ORIGINAL ARTICLE

Diagnostic Accuracy of Fine Needle Aspiration Cytology of Thyroid in Hospital Sultanah Nur Zahirah, Malaysia

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ABSTRACT

INTRODUCTION: Fine Needle Aspiration Cytology (FNAC) is widely used as an initial screening method in the preoperative examination of thyroid lesions. However, diagnostic cytology interpretation remains inconsistent among reporting pathologists worldwide. This study aimed to determine the diagnostic accuracy of FNAC of thyroid lesions at Hospital Sultanah Nur Zahirah (HSNZ), a tertiary hospital in Kuala Terengganu, Malaysia. **MATERIAL AND METHODS:** We conducted a retrospective cross -sectional study at the Department of Pathology, HSNZ, from January 2017 to December 2019. Data of patients were collected from the Laboratory Information System (LIS) and Hospital Information System (HIS). The study included patients with thyroid lesions who underwent both FNAC and subsequent histopathological examination (HPE). **RESULT:** A total of 389 cases of thyroid lesions underwent FNAC, with 162 cases proceeding to surgical resection. The median age of the patients was 43.3 years, with a male to female ratio of 1:5.3. FNAC diagnoses were categorized as follows: 85 cases (52.5%) were benign, 23 (14.2%) as atypia or follicular lesion of undetermined significance, 9 (5.6%) as follicular neoplasm, 21 (13%) as suspicious for malignancy, and 12 (7.4%) as malignant and unsatisfactory. The diagnostic accuracy of FNAC was 85.8%, with sensitivity of 66.7% and specificity of 96.2%. The positive predictive value was 90.5%, and the negative predictive value was 84.2%. **CONCLUSION:** FNAC has proven to be an accurate diagnostic method for screening thyroid lesions. However, continuous improvement in sampling and preparation techniques and cytopathologist training is necessary to enhance its reliability further.

Keywords
Thyroid, Fine Needle Aspiration cytology (FNAC), Bethesda system

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INTRODUCTION

Fine Needle Aspiration Cytology (FNAC) of the thyroid is widely recognized for its simplicity and cost-effectiveness in initial evaluation of thyroid nodules. However, the interpretation of FNAC results presents significant challenges, primarily due to its dependence on operator skill and the substantial experience of doctors required for accurate diagnosis.

The principal difficulty of FNAC of thyroid interpretation lies is differentiating between the relatively uncommon malignant lesions and the more prevalent benign thyroid conditions. Obtaining a definitive pre-operative tissue diagnosis through FNAC is crucial for several reasons. When a benign lesion is indicated, it helps avoid unnecessary surgical interventions. This allows for the implementation of conservative management approaches when appropriate. In cases of malignancy, FNAC facilitates the planning of suitable surgical procedures and enables informed patients counseling.[1]

In 2007, the National Cancer Institute (NCI) Thyroid Fine Needle Aspiration State of the Science meeting in United States of America?, which led to the development and subsequent adoption of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC). This standardized reporting system aimed to improve the consistency and accuracy of FNAC of thyroid interpretation across institution.[2] Despite these

advancement, the evolution of diagnostic accuracy for FNAC of the thyroid over the recent decades remains a subject of debate. Previous studies have reported wide ranges in diagnostic accuracy; sensitivity range between 60% to 97% and specificity between 73% to 99%. The discrepancies are largely attributed to variations in study inclusion criteria and differing definitions of sensitivity and specificity.[3–7] Given the persistent uncertainties related to FNAC of thyroid, this study aims to evaluate the diagnostic performance of FNAC in classifying thyroid nodules. The approach in in this study involves a comparative analysis of BSRTC categorizations with the gold standard histopathological examination (HPE) results obtained from surgically excised nodules. This study seeks to contribute to the ongoing refinement of thyroid nodule diagnosis and management strategies.

