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Oncopathology

"DIAGNOSIS OF THYROID NODULES BY BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY AIDED WITH IMMUNOCYTOCHEMISTRY".

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ABSTRACT **Introduction:** The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) provides a standardized framework for classifying thyroid nodule fine-needle aspiration (FNA) cytology results in management and risk stratification of thyroid nodules. Despite its utility, Indeterminate Categories pose diagnostic challenges. Immunocytochemistry (ICC) offers potential solutions by using specific markers to distinguish between benign and malignant nodules. **Objectives:**1. Analyze the cytological features and group the thyroid cytopathological reports based on the diagnostic criteria of Bethesda system for reporting thyroid cytopathology. 2. Use of immunocytochemistry (CK-19 and Galectin 3) for differential diagnosis of Indeterminate follicular patterned thyroid smears and whenever required for the diagnosis. 3. Analyze whether cytopathological diagnosis correlated with the histopathological diagnosis in cases where biopsy specimens were available. **Methods:** A cross-sectional study was done on 143 patients with thyroid nodule. FNA was done on all the patients and cytological diagnosis were made by using TBSRTC and ICC was performed on Indeterminate Categories (III, IV, V) and histopathological correlation was done in cases wherever the surgical specimens were received. **Results:** All the patients were diagnosed according TBSRTC. Out of 143 patients Category I included 5 cases, Category II included 104 cases, Category III included 11 cases, Category IV included 12 cases, Category V included 6 cases, Category VI included 5 cases. On Category III, IV, V, ICC was done to differentiate Benign lesions from Malignant lesions and histopathological correlation was done. ROM was calculated for every Category. **Conclusion:** TBSRTC was reliable and reproducible and its diagnostic accuracy was increased by using ICC in conjugation with it.

KEYWORDS : Bethesda System, Thyroid Cytopathology, Immunocytochemistry, Thyroid Nodules, Fine- Needle Aspiration.

INTRODUCTION

The thyroid gland is situated in the anterior part of neck, in front of the upper trachea and it is bilobed. Embryologically, it is derived from the floor of the primitive pharynx, as a down growth in the region of the developing tongue. The normal thyroid weighs 15 to 40 g in the adult. Histologically, it is composed of colloid-containing follicles lined by cuboidal cells with uniform round nuclei with a dense chromatin pattern.

Parafollicular C cells, believed to be derived from the ultimobranchial body, comprise a minor component of the thyroid gland. They are polygonal or spindled, with clear to pale cytoplasm, and occur singly or in small groups within the follicular basal lamina or in the inter-follicular interstitium.[1]

Fine needle aspiration cytology (FNAC) has emerged as one of the firstline diagnostic technique for thyroid nodule, as it is safe, cost-effective, minimally invasive, and accurate method for triaging patients with thyroid nodules.[2]FNAC was first described in the 1930's by Martin and Ellis.[3]

In 2007, "The Bethesda system for reporting thyroid cytology (TBSRTC) was proposed at the National Cancer Institute Thyroid FNA State of Science Conference at Bethesda, Maryland. This reporting system includes- layout of the report, adequacy of the sample, diagnostic category, risk of malignancy, and proposed clinical management. TBSRTC standardized the cytology reporting for thyroid lesions thereby, provide a uniform, explicit, and clinically pertinent reporting nomenclature".[4,5]

A 6-tier system named "Bethesda System for Reporting Thyroid Cytopathology" TBSRTC Diagnostic Categories I— Non-diagnostic (ND) II—Benign III—Atypia of undetermined significance (AUS) IV—Follicular neoplasm (FN) V—Suspicious for malignancy (SM), VI—Malignant.[6]

Due to the morphological similarities among various thyroid tumors with Follicular patterns, such as Follicular Adenoma, Follicular Carcinoma and Follicular Variant of Papillary Carcinoma, differentiating these tumors can be difficult. Additionally, nuclear features which are characteristic of Papillary Carcinoma (nuclear grooves and inclusions) can also be seen in other conditions like "multinodular goiter with papillary hyperplasia" and "hyalinizing trabecular adenoma". Immunocytochemistry aids in differentiating the benign lesions from malignant.[7] A panel of markers can be used like CK-19, Galectin 3, HBME-1, TTF-1, CD-56 in indeterminate categories for making more accurate diagnosis along with FNA results.

