Original Research Article

Cytohistologic correlation study of thyroid lesions

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Abstract

Background: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a significant step to standardize the reporting of thyroid fine needle aspiration (FNA). It has high predictive value, reproducibility, and improved clinical significance. **Objective:** The study was aimed to evaluate the diagnostic utility and reproducibility of "TBSRTC" at our institute. **Material and Methods:** The study included 704 thyroid FNAs which were reviewed by two pathologists and classified according to TBSRTC. Cytohistological correlation was done for 125 cases with surgical follow-up. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated. **Results**: Sensitivity, specificity and diagnostic accuracy of the study for malignant lesions were 72.2%, 99.06% and 95.2% respectively. PPV was 92.86% and NPV 95.49%. **Conclusion:** FNAC is an excellent, safe diagnostic procedure with high degree of accuracy, rapid results and less invasive procedure than a tissue biopsy. It plays a crucial role in the selection of patients for surgery.

Keywords: FNAC, Thyroid, Histopathology correlation, benign, malignant

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INTRODUCTION

Thyroid lesions are one of the common conditions encountered in clinical practice. The diseases of thyroid are of great importance because most of them are amenable to medical or surgical treatment. [1] It is often difficult to make an accurate diagnosis by clinical evaluation alone. Hence Fine Needle Aspiration Cytology (FNAC) study of such lesions along with clinical evaluation is emphasized in order to aid towards accurate diagnosis. As all palpable lesions can be assessed by FNAC technique, early diagnosis is often possible. It is a simple, minimally traumatic and an ideal first line diagnostic test. It is also a speedy and an accurate technique being used worldwide.[2] Given the ease of technique and relatively minimal invasive nature of the procedure, it has become a popular diagnostic modality. It is being widely used to differentiate benign from malignant lesions. But there is some "grey zone" of thyroid FNAC where the diagnostic efficacy becomes low, making it less reliable in categorizing the nature of the lesion leading to discrepant cases.[3] We conducted this study to determine the diagnostic efficacy of thyroid FNAC by comparing it with histopathology which is considered gold standard. We also reviewed the discordant cases and looked at causes for cytohistologic discordance. This may help in minimizing the false positive and false negative cases.

MATERIALS AND METHODS

The present study was undertaken to analyse the role of fine needle aspiration cytology in the cytomorphological features of various thyroid lesions with histopathological correlation wherever the surgery was done and to determine its diagnostic accuracy. TBSRTC was followed for reporting and cytological classification of the lesions. The study was undertaken in tertiary care teaching hospital during the period from May 2018 to May 2019. The study comprised of 125 patients who presented with the history of thyroid swelling in whom FNAC was done in our institute and further surgery on thyroid was performed. Patients who have had surgery at our institute but FNAC were not performed preoperatively for thyroid swelling was excluded. A total of 704 FNACs of thyroid were

performed during the period. But only 125 patients had undergone partial or total thyroidectomy and specimens were available for histopathological correlation. Information about the patient's age, sex, ultrasonography findings and cytological report was recorded. Of these patients who underwent surgery for lobectomy or partial or total thyroidectomies were subjected to histopathological examination and then their diagnoses were recorded.

Aspiration was done with full aseptic precautions using 23-gauge needle using a 10 ml syringe. Multiple smears were prepared from the aspirate and those immediately fixed in 95% ethanol were stained using Haematoxylin and Eosin (HandE) and Papanicolaou (Pap) stains and air-dried smears were stained with May Grunwald Giemsa (MGG). Whenever the aspirate yielded fluid, it was cytocentrifuged and the smears were prepared from the sediment and stained using the above-mentioned stains. Cytological diagnosis was correlated with the histopathology report in all the cases. Patients with other neck swellings were excluded from the present study.

The results were categorized as per the recent 2017 Bethesda classification into –

I-Non-diagnostic or unsatisfactory

II-Benign

III – Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance

IV-Follicular neoplasm or suspicious for a follicular neoplasm

V- Suspicious for malignancy

V- Malignant

Aspirates yielding insufficient or low cellularity or those that were of poor quality were considered "unsatisfactory". SPSS software was used for statistical analysis.

RESULTS

The present study was undertaken in tertiary care teaching hospital during the period from May 2018 to May 2019. 125 cases, where thyroidectomy specimens were available for histopathological correlation were included in the study. We correlated FNA diagnosis with histopathological confirmatory diagnosis. These conventionally diagnosed thyroid lesions were then classified according to the Bethesda system.

