diagnostic Cytopathology, 2008; 36(6): 438–41.
14. Ozluk Y, Pehlivan E, Gulluoglu MG, Poyanli A, Salmaslioglu A, Colak N, et al. The use of the Bethesda terminology in thyroid fine needle aspiration results in a lower rate of surgery for nonmalignant nodules: A report from a reference center in Turkey. Int J Surg Pathol. 2011; 19: 761–71.