Cytokeratin 19: In thyroid cytology, CK-19 refers to Cytokeratin 19, which is a type of intermediate filament protein found in epithelial cells. This is a type of acidic protein. CK-19 is commonly used as a marker to distinguish thyroid follicular cells from other types of cells found in FNA samples. CK-19 expression patterns can help differentiate between benign and malignant thyroid lesions. Malignant thyroid tumors such as papillary thyroid carcinoma often show strong and diffuse CK-19 expression, whereas benign lesions may have weaker or focal expression, so it is useful in cases of indeterminate Category (III, IV, V).[8]

Galectin-3: Galectin-3 is a protein that plays a role in cell adhesion, proliferation, differentiation, and apoptosis. It is overexpressed in various cancers, including thyroid cancer, making it a useful biomarker in distinguishing malignant thyroid nodules from benign ones. When combined with other cytological features and markers like CK-19, Galectin-3 expression can significantly improve the accuracy of diagnosing thyroid malignancies, particularly follicular-patterned

lesions that are challenging to distinguish based on morphology alone.[9]

Need Of Study: "The Bethesda System for Reporting Thyroid Cytopathology is a standardized system used to report and interpret thyroid fine-needle aspiration (FNA) biopsy results". When paired with Immunocytochemistry (ICC), the diagnostic accuracy of TBSRTC can be enhanced and can lead to decrease the pitfalls of TBSRTC.

Problem Statement: The term "thyroid nodule" refers to a distinct thyroid lesion. Thyroid nodules present in thyroid gland can be present variably, as palpable or non-palpable (radiologically distinct from the surrounding thyroid parenchyma). Thyroid nodules are common, they are seen in about 8.5% of the population. The thyroid nodules are more common among the women. In India the prevalence of a palpable thyroid nodule is about 12.2%. Thyroid cancers are quite rare, the incidence is around 8.7 per 100000 people per year, though this seems to be increasing over the years.[10]

Aim Of Study: The present study aims the "Diagnosis of Thyroid Nodules by Bethesda system for Reporting Thyroid Cytopathology Aided with Immunocytochemistry".

Objectives:

1. Analyze the cytological features and group the Thyroid cytopathological reports based on the diagnostic criteria of "Bethesda system for Reporting Thyroid Cytopathology".
2. Use of immunocytochemistry (CK-19 and Galectin 3) for differential diagnosis of indeterminate Follicular patterned thyroid smears and whenever required for the diagnosis".
3. Analyze whether cytopathological diagnosis correlated with the histopathological diagnosis in cases where biopsy specimens were available.

Materials And Methods Study Setting

This study was hospital based and conducted in Department of Pathology in collaboration with Department of Otorhinolaryngology in S.N. Medical College, Agra over a period of eighteen months (from Sept 2022 to March 2024).

Study Design- Cross – Sectional study.

Inclusion Criteria: 1. All cases with visible thyroid swelling, which were referred to Cytology lab in Department of Pathology. 2. Ultrasound guided aspirate from nodular thyroid swelling were also included.

Exclusion Criteria: 1. Smear with non-thyroid component from nearby thyroid swelling were excluded from the study. 2. Any cases with previous history of thyroid malignancy and treatment were excluded.

Sample Size: The study was carried out on all cases with clinically confirmed thyroid nodules referred to cytology section of Department of Pathology and fulfilling the inclusion and exclusion criteria.