Retrospectively, the risk of malignancy was calculated in 125 cases in which cyto-histopathological correlation was available.

In this study, patient's age ranged from 19 - 85 years with mean age of 38.72 years.

Majority of the patients were females accounting for 85.09% and males 14.91% with male: female ratio of 1:5.

Of the 125 specimens 79 were non -neoplastic and 46 were neoplastic lesions **(Table No. I).** Out of non -neoplastic lesions, goitre comprised of 72 cases, 6 cases of Hashimoto's thyroiditis and 1 case of hyperplasia. Out of neoplastic lesions, follicular adenoma were 24 cases, Hurthle cell adenoma 4 cases and among the malignant lesions papillary carcinoma comprised of 15 cases and 1 cases each in follicular carcinoma, medullary carcinoma and squamous cell carcinoma each.

Table I: Showing Cyto - histological correlation of 125 cases

		HISTOPATHOLOGICAL DIAGNOSIS											
		Colloid goitre	Nodular goitre	Adenomatoid goitre	Hashimoto thyroiditis	Hyperplasia	Follicular adenoma	Hurthle cell adenoma	Papillary carcinoma	Follicular carcinoma	Medullary carcinoma	Squamous cell carcinoma
Colloid goitre	7	6							1			
Nodular goitre	63		57				2	1	3			
Adenomatoid goitre	9			8			1					
Hashimoto thyroiditis	6				6							
Hyperplasia	1					1						
Follicular neoplasm	22						21			1		
Hurthle cell neoplasm	3							3				
Papillary carcinoma	12		1						11			
Medullary carcinoma	1										1	
Squamous cell carcinoma	1											1
TOTAL	**125**	**6**	**58**	**8**	**6**	**1**	**24**	**4**	**15**	**1**	**1**	**1**

Out of seven cases of colloid goitre diagnosed by FNAC, six cases were histopathologically proven to be colloid goitre and one case turned out to be papillary carcinoma.
Out of sixty three cases of nodular goitre diagnosed by FNAC, 57 cases were histopathologically proved to be nodular goitre. Out of remaining six cases, two cases turned out to be follicular adenoma, one case hurthle cell adenoma, one case papillary carcinoma with MNG and two cases of micro occult papillary carcinoma.
Out of nine cases diagnosed as adenomatoid goitre by FNAC, eight cases histopathologically were consistent with adenomatoid goitre and one case was follicular adenoma.
Out of 22 cases of follicular neoplasm diagnosed by FNAC, 21 cases histopathologically were follicular adenoma and one case was follicular carcinoma.
Out of 12 cases of papillary carcinoma diagnosed by FNAC, 11 cases histopathologically were consistent with papillary carcinoma and one case turned out to be multinodular goitre.
TBSRTC categorization was carried out in all cytologically diagnosed cases. Out of 704 FNAC cases, 20 cases under non diagnostic/unsatisfactory –I category, 606 cases came under benign –II category, one case in Atypia of undetermined significance- III category, 44 cases in follicular neoplasm /suspicious of follicular neoplasm- IV category, 5 cases under Suspicious of malignancy- V category and 28 cases in Malignant- VI category.
Risk of malignancy was calculated for each Bethesda category, category I-10%, category II - 4.93% , category IV - 4.76%,category VI - 92.30% **(Table No. II).**

Table II: Table showing comparison of pre operative FNAC diagnosis with the diagnosis on histopathology after surgical resection and calculation of malignancy risk for each Bethesda category

Diagnosis of pre operative FNAC as per Bethesda system	Actual diagnosis observed on HPE after surgical resection	Number of cases which turned out to be malignant	Malignancy risk (%)
Non diagnostic-I (n10)	Nodular goitre – 2 Multinodular goitre – 5 Follicular adenoma – 1 Hurthle cell adenoma -1 Papillary carcinoma - 1	1	10
Benign –II (n-81)	Colloid goitre – 5 Nodular goitre – 18 Multinodular goitre -31 Adenomatoid goitre -10 Hashimoto thyroiditis -6 Hyperplasia – 1 Follicular adenoma- 4 Hurthle cell adenoma – 2 Papillary carcinoma - 4	4	4.93
Atypia of undetermined significance- III (n-0)		0	0
Follicular neoplasm/ Suspicious of follicular neoplasm-IV (n-21)	Follicular adenoma – 19 Hurthle cell adenoma – 1 Follicular carcinoma - 1	1	4.76
Suspicious of malignancy- V (n-0)		0	0
Malignant -VI(n-13)	Multinodular goitre – 1 Papillary carcinoma – 10 Medullary carcinoma -1 Squamous cell carcinoma – 1	12	92.30

