Clinical and Experimental Health Sciences

The Effects of Immunocytochemistry on Diagnostic Accuracy in Thyroid Fine Needle Aspiration Cytology: A Retrospective Study

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ABSTRACT

Objective: In thyroid cytology, ancillary studies are often utilized for intermediate-category cases to better differentiate between benign and malignant lesion. For this purpose, immunocytochemical markers may be preferred because they are cheaper than molecular studies and can be applied in many laboratories. This study retrospectively compares the diagnostic accuracy of cytology samples with and without immunocytochemistry and calculates the frequency of immunocytochemical marker use, as well as sensitivity and specificity rates.

Methods: Between 2015 and 2023, 1816 samples from 1506 patients with a histological diagnosis after cytological examination (thyroidectomy-lobectomy) were included. Cases without a histological diagnosis were excluded. The Thin Prep® method was used for all cytological sample preparations, and cell blocks were obtained. Demographic information, Bethesda system categories, immunocytochemical markers used, and histological diagnoses were recorded. Cases using at least one immunocytochemical marker were re-evaluated, and staining results were categorized as positive, focally positive, or negative. SPSS 15® software was used to assess data normality and perform statistical analyses.

Results: The most frequently used markers were HBME-1 (n=167), CK 19 (n=106), Galectin-3 (n=75), and CD 56 (n=6). Sensitivity rates for HBME-1, CK 19, Galectin-3, and CD 56 were 91%, 94%, 76%, and 75%, respectively; specificity rates were 63%, 61%, 80%, and 50%, respectively. Comparing groups with and without immunocytochemistry, the risk of malignancy was: 6.95%-6.97% for Bethesda category II; 21.7%-19.0% for Bethesda category III; 76.0%-37.1% for Bethesda category IV; 94.0%-95.0% for category V; and 100% for category VI.

Conclusion: In the follicular neoplasm group (Bethesda category IV) the risk of malignancy was higher in the immunohistochemistry applied group. No significant difference in malignancy risk was observed between groups with and without immunocytochemistry in other categories. Considering that immunocytochemical markers were predominantly applied in diagnostically challenging Bethesda categories, the similar malignancy risks across groups may suggest immunocytochemistry aids in accurate categorization. However, according to the results of this study, routine use of immunohistochemical markers in thyroid cytology is unnecessary except for Bethesda category IV.

Keywords: CK 19, Galectin-3, HBME-1, Immunocytochemistry, Thyroid

1. INTRODUCTION

Fine-needle aspiration cytology (FNAC) is a widely used, cost-effective, and minimally invasive diagnostic method that has been employed for decades in the evaluation of thyroid lesions. While FNAC yields high diagnostic accuracy for many thyroid nodules, differentiating between benign and malignant lesions can be particularly challenging in certain cytological samples. Several classification systems aim to provide reliable risk stratification for these intermediate cases; the most widely used is the Bethesda system, updated in 2023.

The 2023 Bethesda system categorizes thyroid cytology into six categories: 1. Nondiagnostic, 2. Benign, 3. Atypia of Undetermined Significance, 4. Follicular neoplasm, 5. Suspicious for malignancy, and 6. Malignant. While detailed cytological features characterize each category (1), routine cytological evaluation can be challenging, leading to difficulties in accurate categorization (2,3). The Bethesda system provides estimated malignancy risks for each category.

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Table 1. *Sensitivity, Specificity, positive predictive value and negative predictive values for HBME-1, CK 19 and Galectin 3 in various studies 1 – Core needle biopsy results of Xiong et al., 2 – Fine needle aspiration and core needle biopsy results of Song et al. 3 – Cazzaniga et al.'s results on histological samples 4 – Xin et al.'s meta-analysis results.*

	HBME-1				CK 19			Galectin-3		
	XIONG (5)	SONG (9)	CAZZANIGA (7)	XIN (10)	XIONG (5)	SONG (9)	XIN (10)	XIONG (5)	SONG (9)	XIN (10)
Sensitivity	63.53	87.5	77.0	92	77.65	51.5	81.6	89.41	96.16	84.2
Specificity	81.81	68.2	83.0	86	63.63	100.0	87.2	50.0	38.46	83.3
PPV	93.10	80.0	-	-	89.19	100.0	-	87.36	95.0	-
NPV	36.73	78.9	-	-	42.42	57.9	-	55.0	60.0	-

