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RESEARCH ARTICLE

THE BETHESDA SYSTEM FOR THYROID CYTOPATHOLOGY REPORTING: A SINGLE CENTRE STUDY CONTRIBUTORS

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ABSTRACT

Background: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has attempted to standardize reporting and cytological criteria in aspiration smears. **Aim:** 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 100 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/ un satisfactory (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. Cytohistological correlation was done, when surgical material was available. **Results**: The distribution of various categories from 100 evaluated thyroid nodules was as follows: 7% ND/UNS, 20% benign, 3% AUS/FLUS, 23% FN, 3% SFM, and 44% malignant. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated. **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. Use of TBSRTC for thyroid FNAC reporting helps to highlight increased malignancy risk associated with FN, SM and malignant categories as well as provide data in a standardize pattern to ompare between different studies related to cytology of thyroid lesions.

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INTRODUCTION

Fine-needle aspiration (FNA) of the thyroid gland has proven to be an important and widely accepted, cost-effective, simple, safe, and accurate method for triaging patients with thyroid nodules (Sakorafas, 2010). It has an essential role in the evaluation of euthyroid patients with a thyroid nodule as it reduces the rate of unnecessary thyroid surgery for patients with benign nodules and appropriately triages patients with thyroid cancer to appropriate surgery (Cibas, 2009). However, terminology of reporting thyroid FNACs has varied markedly. Various reporting formats of thyroid FNACs have been used varying from two category schemes to six or more category schemes (Wang, 2006). While some of them tried to diagnose various lesions using histology-equivalent categories. It made it difficult for clinicians to interpret the reports. To address terminology and other issues related to thyroid FNACs, the National Cancer Institute (NCI) hosted "The NCI Thyroid Fine Needle Aspiration State of the Science Conference" at Bethesda, Maryland. Its recommendations were widely published (Cibas, 2008; Baloch, 2008). Subsequently a monograph "The Bethesda System for Reporting Thyroid Cytopathology" (TBSRTC) which includes definitions, diagnostic/morphologic criteria, explanatory notes, and a brief management plan for each diagnostic category was published (Ali, 2010). TBSRTC is a six-category scheme of thyroid cytopathology reporting (Table 1). Each category has an implied cancer risk, which ranges from 0% to 3% for the "benign" categoryto virtually 100% for the "malignant" category. It uses threecategories, AUS/FLUS, SFN/ Hurthle cell neoplasm, and SFM, to report thyroid aspirates that fall between benign andmalignant. As a function of these risk associations, each category is linked to evidence based clinical management guidelines (Ali, 2011; Cibas, 2009). The objective of the present prospective study, done in an Indian cancer 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

The present study was carried out at the Department of Pathology, Bhagwan Mahaveer Cancer Hospital and Research Center, Jaipur. The study was done for a duration of three years commencing from 2011 to 2014. It was conducted after obtaining the ethical approval from the Ethical Review Committee. All the patients with thyroid nodule attended our institute were included in the study. A detailed clinical examination done and all clinical data were collected. FNACwas performed in all cases be it ultrasound guided or not and slides were stained with routine haematoxylin and eosin and MGG, then studied for reporting. Resected specimens including lobectomy / sub-total thyroidectomy / total-thyroidectomy were received on frozen section if indicated or else for routine histopathological examination. Formalin fixed paraffin embedded tissue sections were stained with H&E. Slides were prepared and subjected for histopathological diagnosis. Blocks & slides for review were also included. The FNAC slides were reported according toTBSRTC. A total of 6 general diagnostic categories with some categories having two alternative names and some having degree of sub-categorization were recommended in this. Each of the categories has an implied cancer risk that links it to a rational clinical management guideline. Cytological diagnosis was correlated with the histopathology and the efficacy of FNAC was estimated. The statistical values were interdependent and indicating the accuracy of results.Calculation of malignancy rate was done as follow:

ND/UNS: No. of malignant cases on surgical resection /no. of cytohistological correlations inthis category x100

BN: No. of malignant cases on surgical resection/total BN FNA x100

AUS: No. of malignant cases on surgical resection/no. of cytohistological correlation inthis category x100.