Methodology: After a thorough clinical examination, consent was obtained from the patients after explaining the procedure to them. The patients with nodular thyroid lesions were aspirated. The patients were examined in sitting posture, and then made to lie down in a supine position with pillow under the neck to expose the gland from surrounding soft tissues. During the procedure, the patient was asked to lie still and to refrain from swallowing. The site to be aspirated was fixed by immobilizing it between two fingers and the procedure was performed using a 22 G/23G needle only (NA) or using 20 ml syringe along with mentioned needle (FNA). The aspirated material was expressed on glass slides and slides were prepared by conventional method and airdried smears were stained by MGG. Wherever required slides were fixed in 95% ethanol and stained with PAP stain. In Indeterminate thyroid nodules, Immunocytochemistry was done for aiding in diagnosis. Immunocytochemistry (ICC) was processed over the thin smears which were prepared through liquid based cytology and CK-19 and Galectin-3 were used as markers to distinguish the benign and malignant lesions. Smears were examined and analyzed according to "TBSRTC". In Indeterminate cases Immunocytochemistry findings were correlated with cytological findings for proper cytological diagnosis. The cytological findings of thyroid nodule were correlated with histopathological reports wherever possible.

Ethical Consideration: Institution Ethics Committee of SNMC, Agra has granted approval for this study topic

Plan for Data Analysis- All the data were entered into Microsoft Excel 2010. Statistical analysis performed using SPSS version 20.0 (statistical package for social sciences). Results were interpreted using tables.

RESULTS AND OBSERVATIONS

In our study, we gathered 143 cases of fine needle aspiration (FNA) of thyroid nodules. The patient age ranges from 7years to 74 years with majority of patients lied between 21years to 30 years, with a mean age of 34years. The male to female ratio was **1:5.2,** out of 143 patients 23 were males and 120 were females. All the cases were classified according to TBSRTC. Out of the total 143 FNACs performed, five aspirates were inadequate for cytological evaluation, thus classified as Non-diagnostic Category I of TBSRTC. These smears exhibited fewer than six clusters of follicular cells and contained fewer than ten cells per cluster on smears.

Non-neoplastic Category II lesions were the major proportion constituting 104(72.5%) cases among them colloid goiter was diagnosed maximum with 40 cases, next was autoimmune thyroiditis in 35 cases, next was colloid goiter with cystic changes in 16 cases. AUS Category III includes 11(32.4%) cases, Category IV FN/OFN was diagnosed in 12(35.3%) cases. Category IV Suspicious for Malignancy was diagnosed in 6(17.6%) cases and Category VI includes 5(14.7%) cases which were diagnosed as Malignant.

Table-1: Distribution Of Patients According To Categories Of Tbsrtc (n=143)"

Categories	Number	Percent (%)
CATEGORY I- Non-diagnostic	05	3.4%
CATEGORY II- Benign	104	72.5%
Colloid Goiter/Colloid Nodule	40	38.5%
Autoimmune thyroiditis	35	33.7%
Colloid with cystic changes	16	15.4%
Benign Follicular Nodule	05	4.8%
Multinodular Goiter	02	1.9%
Granulomatous Thyroiditis	02	1.9%
De Quervain's thyroiditis	02	1.9%
Hyperplastic Nodule	01	0.97%
Adenomatoid Nodule	01	0.97%
CATEGORY III- Atypia of undetermined significance	11	32.4%
CATEGORY IV- Follicular Neoplasm	12	35.3%
CATEGORY V- Suspicious of Malignancy	06	17.6%
Suspicious for Papillary Carcinoma	05	
Suspicious for Medullary Thyroid Carcinoma	01	
CATEGORY V-Malignant	05	14.7%
Papillary Thyroid Carcinoma	03	
Medullary Thyroid Carcinoma	01	
Anaplastic Thyroid Carcinoma	01	
TOTAL	143	100%

Immunocytochemistry -

Immunocytochemistry was performed on Indeterminate Categories (III, IV, V) along with FNA to improve the diagnostic accuracy of Bethesda System for reporting thyroid cytopathology and also to triage the patient for surgical management.

Out of total 143 patients, 29 patients were diagnosed under Indeterminate Categories (III, IV, V). Along with FNA, immunocytochemistry was performed on thin layered smears which were processed using Liquid based cytology. We performed two markers- CK-19 and Galectin-3, these Two markers were able to differentiate benign lesions from malignant lesions.

