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Original Article

THE EFFECTIVENESS OF FINE NEEDLE ASPIRATION CYTOLOGY IN DIAGNOSING THYROID SWELLINGS AND THE REASONS FOR DISCREPANCIES: A 6-YEAR CYTOHISTOLOGIC CORRELATION STUDY

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Abstract

Background: FNAC is a safe, reliable, cost-effective, and efficient method for initial screening of patients with thyroid nodules.

Aims: The purpose of this study was to evaluate the diagnostic efficacy of FNAC as a screening tool for thyroid nodules, identify cytomorphological features that contribute to diagnostic errors, and suggest improvements.

Materials and Methods: A study included 611 cases of FNAC, with 99 cases being compared to histological diagnosis. Subsequently, discordant cases, including both false negatives and false positives, were retrospectively re-evaluated. Additionally, a thorough review of previous research on the factors that contribute to misdiagnosis was conducted.

Results: When BSRTC categories IV, V, and VI are all classified as cytologically positive, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy are 84.6%, 97.1%, 93.4%, 86.7%, and 91.9%, respectively. The primary reason for false-negative diagnoses was sampling errors (4/5, 80%), while the majority of false-positive diagnoses were attributed to interpretation errors (1/3, 33.3%). Overlapping cytological features in adenomatoid hyperplasia, thyroiditis, and cystic lesions were the primary factors contributing to misinterpretation. Additionally, heterogeneity and unsampled areas were responsible for variations in nodule size and number. This may have resulted in a false negative diagnosis.

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Conclusion: The results of our study have demonstrated that FNAC of thyroid lesions exhibits a significant level of accuracy, sensitivity, and specificity, enabling appropriate initial diagnostic intervention. Cytopathologists should improve their criteria for identifying adenomatous hyperplasia, thyroiditis, and cystic lesions in order to avoid false-positive diagnoses caused by errors in interpretation.

Keyword: FNAC, thyroid, misdiagnoses, false negative, false positive

Introduction:-

Thyroid swelling is a prevalent issue globally. Although thyroid nodules are mostly benign, the incidence of malignancy was found to be around 5%, making it one of the most common endocrine malignancies [1]. The challenge in clinical practice lies in accurately distinguishing between malignant tumors and harmless nodules, which is essential for preoperative tissue diagnosis, surgery planning, and patient counseling. FNAC is considered the gold standard diagnostic test for evaluating thyroid masses, and it should be complemented with other tests such as ultrasound and nuclear scan [2-4]. FNAC is a straightforward, rapid, and cost-effective method for sampling superficial masses in the thyroid gland, typically performed in an outpatient setting with minimal patient discomfort and negligible risk of complications. A malignant diagnosis allows for informed discussions and planning for the next steps, while a benign lesion diagnosis provides immediate relief to the patient. FNAC can also serve as both a diagnostic and therapeutic tool for cystic swellings [3]. The present investigation was conducted to evaluate the diagnostic effectiveness of Fine Needle Aspiration Cytology (FNAC) performed within our organization. This was achieved by establishing a correlation between the results obtained from FNAC and the histological diagnoses. Our objective was to retrospectively review cases where there were disagreements (including both false-negative and false-positive results) in order to evaluate the cytological characteristics that contributed to diagnostic errors and propose measures for improvement.

Material and methods:-

Study subjects, sampling,technique and data acquisition

The current study, spanning six years, consisted of a prospective component covering the period from January 2013 to December 2013, and a retrospective component covering the period from January 2008 to December 2012. The study was conducted at the Department of Pathology, Pt. J.N.M. Medical College and its associated Dr. B.R.A.M.Hospital in Raipur, Chhattisgarh, India. The prospective study involved selecting cases from patients with thyroid masses who were attending the ENT outpatient department and inpatient facilities. Ethical considerations were addressed by obtaining approval from the institutional ethics committee, and written consent was obtained from each patient. FNAs were conducted using palpation or ultrasound guidance, without on-site evaluation. The aspirates were prepared as direct smears. Smear made from the centrifuged deposit in the case of aspirated fluid. Staining of the wet fixed smears was done with Papanicolaou stain/ Haematoxylin and Eosin and air dried smears were stained with MGG (May Grunwald and Giemsa) stain. The cases were initially classified into benign lesions and malignant lesions (including those suspicious for malignancy as well). The final

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histopathological diagnosis was correlated with the FNAC findings to assess the precision of cytodiagnosis.

