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Diagnostic Concordance between Fine Needle Aspiration Cytology and Surgical Biopsy of Thyroid Nodules: A Retrospective Cross-Sectional Study from a Tertiary Referral Hospital in Riyadh, Kingdom of Saudi Arabia

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Design: Retrospective study.

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Main outcome measure: Evaluation of the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FNAC.

Results: Out of the 3867 FNAC results, 518 (13.4%) cases had histopathology results. Analysis of FNAC results revealed that 278 (53.7%) as benign, 98 (18.9%) as malignant, and 90 (17.4%) as indeterminate lesions, whereas 29 (5.6%) were suspicious for malignancy and 23 (4.4%) were non-diagnostic/unsatisfactory. The rate of false negatives was 30% and 18.5% for indeterminate cases and overall FNAC performance, respectively. Concordance between FNAC and histopathology results was observed in 415 (80.1%) cases. The overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FNAC were 60.0%, 97.5%, 95.3%, 73.8%, and 80.0%, respectively.

Conclusion: FNAC was confirmed to be a useful screening procedure for the assessment of patients with thyroid nodules because it is minimally invasive and cost-effective. However, there is a need to address false positive and false negative errors, particularly among indeterminate cases and cases suspicious for malignancy, through careful specimen collection and interpretation of FNAC results in order to improve the diagnostic yield.

Keywords: *fine needle aspiration cytology, histopathology, sensitivity, negative predictive value, positive predictive value.*

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I. Introduction

Fine needle aspiration cytology (FNAC) is a minimally invasive procedure commonly used as a diagnostic tool for the evaluation of single thyroid nodules. It is a simple procedure that is safe, cost-effective, and has a high diagnostic accuracy.[1]The reported overall sensitivity of FNAC for thyroid cancer ranged from 61.5% to 72%, while specificity was around 98% to 99%.[2] For uncommon thyroid malignancies, including anaplastic thyroid carcinoma and metastatic carcinoma, the reported sensitivity of FNAC reached almost 100% and specificity was over 80%.[3] As for solitary thyroid nodules, the reported sensitivity and specificity of FNAC were 80% and 86.6%, respectively.[4] However, several limitations of FNAC have been reported, including its high rates of unsatisfactory sampling, inconclusive reports, and indeterminate interpretations.[1] For papillary thyroid carcinomas (PTC), the sensitivity of FNAC depends on the tumor size. APTC <0.5 cm or >3 cm in size is more difficult to successfully aspirate as compared to tumors that are 0.5 cm to 3 cm in size.[5]

False negative thyroid aspirates are identified in 2.7% to 4% of cases diagnosed via FNAC, usually due to interpretation errors in cases of poorly-developed features of malignancy, scant cellularity in the specimen, and suboptimal material.[6, 7] False positives occur in up to 8% of cases due to the over diagnosis of follicular neoplasms.[7] False negative diagnoses occur in follicular cases, cystic PTCs, and papillary microcarcinomas.[8] It was previously suggested that the appropriate technique and preparation can increase the sensitivity and specificity of FNAC.[9]

Over the past decades, FNAC has been a primary diagnostic and screening tool for thyroid nodules. It has also been used for the cytologic diagnosis of thyroid cancers that require surgery. Therefore, to avoid unnecessary surgery, this method must yield correct and appropriate diagnoses through proper sampling and interpretation of results. The

present study aimed to evaluate the diagnostic performance of FNAC for thyroid nodules.

II. Subjects and Methods

A retrospective review of medical records of patients who underwent FNAC and histopathological examination of thyroid nodules at the Pathology Department of King Saud University Medical City from January 2016 to May 2021 was conducted. Patients with thyroid FNAC results and available histopathological follow-up results were included in the study. Those without histopathological follow-up results and with a final histopathological diagnosis of microcarcinoma were excluded from the analysis. Overall, 3867 FNAC and surgical biopsy results were reviewed, which comprised 1693 (43.8%) FNAC examinations and 2174 (56.2%) histopathological examinations from a total of 2442 patients. Of the 3867 results, 592 (15.3%) patients had both FNAC and histopathology results. After excluding histopathological biopsies that revealed microcarcinoma, we compared the FNAC results and histopathological examinations of 518 patients. Information gathered included the age and sex of the patients, the location of the FNAC specimen collection, and the FNAC and histopathological results.

The findings of thyroid FNAC and histopathology were compared. The characteristics and clinical relevance of FNAC were tested by calculating the values of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) which are all expressed as percentages.