Table-2 Immunocytochemistry on Indeterminate Category:

Categories	Number of cases	CK-19	Galectin-3
AUS	11	Positive-6 case Negative-5 cases	Positive- 6cases Negative-5 cases
FN	12	Positive-7 cases Negative-5 cases	Positive-7 cases Negative-5 cases

Suspicious of malignancy	06	Positive-5 cases Negative-1case	Positive-5 cases Negative-1 case
Total	29	Positive cases-18 Negative cases-11	Positive cases-18 Negative cases-11

Histological Correlation Of Tbsrtc Categories Along With Icc Results In Indeterminate Categories.

Out of total 143 patients , we receieved 45 cases for histological correlation. 5 cases were diagnosed under Category I- Non-diagnostic, out of which one case was received in histology lab and came out benign. 104 cases were diagnosed under Category II -Benign, out of which 19 cases were recevied out of them 17 cases came out benign and 2 cases came out malignant.

11 cases were diagnosed under Category III-Atypia of Undetermined Significance, on all cases we performed Immunocytochemistry on thin layered FNA material by using Marker CK-19 and Galectin-3. We received 7 cases out of total 11 cases of Category III in histology lab, and histological results were compared with cytological results and Immunocytochemistry results. Out of 7 cases, 3 cases came out malignant with positive Immunocytochemical markers and 4 cases came out benign with negative Immunomarkers. All cases on histology diagnosed were concordant with the Immunocytochemical markers.
12 cases were diagnosed under Category IV, along with ICC markers, out of them 7 cases were positive for both markers CK-19, Galectin-3 and remaining 5 cases were negative for both markers.

On histology we received 9 cases out of 12 cases, out of them 6 cases were turned out malignant and 3 cases benign and all cases were concordant with Immunocytochemical results.

6 cases were diagnosed under Category V. Out of them 5 cases were received in histology lab for histological correlation, out of them one case was diagnosed Hashimoto thyroiditis with negative Immunocytochemistry for CK-19 and Galectin-3 on FNA material. Other 4 cases came out malignant with positive Immunocytochemical markers on FNA material, one case came out Medullary thyroid carcinoma and 2 cases as PTC and remaining last case as Invasive encapsulated Follicular variant of PTC.

5 cases were diagnosed under Category VI. Immunocytochemistry was not performed on these cases, as all cases were diagnosed malignant. Out of 5 cases ,4 cases were received in histology lab, and were diagnosed as malignant. 3 cases were diagnosed as Papillary thyroid carcinoma and one case was diagnosed as Medullary thyroid carcinoma.

Risk Of Malignancy:

From the histopathological data malignancy rate of each category of the Bethesda system was calculated. In present study malignancy rate of Category I, II, III, IV, V, VI were calculated and were as follow- 0%, 10.5%, 57.2%, 66.6%, 80%, 100%.

Table-3 Histological Correlation Categories I, Ii, Vi

CATEGORIES	CYTOLOGICAL DIAGNOSIS	HISTOLOGICAL DIAGAANOSIS	
		Benign	Malignant
Category I	Non-Diagnostic(n=5)	Colloid Goiter(n=1)	
Category II	Colloid Goiter(n=40) Colloid Goiter with cystic changes(n=16) Adenomatoid Goiter(n=1) AutoimmuneThyroiditis(n=35)	Colloid goiter(n=10) Colloid Cyst(n=5) Hashimoto thyroiditis(n=2)	Cystic Papillary Carcinoma(n=1) Follicular variant of PTC(n=1)
Category VI	Papillary thyroid carcinoma (n=3) Medullary thyroid carcinoma (n=1)		PTC (n=3) Medullary thyroid carcinoma(n=1)

Table 4- Histo Cytological Correlation Of Indeterminate Categories Along With Icc (cat Iii, Iv, V)

Category	Cases(n)	Cytological diagnosis	Immunohistochemical markers		Histological diagnosis
			CK-19	Galectin-3	
Category III- n= (07)	n=03	AUS	+	+	PTC
	n=01	AUS	-	-	Nodular Goiter
	n=01	AUS	-	-	Hashimoto thyroiditis
	n=01	AUS	-	-	Colloid Goiter
	n=01	AUS	-	-	Follicular Adenoma
Category IV- n= (09)	n=03	FN	-	-	Follicular Adenoma
	n=04	FN	+	+	Follicular variant of PTC
	n=02	FN	+	+	Follicular Carcinoma
Category V- n= (05)	n=01	SOM	-	-	Hashimoto thyroiditis
	n=01	SOM	+	+	Medullary Carcinoma
	n=01	SOM	+	+	Invasive encapsulated follicular variant of PTC
	n=02	SOM	+	+	PTC