False negative and **false positive diagnoses**

FNAC diagnoses were classified into six groups based on The Bethesda System for Reporting Thyroid cytopathology. (I): non-diagnostic (II) Benign, (III) AUS/FLUS, (IV) Follicular neoplasm, (V) Suspicious for malignancy, and (VI) Malignant. Non-diagnostic cases were not included in the analyses. False-negative and false-positive diagnoses were defined as cases in which the results of the fine needle aspiration (FNA) did not correspond with the findings of the final histological examination. A false-negative diagnosis is defined as a nodule that was initially determined to be benign (TBSRTC category II and III) through fine-needle aspiration cytology (FNAC), but it was found discovered to be malignant upon histological examination. Conversely, a false-positive diagnosis was described as a nodule with cytology indicating malignancy (BSRTC category IV, V, and VI) that was later found to be a nonneoplastic lesion or benign neoplasm upon histological analysis after surgery. The misdiagnoses were categorized as "specimen problem," which included sampling errors or suboptimal specimens, and "interpretation error," indicating overdiagnoses or underdiagnoses by cytologists.All slides from the false-negative and false-positive FNAs were reexamined to determine the cause of misdiagnoses.

Statistical analysis

Statistical analysis was conducted to evaluate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. IBM SPSS Statistics (version 19.0) was used for the analysis, and the chi-square test was employed for the primarily categorical variables. Cohen's kappa (κ) coefficient was utilized to assess the agreement between the FNA and pathology results. P value of <0.05 was considered statisticaly significant.

Result

During the period from January 2008 to January 2013, we conducted a comprehensive review of 611 cases of thyroid fine-needle aspiration cytology (FNAC). The distribution of benign and malignant thyroid lesions among the total 611 FNACs was as follows: 554(90.1%) and 57(9.9%), respectively. The age group between 21 and 40 years constituted 59.9% of the cases. The most common age group affected by malignant thyroid neoplasm was the 4th to 6th decade, comprising 31 (54.4%) cases. The majority of cases consisted of females (n=508, 83.14%), while 16.85% (n=103) were male [Table-1].

In the entire study population, there were 99 cases with available histological correlation data. Out of these, 82 cases had benign thyroid lesions, while 17 cases had malignant lesions. The FNA findings were correlated with the corresponding histological diagnosis. There were 8 misdiagnosed cases, including 6 false-negative and 2 false-positive cases. We conducted a retrospective analysis of 8 cases identified as false-negative and false-positive. The analysis revealed that 5 cases (62.5%) were attributed to issues with the specimen, while 3 cases (37.5%) were the result of errors in interpretation. The primary factor contributing to false-negative

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diagnoses was sampling error, which was responsible for 80% of problematic specimen cases. On the other hand, 33.3% of interpretation errors represented false-positive diagnoses [Table 2].

The results of the assessment comparing the findings of fine-needle aspiration cytology (FNAC) with the final histopathology results of the patients are presented in [Table 3]. Upon inspection of the aforementioned table, a significant correlation was identified between the two measurements (κ: 0.557, $p<0.001$). The test sensitivity was found to be 84.62%, while the specificity was determined to be 97.13%. Based on the results of the FNAC test, the positive predictive value (PPV) for malignancy was 93.45%, while the negative predictive value (NPV) for benign cases was 86.70%.