SFN: No. of malignant cases on surgical resection/no. of cytohistological correlation inthis category x100.

SM: No. of malignant cases on surgical resection/no. of cytohistological correlation in this category x100

MGT: No. of malignant cases on surgical resection/no. of cytohistological correlation inthis category x100.

In calculating the malignancy follow-up rate for the benign category, the total number of benign FNA diagnoses was used as the denominator, as similarly performed in otherstudies. [9, 10, 11]For all other diagnostic categories, malignancy follow-up rates werecalculated by using the number of cases with follow-up histology results.

RESULTS

A total of 100 cases were included in the study. The age range was 14 to 80 years and sex ratio was F:M::2.8:1. In all the 100 cases cytosmears were studied and graded according to TBSRTC as shown in table 1. Histopathologic examination was done in total 87 patients, 59 patients proved to be malignant remaining of which were benign. In benign cases 12 cases had follicular adenoma, 2 cases had oncocytoma, remaining cases had goitre or primary thyroid hyperplasia or Hashimoto's thyroiditis.

In malignant lesions maximum 45 patients had papillary carcinoma (figure2a), 8 patients had medullary carcinoma (figure2d & 2e), 2 patients had follicular carcinoma (figure2b), 2 patients had malignant poorly differentiated neoplasm (figure2f), 1 patient had anaplastic carcinoma, 1 patient had anaplastic carcinoma with focus of papillary carcinoma (Table 2). Frozen was done in thirty eight cases. Sixteen cases out of 38 were malignant & also confirmed on routine histopathologic examination. Of the remaining 22 benign cases in frozen section 4 turned out to be malignant on routine histopathologic examination. Out of total 100 FNAC cases 7% were Non diagnostic, 20% were benign, 3% were AUS, 23% were SFN/FN, 3% were suspicious for malignant and 44 % were malignant. Preoperative FNA diagnoses of 87 cases with histological follow up had 6 cases as ND/US, 11 cases as benign, 3cases each of AUS and SM, 23 cases as SFN/FN and 42 cases as malignant. FNA diagnosis according to TBSRTC was compared with diagnoses on HPE and malignancy risk was calculated for each category.

Among 7 cases which had FNA diagnoses as ND/US, 3 turned out to be malignant in HPE. Malignancy risk came out to be50% in this category. There were 20 cases which were diagnosed as benign on FNA in which 4turned out to be malignant on HPE. So malignancy risk was 36.4% in this category. 3 cases were diagnosed as AUS, all were reported malignant in HPE. So the malignancy risk was 100% in this category. Out of 23 cases diagnosed as SFN/FN, 4 turned out to be malignant on HPE. Hence malignancy risk was 17.4% for this category. 3 cases were diagnosed as SM. All of them were confirmed as malignant on HPE. The malignancy risk in this category was 100%. There were 44 malignant cases in FNA, out of which 42 turned out to bemalignant on HPE, confirming the malignancy risk as 100% in this category. The cases diagnosed as benign in both cytology and histology were taken as true negative, while those diagnosed as malignant both in cytology and histology were taken as true positive. Those cases which were benign in cytology and malignant on histology were taken as false negative and cases malignant on cytology and benign on HPE were labeled as false positive. In this study Sensitivity, specificity, PPV, NPV & diagnostic accuracy for FNAC were 76.27%, 89.28%, 100%, 69.44% & 80.46% respectively.Sensitivity & specificity of studies done by Muhammad Akram et al [12], GG Swamy et al[13] and Muhammad Saddique et al[14] were almost similar to our study. (Table 3).

