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Assessment of diagnostic accuracy of Bethesda reporting system with fine needle aspiration cytology of thyroid lesions and its histological correlation

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Abstract
Background: Thyroid FNAC is widely recognized as the top diagnostic tool for evaluating thyroid nodules prior to surgery.
Objectives: Assessing the diagnostic precision of Bethesda system classifications and analysing the correlation between cyto-histopathological findings and FNAC results.
Material and Methods: In this study, a total of 88 thyroid FNA smears were reviewed, and histopathological correlations were made for 45 surgically excised cases.
Results: When considering follicular neoplasm/suspicious for follicular neoplasm as malignant, FNAC showed sensitivity of 88%, specificity of 82%, positive predictive value of 75%, negative predictive value of 92%, and accuracy of 84%.
Conclusion: FNAC stands out as an extremely sensitive and accurate tool for diagnosing diverse thyroid nodules.

Keywords: Thyroid diseases, fine needle aspiration cytology (FNAC), the Bethesda reporting system of thyroid cytology (TBRSTC)

Introduction

The most widespread endocrine conditions worldwide are thyroid diseases [1]. The prevalence of thyroid nodules ranges from 3%-7% through palpation, but when examined with ultrasonography it increases significantly to 19%-67%. [2, 3, 4]. Most of them are benign (90%), whereas thyroid cancer represents just 10% and is on the rise in various parts of the world [5]. FNAC is an emerging test as the first line of diagnostic tests performed on the patient's OPD visit. FNAC is safe, cost-effective, minimally invasive, and highly accurate in the diagnosis of nodular diseases [6, 7]. In general, about 5% of adult thyroid nodules are cancerous, with the majority being non-neoplastic or benign growths [8, 9].

Careful consideration must be given to selecting the specific neoplastic nodules when contemplating surgery for enlarged thyroid glands. Several classifications for thyroid cytology reports have been proposed to assess various terminology, descriptions, and interpretations of cytological appearances and transmit them to clinicians in a clear and replicable way. In this study, we assess the accuracy of the Bethesda reporting system and risk stratification for malignant transformation for thyroid lesions.

The main objective of this study is to determine the usefulness and precision of fine needle aspiration cytology within the scope of the Bethesda reporting system. Furthermore, this analysis specifically examines different histopathological profiles of thyroid tumors while also drawing comparisons between histological and cytological observations.

Materials and Methods

The retrieval of FNACs for thyroid lesions done during the years of 2021 and 2022 was accomplished by reviewing hospital records retrospectively. The patient data and other relevant information like clinical history, size and consistency of swelling, and nature of aspirate were retrieved obtained from the medical centers information database along with participants consents were obtained. Total of 88 cases were retrieved and their corresponding hematoxylin and eosin, Papanicolaou, and Giemsa slides were reviewed. The interpretations

were depicted according to TBSRTC. [Table 1] [10, 11].

Out of 88, 45 cases in which surgery was performed and received for histopathological evaluation were retrieved. All cases were reviewed, and the results were correlated with the cytological reports to evaluate the efficacy of the procedure, and the malignancy rate, especially in suspicious categories, was evaluated.

From benign 62 cases, only 25 cases underwent surgery for mainly cosmetic purposes or pressure symptoms, the rest were resolved by treatment. Six cases of malignant lesions were found as lost follow-up which SFN/FN consider as malignant.

Data was collected and depicted on an Excel sheet. Statistical analysis is performed in two different categories, one with SFN/FN as benign and the other with malignant to assess change in the sensitivity of the test.

Results

The outcome of 88 thyroid cases is tabulated in Table 2, in which Benign II (benign) was the largest at 55%, whereas else category I (ND/UNS) and category IV (FN/SFM) had 10% cases. 4.5% of cases constituted Category III(AUS/FLUS), while Category V (SFM)and Category VI (malignant) constituted 7.9% and 11%, respectively.

In the ND/UNS category, the majority of cases were subcategorized as hemorrhagic fluid only followed by cystic fluid. Only one case was reported as an acellular smear, all cases were advised to repeat FNAC and satisfactory results of those cases were not included in further study, as repeat FNAC was excluded.

