Original Research Paper

Volume -10 | Issue - 3 | March - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pathology

CYTOPATHOLOGICAL EVALUATION OF THYROID LESIONS WITH IMPLEMENTATION OF BETHESDA SYSTEM: A 6.5 YEARS STUDY

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ABSTRACT Thyroid nodules are commonly encountered in clinical practice. Fine needle aspiration (FNA) of these nodules is widely accepted, cost-effective and simple method for diagnosis. This study aims at determining the distribution of diagnostic categories according to The Bethesda system for reporting thyroid cytopathology (TBSRTC), to analyze cytological features and correlate them with histopathology.

We report retrospective and prospective analysis of 869 FNA of thyroid nodules using the Bethesda system. FNA were performed in prospective cases (554), whereas in retrospective cases (315) all smears were reviewed. All cases were categorized into six Bethesda categories. The sensitivity, specificity, positive predictive value, negative predictive value was calculated.

The distribution of 869 evaluated thyroid nodules was as follows: 3.68% Nondiagnostic / unsatisfactory, 86.77% benign, 1.73% atypia of undetermined significance, 3.2% follicular neoplasm, 2.53% suspicious for malignancy and 2.07% malignant. In 141 cases, histopathological correlation was available and of these cytohistological concordance was found in 94% cases. The sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy were 76%, 96%, 84%, 95% and 93% respectively. The risk of malignancy in categories II, III, IV, V and VI was 1.8%, 25%, 29%, 70%, & 100% respectively. Use of TBSRTC in well-defined and consistent manner especially in grey zone areas of thyroid cytopathology, allow appropriate evaluation of thyroid lesions cytologically.

KEYWORDS : Thyroid cytopathology, TBSRTC, Sensitivity, Specificity

INTRODUCTION

Thyroid swellings are a significant clinical problem in the general population. Both non-neoplastic and neoplastic diseases affect it and lead to diffuse or nodular enlargement.[1] FNA of thyroid has been accepted as first-line screening test for patients with thyroid nodules. Its utility has increased significantly particularly because of the availability of ultrasound-guided techniques, which allows for the detection and aspiration of smaller and deep-seated nodules. [2] Consequently, more thyroid cancers are diagnosed at an early stage. This minimally invasive and cost-effective technique is extremely useful in identifying a substantial proportion of thyroid nodules as benign and reducing unnecessary surgery for patients with benign disease.[1]

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was introduced in 2007 for unifying the terminology and morphologic criteria for diagnosis of thyroid lesions along with the corresponding risk of malignancy.[3] The objectives of the present analysis was to classify thyroid lesions in various categories under Bethesda system and to elucidate the diagnostic utility of the Bethesda system in reporting thyroid FNAs. The objectives also were focused to correlate the cytological findings with histopathological reports.

MATERIALS AND METHODS

The present retrospective and prospective study was carried out in our institute during the January 2011 to June 2017.The study comprised of 869 patients who presented with the history of thyroid swelling and referred to cytology section of Department of Pathology for FNAC. Relevant clinical history was taken and examination done.Patients were explained about the procedure and written consent was obtained. The patient was asked to lie in supine position with their neck stretched up. FNAC was performed in all cases by cytopathologist with 23-24 gauge needles. For FNAC of smaller and deep-seated nodules ultrasound-guided technique was used. Smears were wet fixed in 95% alcohol and dry smears were also made. Dry smears were stained with May-Grünwald-Giemsa (MGG) and wet fixed smears with Papanicolaou (Pap) stains as per the standard guidelines.

Smears were examined and categorized according to the TBSRTC[3] into six groups; (I) Non diagnostic, (II) benign, (III) atypical follicular lesion of undetermined significance,(IV) suspicious of follicular neoplasm/ follicular neoplasm, (V) suspicious for malignancy and (VI) malignant.