DISCUSSION

It is a prospective study in which we followed the Bethesda system for reporting thyroid cytopathology (TBSRTC). In this study, FNAC findings showed maximum 44% cases in Bethesda grade VI i.e. malignant category and minimum number patients in category III & V i.e. AUS/FNUS and suspicious for malignancy. Comparison of percentage of cases in each category in present study & other studies is shown in table 1. The incidences in Bethesda I, III, IV, V were comparable with other studies. The number of cases in grade II (benign category) were less and in grade 6(malignant category) were exceptionally high in present study as this institute was a tertiary care cancer institute and many cases were referred from other hospitals. In Bethesda grade I and grade II the incidence of malignancy was higher as malignancy like papillary carcinoma which can be multifocal or small or cystic and can only be detected on multiple sectioning in final

Table 1. Comparison between present study & different studies in distribution of Bethesda grades

Study	Year	Category I	Category II	Category III	Category IV	Category V	Category VI
Ali &Cibas et al. (2011)	2011	Up to 10%	60-70%	Approx. 7%	Up to 35%	2.4-7.9%	3-7%
V.Y et al. (2010)	2010	18.6%	59%	3.4%	9.7%	2.3%	7%
Theoharis et al. (2007)	2009	11.1%	73.8%	3%	5.5%	1.3%	5.2%
E.A. Sinna et al. (2012)	2012	7.1%	33.1%	13.5%	16.5%	10.1%	19.5%
Tejinder Singh et al. (2013)	2013	1.25%	61.25%	10%	20%	3.75%	3.75%
Santosh et al. (2013)	2013	1.2%	87.5%	1%	4.2%	1.4%	4.7%
Muratli et al. (2014)	2014	10.8	59.5	8.7	0.6	2.8	17.6
Al-Shraim et al. (2012)	2012	6.2%	57.3%	13.6%	16.1%	1.5%	5.3%
Mehra et al. (2015)	2015	7.2	80	4.9	2.2	3.6	2.2
Mamtha et al. (2015)	2015	10.84	60	12.5	3.34	4.16	9.16
Present study	-	7%	20%	3%	23%	3%	44%

Table 2. Depicts the malignancy risk associated with different categories of TBSRTC after histopathological examination

Bethesda grading (no. of cases in present study)	Final HPE Impression present study	No of malignant cases in present study	Risk of Malignancy (%) by The Bethesda system	Risk of Malignancy (%) in present study
Bethesda grade I (n=7)	2 Follicular adenoma 1 goitre 3 papillary ca	3	1-4%	50
Bethesda grade II (n=20)	1 inflammatory pathology 2 primary thyroid hyperplasia 3 goitre 1 follicular adenoma 3 papillary ca 1 Follicular ca	4	0-3	36.5
Bethesda grade III (n=3)	2 papillary ca 1 medullary ca	3	5-15%	100
Bethesda grade IV (n=23)	2 primary thyroid hyperplasia 1 Hashimoto thyroiditis 3 goitre 2 oncocytoma 10 Follicular adenoma 4 papillary ca	4	15-30%	17.4
Bethesda grade V (n=3)	3 papillary ca	3	60-75%	100
Bethesda grade VI (n=44)	30 papillary ca 1 follicular ca 7 medullary ca 1 anaplastic ca 1 anaplastic & papillary ca 2 malignant poorly differentiated neoplasm	42	97-99%	100
Total=100	87			

Table 3. Comparison of different studies showing sensitivity and specificity of FNAC

Study	Sensitivity	Specificity
Muhammad AkramDogar et al. (1997)2007	71.42%	95.34%,
GG Swamy et al. (2007) 2011	75%	95.83%
Fazal Wahid et al. (2011) 2011	88.09%	77.50%
Sandhya et al. (2011)	90%	100%
Shirish et al. (2012)	90%	100%
Mohammed et al. (2011)	61.53%	98.9%
Muhammad Saddique et al. (2011) (2008)	75%	95.83%
Richa et al. (2012) 2012	89.47%	86.11%
Present study	76.27%	89.28%