In our study of 125 cyto histologically correlated cases, 13 cases (10.4%) were malignant on both FNAC and histopathology. 5 cases (4%) were benign on FNAC but malignant on histopathology. 106 cases (84.8%) were benign both on FNAC and histopathology **(Table No.III).**

Table III: Statistical data of cyto-histologically correlated 125 cases

FNAC	HISTOPATHOLOGY		
	MALIGNANT n (%)	BENIGN n (%)	TOTAL
MALIGNANT	13(10.4)	1(0.8)	14
BENIGN	5 (4)	106 (84.8)	111
TOTAL	**18**	**107**	**125**

Only 1 case (0.8%) was malignant on FNAC but benign on histopathology. X^2 - 78.731, df – 1, p value - 0.0001: Statistically significant.

In the present study, value of Kappa was 0.786, which signifies good agreement between FNAC and histopathological diagnosis which is the gold standard.

DISCUSSION

The goal of thyroid FNA is to successfully differentiate benign from malignant lesions and to triage patients requiring surgery. The six-tired Bethesda system provides standardized nomenclature for reporting thyroid FNA smears which enables better communication and understanding between clinicians and pathologists. The advantage of this systematic approach is that each of the six Bethesda categories has implied risk of malignancy which helps the clinicians to plan appropriate therapy necessary for the patient.[4] The value of a diagnostic test lies in its ability to detect the presence of disease when it is present (sensitivity) and reliably verify the absence of disease when it is not present (specificity). The reported sensitivity and specificity of the thyroid FNAC ranges from 43 to 99% and 72 to 100% respectively. Our findings are similar to those reported in other series.[5] In the present study, six cases of colloid goitre were diagnosed by fine needle aspiration cytology, out of which five cases were histopathologically proven to be colloid goitre but one case turned out to be papillary carcinoma on histology. On reviewing the histology slides, there were seen focal areas of dilated papillae filled with colloid and probably the aspiration needle has not hit that site. This can be avoided by aspirating from multiple sites of glands. In our case even on re-aspiration only colloid material was seen. Since most of the papillary carcinomas undergo cystic degeneration, cystic papillary carcinomas yield fluid aspirate with scant follicular cells, which masks the diagnosis of papillary carcinoma giving a false negative result. Braga M *et al.* (2001) found that cystic thyroid nodules are considered to be one of the major causes of non diagnostic and false negative results on conventional fine needle aspiration, thus limiting the potential of this method for the evaluation of complex thyroid nodules.[6] Ultrasound guided fine needle aspiration cytology is suggested as an excellent modality for the evaluation of the complex nodules and also for the re-evaluation of those nodules with non-diagnostic result on the conventional fine needle aspiration. Goellner JR in his study commented that cyst fluid showing no pathologic change and containing only degenerative foam cells should be interpreted as "nondiagnostic" rather than "negative".[7] In the present study, 63 cases of nodular goitre **(Figure 1)** were diagnosed by fine needle aspiration cytology out of which 57 cases histopathologically proved to be nodular goitre **(Figure 2).** Out of remaining six cases, two cases turned out to be follicular adenoma, one case Hurthle cell adenoma, one case papillary carcinoma with MNG and two cases of occult micro papillary carcinoma.