Nondiagnostic category i.e.I included sample with inadequate material, poor quality smear and that containing cyst fluid only. Categories II, III and IV were considered cytologically benign and categories V and VI were considered malignant. All cases were followed up and correlated with final histopathological report wherever possible. In 141 cases where surgery was done, and histopathology specimen received. All cases of malignant histopathological diagnosis in cases of Bethesda II, III&IV categories were considered false negative whereas benign histopathological diagnosis in Bethesda category V&VI were considered false positive.

Sensitivity, specificity, positive predictive value, and negative predictive value and diagnostic accuracy were calculated using histopathology diagnosis as gold standard. For calculating statistical parameters ND/UNS cases were excluded as non-definitive diagnosis.

RESULTS

The present study was carried out in a tertiary care institute during the January 2011 to June2017. In this study, 869FNACs done were classified according to the Bethesda system and out of them, 141 histopathological specimens obtained from this group were evaluated. The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated.

Out of 869 patients with thyroid swelling, majority were females (745 cases, i.e.85%) and 124 were males (M: F = 1:7). The age ranged from 15 to 73 years with mean age of 37.9 years. Majority (69.45%)of case were in 31-50 years age group.

The distribution of 869 cases is shown in Table 1. Category II (Benign) was the most common contributing for 86.77%cases followed by category I(non-diagnostic, 3.68%) [Figure 1a] and IV (SFN/FN, 3.20%). Category V (suspicious for malignancy), VI (Malignant), and III (atypia of undetermined significance) accounted for 2.53%, 2.07%

and 1.73% respectively. Non-neoplastic lesions accounted for 786 cases of which colloid goiter was the most common lesion (58.9%) [Figure 1b] followed by lymphocytic thyroiditis [Figure 1c]. The malignant lesions showed papillary carcinoma [Figure 2 b-d], medullary carcinoma [Figure 3 a& b], poorly differentiated carcinoma [Figure 3c] and nonHodgkin's lymphoma [Figure 3d].

We compared the diagnosis on FNAC based on Bethesda system, with the corresponding histopathological diagnosis. Out of 869 cases of FNAC, in 141 cases, histopathological correlation was available. Table2 shows cyto-histopathological correlation of thyroid lump and the incidence of malignancy in various TBSRTC categories. Incidence of malignancy was highest in category VI (100%) followed by category V (29%) and IV (25%). Cytohistological concordance was found in 133 cases (94.32%) whereas eight cases were discordant (5.67%). Out of these discordant cases, two false positive cases reported as suspicious of papillary carcinoma thyroid, which on histopathological examination was found to be hyperplastic goiter (1) and goiter with adenomatoid nodule(1), whereas six false negative cases reported as benign on cytology turned out to be follicular carcinoma (2) and papillary carcinoma (4) on histopathological examination.

The sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy were 76%,96%, 84%, 95% and 93% respectively. The risk of malignancy in categories II, III, IV, V and VI was 1.8%, 25%, 29%, 70%, & 100% respectively. Overall, there was a false positive rate of 1.41% and false negative rate of 4.25%.

DISCUSSION

The Thyroid lump is common clinical presentations with a reported prevalence rate of 4 to 7%.[4] Majority of thyroid swellings are non-neoplastic and do not always require surgical intervention. As less than 5 % of thyroid nodules are malignant, it is very important to establish the exact nature of lesion to prevent unnecessary surgery which can cause hypothyroidism, hypoparathyroidism and laryngeal nerve palsy.[5] The initial preoperative screening procedures include ultrasonography, fine needle aspiration cytology (FNAC) and radio nucleotide scan. Fine needle aspiration cytology is still the first diagnostic tool to establish the nature of thyroid lump as it is very rapid, easy, cost effective, minimally invasive out-patient based diagnostic tool which is well tolerated among people and moreover it has a greater accuracy.[2] The Bethesda system of thyroid cytology reporting makes the reports clinically relevant and helps the clinicians to take appropriate therapeutic interventions.[3]