Table 1 Demographic and clinical data of the study patients

Characterstics			**n (%) or mean ±SD**
Age	Benign lesion (n=554)		34 ±12
	Malignant lesion (n=57)		48 ±14
Sex	Benign lesion (n=554)	Male	90 (16.2%)
		Female	464 (83.8%)
	Malignant Lesion (n=57)	Male	13 (22.8%)
		Female	44 (22.8%)
FNAC cases (n=611)	Benign lesion		554 (90.70%)
	Malignant lesion		57 (9.30%)
Histopathological confirmed cases(n=99)	Benign lesion (n=82)	Colloid goiter	48 (48.5%)
		Adenomatoid goiter/hyperplasia	19 (19.2%)
		Thyroiditis	02 (2%)
		Follicular adenoma	11 (11.2%)
		Hurthle cell adenoma	02 (2%)
	Malignant lesion (n=17)	Papillary carcinoma	08 (8.2%)
		Follicular variant of papillary carcinoma	02 (2.2%)
		Follicular carcinoma	05 (5.3%)
		Medullary carcinoma	01 (1.2%)
		Anaplastic carcinoma	01 (1.2%)

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Table 2 Analysis of Misdiagnosed Cases

		Specimen problem	Interpretation problem
False negative diagnoses (n=6)	Papillary thyroid microcarcinoma	3	-
	thyroid cancer in multinodular goiter	1	1
	Follicular variant papillary thyroid carcinoma	-	1
False positive diagnoses (n=2)	Cystic nodules	-	1
	Thyroiditis	1	-
Total		**5 (62.5%)**	**3 (37.5%)**

Table 3 Conformity of the FNAC and histopathology results of the study patients

PPV, positive predictive value; NPV, negative predictive value; κ, Cohen's kappa coefficient; FNR, false-negative rate; FPR, false-positive rate.

Variables		**Histopathological diagnosis**		**Total**
		Malignant lesion	**Benign lesion**	
		n	n	
Cytological diagnosis	**Malignant lesion**	11	02	13
	Benign lesion	06	80	86
Total		17	82	99
Statistical Statistical analysis Result		Sensitivity		84.62%
		Specificity		97.13%
		Accuracy		91.92%
		FNR		35.30%
		FPR		2.44%
		PPV		93.46%
		NPV		86.70%
		κ		0.68671
		p-value		<0.0001

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Discussion

Fine-needle aspiration (FNA) serves as an uncomplicated, secure, cost-efficient, and precise diagnostic method for the initial assessment of patients with thyroid nodules [5-7]. The primary objective of FNA is to identify neoplastic nodules that require surgical removal while avoiding unnecessary surgery for nonneoplastic lesions.

In our investigation, when both malignant and suspicious for malignancy thyroid lesions were considered cytologic-positive, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were 84.6%, 97.1%, 90.2%, 93.4%, and 86.7%, respectively. The positive predictive value (PPV) and diagnostic accuracy exceeded 90.0%, highlighting the importance of thyroid fine-needle aspiration (FNA) in preoperative diagnosis. It is widely acknowledged that the clinical utility of thyroid FNA stems from its ability to consistently facilitate the identification of benign thyroid nodules and its low false negative rate. This enables surgeons to rely on FNA as a dependable test for guiding operative decision-making. Consequently, the lower the false-negative rate, the more valuable thyroid fine-needle aspiration (FNA) becomes. The false-negative rates of fine-needle aspiration (FNA) for thyroid nodules reported in most studies are below 5% [7-13]. Nonetheless, higher rates (ranging from 7.5% to 21%) have also been documented in other study series [14–20]. In our current study, the false-negative rate (6.9%) was similar to those reported in previous studies, indicating that our negative thyroid FNA results were quite reliable. However, the relatively low NPV (86.7%) shows that even if a thyroid nodule is initially diagnosed as benign by FNA, it may still have malignant potential.In our analysis, the majority of false-negative diagnoses in our study were attributed to issues with the specimen (80%, 4/5). In order to determine the adequacy of FNAC materials, it is necessary to observe at least six cell populations, each containing 10-20 well-preserved follicular epithelial cells. The most common cause of false-negative results is insufficient material.[21] In such instances, it is recommended to repeat the FNAC procedure under the guidance of ultrasonography. Studies have shown that utilizing US assistance in performing a subsequent FNAC reduces the rate of non-diagnostic outcomes from 3% to 15%. Furthermore, it has been determined that 50% of nodules that are persistently non-diagnostic, as a result of fine needle aspiration cytology (FNAC), are found to be malignant. As a result, it is advised that these patients undergo surgical intervention or receive close monitoring. [22-23]

