Section: Pathology

Original Research Article

ROLE OF CD56 AND GALECTIN-3 AS IMMUNOHISTOCHEMICAL MARKERS IN THE DIFFERENTIAL DIAGNOSIS OF FOLLICULAR THYROID TUMORS

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ABSTRACT

Background: Differentiating between benign and malignant follicular thyroid neoplasms poses a significant diagnostic challenge, particularly in cases of minimally invasive follicular carcinoma (MIFC) where capsular and vascular invasion may be subtle or equivocal. Immunohistochemical markers such as CD56 and Galectin-3 have been proposed as valuable adjuncts to routine histopathology. **Aim:** To evaluate the diagnostic utility of CD56 and Galectin-3 expression in distinguishing follicular adenoma (FA) from follicular thyroid carcinoma (FTC), and to determine whether a combined marker panel enhances diagnostic accuracy.

Materials and Methods: This retrospective study included 50 surgically resected follicular thyroid tumours, comprising 36 benign cases (35 FA and 1 hyalinising trabecular adenoma) and 14 malignant cases (9 MIFC, 4 widely invasive FTC, 1 Hurthle cell carcinoma). Formalin-fixed, paraffin-embedded sections were stained using CD56 and Galectin-3 antibodies. Expression was evaluated semi-quantitatively by intensity and percentage of stained cells. Statistical analysis included sensitivity, specificity, predictive values, ROC curves, and Pearson chi-square testing.

Results: CD56 showed positive membranous expression in 94.4% of benign lesions and was absent or reduced in 78.6% of malignant tumours. It demonstrated high specificity (94.4%) as a negative marker for malignancy. Conversely, Galectin-3 showed positive cytoplasmic staining in 85.7% of FTC cases and only 5.6% of benign cases, with a sensitivity of 85.7% and specificity of 94.4%. The combination of CD56 and Galectin-3 yielded a sensitivity of 86% and specificity of 97%, significantly enhancing diagnostic accuracy ($p < 0.0001$).

Conclusion: CD56 and Galectin-3 are reliable immunohistochemical markers in the evaluation of follicular thyroid neoplasms. While CD56 is more specific for benign lesions and Galectin-3 more sensitive for malignancy, their combined use significantly improves the ability to differentiate follicular adenoma from carcinoma, especially in histologically borderline cases. These markers serve as useful adjuncts but do not replace conventional histopathological evaluation.

Keywords: Follicular thyroid carcinoma, Follicular adenoma, CD56, Galectin-3, Immunohistochemistry, Minimally invasive follicular carcinoma, Thyroid neoplasms, Differential diagnosis, Ancillary markers.

INTRODUCTION

Thyroid cancer is the most common malignancy of the endocrine system, accounting for the majority of endocrine-related neoplasms. Among these, approximately 95% arise from follicular epithelial cells of the thyroid gland, giving rise to a spectrum of well-differentiated to poorly differentiated carcinomas.[1] Globally, thyroid cancer exhibits a distinct female preponderance, with women being affected three to four times more frequently than men, and it ranks as the sixth most common cancer in women.[2] The peak incidence typically occurs between the third and sixth decades of life, with a relatively low prevalence in pediatric populations.

Follicular adenoma (FA) and follicular thyroid carcinoma (FTC) are neoplasms of epithelial origin that exhibit follicular differentiation. While follicular adenoma is a benign encapsulated neoplasm, follicular carcinoma is defined by capsular and/or vascular invasion, which is the key histopathological criterion distinguishing it from its benign counterpart. However, this distinction can be histologically subtle and often complicated by sectioning artifacts, poor tissue orientation, or incomplete capsular evaluation, leading to diagnostic uncertainty.[3,4,5]

Autopsy studies have estimated the incidence of follicular adenoma to be around 3%–4.3% of thyroid lesions, indicating its relative rarity compared to papillary thyroid carcinoma.[3,4] Nevertheless, FTC remains the second most common thyroid carcinoma after papillary carcinoma, and poses a particular diagnostic challenge when it manifests as minimally invasive follicular carcinoma (MIFC). In such cases, clear-cut evidence of capsular or vascular invasion may be limited, resulting in potential misclassification or underdiagnosis.

Given these limitations in routine histopathology, there has been a growing interest in identifying reliable immunohistochemical (IHC) markers that could aid in differentiating benign from malignant follicular neoplasms. Two such markers are CD56 (Neural Cell Adhesion Molecule) and Galectin-3, both of which have shown potential diagnostic relevance in thyroid pathology.[6]

- CD56 is typically expressed in benign follicular epithelium and is generally lost or reduced in malignant lesions, particularly in papillary and follicular carcinomas.
- Galectin-3, a β-galactoside-binding lectin involved in cell growth, adhesion, and apoptosis, is frequently overexpressed in malignant thyroid tumors, making it a useful positive marker for malignancy.

These markers may serve as valuable adjuncts to histopathological evaluation, particularly in borderline or equivocal cases, and may help reduce the risk of diagnostic error, unnecessary surgery, and overtreatment.

Aim of The Study

This study aimed to investigate the immunohistochemical expression of CD56 and Galectin-3 in benign and malignant follicular thyroid neoplasms, and to evaluate their diagnostic utility in differentiating follicular adenoma from follicular carcinoma. The goal was to determine whether a combination panel of these markers could enhance diagnostic accuracy and serve as a supportive tool in routine thyroid histopathology.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Pathology, Maheshwara Medical College, Hyderabad, over a one-year period from July 2024 to June 2025. The study included a total of 50 cases of surgically resected benign and malignant follicular thyroid tumours that were diagnosed based on routine Hematoxylin and Eosin (H&E) staining. Prior approval from the Institutional Ethical Committee was obtained before initiating the study.