The data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

This study was approved by the relevant Institutional Review Board. The need for informed patient consent was waived due to the retrospective nature of this study. None of the patients could be identified in the course of the study or during the publication and analysis of results.

III. Results

Overall, 518 patients were included which consisted of 420 (81.5%) women and 96 (18.5%) men. Location of the nodules differed among the patients, with 193 (37.3%) of the nodules involving the right thyroid gland, 168 (32.4%) involving the left thyroid gland, 142 (27.4%) involving both the left and right thyroid glands, and 15 (2.9%) had nodules involving the midline or isthmus (Fig 1).

Results of FNAC indicated that 278 (53.7%) are benign lesions, 98 (18.9%) malignant lesions, 90 (17.4%) indeterminate lesions, 29 (5.6%) lesions suspicious for malignancy and 23 (4.4%) lesions that were non-diagnostic/unsatisfactory. The most common type of benign lesion identified using FNAC was follicular nodule which was identified in 238 (85.6%) patients. PTC was the most common malignancy (86.7%) identified using FNAC (Table 1). Through histopathology, 271 (52.3%) benign lesions and 247 (47.7%) malignant lesions were identified. The most common benign lesions detected using histopathology were follicular nodules in 221 (81.5%) patients, whereas papillary carcinoma was the most common malignant diagnosis based on histopathology (n=200, 81.0%)(Table 2).

Table 1: FNAC findings in thyroid specimens (n = 518)

Diagnosis on FNAC	n (%)
Benign	278 (53.7%)
Follicular nodules	238 (85.6%)
Hashimoto's thyroiditis	31 (11.2%)
Hurthle cell adenoma	9 (3.2%)
Malignant	98 (18.9%)
Papillary carcinoma	85 (86.7%)
Follicular carcinoma	2 (2.0%)
Medullary carcinoma	3 (3.1%)
Anaplastic large cell carcinoma	3 (3.1%)
Hurthle cell carcinoma	5 (5.1%)
Indeterminate	90 (17.4%)
Suspicious for malignancy	29 (5.6%)
Unsatisfactory/non-diagnostic	23 (4.4%)

Abbreviations: FNAC, fine needle aspiration cytology

Table 2: Histopathological diagnosis in thyroid specimens (n = 518)

Histopathological diagnosis	n	%
Benign	271	52.3%
Multinodular goiter	221	81.5%
Hashimoto's thyroiditis	41	15.1%
Hurthle cell adenoma	9	3.3%
Malignant	247	49.1%
Papillary CA	200	81.0%
Follicular CA	30	12.2%
Medullary CA	6	2.4%
Anaplastic large cell CA	4	1.6%
Hurthle cell CA	7	2.8%

Abbreviations: CA, carcinoma

Of the 98 malignant lesions identified through FNAC, eight (8.2%) were considered benign through histopathological examination. Out of the 278 benign lesions identified through FNAC, 82 (29.5%) were considered malignant through histopathological examination. Four (17.4%) lesions considered unsatisfactory through FNAC examination were classified as malignant through histopathology. In three (10.3%) FNAC cases reported as suspicious for malignancy, FNAC revealed a benign lesion. A malignant lesion was found through histopathology in half of the lesions considered indeterminate by FNAC (Table 3).

Table 3: FNAC diagnosis versus final pathological diagnosis of specimens (n = 518)

FNAC diagnosis	Total (%)	Final pathological diagnosis (n=518)	
		Malignant	Benign
Positive for malignancy	98 (18.9%)	90 (91.8%)	8 (8.2%)
Negative for malignancy	278 (53.7%)	82 (29.5%)	196 (70.5%)
Unsatisfactory/Non-diagnostic	23 (4.4%)	4 (17.4%)	15 (82.6%)
Indeterminate	90 (17.4%)	45 (50.0%)	45 (50.0%)
Suspicious for malignancy	29 (5.6%)	26 (89.7%)	3 (10.3%)
Total	518	247 (47.7%)	271 (52.3%)

Abbreviations: FNAC, fine needle aspiration cytology

FNAC showed the following sensitivities, specificities, PPVs, and NPVs, respectively: 100%, 40.0%, 94.7%, and 100% for positive cases; 20.0%, 100%, 100%, and 75.7% for negative cases; 25.0%, 100%, 50.0%, and 81.8% for unsatisfactory cases; 40.0%, 100%, 100%, and 62.8% for indeterminate cases; and 100%, 33.3%, 92.9%, and 100% for lesions suspicious for malignancy. The rate of false negative results in indeterminate cases was 30.0%, whilst that for FNAC was 18.5%. Concordance between FNAC and histopathology results was observed in 415 (80.1%) cases. Overall, FNAC exhibited sensitivity, specificity, PPV, NPV, and accuracy of 60.0%, 97.5%, 95.3%, 73.8%, and 80.0%, respectively.