In past, terminology regarding thyroid fine needle aspiration cytology (FNAC) has varied significantly from one laboratory to another creating confusion among clinicians working at multiple institutes. Hence, a uniform reporting system for thyroid FNA that will facilitate effective communication among health care providers was needed. An encouragement for the thyroid proposal was the Bethesda system for reporting cervical cytology interpretations, first developed at an NCI workshop in 1988 and widely accepted in the United States for reporting Papanicolaou test results. The Bethesda system for reporting thyroid cytopathology (TBSRTC) was introduced in 2007 by the National Cancer Institute (NCI) Bethesda, Maryland, United States, to bring the uniformity in reporting and nomenclature of thyroid lesions.[6]

TBSRTC is a six-category scheme of thyroid cytopathology reporting. Each category has an implied cancer risk, which ranges from 0% to 3% for the "benign" category to virtually 100% for the "malignant" category. [3] TBSRTC facilitates effective communication among cytopathologist, endocrinologist, surgeons, radiologists, clinicians and very useful for cytological-histologic correlation for thyroid diseases. This system represents a major step towards standardization, reproducibility, improved clinical significance, and greater predictive value of thyroid fine needle aspirates.[7]

Fine needle aspiration biopsy (FNAB) has been used since the 1950s, and is cost effective, easy, and well tolerated among individuals.[8] However, FNAC of thyroid lump has several limitations including inadequate sampling and most important being in its inability to differentiate between benign and malignant follicular lesions. Also cystic change in thyroid lesion is a common diagnostic pitfall in cytology.[4]USG-guided FNAC results in better sample yield leading to the reduced inadequacy of sample and enhancing overall accuracy. Hence, multiple passes to cover all areas of interest, and USG-guided aspiration reduces sampling error. Use of TBSRTC in a well-defined and consistent manner, especially in gray zone areas of Thyroid cytopathology, allow appropriate evaluation of thyroid lesions cytologically.[3,9]

Thyroid diseases are frequently encountered in young and middle-aged groups with majority of patients being females in reproductive age groups. In present study, the age distribution ranged from 2nd to 8th decade and maximum number of cases was in the age group 31-50 years. A female preponderance was noted in our study with 745 (85.73%) cases. Similar female preponderance was noted by Garg et al.[10] As reported by Garg et al 78% per cent of the thyroid diseases were found in the age group 21-60 years.[10] Similarly in present study, 69.45% cases were in the 31-50 years age group.

After applying Bethesda to the same cases (869), they were categorized in six categories as, I (3.68%), II (86.77%), III (1.73%), IV (3.20%), V (2.53%), and VI (2.07%). Study of 431 cases by Khadatkar et al[7] of 431 cases showed distribution as I (7.7%), II (82.3%), III (3.1%), IV (1.45%), V (0%), and VI (5.3%). Jo et al[11] conducted study of 3,080 thyroid FNA samples from over the period of 18 years and classified thyroid lesions according to TBSRTC. Of these 3,080 FNAC samples, 18.6% were non-diagnostic, 59.0% were benign, 3.4% were atypical follicular lesion of undetermined significance (AFLUS), 9.7% were "suspicious" for follicular neoplasm (SFN), 2.3% were suspicious for malignancy (SM), and 7.0% were malignant. Higher percentage of benign lesions was observed in our study which is comparable to study by Khadatkar et al.[7]

Statistical analysis in study by Chaudhary et al[2] revealed a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 75.2%, 98.2%, 90.0%, 94.7% and 94.03% respectively. The present study showed a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 76%, 96%, 84%, 95% and 93% respectively. These results were comparable to Chaudhary et al[2] and the others where the FNAC of thyroid has reported sensitivity ranging from 60% to 99%, specificity 80% to 100%, positive predictive value 85% to 97%, negative predictive value 88% to 99% and accuracy 89% to 99%.[1,2,6,7] Reasons for these varied results may be due to number of cases, subjective errors and sampling errors.