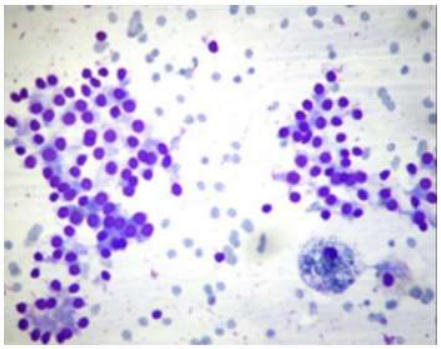

Figure 1: Photomicrograph of nodular goitre with cystic change showing sheets of follicular cells with cyst macrophages in thin colloid background. FNAC, (Leishman, 10X)

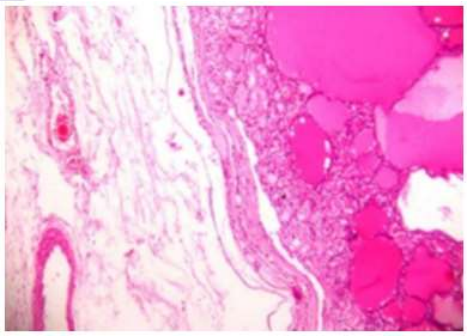

Figure 2: Photomicrograph of nodular goitre showing multiple colloid filled areas (HandE, 10X)

Two cases of follicular adenoma were missed on cytology due to the presence of thick colloid and hemorrhage in which cells were trapped. Hence, there was masking of repetitive follicles. One case of Hurthle cell adenoma was missed on cytology due to the presence of mainly hemorrhage with sparse follicular cells and Hurthle cells. This could have overcome by performing fine needle aspiration under ultrasound guidance. But in our study, inspite of guided FNAC, only hemorrhagic material and sparse follicular and Hurthle cells were seen. One case of papillary carcinoma with MNG was missed on cytology. On reviewing the cytology slides there were mainly follicular cells in sheets and in singles with many cyst macrophages in the background **(Figure 3).** There were no cytological features consistent of papillary carcinoma in the slides reviewed. Probably the aspiration needle has hit the MNG dominant nodule of thyroid gland but the nodule

was showing cytological features of MNG, cystic areas with papillary excrescences were not hit by our needle.

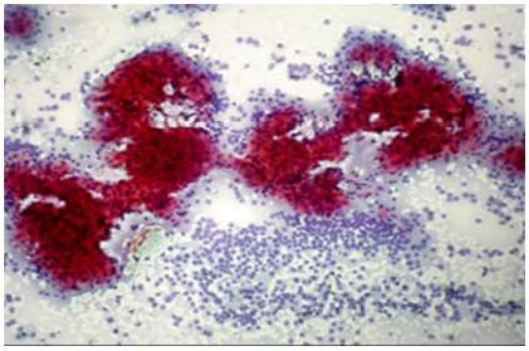

Figure 3: Photomicrograph of Papillary carcinoma showing highly cellular smears with cells arranged in complex branching papillary pattern. FNAC. (Pap. 10X)

Two cases of occult micro papillary carcinoma were missed on cytology. This was an incidental finding on histology and is one of the limitations of fine needle aspiration cytology. The term occult papillary carcinoma is used for tumours smaller than 1.5 cms in diameter and nowadays it is preferred for tumours with no clinical signs. In our study, one patient was a 29-year-old female who presented clinically as left lobe swelling measuring 3x3 cms in size. Other patient was a 36-year-old female who presented clinically as left lobe swelling measuring 1x3.5 cms in size. Occult papillary carcinoma of the thyroid may be discovered incidentally during surgery for an unrelated thyroid disease. They may present clinically with regional metastasis but the prognosis is excellent and not life threatening. These cases are usually missed by thyroid scintigraphy due to their small size. Most of these cases are found by accident and are confined to the thyroid according to large surgical and necropsy series by different authors. In the present study, nine cases were diagnosed as adenomatoid goitre by cytology out of which eight were consistent with adenomatoid goitre and one case was follicular adenoma on histopathology. Discordance in this case was mainly due to hemorrhage on cytology smears which are masking the repetitive follicles. Hall TL *et al.* in their study of 17 cases of follicular neoplasm on FNAC, 10 cases were confirmed on histopathology with a diagnostic accuracy of 58.8%. This less diagnostic accuracy is explained by the fact that, there always exist confusion between hyperplastic nodular goitre and follicular adenoma. This error is generally accepted as unavoidable because of cytomorphologic similarity and the need to maintain a high degree of sensitivity to the presence of a neoplastic process requiring surgical biopsy.[8] In the present study, there were 22 cases of follicular neoplasm diagnosed by cytology out of which 21 cases were follicular adenoma and one case was follicular carcinoma on histopathology. Limitation of thyroid cytology is its inability to distinguish follicular adenoma from follicular carcinoma. Diagnosis requires detailed histological examination for vascular or capsular invasion and cannot be readily made out on routine fine needle aspiration specimens. In the study of Gupta M *et al.,* 9 of the 12 cases of papillary carcinoma were correctly diagnosed on FNAC with a diagnostic accuracy of 75%. [9] In our study, 11 out of 12 cases were correctly diagnosed on FNAC with a diagnostic accuracy of 91.6%. In our study, there were 12 cases of papillary carcinoma diagnosed by cytology out of which 11 cases were consistent with papillary carcinoma but one case turned out to be MNG on histopathology. Papillary thyroid carcinoma is the most common malignant tumor of the thyroid. Its pathological diagnosis is based on classic nuclear features **(Figure 4).** Although majority of papillary cancers can be diagnosed and classified on the basis of set pathological criteria, there exists a group of cases in which benign thyroid tissue or lesions can mimic nuclear cytologic features or the architecture and growth pattern of papillary thyroid cancers, posing a diagnostic problem.