PTC- papillary thyroid carcinoma; AUS-Atypia of undetermined significance ; FN – Follicular neoplasm ; SOM- Suspicious of malignancy

Statistical Analysis:

True positive, true negative, false positive and false negative results were obtained. From these values sensitivity, specificity, positive predictive value, negative predictive value was calculated.

	Indicators	Percentage
1.	Sensitivity = TP/(TP+FN)	89.5%
2.	Specificity = TN/(TN+FP)	71.4%
3.	Positive Predictive Value = TP/(TP+FP)	68%
4.	Negative Predictive Value = TN/(TN+FN)	90.9%

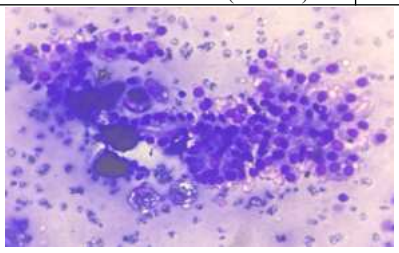

Fig 1 A- AUS Cat III, Follicular epithelial cells along with cystic macrophages

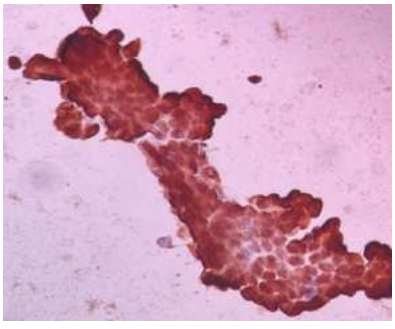

Fig 1b- CK-19 showing cytoplasmic and membranous positivity in follicular epithelial cells- On histology diagnosed as Cystic PTC.

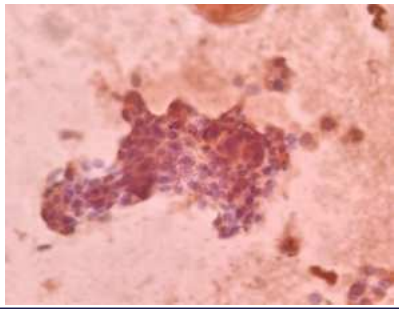

Fig 1c- Galectin-3 showing cytoplasmic positivity in follicular epithelial cells – On histology diagnosed as Cystic PTC.

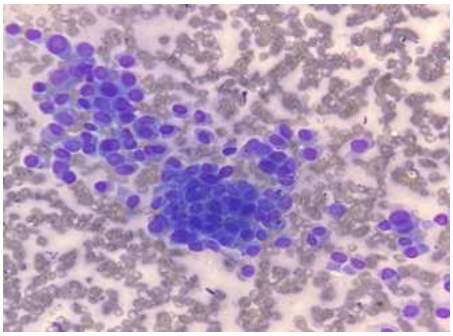

Fig 2a- AUS Cat III follicular cells in hemorrhagic background showing Anisokaryosis.

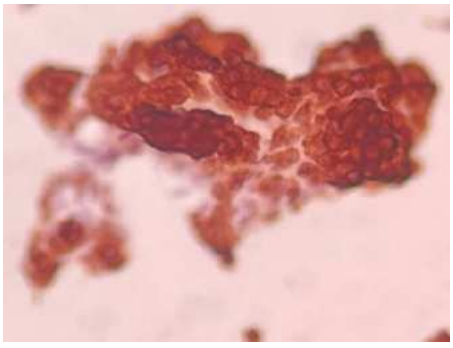

Fig 2b- CK-19 Showing cytoplasmic and membranous positivity of follicular cells -On histology diagnosed as PTC

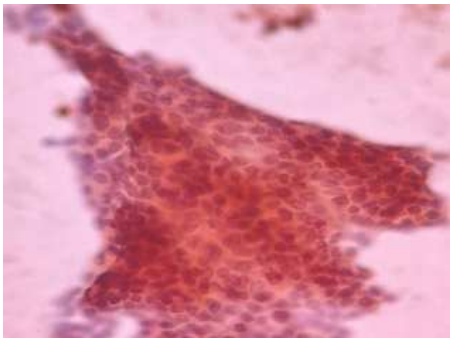

Fig2c- Galectin-3 Showing cytoplasmic positivity of follicular epithelial cells- Diagnosed as PTC.