MATERIAL AND METHODS

Cases and sample selection

This retrospective cross-sectional study was conducted at the Department of Pathology, Hospital Sultanah Nur Zahirah (HSNZ), a tertiary hospital in Kuala Terengganu, Malaysia. The study period spanned from January 1, 2017, to December 31, 2019.

Prior to the commencement of the study, ethics committee approval was obtained from our institution's ethics committee (protocol number: USM/JEPeM/19120975).

We examined a total of 162 thyroid cases for which both preoperative cytology findings and subsequent post-surgical histological diagnoses were available in HSNZ. Data of cases data were extracted from two primary sources: Laboratory Information System (LIS) and Hospital Information System (HIS).

Patients who met the inclusion criteria were those that had histopathological confirmation and accessible preoperative FNAC results within the study period. Exclusion criteria were cases with unavailable FNAC or histopathological reports, referral cases to HSNZ with incomplete documentation, and cases with missing FNAC or histopathological examination (HPE) slides. Clinicopathological data for each case was retrieved from electronic medical records. To facilitate subsequent data analysis, each case was assigned a unique pathology laboratory number, and information was recorded on separate proforma forms. The evaluation included the following variables: age, gender, ethnicity, duration and size of neck swelling, and family history of malignancy.

Statistical analysis

Data entry, calculations, and analysis were performed using IBM SPSS statistics for Windows, Version 26.0. Descriptive statistics were used to present demographic variables. Chi-Square test was employed to assess the association between FNAC and HPE reports. A value < 0.05 was considered statistically significant.

The accuracy of FNAC was evaluated against the gold standard method which is the histopathological evaluation. After excluding unsatisfactory smears, cytological results were categorized as follow: Negative result based on BSRTC (2007), is case with benign interpretation. Positive results are case interpreted as one of the following categories: atypia of undetermined significance or follicular lesion of undetermined significance, follicular neoplasm/Suspicious for a follicular neoplasm, suspicious for malignancy, and malignant. False negative defined as cases with negative result by cytological examination but interpreted by histopathological examination as: follicular carcinoma, papillary thyroid carcinoma, follicular carcinoma; Hurthle cell variant, and diffuse large B-cell lymphoma (DLBCL).

False positive was defined as cases with positive cytological examination and interpreted by histopathological examination as nodular hyperplasia, follicular adenoma, Hurthle cell adenoma, Hashimoto's thyroiditis and cyst content. True negative was defined as cases reported as benign by cytological examination and confirmed by histopathological examination as one of the following categories: nodular hyperplasia, follicular adenoma, Hurthle cell adenoma, Hashimoto's thyroiditis and cyst content. True positive cases were defined as cases diagnosed by cytopathology as atypia of undetermined significance or follicular lesion of

undetermined significance, follicular neoplasm/ Suspicious for a follicular neoplasm, suspicious for malignancy, and malignancy and confirmed by histopathology as follicular carcinoma, papillary thyroid carcinoma, follicular carcinoma; Hurthle cell variant, and DLBCL.

RESULTS

Clinicopathological features

During the period of study, a total of 389 patients had undergone FNAC testing at HSNZ. Of these, 162 patients met the inclusion criteria for this study. The age of the patients ranged from 15 to 76 years, with a mean age of 43.3 years. Thyroid lesions were found to be more prevalent in females, constituting 84% (136/162) of the cases, compared to males, who accounted for 16% (26/162), resulting in a female-to-male ratio of 5.3:1. The vast majority of patients (94.4%) reported no family history of thyroid disease. Table I presents the clinicopathological characteristics of thyroid cases included in the present study.