histopathologic examination and FNAC being a blind procedure needle may not hit the accurate site. In some cases tumour was associated with goitre or thyroiditis and these were predominantly aspirated on FNAC (Table 2). Three cases were in grade III (figure1a). All of were turned out to be malignant (2 had papillary carcinoma and 1 had medullary carcinoma) on final histopathologic examination. Atypia was of insufficient degree to qualify for any of the suspicious categories and obscuring blood and clotting artefact precludes definitive evaluation. One of these patients had previous history of papillary carcinoma and other had strong clinical suspicion of malignancy leading to surgery followed by frozen section & final histopathologic examination (Table 2). Twenty-three (23%) cases were in Bethesda grade IV (figure1b). Four cases out of these turned out to be papillary carcinoma on histopathologic examination. Discrepancy can be due to subtle features of papillary thyroid carcinoma in these cases that were not appreciated on the FNAC sample (Table 2). In grade IV the risk of malignancy is 17.39% comparable to the risk predicted by the Bethesda System (15-30%). Three cases which were categorized in Bethesda grade V (figure1c) i.e. suspicious for papillary neoplasm proved to be papillary carcinoma on final histopathologic examination. These cases had sparse to moderately cellular smear. Smear had predominantly benign

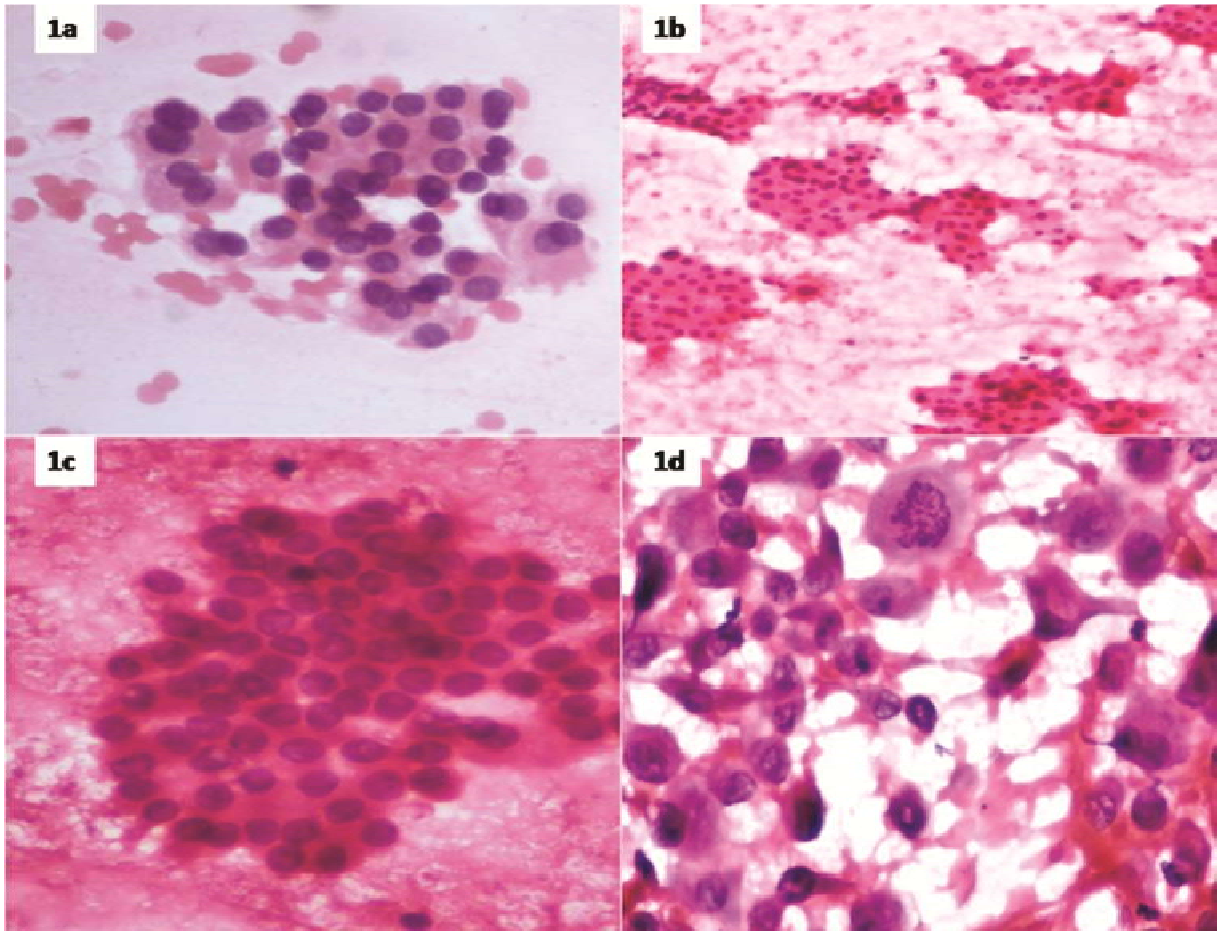

Figure 1. (FNA smear): (1a): AUS, Bethesda grade III, (H&E,x40);(1b): follicular neoplasm, Bethesda grade IV, (H&E,x10); (1c): Suspicious for papillary carcinoma, Bethesda grade V, (H&E,x40);(1d): Medullary carcinoma, Bethesda grade VI, (H&E,x40)