Two of the four cases involved papillary thyroid microcarcinoma (PTMC). PTMC is defined by the World Health Organization (WHO) as a papillary thyroid carcinoma (PTC) with a longest diameter of ≤1.0 cm, typically found incidentally. [24]. The presence of an unsampled microcarcinoma in the context of an adenomatous goiter has been identified as a common cause of false-negative diagnoses by fine-needle aspiration (FNA) in several studies [25-29]. It is important to note that sampling of entire nodule can be challenging. This can result in an increased false-negative rate for larger nodules, as reported by some authors [16, 17, 30-34]. Several researchers have reported false-negative rates as high as 17 to 19.3% for thyroid nodules measuring 3 to 4 cm or larger. We align with this perspective, as nodule heterogeneity has been identified as a contributing factor to misdiagnoses. This may potentially explain the challenges in evaluating these nodules using traditional cytologic methods.

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Another significant concern regarding false-negative diagnoses is the presence of multiple nodules, as sampling error may occur when the cells captured by the needle are not from the intended nodule. In our study, two cases of multinodular goiter that was initially diagnosed cytologically were ultimately confirmed to be papillary carcinoma and follicular carcinoma through histopathology. Studies have indicated a high incidence of malignancy in patients with multinodular goiter compared to the general population [35]. Additionally, the presence of multiple nodules can complicate the evaluation of the entire thyroid [36]. This highlights the importance of conducting multiple passes in various parts of a large nodule or from different nodules to reduce the risk of false-negative findings caused by heterogeneity.

Our study indicates that errors in interpretation were not the primary cause of false-negative diagnoses. Follicular variant of papillary thyroid carcinoma (FVPTC) was erroneously classified as benign through cytopathologic evaluation. Previous researchers have also observed that follicular variant of papillary thyroid carcinoma (FVPTC) is a significant contributing factor to false-negative results in thyroid fine-needle aspiration (FNA) tests. It is worth noting that the effectiveness of thyroid FNA is limited by its inability to accurately distinguish between follicular lesions [13, 20, 37–40]. Zhu et al. [20] reviewed multiple studies and observed that the histopathologic characteristics of FVPTC often overlap with those of follicular neoplasms, hyperplastic adenomatoid nodules in goiter, or even lymphocytic thyroiditis. This is because the characteristic nuclear features, although usually present with subtle changes, are also observed in these other conditions. They also acknowledge that for these follicular lesions, cytopathology serves as a screening tool rather than a diagnostic test. Şule Canberk et al. [41] have also emphasized the importance of three key principles in order to prevent misinterpretations and improve clinical management. These principles include recognizing the limitations of cytomorphology, being attentive to the presence of certain features such as sheets/macrofollicles, abundant colloid, lymphocytes, and obscuring blood, and avoiding the downgrading of nuclear atypia.

One instance involved the cytological diagnosis of a cystic nodule as papillary thyroid carcinoma (PTC), which was later confirmed to be a multinodular goiter upon histopathological examination. The effectiveness of fine-needle aspiration cytology (FNAC) in evaluating cystic nodules is limited, and there have been well-documented cases of false-negative diagnoses of malignant cysts [20, 46–50]. we conducted a retrospective analysis of the smears. In accordance with the findings of Faquin et al. [44], the "atypical" cells displayed various cytomorphologic characteristics. These included elongated cells with a spindle shape, as well as polygonal epithelioid cells with enlarged nuclei, nuclear grooves, fine chromatin, and prominent nucleoli. However, these cells did not display nuclear crowding, such as intranuclear pseudoinclusions, nor did they possess the papillary architecture typical of cystic papillary carcinomas. Malheiros et al. [51] recommend that a definitive diagnosis of PTC should only be made if unequivocal nuclear features of PTC are identified. Consequently, we stress the significance of accurately identifying atypical cyst-lining cells and evaluating their background in order to differentiate benign cystic thyroid nodules from malignant ones and prevent unnecessary surgical interventions.