To improve diagnostic accuracy, ancillary studies can be used. These studies may include molecular tests (such as mutation analyses, gene expression studies, and miRNA analysis) or immunocytochemical methods. Molecular studies have become increasingly prominent in the updated Bethesda system (4,5). Many immunocytochemical markers are available, including HBME-1, CK19, galectin-3, Cited-1, CD117, CD56, and E-cadherin (4,5). However, the large number of available markers and their varying sensitivity and specificity can lead to different approaches among pathologists (Table 1). There is a growing consensus on standardizing the use of immunocytochemistry. For instance, Margari et al. proposed a diagnostic algorithm that begins with CK19, followed by HBME-1 and galectin-3 (6).

This study focuses on the commonly used markers: HBME-1, which demonstrates higher sensitivity and specificity in papillary carcinoma than in follicular neoplasms (7) and exhibits increased positivity in non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFT-P) and follicular variant papillary thyroid carcinoma (8,9); CK 19, a keratin family member expressed more frequently in papillary carcinomas than in normal thyrocytes (10); galectin-3, an anti-apoptotic protein with potential utility in papillary carcinoma diagnosis (11); and CD56, a marker with expression that decreases in papillary carcinoma (12-14).

The use of markers expected to be positive in papillary carcinoma, in conjunction with negative markers, may improve diagnostic accuracy (14). BRAF mutations are common in papillary thyroid carcinoma and less frequent in anaplastic and poorly differentiated carcinomas (15); immunohistochemical BRAF mutation analysis often correlates with molecular findings (15). While the cytological features of medullary thyroid carcinoma are well-established, preoperative diagnosis can be challenging. Immunocytochemistry using markers such as synaptophysin, chromogranin, CEA, and calcitonin may be necessary to confirm or exclude the diagnosis (16-18).

This retrospective study compares the diagnostic accuracy of thyroid cytology with and without immunohistochemistry and examines the selection of immunocytochemical markers by pathologists.

2. METHODS

Between 2015 and 2023, 1816 samples from 1506 patients whose histological diagnoses were confirmed with thyroidectomy or lobectomy and who had previous thyroid fine needle aspiration cytology (FNAC) at Haseki Training and Research Hospital were included in this study. (This study was approved by Ethics Committee of Haseki Training and Research Hospital, Noninvasive Clinic Ethics Committee (Approval date: 23.05.2024.; Number:26-2024). Thin Prep® method was used in the preparation of all cytological samples and cell blocks were obtained.

Immunocytochemical (ICC) analysis was performed at the discretion of the reporting pathologist during routine diagnostic evaluation. BenchMark®, Clone HBME-1 for HBME-1, BenchMark® A53-B/A2.2b for CK19, BenchMark® 9C4 for Galectin-3 and Ventana® MRQ-42 for CD56 clones were used in routine study in the hospital.

The cases were divided into two groups: those in which immunocytochemistry was used and those in which immunocytochemistry was not used when making a cytological diagnosis. The age, gender, diagnosis groups of these groups according to the Bethesda classification system, and the diagnoses they received after resection were noted. Histological diagnoses were divided into malignant and non-malignant groups according to the WHO Classification of Tumours of Endocrine Organs. Which markers were used in the group where immunocytochemical markers were applied was noted. Sensitivity was defined as the proportion of ICC-positive cases among malignant diagnoses, and specificity as the proportion of ICC-negative cases among benign diagnoses.

The data were evaluated using Microsoft Exel and SPSS programs. Comparisons between groups with and without the use of immunocytochemistry (ICC) were conducted using the chi-square test. In cases where expected cell frequencies were less than 5, Fisher's exact test was applied instead. A *p*-value less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Patient Demographic

The study included 1816 samples from 1506 patients. Of the 167 patients in the immunocytochemistry group, 132 (79%) were female and 35 (21%) were male; their mean age was 47.0 years (range, 19–84 years). In the non-immunocytochemistry group (n=1339), 1098 (82%) were female and 241 (18%) were male; their mean age was 48.6 years (range, 14–85 years). The mean nodule diameter was 24.07 mm (range, 5–80 mm) in the immunocytochemistry group and 24.07 mm (range, 5–55 mm) in the non-immunocytochemistry group.