IV. Discussion

Several studies on the diagnostic sensitivity and reliability of FNAC for detecting the presence or absence of thyroid diseases have reported an FNAC sensitivity ranging from 43% to 99% and thyroid FNAC specificity ranging from 72% to 100%. [7, 8, 10]

In the current study, we found a 19.9% discordance between FNAC and histopathology results, which generally varies between 30% to 40%, depending on the rate of false positives and false negatives.[11] The most commonly reported causes of discordance between FNAC and histopathology include interpretation errors (false positives), sampling errors (false negatives), and unsatisfactory samples.[12] Discordance often occurs among cases with overlapping cytological features, particularly among adenomatous nodules, follicular neoplasms, follicular variants of PTC, and Hashimoto's thyroiditis.[12]

In this study, we had 96 (16.5%) false negatives, most of which were misdiagnosed as negative for malignant lesions or were due to non-diagnostic FNAC sampling and indeterminate sample issues. Many of the FNAC-diagnosed as false negative follicular lesions were found to be malignant PTCs. The high false negative rates in cases with large thyroid nodules can be explained by the difficulty in precisely sampling the entire nodule. [13, 14] Nodule heterogeneity has been suggested as one of the reasons why it is difficult to evaluate certain thyroid nodules by FNAC.[15] Sampling errors occur when the targeted nodule is missed or hidden in cases of a multinodular thyroid.

Seven of the thyroid FNACs with histopathologically proven false positive diagnosis included focal nuclear atypia and Hashimoto's thyroiditis, which were misdiagnosed as PTC. Focal nuclear atypia is often mistaken for PTC due to the overlapping features including papillary hyperplasia and

chromatin clearing, which are very common in hyperplastic nodules.[16, 17] Hashimoto's thyroiditis can be mistakenly diagnosed as PTC due to the atypical nuclear features, including nuclear grooves, overlapping nuclei, and nuclear clearing.[18] One way to distinguish Hashimoto's thyroiditis from papillary microcarcinomas is when solid cell nests are numerous and also by immunohistochemistry, particularly of p63, thyroid nuclear factor-1, thyroglobulin, Hector Battifora mesothelial-1, and calcitonin.[18, 19]

Overall, our study revealed an FNAC sensitivity, specificity, PPV, NPV, and accuracy of60.0%, 97.5%, 95.3%, 73.8%, and 80.0%, respectively. The sensitivity and accuracy we observed are relatively lower compared to results of recent studies with similar methodologies showing a sensitivity of 80% and an accuracy over 90%. [20-22] The lower sensitivity of FNAC in this study was due to a large number of false negatives in the indeterminate cases and in those with follicular neoplasm with papillary-like nuclear features. Indeterminate cases arise when pathologists are challenged in defining the FNAC results as clearly benign or clearly malignant. This is due to questionable features, such as the presence or absence of vascular capsular invasion, papillary-like nuclear features, and atypia of undetermined significance.[23] Several procedures have been found to improve the detection of malignancy in indeterminate smears, including real-time polymerase chain reaction of molecular markers that have been shown to have high sensitivity and specificity,[24,25] as well as elastography.[26, 27]

Recently, additional measures have been suggested to reduce the diagnostic error in thyroid FNAC and histopathology.[11] These include the use of uniform terminology for reporting cases, together with a review of the clinical and ultrasound findings and a multidisciplinary approach.[11] Furthermore, proper and strict specimen collection, implementation of specimen adequacy rules, and awareness of certain FNAC pitfalls may also improve the interpretation of FNAC and diagnosis of thyroid nodules.[7, 8]

We recognize that our study has some limitations. Selection bias may result from the retrospective nature of the study along with the study being conducted in a single center. However, we were able to draw and highlight some important findings on the reliability of FNAC in the assessment of thyroid nodules.

V. Conclusion

Our study confirmed the usefulness of FNAC as a screening procedure for the assessment of patients with thyroid nodules. However, this study showed low sensitivity and NPV of FNAC because of the relatively high number of false negatives. Nevertheless, it is crucial, particularly among indeterminate cases and those suspicious of malignancy, to exercise meticulous specimen collection and careful interpretation of FNAC results to improve diagnosis.

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Fig. 1: Sources of thyroid specimens (thyroid gland localization) for 518 FNAC and histopathological examinations