In the benign category, 31.81% of total cases were consistent with nodular hyperplasia of the thyroid (figure 1A) followed by 17% of total cases that were consistent with colloid goiter with cystic degeneration these benign lesions thyrofolicular cells arranged in monolayer sheets with microfollicular arrangements and minimal amounts of anisonucleosis and h”urthels changes(2% cases). Only colloid or blood-mixed colloid present were present in 8.9% of cases, while 17% of cases showed cystic macrophages along with thyrofollicular cells in a background of colloid. All specimens had low to moderate cellularity. Another subcategory consistent with Hashimoto's thyroiditis had 4.54% of cases with moderate cellularity. The lymphocytes were infiltrated surrounding thyrofollicular cells. (figure 1B) Some of the cells showing h’urthel cells change, pale eosinophilic abundant cytoplasm with pleomorphic nuclei. 2.27% of cases showed multinucleated giant cells with a vague granulomatous cluster of epitheliod histiocyte with scant degenerated thyrofollicular cells over a hemorrhagic background which is labeled as granulomatous thyroiditis.

In the category AUS/FLIS,4.54% of cases reported. Predominantly showed micro follicles in moderate cellularity with scanty colloid. Only one smear showed focal areas of nuclear pleomorphism, grooving, and coarse chromatin, whereas else prominent component has benign features.

In this study, category FN/SFN constituted 10%, and 77.7% of these mainly showed repeated microacinar patterns with a fair amount of anisonucleiosis in the background of very scant or absent colloid. (figure 1C) 22.23% of cases reported as follicular neoplasm h”urthle cell type.

SFM category constitutes 7.9% of cases out of these 71.4% were suspicious of papillary carcinoma and 28.57% were suspicious of medullary carcinoma. (figure 1D) All of these cases were shown patchy and incomplete nuclear changes.

In malignant category, 11% of cases were included, maximum cases 40%, were labeled as medullary carcinoma of the thyroid followed by papillary carcinoma of thyroid (30% cases) and anaplastic carcinoma of thyroid (30% cases).

A total of 88 cases were studied cytologically, and a histopathological specimen of 45 cases was received and studied by two separate pathologists. (table 3).

Surgical specimens of 2 cases (22.22%) were received from the ND/UNS category and reported as nodular hyperplasia of thyroid histologically. (figure 2A) From 49 cases of benign category cytologically,21 cases (42.85%) were undergone for surgical resection, out of them only 1 case was reported as papillary carcinoma of thyroid. As papillary carcinoma may represent cystic changes in cytology more often. Out of 2 cases of AUS/FLUS, one case converted in follicular adenoma due to no capsular invasion, and one which was shown focal nuclear pleomorphism and grooving cytologically labeled as papillary carcinoma of thyroid

A difference between follicular neoplasm and adenoma more relay on capsular invasion histologically, of 7 cases of FN/SFN category, 4 were follicular adenoma and 2 were follicular carcinoma on histopathological evaluation, while one case was reported as a follicular variant of papillary carcinoma. (figure 2B).

Among the five cases of SFM analysed histologically, one was found to be a follicular adenoma while two of them each were identified as papillary carcinoma (figure 2C) and medullary carcinoma. (figure 2D).

8 out of 10 cases of malignant category, were evaluated the same as malignant histologically. None of cases of malignant cytology proved to be benign histologically.

Category-wise report of histological findings summarized in the form of malignant and benign in Table 4. Statistically, all data was evaluated in two different various in which one was calculated as FN/SFM as benign and in other as malignant. When FN/SFM is included in the malignant sensitivity of the Bethesda reporting system increases with a marked decrease in positive predictive value. (table 5).

Figure format

Table 1: The Bethesda system for reporting thyroid cytopathology; recommended diagnostic categories, implied risk of malignancy, and recommended clinical management [10, 11].

Diagnostic category	Risk of malignancy (%)	Usual management*
I. Nondiagnostic or unsatisfactory Cyst fluid only Virtually acellular specimen Other (obscuring blood, clotting artifact, etc.)		Repeat FNA with ultrasound guidance
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	0-3	Clinical follow up
III. Atypia of undetermined significance or follicular lesion of undetermined significance	5-15**	Repeat FNA
IV. Follicular neoplasm or suspicious for a follicular neoplasm Specify if Hu¨rthle cell (oncocytic) type	15-30	Surgical lobectomy
V. Suspicious for malignancy Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other	60-75	Near total thyroidectomy or surgical lobectomy
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 lymphoma Other	97-99	Near total thyroidectomy***

*Actual management may depend on other factors (e.g., clinical and sonographic) besides the FNA interpretation.
**Estimate extrapolated from histopathologic data from patients with “repeated atypicals”.
***In the case of “suspicious for metastatic tumor” or a “malignant” interpretation indicating metastatic a tumor rather than a primary thyroid malignancy, surgery may not be indicated

Table 2: Outcome of 88 cases of FNAC of thyroid lessons according to the Bethesda reporting system