Table I: The clinicopathological features of thyroid cases included in the present study (n=162)

Variables	N (%)
Age	
15 to 35 years old	52 (32.1)
36 to 55 years old	80 (49.4)
56 to 75 years old	29 (17.9)
76 years old and above	1 (0.6)
Gender	
Male	26 (16)
Female	136 (84)
Ethnicity	
Malay	159 (98.1)
Chinese	2 (1.2)
Others	1 (0.6)
Family history of thyroid	
Yes	9 (5.6)
No	153 (94.4)
Duration of neck swelling	
1-11 months	48 (29.6)
1 – 5 years	71 (43.9)
5 – 10 years	17 (10.5)
More than 10 years	26 (16.0)

Cytology diagnosis according to BSRTC

Based on the BSRTC, 85 cases were diagnosed as benign (52.5%), 23 cases (14.2%) as atypia or follicular lesion of undetermined significance, 9 cases (5.6%) as follicular neoplasm, 21 cases (13%) as suspicious for malignancy, and 12 cases (7.4%) as malignant. Additionally, due to inadequate sampling, 12 cases (7.4%) could not be diagnosed despite repeated aspirations in different settings and were categorized as non-diagnostic cases (Figure 1).

Histopathological Examination (HPE)

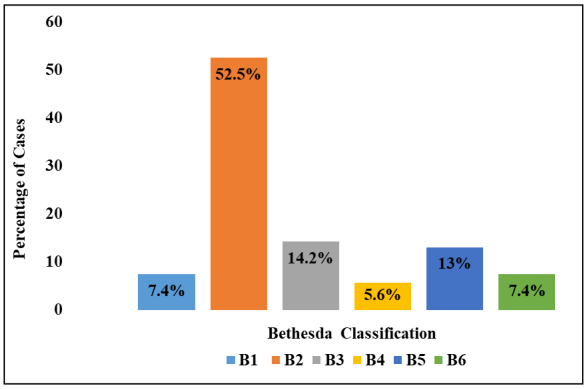

Figure 1. The diagnosis of FNAC thyroid cases based on Bethesda Classification. B1: Non-diagnostic or unsatisfactory; B2: Benign; B3: Atypia of undetermined significance or Follicular lesion of undetermined significance; B4: Follicular Neoplasm or Suspicious for a Follicular Neoplasm; B5: Suspicious for Malignant; B6: Malignant.

The distribution of cases according to HPE, revealed that the majority were benign. Specifically, 92 cases (56.8%) were diagnosed as nodular hyperplasia, 9 cases (5.6%) as follicular adenoma, 3 cases (1.9%) as Hurthle cell adenoma, and one case (0.6%) as Hashimoto's thyroiditis. Regarding malignant diagnoses, papillary thyroid cancer (PTC) was predominant, comprising 47 cases (29%) with follicular variation and one case (0.6%) of micropapillary PTC. Additionally, there were 7 cases (4.3%) diagnosed as follicular carcinoma and one case (0.6%) of DLBCL in the context of lymphocytic thyroiditis. (Table II).

Table II: The distribution of FNAC thyroid cases according to the histopathological diagnosis.

Type	Number	%
Benign Conditions		
Cyst content	1	0.6
Nodular Hyperplasia	92	56.8
Follicular Adenoma	9	5.6
Hurthle Cell Adenoma	3	1.9
Hashimoto Thyroiditis	1	0.6
Malignant Conditions		
Papillary Thyroid Carcinoma	47	29
Follicular Carcinoma	7	4.3
Follicular Carcinoma, Hurthle Cell	1	0.6
DLBCL in background lymphocytic thyroiditis	1	0.6
Total	162	100

Cytology and Histopathology results correlation

The correlation between FNAC and HPE results revealed interesting findings. Out of the 85 cases cytologically classified as benign (non-neoplastic), HPE confirmed 70.8% (75 cases) as non-neoplastic. However, 16.1% (9 cases) were histologically diagnosed as malignant, consisting of follicular and papillary carcinoma. Among the cases initially diagnosed as follicular neoplasm, HPE revealed that 5.6% (5 cases) were malignant, while 4.4% (4 cases) were benign.