DISCUSSION:

In this study thyroid fine needle aspirations were categorized according to The Bethesda system for reporting thyroid cytopathology, a six-tier category. The study period was from September 2022 to March 2024 of 18 months. During the study period, a total of 143 cases of thyroid fine needle aspirations were collected and categorized according to "The Bethesda System for Reporting Thyroid Cytopathology". For more accurate diagnosis Immunocytochemistry was performed by using markers CK-19 and Galectin-3 on intermediate Categories (III, IV, V). Later on, cytological diagnosis was compared with histological diagnosis in cases where surgical specimens were received.

Our study included patients age ranged from 7-74 years, and majority of patients were belonged to age group of 31-40 years which was in concordance with the study of Shiksha et al.[11] The study of Agarwal P et al.[12] showed some slight changes in mean age in comparison with our study. Kamboj M et al.[13] study showed higher values for mean age this can be because of higher values of samples were included in study.

The Female to male ratio obtained in the present study is 5.2:1 Thyroid lesions are more prevalent in females, this was seen in present study and it was also seen in all studies that females are more prevalent than males. Our results were comparable with studies of Zarif et al,[14] Jeelani et al,[15] and Shiksha et al.[11] In the study of Agarwal P et.[12] al the ratio of female to male ratio was higher.

The incidence of lesions in all categories of present study was comparable with the study of Agarwal P et al,[12] Durgun et al,[16] Shiksha et al.[11] Incidence of category I lesions in our study were far lower than the studies of Kamboj et al,[13] Mathew R et al,[17] Shankar P S et al.[18] owing to the repetition of FNA if they are inconclusive.

The incidence of malignancy rate in patients which were diagnosed using TBSRTC, in our study are as- for Category I the ROM was 0% only one patient which was diagnosed under Category on FNA came for histopathological correlation and diagnosed benign. For Category II the ROM calculated was 10.5% two cases which were diagnosed as benign on FNA material came malignant on histology. For Category III is 57.2%, Category IV is 66.6%, Category V is 80%, Category VI is 100%. The percentage of occurrence of malignancies in each category of the present study was in concordance with Durgun et al,[16] Kamboj et al,[13] Agarwal et al,[12] Zarif et al.[14] The percentage of ROM was different in Category I because most of the cases were non-diagnostic due to inadequacy criteria hence they have equal chances of being diagnosed as benign and malignant.

The statistical indices for our study were comparable with the study of Durgun et al,[16] Zarif et al.[14] The study of Kamboj et al,[13] Mathew R et al.[17] shows higher sensitivity, specificity and NPV than our study it can be due to histopathological correlation in much more cases than in our study.

CONCLUSION

The study employing "The Bethesda System for Reporting Thyroid Cytopathology" complemented by Immunocytochemistry, has proven effective in categorizing thyroid nodules and predicting malignancy. With a high adequacy rate and consistent histopathological correlations, the system demonstrated robust diagnostic utility across various categories. The findings underscore the system's ability to guide clinical management, especially in distinguishing benign from malignant nodules, thereby aiding in informed treatment decisions.