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Another histologically confirmed case of adenomatous hyperplasia has been misinterpreted as suspicious for papillary thyroid carcinoma (PTC) in FNAC. Benign thyroid hyperplastic nodules typically exhibit follicular epithelial cells that are arranged in a honeycomb pattern and possess small, round, dark nuclei. However, hyperplastic nodules may present with focal nuclear atypia, which can be mistaken for papillary thyroid carcinoma (PTC). These atypical features include grooves, an oval shape, chromatin clearing, and overlapping. Marc P et al. [46] have emphasized that when a fine needle aspiration (FNA) reveals papillary structures with sparse nuclear features of papillary thyroid carcinoma (PTC) or features that are mixed with an otherwise benign-appearing follicular component, benign thyroid nodules with papillary hyperplasia should be considered. Other researchers have highlighted that nuclear overlapping and crowding are rare findings in specimens of benign thyroid hyperplasia [48-51]. Furthermore, the presence of an excessive amount of loose or watery colloid can prevent overdiagnoses by cytopathologists [52, 53]. The considerable similarity in morphological characteristics among papillary thyroid carcinoma (PTC) in adenomatous hyperplasia, chronic lymphocytic thyroiditis, and pure thyroiditis can pose a challenge for cytopathologists. Even experienced cytopathologists may have uncertainty when differentiating between these entities.

Our study has certain limitations, the most significant being its retrospective nature and the fact that it was conducted at a single center. Furthermore, the sample size was very limited due to strict criteria regarding the correlation between cyto-histopathology. This resulted in the exclusion of numerous FNAC cases that did not have histopathology reports. Secondly, the study fails to consider various risk factors, such as occupation and history of exposure to radiation. Thirdly, due to patients facing significant distances and financial constraints, no follow-up data were made available. Despite these limitations, this research serves as the first investigation that examines the association between FNAC and their corresponding histopathology in the context of diagnosing thyroid cancers. Additionally, it evaluates the accuracy rate, sensitivity, specificity, positive predictive value, negative predictive value, false negative rate, and false positive rate of fine needle aspiration cytology (FNA) as a diagnostic tool for thyroid nodules.

Conclusion

The results of our study have demonstrated that fine-needle aspiration cytology (FNAC) of thyroid lesions exhibits a significant level of accuracy, sensitivity, and specificity, enabling appropriate initial diagnostic intervention. False-negative diagnoses were primarily attributed to issues with the specimens obtained, whereas false-positive diagnoses were predominantly caused by errors in interpretation. To minimize the occurrence of false negatives resulting from specimen issues, it is advisable to perform multiple passes in different regions of a large nodule or in distinct nodules. Cytopathologists should enhance their criteria for identifying adenomatous hyperplasia, thyroiditis, and cystic lesions to prevent false-positive diagnoses resulting from interpretation errors. Moreover, FNAC (Fine Needle Aspiration Cytology) is a safe, reliable, cost-effective, and efficient method that should be used as the primary investigative tool for thyroid lesions.

Abbreviations : FNA: Fine-needle aspiration; FNAC: Thyroid fine-needle aspiration cytology; NPV: Negative predictive value; PPV: Positive predictive value; PTC: Papillary thyroid carcinoma; PTMC: Papillary thyroid microcarcinoma; SFN/FN: Suspicious for follicular

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neoplasm or Follicular neoplasm; SM: Suspicious for malignancy; TBSRTC: The Bethesda System for Reporting Thyroid cytopathology.

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Author contributions

All authors have made notable contributions to the research presented in this work, whether it be in the conceptualization, design of the study, implementation, data acquisition, analysis and interpretation, or in all of these domains. Furthermore, they all participated in the drafting, revising, and critical review of the article. Additionally, they provided their endorsement for the final version to be published and have reached a consensus on the journal in which the article has been submitted. Lastly, they have agreed to assume responsibility for all aspects of the work.

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Institutional review board statement

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Declaration of competing interest

No conflict of interest associated with this publication.

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