Serial number	Cytological categories	Subcategories	Number of cases	Total number of cases in each category
1	Nondiagnostic/unsatisfactory	Cyst fluid only	2 (2.27%)	9 (10%)
		Acellular smear	1(1.1%)	
		Only hemorrhagic smear	6(6.8%)	
2	Benign	Nodular hyperplasia of the thyroid	28 (31.81%)	49 (55%)
		Colloid goiter with cystic degeneration	15 (17%)	
		Hashimoto thyroiditis	4 (4.54%)	
		Granulomatous thyroiditis	2 (2.27%)	
3	Atypia of undetermined significance/follicular lesion of undermined significance (AUS/FLUS)			4 (4.5%)
4	Follicular neoplasm /suspicious for a follicular neoplasm (FN/SFN)			9 (10%)
5	Suspicious for malignancy	Suspicious for papillary carcinoma	5 (5.68%)	7 (7.9%)
		Suspicious for medullary carcinoma	2 (2.27%)	
6	malignant	Papillary carcinoma of the thyroid	3 (3.40%)	10 (11%)
		Medullary carcinoma of the thyroid	4 (4.54%)	
		Undifferentiated/Anaplastic carcinoma of the thyroid	3 (3.40%)	
7	Total		88(100%)	88

Table 3: Shows a comparison of 45 cases that were received surgically and histologically evaluated

Cytological categories	Number of cases where surgical specimens were received (n-45) [a]	Percentage of category	Histopathological diagnosis	Number of cases
ND/UNS[b] (n-9)	2	22.22	Nodular hyperplasia of thyroid	2
Benign (n-49)	21	42.85	Nodular goiter	15
			Follicular adenoma	2
			Lymphocytic thyroiditis	3
			Papillary carcinoma	1
AUS/FLUS[c] (n-4)	2	50	Follicular adenoma	1
			Papillary thyroid carcinoma	1
FN/SFN[d] (n-9)	7	77.78	Follicular adenoma	4
			Follicular carcinoma	2
			Follicular variant of papillary carcinoma of thyroid	1
SFM[e] (n-7)	5	71.42	Follicular adenoma	1
			Papillary carcinoma of thyroid	2
			Medullary carcinoma of thyroid	2
Malignant (n-10)	8	80	Papillary carcinoma of thyroid	3
			Medullary carcinoma of thyroid	3
			Undifferentiated carcinoma	2

[a]n = total number of cases/UNS = nondiagnostic/unsatisfactory, [c]AUS/FLUS = atypia of undetermined significance/follicular lesion of undetermined significance, [d]FN/SFN= follicular neoplasm/suspected for a follicular neoplasm, [e]SFM =suspected for malignancy

Table 4: To histopathological correlation of 45 surgically resected cases

Cytological diagnosis according to Bethesda reporting system (n[a])	Histopathological diagnosis in benign and malignant categories	
	Benign	Malignant
ND/UNS [b](n=2)	2	0
Benign (n=21)	20	1
AUS/FLUS[c] (n=2)	1	1
FN/SFN[d] (n=7)	4	3
SFM[e] (n=5)	1	4
Malignant (n=8)	0	8

[a]n = a total number of surgically resected cases [b]ND/UNS = nondiagnostic/unsatisfactory, [c]AUS/FLUS = atypia of undetermined significance/follicular lesion of undetermined significance, [d]FN/SFN= follicular neoplasm/suspected for a follicular neoplasm, [e]SFM =suspected for malignancy

Table 5: Statistical evaluation of our study

Statistical parameters	FN/SFN *as benign	FN/SFN* as malignant
Sensitivity	70.5%	88%
Specificity	96.4%	82%
Positive predictive value	92%	75%
Negative predictive value	84%	92%
Accuracy	86%	84%

*FN/SFN -follicular neoplasm/suspicious for follicular neoplasm

Table 6: Statistical analysis of our study comprised of two different test groups FN/SFN as benign /FN/SFN as malignant and a comparison of our study with recent similar studies

Study	Sensitivity	Specificity	PPV	NPV
FN/SFN *as benign	70.5%	96.4%	92%	84%
FN/SFN* as malignant	88%	82%	75%	92%
Al-Sayer *et al*. [22]	86	93	80	96
Cusick *et al*. [23]	76	58	72	64
Altavilla *et al*. [24]	71.4	100	100	94.4
Ko *et al*. [25]	78.4	98.2	99	66.3
Kessler *et al*. [26]	79	98.5	98.7	76.6
Gupta *et al*. [27]	80	86.6	80	86.6