Literature shows risk of malignancy among the various non-malignant categories was highest in category IV followed by categories III and II.[3,8] These cases should therefore be followed up to detect any progression to malignancy. Present study showed the risk of malignancy to be highest in category IV (29%).It confirms the diagnostic role of TBSRTC in the reporting of thyroid lump and/or surgical intervention.[4,9]The overall accuracy of 93% in our study is comparable to Chaudhary et al(94.03%).[2]

Diagnostic accuracy of thyroid FNA is highly variable. Most diagnostic failures are due to ND samples or pathologist issuing diagnosis on samples with inadequate material. Efforts toward improvement in proficiency in FNA sampling and specimen preparation should be given high priority. The diagnosis of a benign thyroid lesion should be made only on adequate samples, whereas the presence of atypical cells or cellular pattern, always should be addressed regardless of cellularity and it precludes the interpretation of an inadequate sample.[3]US-guided FNA lowers the rates of ND aspirations by allowing sampling of the cellular portions of predominantly cystic nodules and thus increased accuracy can be achieved by the use of USG-FNA in the evaluation of thyroid nodules in reducing the need of unnecessary surgery.[3,9]The inadequacy rate in our study was 3.68%. Ali[9] suggested that the rate of ND test should be below 10%. All thyroid FNAs must be technically adequate with well-represented and well-prepared smears for interpretation. All of them should be re-aspirated after a minimum period of 3 months. The 3-month interval was recommended to prevent false positive interpretations due to reactive or reparative changes, as recommended by Committee VI (Post-FNA Technique and Treatment Options).[3]

In the present study there was predominance of benign lesions than the malignant ones. The category II had 786 cases (86.77%) with benign follicular nodule being the predominant group followed by lymphocytic thyroiditis. The "benign" category had a range of 59% to 87.5% in different studies[11]which shows good correlation with our study. The diagnostic criteria of all the subcategories are well characterized in TBSRTC monograph.[3]In our study a benign follicular nodules including colloid goiter were reported in 575 cases and

lymphocytic thyroiditis was diagnosed by cytology in 177 cases.

The controversial area in Bethesda classification is newly introduced category III i.e. atypia of undetermined significance. This category AUS/FLUS is reserved for specimens that contained cells (follicular, lymphoid, or other) with architectural and/or nuclear atypia that is not enough to be classified as suspicious for a follicular neoplasm or suspicious for malignancy. Bethesda has recommended its judicial use with careful monitoring. [12]We had 15 cases (1.73%) in group AUS/FLUS. An AUS result has been reported in 3.2–29% of thyroid cases in other studies. [6,8,12] TBSRTC suggests that the frequency of AUS interpretations should be in the range of approximately 7% of all thyroid FNA interpretations. However, suboptimal preparation, papillary microcarcinoma, and coexisting Hashimoto's thyroiditis precluded cytopathologist from making definitive diagnoses resulting in AUS/FLUS cases.[12] The recommended management for an initial AUS/FLUS interpretation is the clinical correlation and, for most cases, a repeat FNA at an appropriate interval.[3]

Garg et al[10] compared various studies between 2013 and 2017 and found 3.58% to 9% cases in category IV. In the present study, 28(3.2%) cases were diagnosed as follicular neoplasm / suspicious of follicular neoplasm by FNA with good correlation with other studies. Cytologically tightly cohesive follicular cells and repetitive follicular pattern favor neoplastic condition. We received surgical specimen in 07 cases (out of these 28)in which follicular adenoma (02), follicular carcinoma (04) and follicular variant of papillary carcinoma in one case was confirmed on final histopathology. Data from literature shows 27–68 % of malignancies, in which a diagnosis of follicular neoplasm was made in FNA, are interpreted as papillary carcinoma on histopathology.[8,9,12] This may be due to focal subtle nuclear features of papillary carcinoma in some tumors which were not appreciated on the FNA samples. No reliable cytological feature distinguish follicular adenoma from follicular carcinoma and distinction between the two is based solely on demonstration of histologic evidence of capsular/and or vascular invasion.[1]

In present study, 22 (2.53%) cases were diagnosed as Suspicious of malignancy by FNA in category V (out of which 18 were suspicious for papillary carcinoma and 04 were others) which is in good correlation with percentage reported by Gerg et al[10] (1.37%) and Chaudhary et al[2] (3.6%) in their studies. This diagnosis was made in cases which showed some or focal features of malignancy, but the findings were not sufficient to make a conclusive diagnosis. The features of papillary carcinoma include nucleomegaly, powdery chromatin, nuclear membrane irregularity, nuclear grooves and moulding, intranuclear pseudo inclusions and papillary structures with distinct anatomical borders. We received 10 patient's surgical specimen from category V, of which 08 turned out to be malignant (05 Papillary carcinoma) and two benign. In most of these cases the nuclear features of papillary carcinoma were focal and subtle.