The FNAC-HPE correlation showed that in Bethesda II (benign) category, 88.2% of cases were confirmed as benign, while 11.8% were found to be malignant. In Bethesda III (AUS/FLUS), 65.2% were benign and 34.8% were malignant. For Bethesda IV (follicular neoplasm), 44.4% were benign and 55.6% were malignant. In both Bethesda V (suspicious for malignancy) and VI (malignancy), 100% of cases were confirmed as malignant by HPE (Table III).

Table III: Correlation between the cytology and histopathology results

Bethesda Classification	Histopathology n (%)		Total (%)
	Benign	Malignant	
B1	11 (6.8)	1 (0.6)	12 (7.4)
B2	75 (46.3)	10 (6.2)	85 (52.5)
B3	15 (9.3)	8 (4.9)	23 (14.2)
B4	4 (2.5)	5 (3.1)	9 (5.6)
B5	0 (0.0)	21 (13.0)	21 (13.0)
B6	0 (0.0)	12 (7.4)	12 (7.4)
Total	105 (64.8)	57 (35.2)	162 (100%)

The sensitivity and specificity of FNAC of the thyroid

In Table IV, the sensitivity and specificity of FNAC of the thyroid compared to the gold standard method (HPE) was presented. Out of a total of 101 cases, representing 62.3%, benign cytological findings were confirmed as benign by HPE, indicating true negative cases. Conversely, there were 19 cases (11.7%) initially diagnosed as benign by FNAC but were found to be carcinomas upon HPE, indicating false negative cases. In all 38 cases (23.5%) were diagnosed as malignant both on FNAC cytology and histopathological examination, indicating true positive cases. However, four cases (2.5%) initially diagnosed as carcinoma by FNAC were revealed to be goitre upon HPE, representing false positive cases. Overall, FNAC achieved a total diagnostic accuracy of 85.8%, with a sensitivity rate of 66.7% and specificity of 96.2%. The positive predictive value (PPV) was 90.5%, and the negative predictive value (NPV) was 84.2%.

Table IV: The sensitivity and specificity of FNAC of thyroid lesions

Variables	Histological, n (%)		Combo value
	Benign	Malignant	
FNAC			
Benign	101	19	Sensitivity (39/ 38+19) = 66.7%
Malignant	4	38	Specificity (101/ 101+4) = 96.2%
			PPV (38 / 38+4) = 90.5%
			NPV (101 / 101+19) = 84.2%
			Accuracy (101+38)/(162) = 85.8%

*Chi Square significant at p value < 0.05
*Sensitivity = ability of the test to detect true malignant case
*Specificity = ability of the test to detect true benign case
*PPV = Positive Predictive Value
*NPV = Negative Predictive Value

DISCUSSION

Thyroid cancer has been reported to rank seventeenth among the most prevalent cancers in men and ninth among women, according to earlier findings by Azizah et al.[8] FNAC has emerged as the most cost-effective approach for assessing thyroid nodules. Many healthcare facilities offering this procedure have significantly reduced the number of patients requiring surgical intervention.[9,10]

In our study, we aimed to assess the diagnostic accuracy of the FNAC of thyroid by comparing the FNAC diagnoses with HPE. We observed a predominance of female cases. With female-to-male ratio of approximately 5.3:1 which aligns with previous literature.[10,11]

This gender disparity reflects a higher prevalence of thyroid disorders in women. Interestingly, the majority of included patients had no family history of thyroid disease, suggesting that environmental or other non-genetic factors may contribute significantly to the development of thyroid lesions. It is well established that the primary environmental determinant affecting the prevalence of goitre is iodine levels. However, other environmental factors impacting entire populations have also been recognized, including goitrogens present in food and

drinking water.[12]

Consistent with findings in previous studies,[10,13] the majority of cases in our study were benign conditions (65.4%). Among these, nodular hyperplasia was the most commonly diagnosed condition, comprising approximately 86.7% of all benign cases, followed by follicular adenoma, which accounted for 8.4% of benign cases. Regarding malignancies, papillary thyroid carcinoma was the most frequently diagnosed, representing approximately 83.9% of all malignant cases, followed by follicular carcinoma at 12.5%.

