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EVALUATION OF THE POSITIVE PREDICTIVE VALUE OF ATYPICAL THYROID CYTOLOGY CASES ACCORDING TO BETHESDA SYSTEM.

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ABSTRACT… Objectives: For the past 20 years Fine Needle Aspiration Cytology (FNAC) has evolved as the most sensitive diagnostic tool for the initial screening of patients with thyroid nodules. Unfortunately FNAC is complicated by a recognized false negative rate of approximately 5%. The clinicians could face the difficulty in the management of patient when a cytological diagnosis is atypical only. The objective of study is to evaluate the positive predictive value (PPV) of atypical thyroid cytology cases according to the Bethesda system taking histopathology as gold standard. **Study Design:** Cross sectional study. **Setting:** Department of Pathology at Shaikh Zayed Hospital, Lahore. **Period:** Six months i.e. from 25.11.2014 to 25.5.2015. **Materials and Methods:** Patients presenting with solitary thyroid nodules in the outpatient department and fulfilling the inclusion criteria were included after evaluation by thyroid function tests and thyroid scan, FNAC was performed and reported according to Bethesda system of thyroid reporting. Later on, cases underwent lobectomy, total or hemi-thyroidectomy, the tissue was received in 10% formalin solution in our pathology department and then processed, stained and examined. FNAC results of atypical cases were then compared with the definitive histological diagnosis which were considered the gold standard. The slides were examined and any differences were sought by consensus of two pathologists. Eighty cases were observed with 95% confidence level, 11% margin of error, using non-probability purposive sampling technique for sample collection. Data was analyzed by SPSS version 15 (P value <0.05). **Results:** The mean age of patients was 38 years with SD $\pm$ 2.16. There were 22 (28%) males and 58 (72%) females in our study. In this study, positive predictive value for Atypia of undetermined significance/ Follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm (FN), suspicious for malignancy and positive for malignancy were 33.3%, 25%, 66.6% and 100% respectively. Overall PPV of atypical cytology was 35.71%. Overall accuracy of FNAC was 86.30%, 87.50% sensitivity and 86.15% specificity, PPV value 43.75% and negative predictive value was 98.25%. **Conclusion:** Results showed that Bethesda system of reporting is helpful for the management of patients who falls in to undetermined categories as it categorically divide atypical cytology cases in to three definite categories AUS, FN and suspicious for malignancy and these categories have different risks of malignancy. Thus can help to determine a better patient outcome due to proper clinical management of thyroid swellings.

Key words: Atypical Thyroid Cytology, Bethesda System, Gold Standard, Histopathology, Positive Predictive Value.

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INTRODUCTION

Thyroid neoplasm is the most common form of endocrine malignancy. The incidence of palpable thyroid swelling is 4-7%. As there is a 14% life time risk of developing a thyroid nodule, screening thyroid nodules has emerged as a common medical problem[1], but only 5-10% of thyroid nodules are malignant on histology. It is neither essential nor possible to surgically remove every thyroid swelling.[2] For initial screening, FNAC is considered accurate, cost effective and sensitive diagnostic tool. The sensitivity and specificity of thyroid FNAC ranges from 65 to 98% and 73 to 100% respectively.[3] Approximately 5% of false negative cases complicate FNAC which may be due to procedure technique, slide preparation and experience of cytopathologist. Quite often clinicians face difficulty in the management of

patient with atypical category of cytological diagnosis which may result in overtreatment in some of the patients which is considered FNAC limitation.[4] For uniform reporting standards, Bethesda System For Reporting Cytopathology (TBSRTC) was introduced.[5] The present study is based on the objective to evaluate the positive predictive value of atypical thyroid cytology cases according to the Bethesda system taking histopathology as gold standard.