*FN/SFN -follicular neoplasm/suspicious for follicular neoplasm

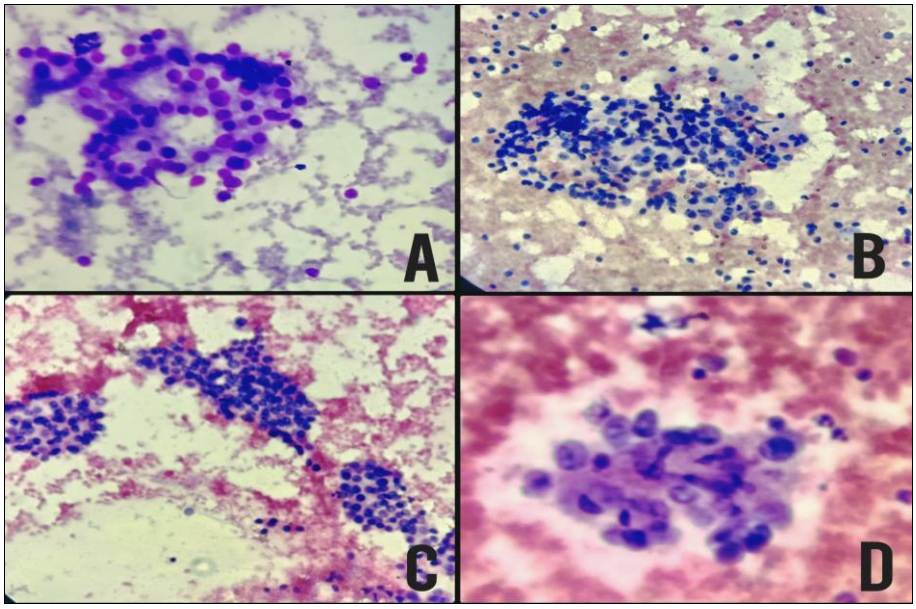

Fig 1: A- microfollicular arrangements of thyrofollicular cells in nodular hyperplasia of thyroid(Giemsa stain,40X); B-lymphocytic infiltration along with h"urthel cell changes in Hashimoto's thyroiditis(H&E,20X);C-nuclear overlapping with repeated micro acinar pattern in follicular neoplasm(H&E,20X);D-medullary carcinoma of thyroid (H&E,40X)

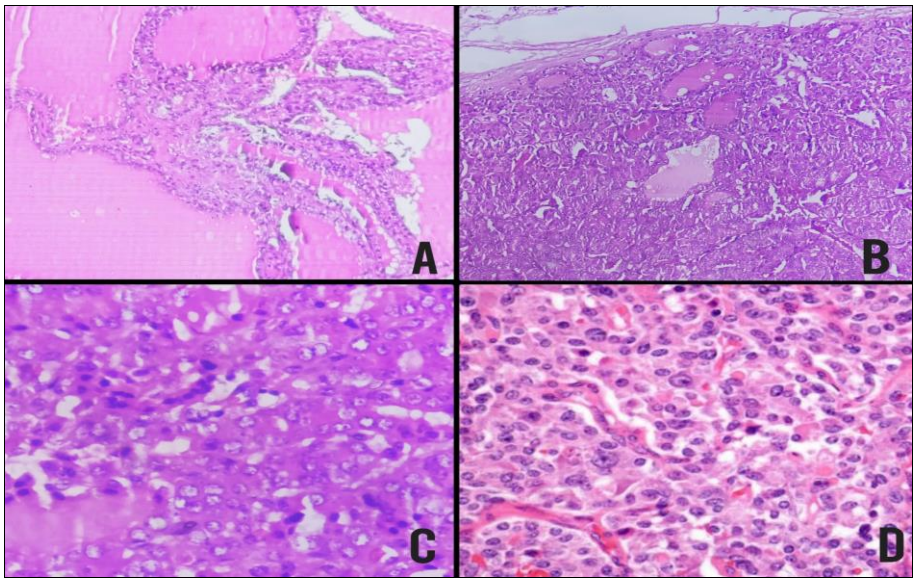

Fig 2: A-nodular hyperplasia of thyroid (H&E,40X); B-follicular arrangements of tumor cells in follicular variant of papillary carcinoma of thyroid (H&E,20X); C-orphan annie nuclei with high mitotic activity in papillary carcinoma of thyroid (H&E,40X); D- medullary carcinoma with amyloid deposition(H&E,40X)

Discussion

In this paper, we evaluated the accuracy of TBSRTC in thyroid aspiration cytologically, a one-year retrospective study in GMERS Medical College, sola.