Inadequate smears in cytology lab are an unavoidable aspect of the procedure. In our study, approximately 7.4% (12 cases) of included patients had smears deemed inadequate for evaluation. The adequacy of thyroid FNA depends on the number of cells observed under the microscope. To deem a thyroid FNA adequate for evaluation, we need to observe six clusters of follicular cells, each cluster containing no fewer than ten cells. The normal or suggested range for inadequate samples typically falls between 2% and 20%,[14] thus our findings fall within this acceptable range.

To assess the diagnostic accuracy of FNA of thyroid, we correlated cytopathological diagnoses with histopathological results. Sensitivity, defined as "the ability of the test to correctly identify patients with a disease"[15] is a crucial measure of FNAC effectiveness. In our study, FNAC demonstrated a sensitivity of 66.7%, indicating that it correctly identified approximately two-thirds of malignant thyroid cases while missing about one -third. This sensitivity result falls within the range reported in recent literature, higher than study reporting (42.8%) [16] but lower than others reporting (82.3%),[14] (94%).[17] The significant variation in sensitivity across studies suggests that the success of thyroid FNAC may largely depend on the operators expertise.

Regarding specificity, which is defined as "the ability of a test to correctly identify people without the disease",[15] our study observed a high value of 96.2%. This high percentage indicates FNAC's strong ability to rule out benign conditions in the majority of cases diagnosed as benign histopathological examination. Similar to sensitivity, previous studies have shown variations in FNAC specificity for thyroid lesions, with percentages ranging from 64.3% to 98.5%. [14,16,17]

In our study, the correlation between cytopathology and histopathological examination revealed a false negative rate of 11.7%. This rate is higher than ideal, as previous studies investigating the accuracy of FNAC of thyroid have shown a wide variation in false negative results, ranging from 5% to 21%, with most studies reporting 5% or less.[18,19] Moreover, the American Thyroid Association guidelines recommend that the false negative rate should be within 0-5%.[20] These findings highlight the need for continued improvement in FNAC techniques and interpretation to reduce false negative rates and enhance overall diagnostic accuracy in thyroid lesions assessment in our hospitals.

The discrepancies between cytology and histopathology examinations in thyroid nodule diagnosis can be attributed to various factors, depending on the condition under investigation. Generally, false positive and false negative results, as well as the non-diagnostic aspirates, are related to both the nature of the lesion and the experience of the cytopathologist.[21] For example, a previous study emphasized that up to 50% of FNAs performed on thyroid nodules measuring ≥4 cm were inaccurately classified as benign.[22] Moreover, multiple nodules present a challenge for cytopathologist, as they need to assess the entire lesion by taking several aspirates from different sites.

Earlier reports have highlighted that atypical nuclear features in cases of papillary carcinoma may result in missed diagnoses and false negative results. Additionally, papillary carcinoma cases with a diameter less than 0.5 cm and adjacent to benign follicular neoplasm; often yield false negative results.[21]

Our study found a 2.5% false positive rate. It's important to note that certain morphological features such as nuclear grooves, papillary architecture, absence of colloid

material, and intranuclear inclusions are consistent with papillary carcinoma diagnosis. However, these features may also be present in benign conditions such as Hashimoto thyroiditis, nodular hyperplasia, Hurthle cell adenoma, and follicular adenoma, leading to false positive interpretations. Another source of false positives in papillary carcinoma; is the follicular variant cases, which may lack typical nuclear features and exhibit cytomorphological features shared with follicular neoplasms[21]. In these instances, a preoperative diagnosis of "follicular lesion suggestive of papillary carcinoma" often leads to a cautious surgical evaluation until a conclusive diagnosis can ascertain the suitable course of treatment.[23]

The implications of false negative and false positive diagnoses are significant. False negatives may lead to delayed diagnosis and treatment of thyroid carcinomas, potentially impacting patient clinical outcomes. Conversely, false positives may result in unnecessary surgeries or treatments, emphasizing the importance of minimizing such scenarios.