MATERIALS & METHODS

This is a cross sectional study conducted at Department of Pathology, Shaikh Zayed Hospital, Lahore. Cases were collected for six months from November 2014 to May 2015. Sample size was calculated with 95% confidence level, 11% margin of error taking an expected positive predictive value of FNAC as 55.9%[6] by non-probability purposive sampling technique. Female patients were 58 while 22 were male presented with solitary thyroid nodule with 25 to 70 years of age who had atypical cytological diagnosis followed by surgical treatment were included in the study whereas the toxic goiter for example Grave's disease presented as hyperthyroidism confirmed by clinical evaluation and laboratory parameters were excluded from the study. Demographic features that is sex, age and address and telephone contacts (for follow up) were recorded. After evaluation by thyroid function tests and thyroid scan, FNAC was performed using 25 gauge needle. One direct smear was prepared from aspirated material. Two slides were fixed in 10% formalin for staining with hematoxylin and eosin and PAP. Four slides were air dried for Giemsa staining. Bethesda system of thyroid was used for cytological reporting. Cases underwent total or hemi-thyroidectomy, the tissue were fixed in 10% formalin solution in our pathology department and then processed, stained and examined. FNAC results were then compared with the definitive histological diagnosis which were considered the gold standard. In order to minimize inter-observer variation, the slides were examined by three consultant histopathologists separately and any differences were sought by consensus of two pathologists. The study was approved by College of Physicians and surgeons Pakistan. All the data was entered and analyzed by using SPSS version 15 (P value < 0.05) as significant. Quantitative data like age was presented by mean and S.D. Qualitative data like gender was presented by frequency and percentages. All the results were presented in the form of tables and charts. Confounding factors were control by stratification at the time of analysis. There were no emotional threat to patient. Ethical committee approved certificate was attached.

RESULTS

Total 80 patients were included in the study. Fifty eight (72%) were females and 22 (28%) were males with mean age ± SD of 38 ± 2.16 years. The number of diagnosed atypical cases were 14 which were reclassified in to three categories: AUS 3(4%), FN 8 (10%) and suspicious for malignancy 3(4%). FNAC findings were analyzed and compared with histopathology according to the Bethesda system (Table-I). The positive predictive value values for AUS, FN, suspicious for malignancy and positive for malignancy were 33.3%, 25%, 66.6% and 100% respectively. Overall PPV of atypical cytology was 35.71% as shown in Table-II. Overall accuracy of FNAC was 86.30%, 87.50% sensitivity and 86.15% specificity, PPV value 43.75% and negative predictive value was 98.25%.

		Histopathology, n (%)	
Categories	**FNAC, n (%)**	**Benign**	**Malignant**
Unsatisfactory	7(9%)		
Benign	57(71%)	56(70%)	1(1%)
Atypia/follicular lesion of undetermined significance	3(4%)	2(3%)	1(1%)
Suspicious for follicular neoplasm	8(10%)	6(7%)	2(3%)
Suspicious for malignancy	3(4%)	1(1%)	2(3%)
Malignant	2(2%)	0	2(2%)
Total	80(100%)	65(81%)	8(10%)

Table-I. Cytologic and histologic correlation according to Bethesda system.

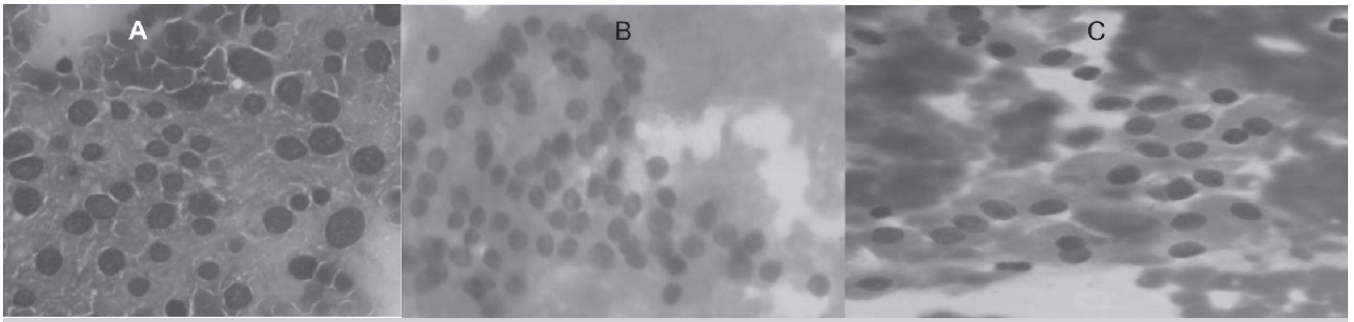

Image-A. Showing nuclear enlargement and architectural atypia, atypia of undetermined significance (AUS) was given (H&Ex40). B. suspicious nuclear grooves and occasional pseudo inclusions, AUS is the proper diagnosis (H&Ex40). C. Hurthle cell change Follicular neoplasm / Hurthle cell neoplasm (FN/Hurthle cell neoplasm) is the correct diagnosis (H&Ex40).