3.2. Bethesda Category Analysis

Table 2 presents the Bethesda categories and final diagnoses for cases with non-benign histological diagnoses (excluding follicular nodular disease and thyroiditis).

3.2.1. Bethesda Category I

Immunocytochemistry was not performed (insufficient thyrocytes). Of the 269 cases, histological diagnoses included 23 papillary thyroid carcinomas, 2 anaplastic carcinomas, 1 lymphoma, and 28 microcarcinomas (9% malignancy risk).

3.2.2. Bethesda Category II

In the immunocytochemistry group (n=43), diagnoses included 3 papillary thyroid carcinomas, 5 microcarcinomas, and 1 neoplasm of uncertain malignant potential (6.97% malignancy risk). The non-immunocytochemistry group (n=819) showed 56 papillary thyroid carcinomas, 3 NIFT-P, 1 medullary thyroid carcinoma, and 93 microcarcinomas (6.95% malignancy risk).

3.2.3. Bethesda Category III

The immunocytochemistry group (n=46) showed 1 lymphoma, 9 papillary thyroid carcinomas, 1 medullary carcinoma, and 7 microcarcinomas (21.7% malignancy risk). The non-immunocytochemistry group (n=383) showed 31 papillary thyroid carcinomas, 2 medullary carcinomas, 7 microcarcinomas, and 1 NIFT-P (19% malignancy risk).

3.2.4. Bethesda Category IV

The immunocytochemistry group (n=13) showed 10 papillary thyroid carcinomas and 3 microcarcinomas (76.9% malignancy risk). The non-immunocytochemistry group (n=70) showed 26 papillary thyroid carcinomas and 12 microcarcinomas (37.1% malignancy risk).

3.2.5. Bethesda Category V

The immunocytochemistry group (n=55) showed 30 papillary thyroid carcinomas, 21 microcarcinomas, 1 medullary carcinoma, and 1 NIFT-P (56.3% malignancy risk). The non-immunocytochemistry group (n=81) showed 49 papillary thyroid carcinomas, 1 lymphoma, 1 neoplasm of uncertain malignant potential, and 27 microcarcinomas (61.7% malignancy risk). Including microcarcinomas ≥5 mm in size (radiologically indicated), the malignancy risk increased to 94% in the immunocytochemistry group and 95% in the non-immunocytochemistry group.

Table 2. *Bethesda Categories and histological diagnoses according to the use of immunocytochemistry in neoplastic cases.*

	Histological diagnosis	BK 2	BK 3	BK 4	BK 5	BK 6
Immunocytochemistry Applied	Thyroid papillary carcinoma	3	9	10	30	15
	Microcarcinoma	5	7	3	21	3
	Medullary carcinoma	0	1	0	1	1
	NIFT-P	0	0	0	1	0
	Other	1	1	0	0	0
Immunocytochemistry Not implemented	Thyroid papillary carcinoma	56	31	26	49	13
	Microcarcinoma	93	7	12	27	4
	Medullary carcinoma	1	2	0	0	1
	NIFT-P	3	1	0	0	0
	Other	0	0	0	2	0

Table 3. *Markers applied and number of cases in which they were used.*

Applied immunocytochemistry	Number of Cases (n)
HBME-1	167
CK 19	106
CD 56	6
Galectin-3	75
Calcitonin	26
Synaptophysin	4
Cea	16
Braf	1