Many cytopathologists concur that several factors play crucial roles in determining the accuracy of FNAC. These factors encompass clinical and imaging observations, lesion size, aspiration characteristics, the expertise of the individual performing the aspiration,[24] and the incapacity of FNAC of thyroid to differentiate between benign and malignant follicular lesions without the presence of nuclear characteristics typical of papillary carcinoma, FNAC faces challenges in accurately diagnosing follicular neoplasms. The indeterminate diagnosis of follicular neoplasm encompasses various thyroid lesions, such as cellular adenomatoid nodules, follicular adenomas, and follicular carcinomas, which exhibit heterogeneity.[25]

The present study provides a critical evaluation of FNAC diagnostic accuracy within the setting of hospitals in Malaysia, thus providing an essential benchmark for cytopathology practice in Malaysian. By sharing our current diagnostic performance, the data serves as a crucial reference point for understanding the strengths and limitations of thyroid FNAC Malaysia. The findings emphasized the need for continuous quality improvement initiatives. With a sensitivity of 66.7% and specificity of 96.2%, our results donate that while the overall diagnostic accuracy is robust, there remains room for improvement, mainly in reducing false negative cases. When we compared our results with international standards both alignments and disparities were observed, providing stakeholders with clear insights into our current diagnostic capabilities. The current research is useful for focused training, method refining, and creating benchmarks to guide future quality improvement efforts in thyroid cytopathology in Malaysian institutions.

The observed false negative rate of 11.7%, which exceeds the American Thyroid Association's recommended benchmark of 0-5%. This significant false negative rate emphasises the crucial need for a thorough review of FNAC thyroid practice in our environment. The clinical consequences are important, since false negative findings may result in delayed detection and treatment of thyroid carcinomas. Our findings indicate an urgent need for targeted interventions, including improvement operator training, enhancing sampling techniques, and more stringent cytopathological interpretation standards. The false negative rate highlights possible issues such as poor sampling, limits in detecting minor morphological alterations, especially in instances with unusual or overlapping morphological characteristics. This data is a significant call to action for local healthcare facilities to engage in ongoing medical education, adopt stricter quality control methods, and maybe introduce new diagnostic protections to reduce missed cases.

This study on FNAC of thyroid nodules has several limitations. The study was carried at a single tertiary hospital in Malaysia with a sample size of 162 cases, in addition the retrospective cross-sectional nature limits generalizability. Moreover, the research was confined to a specific three-year period (2017-2019), potentially not reflecting more recent practices. These limitations underscore the need for further research to improve thyroid nodule diagnostic practices.

CONCLUSION

In conclusion, FNAC emerges as a valuable diagnostic tool for evaluating thyroid nodules, offering high specificity and moderate sensitivity in distinguishing between benign and malignant lesions. While FNAC represents a cornerstone in thyroid nodule assessment, ongoing efforts to refine sampling techniques and enhance interpretation accuracy are essential for optimizing diagnostic outcomes in clinical practice.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study was approved by the National Medical Research Register and Medical Research & Ethics Committee (MREC) with (NMRR-ID19-3559-51702 S4 R1). It was also approved by the Human Research Ethical Committee, Universiti Sains Malaysia, protocol number (USM/JEPeM/19120975).

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analysed during the current study are available from the corresponding author and reasonable request.

COMPETING INTEREST

The authors declare that they have no competing interests.

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AUTHORS'S CONTRIBUTIONS

Conception and design: N.N.A & W.F.W.A.R, Data analysis and article drafting: A.S., N.H.I, NNA, Critical revision and Editing: WFWA.R, A.A.M.Z, Project supervision: W.F.W.A.R

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