Cytological	Cases no	Histological Diagnosis		Frequency	PPV
Bethesda 3 (AUS)	3	Benign	Multinodular hyperplasia Hashimoto thyroiditis	1 1	
		Malignant	Follicular variant of papillary carcinoma	1	33.3%
Bethesda 4 (FN)	8	Benign Malignant	Adenomatous hyperplasia Follicular adenoma Hurthle cell adenoma Hashimoto thyroiditis Follicular carcinoma Follicular variant of papillary carcinoma	1 3 1 1 1 1	25%
Bethesda 5 (Suspicious for malignancy)	3	Benign Malignant	Hashimoto thyroiditis Papillary carcinoma	1 2	66.6%
Total	14				35.71%

Table-II. Cytologic and histologic correlation of atypical cases with PPV according to the Bethesda system (n=14)

DISCUSSION

Unfortunately FNAC is complicated by a recognized false negative rate of approximately 5%. Cytopathologists should interpret the results of FNAC that clearly indicate the management approach. The terminology for thyroid FNA has varied significantly from one laboratory to another, creating confusion in some cases and hindering the sharing of clinically meaningful data among multiple institutions.[1] The clinicians could face the difficulty in the management of patient when a cytological diagnosis is atypical only. It may result in overtreatment in some of the patients. In the solitary thyroid nodule given as benign, the surgeons usually follow-up the patient for certain time period and then reevaluate the patient while in indeterminate categories a definite surgical treatment is required. Each diagnostic category in Bethesda has an implied risk of malignancy (ranging from 0% to 3% for the benign category to virtually 100% for the malignant category) that links it to a rational clinical management guideline.[1] A comprehensive study done by Theoharis CGA et. al[2] at Yale University School of Medicine showed that the proposed classification system is very good for reporting thyroid FNAs and this system guide patient management. According to them specificity for diagnosing malignant cases were 93% while specificity for all neoplasms were 68% and risk of malignancy for FN, suspicious and positive for malignancy were 34%, 87% and 100% respectively. They agreed that every diagnostic category is useful when there is any uncertainty. Another study done by

department of pathology King Edward Medical University Lahore Pakistan by Bukhari et. al on cytohistologic correlation using Bethesda system, showed a high diagnostic accuracy of FNAC involving 120 cases. The sensitivity was 100%, 82.5% specificity and the positive predictive value was 45%.[4]

In our study the FNAC cases diagnosed as atypical with few intranuclear grooves were included in the suspicious for malignancy category and were proved to be papillary carcinoma on histology while one case turned out to be benign. The other pattern was nuclear enlargement with mild architectural atypia with suspicious intranulear grooves. These cases were placed in AUS category among which two cases were found to be benign while one case was of follicular variant of papillay carcinoma. Other findings included were Hurthle cell change, microfollicular pattern. They were placed in FN, two cases were malignant only, and one was of follicular carcinoma and other of follicular variant of papillary carcinoma while others came out to be benign on histology (photomicrograph). These findings are similar to the study done by Chung YS et.al in which most common finding in atypical cases were few nuclear grooves and intranuclear inclusions in low cellularity aspirates. On histopathology most common diagnosis was papillary carcinoma. The malignancy rate according to the main cytological features was 77.3%. According to them based on Bethesda system 39.2% of the cases diagnosed as atypical could be grouped in to the category of suspicious for malignancy and yielded a malignancy rate of 76.9%. The Bethesda emphasizes that the diagnostic rate of atypical cases should be less than 7%. Thus the Bethesda system seemed to provide stricter boundaries for the atypical cytology and to aid in reducing the rates thereof.[5]

Bongiovanni et.al evaluated 6362 cases of FNAC and after cyto-histologic correlation they gave accuracy of 68.8%, 97% sensitivity, 50.7% specificity and positive predictive value as 55.9%. In their study incidence of malignancy of AUS category was 5.9% while in our study it is quite high as 33.3%.[6]