Table 4. *Results according to histological diagnoses and Bethesda categories*

		Histological Final Diagnosis			Bethesda Categories				
		Malignant	Benign	Uncertain	BK 2	BK 3	BK 4	BK 5	BK 6
Hbme-1	Positive	67	9	1	3	8	4	45	17
	Focal positive	10	9	1	4	11	1	3	1
	Negative	7	31	4	26	11	5	0	0
	Could not be evaluated	12	16	0	9	11	2	6	0
CK-19	Positive	45	7	1	0	8	3	33	9
	Focal positive	5	5	1	6	2	1	2	0
	Negative	3	19	2	16	7	1	0	0
	Could not be evaluated	8	10	0	6	7	1	4	0
cd56	Positive	0	0	0	0	0	0	0	0
	Focal positive	1	1	0	0	0	0	2	0
	Negative	3	0	0	0	2	0	1	0
	Could not be evaluated	0	1	0	1	0	0	0	0
Galectin-3	Positive	22	2	0	1	0	1	16	6
	Focal positive	7	2	1	0	5	0	5	0
	Negative	9	17	3	14	8	1	5	1
	Could not be evaluated	8	4	0	4	2	2	4	0

Table 5. *Sensitivity and Specificity of ICC markers for Bethesda Categories*

Sensitivity	Bethesda Category	CK-19	Galectin-3	HBME-1
	BK 2	0.00	0.07	0.10
	BK 3	0.83	0.38	0.52
	BK 4	0.80	0.50	0.50
	BK 5	1.00	0.81	0.89
	BK 6	1.00	0.86	1.00
Specificity	Bethesda Category	CK-19	Galectin-3	HBME-1
	BK 2	0.84	1.00	0.76
	BK 3	0.73	0.62	0.53
	BK 4	0.50	1.00	0.71
	BK 5	0.00	0.50	0.00
	BK 6	N/A	1.00	N/A

3.2.6. Bethesda Category VI

Both the immunocytochemistry group (n=19) and the non-immunocytochemistry group (n=18) showed 100% malignancy risk. The immunocytochemistry group showed 1 medullary carcinoma, 15 papillary carcinomas and 3 microcarcinomas. The non-immunocytochemistry group showed 1 medullary carcinoma, 13 thyroid papillary carcinomas and 4 microcarcinomas.

3.3. Marker Usage

The relevant pathologist decided during the routine procedure whether immunocytochemistry would be used and which markers would be used. While in some cases, a single marker was used, it was often observed that several markers were used together (Table 3). The most frequently used markers were HBME-1 (n=167), CK 19 (n=106), Galectin-3 (n=75) and CD56 (n=6). While the most used marker alone was HBME-1, the most frequently used markers were the combination of HBME-1, CK19 and Galectin-3 (n = 74). In some cases, CD 56 appears to be added as a negative marker. Synaptophysin, chromogranin, monoclonal CEA, and calcitonin were used to exclude or confirm medullary carcinoma. In one case, immunohistochemical studies, such as ER, PR and CDX2 were used together with TTF-1 to exclude the possibility of metastasis in a case where papillary structures were clearly observed but nuclear features of thyroid papillary carcinoma were unclear.

3.4. Marker Performance

Table 4 summarizes the immunocytochemical markers used, Bethesda categories, and final diagnoses. Sensitivity and specificity rates for HBME-1, CK 19, Galectin-3, and CD 56 were 91%, 94%, 76%, and 75%, respectively, and 63%, 61%, 80%, and 50%, respectively. Table 5 shows the sensitivity and specificity rates according to Bethesda categories.

3.5. Overall Malignancy Risk

When malignancy rates were compared between immunocytochemistry and non – immunocytochemistry

group across Bethesda categories, a statistically significant difference was observed only in Bethesda Category IV (p = 0.019). In this category, ICC use was associated with a substantially higher rate of malignancy detection (76.0% vs. 37.1%). In contrast, no significant differences were found in categories II (p = 1.000), III (p = 0.813), V (p = 1.000), and VI (p = 1.000), likely due to either low baseline risk (in categories II and III) or universally high malignancy rates (in categories V and VI). These findings suggest that ICC may provide the most diagnostic utility in the indeterminate Bethesda IV category.

4. DISCUSSION

In thyroid cytology, a distinction can often be made between benign and malignant nodules. However, pathologists may have a challenge deciding between Bethesda categories for various reasons, such as autoimmune thyroiditis, reactive changes and degenerative changes around the cyst, Graves' Disease, granulomatous thyroiditis, and thyroid lesions in the intermediate category in the follicular pattern (2,3).