REFERENCES

1) Fletcher, C. (2021). Tumors of thyroid gland. In J. K. C. Chan & W. Chenk (Eds.), Diagnostic histopathology of tumors (4th ed., Vol. 2, pp. 1177). Elsevier.
2) Tunbridge, W. M., Evered, D. C., Hall, R., Appleton, D., Brewis, M., Clark, F., ... & et al. (1977). The spectrum of thyroid disease in a community: The Whickham survey. Clinical Endocrinology, 7, 481-493.
3) Menon, V. U., Sundaram, K. R., Unnikrishnan, A. G., Jayakumar, R. V., Nair, V., & Kumar, H. (2009). High prevalence of undetected thyroid disorders in an iodine-sufficient adult South Indian population. Journal of the Indian Medical Association, 107, 72-77.
4) Soderstrom, N. (1952). Puncture of goiters for aspiration biopsy: A preliminary report. Acta Medica Scandinavica, 144, 237-244.
5) Wang, H. H. (2006). Reporting thyroid fine-needle aspiration: Literature review and proposal. Diagnostic Cytopathology, 34, 67-76.
6) Cibas, E. S., Ali, S. Z., & NCI Thyroid FNA State of the Science Conference. (2009). The Bethesda System for reporting thyroid cytopathology. American Journal of Clinical Pathology, 132, 658-665.
7) Bhasin, T. S., Mannan, R., Manjari, M., Mehra, M., Sekhon, A. K., Chandey, M., ... & et al. (2013). Reproducibility of 'The Bethesda System for reporting thyroid cytopathology': A multicenter study with review of the literature. Journal of Clinical and Diagnostic Research, 7, 1051-1054.
8) Crowe, A., Linder, A., Hameed, O., Salih, C., Roberson, J., Gidley, J., ... & et al. (2011). The impact of implementation of the Bethesda System for reporting thyroid cytopathology on the quality of reporting, "risk" of malignancy, surgical rate, and rate of frozen sections requested for thyroid lesions. Cancer Cytopathology, 119, 315-321.
9) Cibas, E. S., & Ali, S. Z. (2009). Bethesda system for reporting thyroid cytopathology. American Journal of Clinical Pathology, 132(11), 658-665.
10) Unnikrishnan, A. G., Kalra, S., Baruah, M., Nair, G., Nair, V., Bantwal, G., & Sahay, R. K. (2011). ESI guidelines for patients with thyroid nodules. Indian Journal of Endocrinology and Metabolism, 15(1).
11) Shiksha, A., Kumar Patel, P., & Ankita. (2022). The Bethesda System for Reporting Thyroid Cytopathology and its histopathological correlation. International Journal of Pharmaceutical and Clinical Research, 14(8), 443-449.
12) Agarwal, P., Dahiya, S., & Shams, A. (2021). Cytomorphological spectrum of thyroid lesions using Bethesda system of reporting with histopathological correlation: A study of 87 cases. Indian Journal of Pathology and Oncology, 8(2), 212-217.
13) Laishram, R. S., Zothanmawii, T., Joute, Z., Yasung, P., & Debnath, K. (2017). The Bethesda system of reporting thyroid fine needle aspirates: A 2-year cytologic study in a tertiary care institute. Journal of Medical Society, 31, 3-7.
14) Zarif, H. A., Ghandurah, S. E., Al Garni, M. A., Binmahfooz, S. K., Alsaywid, B. S., & Satti, M. B. (2018). Thyroid nodules cytopathology applying the Bethesda system with histopathological correlation. Saudi Journal of Medicine and Medical Sciences, 6, 143-148.
15) Jeelani, T., Rafiq, D., Nazir, W. U., Shafi, Y., Bashir, N., Charak, A., ... & Ahmad, S. (n.d.). Histopathological and cytological correlation of thyroid nodules with emphasis on Bethesda system for reporting thyroid cytology - A 7-year study.
16) Durgun, C. (2023). Correlation of thyroid fine needle aspiration biopsy with histopathological results. Open Access Original Article. https://doi.org/10.XXXXXXX
17) Mathew, R., Upadhyaya, K., & Sudhakar, S. (2022). Role of the Bethesda system for reporting fine needle aspiration cytology of lesions of the thyroid and its histopathological correlation. Tropical Journal of Pathology and Microbiology, 8(5), 60-64.

18) SShankar, S. P., Meenakshisundaram, K., Rajalakshmi, V., Selvakumar, A. S., & Giridharan, B. (2016). The Bethesda system for reporting thyroid cytopathology: A two-year retrospective review in a tertiary care hospital. Indian Journal of Pathology and Oncology, 3(1), 48-54.