In our study most common diagnosis on histopathology among benign cases were nodular hyperplasia (NH) and one case came out to be of malignant, follicular variant of papillary carcinoma. Three cases diagnosed as AUS on FNAC, two cases turned out to be benign diagnosed as Hashimotos thyroiditis and nodular hyperplasia on histology while only one was malignant. Most common malignant tumor was papillary carcinoma while one case turned out to be of follicular carcinoma diagnosed as suspicious for follicular neoplasm on cytology. In indeterminate cases five cases were found to be malignant on histology (Table-II). These results are incordance with the findings published by Samreen et. Al. They evaluated diagnostic accuracy of 528 FNAC cases as 80.3%, specificity 85.1% and sensitivity 64.3%. They used Bethesda system for cytology interpretation and compared histopathology of 61 cases, thus calculated risk of malignancy for AUS, FN and suspicious for malignancy as 33.4%, 25% and 100% respectively.[7] Their results are almost similar to our study. A study done at Rex Hospital in 2012 showed 35% malignancy rate of AUS category and they recommended a careful use of this category.[8]

A study conducted in 2010, malignancy risk for atypia of undetermined significance or follicular lesion was 17%, follicular neoplasm or suspicious of follicular neoplasm was 25.9% and suspicious for malignancy was 70%. Nayar and Ivanovic calculated malignancy risks as intermediate for neoplasm 6%, follicular neoplasm 14%, suspicious for malignancy 53%.[9] Thus there has been wide variation and subjectivity in the interpretation and reporting of uncertain categories and aspirates with atypical features. The nonuse of standardized terminology and the varying diagnostic schema used by different institutes has led to inconstant practice among pathologists, clinicians and surgeons.

Choudhary et.al in 2016 did cyto-histopathological correlation of 386 cases according to this system and they found sensitivity, specificity and positive predictive value as 75.2% 98.2% and 90.0% respectively.[10]

Reddy et.al in 2018 evaluated 484 cases, out of which 54 cases were available for cyto-histological correlation. Out of 54 cases 14 were placed in indeterminate categories 10 were FN, 3 were suspicious for malignancy, and 1 case was of AUS. They concluded that the Bethesda system has high accuracy (90.7%), positive predictive value of 80% and negative predictive value of 93.1%.[11]

Nandedkar et.al in 2018 also found similar results after evaluating 580 cases by this system. They did cytohistologic correlation in 148 benign cases and 18 malignant cases and calculated sensitivity of FNAC as 85.7%, specificity 98.6%, and diagnostic accuracy 97.7%.[12]

In another study conducted by Kim DW et. al[13] the sensitivity and negative predictive value of performing an US-FNAC for the diagnosis of non-palpable thyroid nodules were high as compared with values obtained for other studies; however, positive predictive value was low. The small positive predictive value (PPV = 37%) indicates that many of the positive results from this testing procedure are false positives. Thus it will be necessary to follow up any positive result with a more reliable test (Histopathology) to obtain a more accurate assessment as to whether cancer is presented. Thus, FNAC has certain limitations especially when follicular neoplasm is considered, as the criteria of diagnosis is based on histology whether capsular invasion is present or not. The Bethesda system included these cases in category of Follicular neoplasm/ Hurthle cell neoplasm. The definite diagnosis of benign and malignant are decided on histology and thus the treatment plan is surgery. This information was lacking in the word atypical only.

CONCLUSION

These results showed that this classification system is helpful for the management of patients who falls in to indeterminate categories as it categorically divide atypical cytology cases in to three definite categories AUS, FN and suspicious for malignancy and these categories have different risks of malignancy. Thus can help to determine a better patient outcome due to proper clinical management of thyroid swellings.

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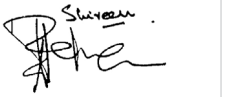
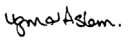
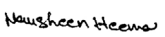
1	Shireen Hamid	Writer.	
2	Aman ur Rehman	Supervision.	
3	Muhammad Kashif Baig	Co-helper for biostatics.	
4	Uzma Aslam	Review and editing.	
5	Nausheen Heena	Review and editing.	
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