Cytological assessment of thyroid nodules may occasionally present interpretative challenges, particularly when nuclear enlargement and pleomorphism are observed in otherwise benign-appearing samples. These features may lead to diagnostic uncertainty between the benign category and atypia of undetermined significance (AUS). An illustrative case is shown in Figure 1, where negative immunoreactivity for HBME-1 and CK19 likely contributed to the cytological interpretation of the nodule as benign. The final histopathological diagnosis in this case was follicular nodular disease. A second example, presented in Figure 2, demonstrates similar cytological and immunostaining findings; however, the histological diagnosis was follicular adenoma. In this case, the dominance of microfollicular architecture may have been overlooked in the cytological evaluation, potentially leading to misclassification. In the case shown in Figure 3, a cluster of thyrocytes exhibits nuclear enlargement, membrane irregularities, and nuclear grooves. In this instance, positive immunostaining for HBME-1 and CK19 may support a cytological classification of suspicious for malignancy. The histological diagnosis of this case was thyroid papillary carcinoma.

In cases where there is difficulty between the Bethesda categories, molecular studies can guide the distinction between benign and malignant. Molecular studies are excluded from the scope of this study. The reason for this is that molecular study was performed on only one cytology sample (next-generation sequencing was performed in the patient with BK3 twice and BRAF V600E mutation was detected). As molecular testing has only recently been introduced at the institution where the study was conducted, it is likely that clinicians will increasingly request such analyses in a greater number of cases over time.

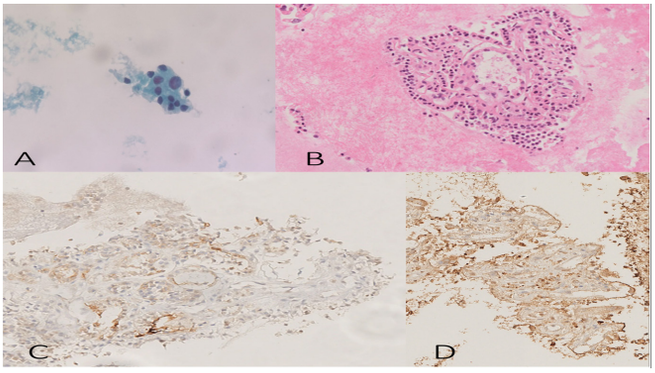

Figure 1. *A sample evaluated as Bethesda Category II. A: Nuclear enlargement and pleomorphism in thyrocytes (ThinPrep®, PAP stain, ×400), B: Benign-appearing thyrocytes with abundant cytoplasm and pleomorphism in the cell block (Hematoxylin & Eosin, ×400), C: Negative immunostaining for CK19, D: Negative immunostaining for HBME-1.*

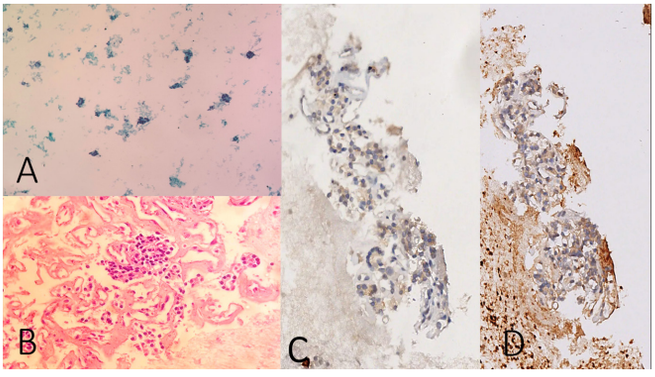

Figure 2. *A case of follicular adenoma evaluated as Bethesda Category II in routine practice. A: Benign-appearing, microfollicular-dominant thyrocytes (ThinPrep®, PAP stain, ×400), B: Benign-appearing thyrocytes in the cell block (Hematoxylin & Eosin, ×400), C: Negative immunostaining for CK19, D: Negative immunostaining for HBME-1.*