In this study, 18 (2.07%) cases were reported as malignant on cytology in category VI of TBSRCT. Of these 13 cases were of papillary carcinoma, 03 of poorly differentiated malignancy, one each of NonHodgkin lymphoma and medullary carcinoma. Histopathological confirmation was available in 09 cases and all of them turned out to be malignant showing 100% accuracy rate and risk of malignancy for category VI. Other recent studies have reported 3.6% to 5% cases in this category with 97% to 100% accuracy of cytological diagnosis confirmed by histopathology.[10]

The correlation of cytological and histopathological diagnoses is an important quality assurance method as it allows cytopathologist to calculate their false positive and false negative results. The false negative rate (FNR) is defined as the percentage of cases with benign cytology but proven to be malignant after histopathological examination. The false positive rate is defined as percentage of cases with a malignant FNA proven to be benign on histological examination.[1] In the present study out of 869 cases of FNAC histopathological correlation was available in 141 cases. Cytohistological concordance was found in 133 cases (94%) whereas eight cases (6%) were discordant.

Most published studies report a false negative rate in the range of 1–10 %.[6,9,12] In our series the false negative rate was 4.25% and out these six cases, four were papillary carcinoma with the adjacent thyroid tissue showing features of thyroiditis or colloid nodules. In these cases, the aspirate was from the nonmalignant parts of the lesion and the small foci of malignancy were missed. These types of errors can be minimized by using ultrasound guided aspirations and by correlating the cytology diagnosis with scan findings. In present study false positive cases were 1.41% which were given suspicious for malignancy on cytology but turned out to be hyperplastic and adenomatoid goiter. This is probably due to aspiration from hypercellular areas of goiter which led to overdiagnosis.

CONCLUSION

In conclusion, FNA cytology is recommended as the first line investigation for evaluation of thyroid lesions as it is simple, cost effective, and rapid diagnostic procedure with high accuracy. Implementation of TBSRTC has improved the quality of reporting by lowering the number of ambiguous and implicit diagnoses. However, non-malignant cytological interpretation should be viewed with caution as there are false negative cases and such cases should undergo regular clinico-radiological follow up for any progression that will require repeat FNAC. Correlation of cytology and histopathology is an important quality assurance measure.

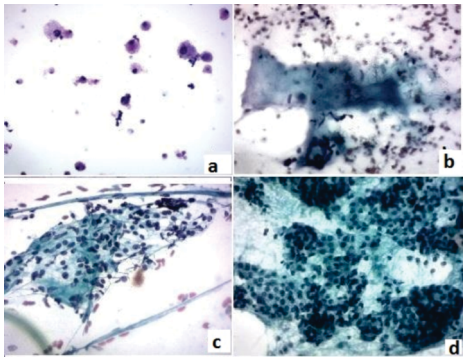

Fig 1: (a) TBSRTC category I- Cyst macrophages only (MGG 400x). (b) TBSRTC category II Benign-colloid goitre-thyroid follicular cells with abundant thick colloid (PAP 400x). (c) TBSRTC category II lymphocytic thyroiditis- lymphocytes admixed with follicular cells(PAP400x). (d) TBSRTC category III (AUS/FLUS) thyroid follicular cells with architectural and cytological atypia (PAP 100x).