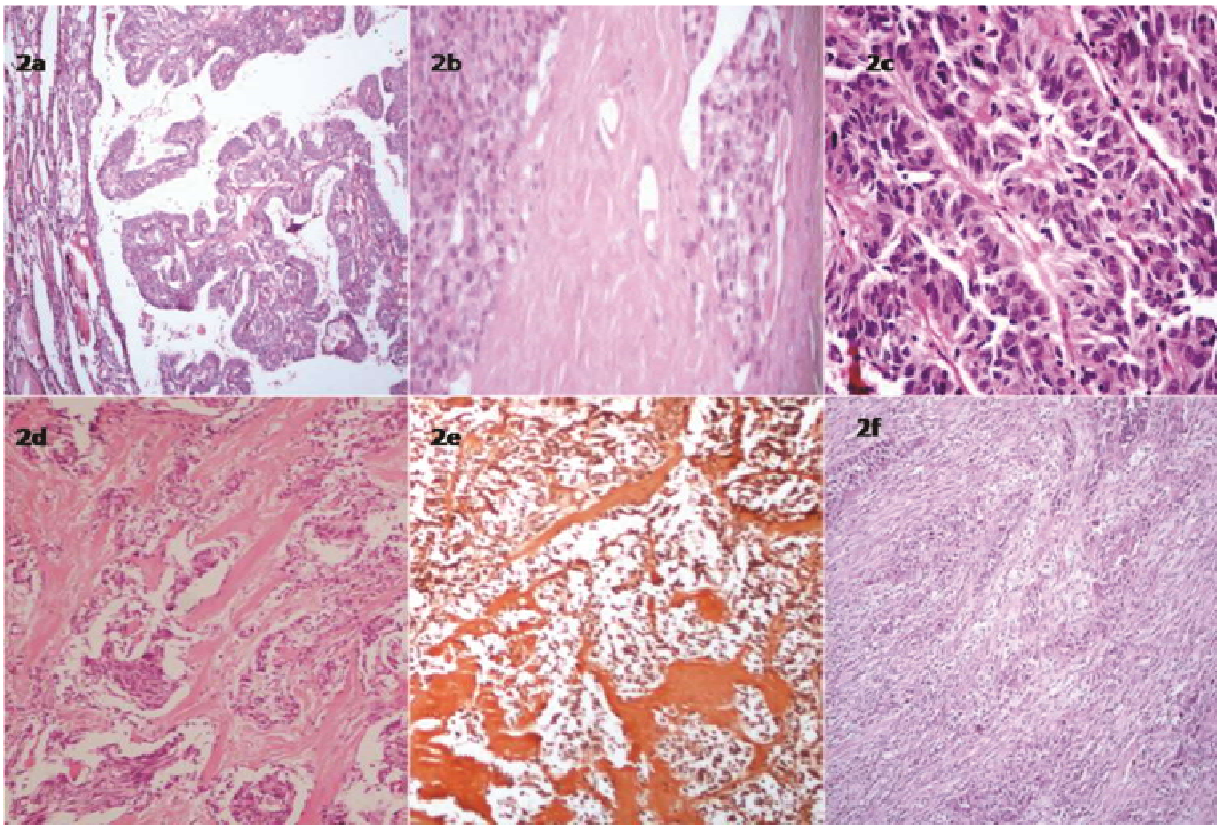

Figure 2(HPE): (2a): Micro-papillary carcinoma thyroid (H&E,x10); (2b): Follicular carcinoma ,vascular invasion(H&E,x10); (2c): Tall cell variant of papillary carcinoma, (H&E,x40); (2d): Medullary carcinoma, sheets of spindloidtumor cells with pink homogenous material (amyloid), (H&E,x10); (2e): Amyloid showing Congo red positivity in medullary carcinoma,(x10); (2f): Poorly differentiated carcinoma, diffuse sheets of tumor cells, (H&E,x10)

follicular cells mixed with some cells having enlarged pale nuclei, some cells having nuclear grooving and moulding but intra nuclear inclusions were not seen. So, findings were not conclusive for papillary carcinoma (Table 2). All the cases in grade VI (figure1d) those were received for histopathologic examination turned out to be malignant. There was 100% cyto-histological correlation in this category. Although HPE provided confirmatory diagnosis in most of the cases, some cases mentioned below had doubtful features on histopathology & were confirmed by IHC. Two cases had been reported as medullary carcinoma & malignant neoplasm respectively on FNAC. On HPE both had been reported as medullary carcinoma (had solid sheets & packets of polygonal spindle tumor cells traversed by delicate fibro-vascular septa with some pink staining material in small deposits). Serum calcitonin was within normal limits in both cases. On IHC one case proved to be solid & trabecular variant of papillary carcinoma and the other case proved to be minimally invasive follicular carcinoma on IHC. Markers for medullary carcinoma like synaptophysin, chromogranin, calcitonin, CEA, Mib1 were negative in these cases. One case which had been reported as malignant neoplasm on FNAC & malignant poorly differentiated neoplasm on HPE (had larger cells forming solid & focally follicular pattern) also proved to be poorly differentiated thyroid carcinoma with extensive angiolymphatic invasion & extra thyroidal extension. On IHC, EMA, CK, TG, TTF-1 markers were positive in this case. One case which had been