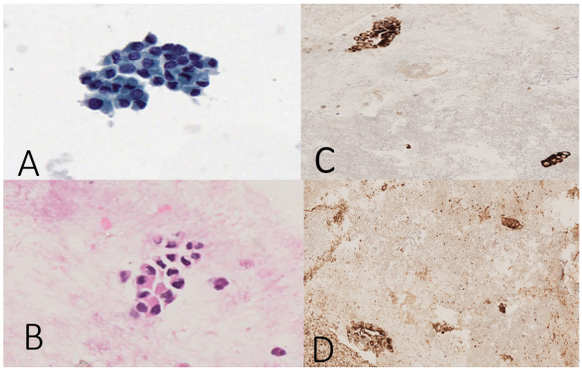

Figure 3. *A case of papillary thyroid carcinoma evaluated as Bethesda Category V in routine practice. A: Thyrocytes exhibiting nuclear enlargement, membrane irregularities, and grooves (ThinPrep®, PAP stain, ×400), B: A few atypical cells observed in the cell block (Hematoxylin & Eosin, ×400), C: Positive immunostaining for CK19, D: Positive immunostaining for HBME-1.*

As mentioned previously, the use of immunocytochemistry in thyroid cytology has been examined in various studies. In a study by He et al., Cyclin D1 was investigated and found its sensitivity to be 88.5% and specificity to be 100% (19). Dixit et al. suggested that the combined use of CD117 and Galectin-3 eliminates the problem of distinguishing between benign and malignant intermediate lesions (14). What does BRAF, CD173, Cadherin-16 (CDH16), somatostatin and CXCR4 receptor, S100 calcium binding protein A1 (S100A1), p53 and MDM-2, Bcl2, PD-1 and PD-L1 and periostin, which are mostly studied in histological samples, play a role in thyroid cytology? Time will tell how much space it can find (20-26). As the number of antibodies that can be used for this purpose and the experience with these antibodies increase, pathologists' preferences may also change. Although these antibodies were not used in our study, the results are not as promising as the result of Dixit et al. (14). In our current study, sensitivity rates for HBME-1, CK 19, Galectin-3 and CD 56 were calculated as 91%, 94%, 76% and 75%, respectively, and specificity rates were calculated as 63%, 61%, 80% and 50%, respectively.

A factor that causes immunocytochemical markers to give false positive and negative results in cytological samples may be sampling errors. Since FNAB samples represent only a part of the thyroid lesion, focal staining may cause difficulty in evaluation. A higher number of evaluated cells will allow for more appropriate evaluation. It can be suggested that more successful results can be obtained in core biopsies, where the number of cells is higher than in fine needle aspiration cytology, but there is not enough evidence to say that the diagnostic performance is better, and since there were no cases in which core biopsy was performed in this study, an evaluation on this subject could not be made (27,28).

One of the limitations of this retrospective study is that pathologists evaluated immunocytochemical results together with cytological findings in the decision-making process, and it was not possible to determine which findings they prioritized when determining Bethesda categories. The subjective nature of Bethesda categorization and differences in ICC assessment can be considered limitations of this study.

Bethesda Category IV (Follicular neoplasm) is one of the intermediate categories and may represent hyperplastic nodule, follicular adenoma, NIFT-P, and follicular carcinoma (29,30). However, in the follicular subtype of thyroid papillary carcinoma, papillary carcinoma nucleus features may not be evident and may be classified in this category. In this study, the diagnoses that increase the risk of malignancy in the Bethesda Category IV group where immunocytochemistry was applied are the follicular subtype of papillary carcinoma. Therefore, it can be suggested that the use of immunocytochemistry may be beneficial in the group considered to be Bethesda Category IV. The absence of a case diagnosed with follicular carcinoma in this study is one of the limitations of this study.

5. CONCLUSION

This study highlights the potential diagnostic value of immunocytochemistry in the evaluation of thyroid nodules, particularly in cytologically indeterminate cases. While the use of ICC did not significantly alter malignancy detection rates in Bethesda categories II, III, V, and VI, a statistically significant increase in malignancy detection was observed in Bethesda Category IV. These findings suggest that ICC may serve as a useful adjunctive tool in improving diagnostic accuracy and guiding clinical decision-making in this diagnostically challenging subgroup.

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Design of the study: AM,CBI,EGU
Acquisition of data for the study: AM,SGB,,EGU
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Drafting the manuscript: AM,CBI,EGU
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