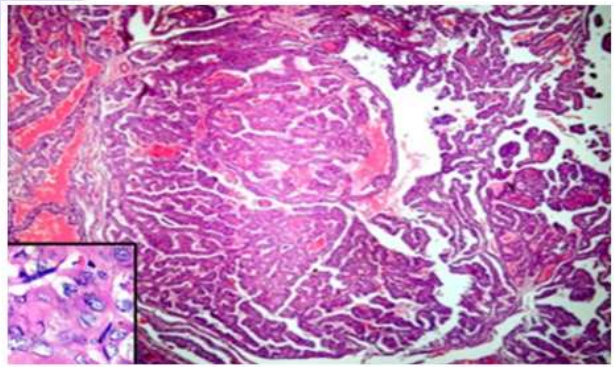

Figure 4: Photomicrograph of Papillary carcinoma showing papillae with fibrovascular core. (HandE 10X) Inset showing ground glass nuclei and nuclear grooving

Papillary formations can occur as a focal change or in the form of a dominant nodule in multinodular goitre, Hashimoto's thyroiditis and Graves disease. These papillary patterned lesions can be partly or totally composed of oncocytic cells and show complex papillae with well formed vascular cores or stroma poor edematous papillae with subfollicles. Fine needle aspirations of cytology specimens of solitary papillary hyperplastic nodules demonstrate cellular smears, transgressing vessels, papillary clusters, nuclear atypia, and pleomorphism, the presence of Intranuclear grooves, multinucleated giant cells and cells with vacuolated cytoplasm. In view of these features, such cases could be misclassified as suspicious of or consistent with papillary carcinoma. However in our case cytological features which mimicked papillary carcinoma features were having high cellularity, papillary clusters with anatomical borders,

presence of intranuclear inclusions and multinucleated giant cells. Khurana kk *et al.* in his study found few features on cytology which can help distinguishing solitary papillary hyperplastic nodules from papillary carcinoma. They were the presence of flame cell change, watery or inspissated colloid, short non- branching papillae and lack of well formed intranuclear inclusions.[10] However these changes were not seen in our case. Sekhri T *et al.* in their study, 2 cases of Hurthle cell neoplasm on FNAC were reported as Hurthle cell adenoma on histopathology with a diagnostic accuracy of 100%.[11] In the present study, 3 cases of Hurthle cell neoplasm was reported on FNAC which was confirmed on histopathology with a diagnostic accuracy of 100% similar to the study of Sekhri T *et al.* In the present study, six cases of Hashimoto's thyroiditis, one case of hyperplasia, one case of medullary carcinoma and one case of squamous cell carcinoma were diagnosed on cytology and they were concordant with histopathological diagnosis respectively The present study showed sensitivity of 72.2%, specificity of 99.06% PPV of 92.86%, NPV of 95.49% and diagnostic accuracy of 95.2 % which was similar to the observations made by GG Swamy *et al.* and Nurismah M *et al.*[12,13] Nandedkar *et al.* found high incidence of category II lesions since the patients directly visit a tertiary care center for primary diagnosis without any referral which was also the case in our study.[14]

CONCLUSION

The Bethesda System for Reporting Thyroid Cytopathology has standardized the diagnostic approach to reporting thyroid FNA ensuring better cyto-histological correlation. Universal application of this standardized nomenclature may improve interlaboratory agreement and lead to more consistent management approach.

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