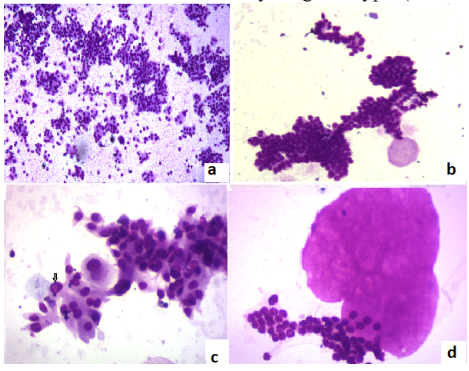

Fig 2: (a) TBSRTC category IV (FN/SFN) follicular cells in micro follicles (MGG 100x). (b) TBSRTC category V suspicious of Papillary carcinoma (MGG 100x) (c) TBSRTC category VI Papillary carcinoma- follicular cells with intranuclear inclusions (MGG 400x) (d) TBSRTC category VI Papillary carcinoma- follicular cells having anatomical border with chewing gum colloid (MGG 400x)

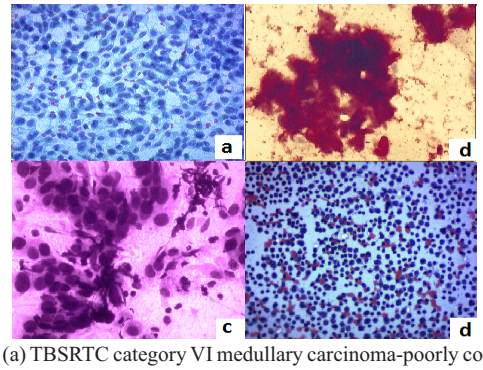

Fig 3: (a) TBSRTC category VI medullary carcinoma-poorly cohesive

cells with plasmacytoid appearance (PAP 400x). (b) TBSRTC category VI medullary carcinoma-clumps of amyloid (Congo red 400x) (c) TBSRTC category VI Poorly differentiated carcinoma-cluster of large cells with hyperchromasia. (MGG 400x). (d) TBSRTC category VI lymphoma-abnormal lymphoid cells. (MGG 400x).

Table1.Number of cases in various diagnostic categories and subcategories according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

Sr.No.	Cytological categories	Subcategories	Number of cases	Total no of cases in each category (%)
1	Non diagnostic/unsatisfactory (ND/UNS)	-	32	32(3.68)
2	Benign	Consistent with 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	575 177 02	754(86.77)
3	Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)	-	15	15(1.73)
4	Follicular neoplasm/suspicious for follicular neoplasm(FN/SFN)	-	28	28(3.20)
5	Suspicious for malignancy (SFM)	Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma others	18 04 00 00 00	22(2.53)
6	Malignant	Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated(anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic carcinoma Non-Hodgkin lymphoma Others	13 03 01 00 00 00 00 01 00	18(2.07)
Total			869	869(100)

(1) Figures in brackets indicate percentages.
(2) "Other" subcategory in benign category consisted of cases of chronic nonspecific abscess.
(3) "Other" subcategory in suspicious for malignancy category consisted of a case of suspicious for malignancy, not otherwise specified

Table 2. Cytological/histopathological diagnosis correlation

Cytopathological categorization	Number of cases where surgical specimens were received (n=141)	Per cent of the category	Histopathological diagnosis	Number of cases	Risk of malignancy
ND/UNS (n= 32)	-	-	-	-	-
Benign(n= 754)	111	79	Nodular goitre Follicular adenoma Papillary thyroid carcinoma Colloid goitre	72 09 02 28	1.8%
AUS/FLUS(n=15)	04	03	Follicular adenoma Papillary thyroid carcinoma	03 01	25%
FN/SFN(n=28)	07	05	Follicular adenoma Papillary thyroid carcinoma Follicular carcinoma	02 01 04	29%
SFM(n=22)	10	07	Hyperplastic goitre Adenomatoid goitre Papillary thyroid carcinoma Follicular adenoma Medullary carcinoma	01 01 05 01 02	70%
Malignant (n=18)	09	06	Papillary thyroid carcinoma Medullary carcinoma	07 02	100%

(1) 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.

(2) n = total number of cases

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