reported as papillary carcinoma on FNAC & HPE (had tumor cells arranged in papillae with some nuclear features of papillary carcinoma) proved to be follicular adenoma on IHC. One case had been reported as follicular neoplasm on FNAC and follicular adenoma (had lack of capsular and vascular invasion with lack of distinctive nuclear features of papillary carcinoma) on HPE, proved to be follicular variant of papillary carcinoma on IHC. One case had been reported as malignant neoplasm on FNAC and malignant poorly differentiated neoplasm on HPE turned out to be high grade plasmablastic plasmacytoma on IHC. This case was positive for LCA, CD138, MUM 1& CD30 on IHC. One case had been reported as malignant neoplasm on FNAC. Possibility of Tall cell variant of papillary carcinoma/spindle cell variant of medullary carcinoma was given on HPE (had predominant tumor cells whose heights were at least three times their widths). This case had normal serum calcitonin & CEA. On IHC this case turned out to be tall cell variant of papillary carcinoma (figure2c). One case that had been diagnosed as colloid goitre on FNAC and minimally invasive follicular carcinoma on HPE, proved to be diffuse follicular variant of papillary carcinoma thyroid on IHC.

Conclusion

According to this prospective study the Bethesda System is very useful as a standardized system of reporting thyroid cytology. This is helping to improve communication between cytopathologist and clinicians and inter laboratory agreement, leading to more consistent management approaches. The high malignancy risk for the AUS/FLUS, SM & Malignant categories reflect the importance of these categories in the six tier Bethesda system. Our malignancy rate for AUS (100%), underscores the importance of using this terminology carefully and sparingly and that if applied strictly its subsequent malignancy rate may not be always low as reported in TBSRTC. Prospective studies using the TBSRTC will lend further insight into our results and the usefulness of TBSRTC.

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