TBSRTC does not recommend surgery for first 3 categories as they show low risk for malignant, thus clinical management and close follow-up are recommended. Category IV to VI shows an increased risk of malignancy, as we expected surgical resections of nodules or thyroidectomy as per Bethesda guidelines.

In this study, 10% of cases were in the ND/UNS category, other recent studies found that cases ranged from 1.2% to 16.4% [12-19]. To avoid misinterpretations caused by reparative changes, TBSRTC recommends waiting at least 3 months before resuming respiration.

The number of cases in the category depends on the skill of aspirators, hence pre-ad aspiration training is advised by committee.

Two surgical samples were submitted for examination, with both demonstrating nodular hyperplasia of the thyroid under histological analysis. The intention behind this surgery is entirely cosmetic, meeting the immediate needs of patients who refuse to wait three months.

The benign category had 55% cases with benign nodular hyperplasia of the thyroid followed by thyroiditis, this category had a range of 34% to 87.5% in other recent studies [12-19]. 21 cases of benign lesions underwent surgery and specimens were received because of pressure symptoms or cosmetic reasons. 15 cases were nodular goiter, 2 follicular adenomas, 3 lymphocytic thyroiditis, and only one case turned out as papillary carcinoma histologically. PTC is an incidental finding as this lesion was cystic and very small radiologically. However, The TBSRTCs recommendation on diagnostic terminology and morphologic criteria fails to acknowledge the presence of giant cells and epithelioid cells in LT as documented in previous literature [20-21]. The

AUS/FLUS category is specifically designated for samples with cells showing architectural and/or nuclear abnormalities, but not enough to be considered suspicious for a follicular tumor or malignancy. The atypia is more marked than can be ascribed confidently to benign changes. The appropriate course of action for an initial AUS/FLUS reading involves coordinating with healthcare professionals and arranging a timely repeat FNA if necessary. 1 out of 2 cases of AUS/FLUS were reported as papillary carcinoma, cytological smears of this case had not nuclear feature of PTC.

However, a recommendation for differentiation between follicular adenoma and follicular neoplasm is not clear in TSBTSTC. The diagnosis is based on the amount of microacinar or thyrofollicular cells in proportion to colloid and degree of anisonucleosis. 7 cases of FN/SFN were surgically resected. 4 cases turned out to be follicular adenoma and 3 cases turned malignant among them 2 were follicular carcinoma and one was a follicular variant of papillary carcinoma.

Histologically 5 cases of SFM, and only one case was labeled as follicular adenoma, in which nuclear pleomorphism is high grade but no capsular invasion was studied in repeated sectioning on histologically. Others turned out to be malignant papillary carcinoma and medullary carcinoma.

The NCI Thyroid Fine Needle Aspiration State of the Science Conferences Committee V has outlined recommendations for ancillary study indications, specific studies to conduct, and sample preparation protocols. It has been recommended to use immunohistochemistry panels for potentially cancerous growths such as medullary carcinoma (calcitonin, thyroglobulin, CEA, and chromogranin), anaplastic carcinoma (pan-cytokeratin), and metastatic carcinoma (TTF-1). It is recommended that these activities take place in the FNA cell block, with a dedicated pass allotted for studying [28].

A recent study showed that the malignant category ranged from 2.9% to 11% [12-19]. A total of 10 (11%) cases fell under the malignant category in this study. We received 8 cases for histological evaluation. All were diagnosed same histologically.

Table 6 provides a comparison of statistical parameters from other studies conducted in the past two decades. The results of statistical parameters can be modified by the approach taken to analyse the data. Suspected lesions being classified as positive can lead to increased sensitivity and reduced specificity. For the purpose of statistical analysis, we have grouped together the categories SFM and malignant.

The literature is now featuring numerous articles that utilize TBSRTC [29-31]. Thyroid cytology smears are now classified using the modern TBSRTC, which divides them into six specific categories. Additional validation is required through further prospective studies involving a greater number of cases with histopathological correlation. Consensus among institutions from diverse countries to employ TBSRTC will greatly simplify the process of sharing data for surveys and research worldwide.

Conclusion

The Bethesda guidelines were utilized in our study for a retrospective analysis of thyroid aspiration smears carried out by TBSRTC. Easy-to-read guidelines, complete with color graphs, simplify the diagnostic process. Hence, risk ratio and treatment suggestions are explained it be helpful for management. The precise likelihood of malignancy is hard to determine, highlighting the necessity for a thorough study with histopathological correlation in ambiguous or questionable scenarios.

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