Inclusion and Exclusion Criteria

The study population included all histopathologically diagnosed cases of follicular adenoma (FA), its variants, and follicular carcinoma (FC) and its subtypes, including minimally invasive, widely invasive, and Hurthle cell carcinoma (HCC). Cases with autolysis, poorly fixed tissue, extensive necrosis, or thyroid neoplasms of non-follicular origin (e.g., papillary, medullary, or anaplastic carcinomas) were excluded from the analysis.

Sample Distribution and Clinical Data

Of the 50 included cases, 36 (72%) were benign (comprising 35 follicular adenomas and 1 hyalinising trabecular adenoma), while 14 cases (28%) were classified as malignant (9 minimally invasive follicular carcinomas, 4 widely invasive follicular carcinomas, and 1 Hurthle cell carcinoma).

Demographic and clinical information—such as age, gender, ultrasonographic findings, fine-needle aspiration cytology (FNAC) reports, and surgical history—was retrieved from medical records and surgical case files. Gross pathological details including tumour size, nodule consistency, and capsular characteristics were collected from surgical pathology registers.

Tissue Processing and Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue blocks were used for sectioning and staining. All sections were stained with H&E for routine histopathological diagnosis. For immunohistochemical analysis, additional sections were subjected to staining with CD56 and Galectin-3 antibodies.

- CD56 expression was evaluated based on membranous staining of follicular epithelial cells. The intensity of staining was scored as: 0 (no staining), 1+ (weak), 2+ (moderate), and 3+ (strong). The percentage of positive cells was categorized as 0: <10%, 1+: 10–25%, 2+: 26–50%, and 3+: >50%.

- Galectin-3 expression was assessed via cytoplasmic staining, using the same semi-quantitative scoring scale. A positive result required clear cytoplasmic staining in at least 5% of tumour cells.

To minimize nonspecific background staining, blocking solutions were applied prior to antibody incubation. Sections were counterstained and examined independently by two pathologists.

Statistical Analysis

Statistical analysis was performed using SPSS version 11.0. The Pearson chi-square test was used to determine statistical significance between marker expression and tumour type. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratios, and receiver operating characteristic (ROC) curves were calculated. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Findings

Out of the 50 patients included, 41 were female (82%) and 9 were male (18%), reaffirming the female preponderance in thyroid disorders. Most patients presented with nodular thyroid swellings, with 94% (n=47) having nodular lesions and 6% (n=3) having diffuse involvement.

The age range for benign cases was 20 to 72 years (mean 37 ± 9.4 years), while that for malignant cases ranged from 30 to 74 years (mean 42 ± 13.6 years). Among benign tumours, 61% of patients were aged 20–40 years, and 33% were aged 41–60 years. Among malignant tumours, the 41–60-year age group also formed the majority (43%), followed closely by 20–40 and 61–80-year age groups.

Tumour size was a notable predictor of malignancy. Large lesions (>4 cm) were more frequently seen in follicular carcinoma (57%) than in adenomas (8.5%). In contrast, small-sized lesions (1–2 cm) were found only in benign cases (28.6%), and moderate-sized lesions (2–4 cm) were observed in both benign (62.9%) and malignant (42.9%) tumours.

Histopathological examination of the 14 malignant cases revealed capsular invasion in 6 cases (42.9%), vascular invasion in 2 cases (14.3%), and both vascular and capsular invasion in 6 cases (42.9%).

Immunohistochemical Expression Patterns

CD56 Expression

Among the 36 benign tumours, CD56 was positively expressed in 34 cases (94.4%), with 17 cases showing moderate (2+) staining and 15 cases showing intense (3+) membranous positivity. Only one case (2.7%) was completely negative. In contrast, CD56 expression was lost or minimal in 11 out of 14 (78.6%) malignant cases, with only 3 malignant cases (21.4%) showing weak-to-moderate staining.

This suggests that CD56 expression is preserved in benign follicular tumours and significantly reduced or absent in follicular carcinoma, supporting its utility as a negative marker for malignancy.

Galectin-3 Expression

Galectin-3 expression was strongly positive in malignant cases, with 12 out of 14 (85.7%) carcinomas showing cytoplasmic staining. Among these, 6 had moderate (2+) and 2 had strong (3+) staining intensity. Only 2 out of 36 benign tumours (5.6%) exhibited any Galectin-3 positivity, both of which were weak (1+). Hence, Galectin-3 proved to be a reliable positive marker for malignancy.

Table 1: Demographic data of the study (n = 50)

Category	No. of Cases	Percentage (%)
Follicular adenoma	35	70
Hyalinising trabecular adenoma	1	2
Widely invasive follicular carcinoma (WIFC)	4	8
Minimally invasive follicular carcinoma (MIFC)	9	18
Hurthle cell carcinoma (HCC)	1	2
Females	41	82
Males	9	18
Nodular lesions	47	94
Diffuse lesions	3	6

Age-wise Distribution

Age Group	Benign (%)	Malignant (%)
20 to 40 years	61% (n=22)	43% (n=6)
41 to 60 years	33% (n=12)	43% (n=6)
61 to 80 years	6% (n=2)	14% (n=2)

Size of Lesion

Size	Follicular Adenoma (n=35)	Follicular Carcinoma (n=14)
1 to 2 cm	28.6% (n=10)	0% (n=0)
2 to 4 cm	62.9% (n=22)	42.9% (n=6)
> 4 cm	8.5% (n=3)	57.1% (n=8)

Histopathological Invasion in FTC (n = 14)

Invasion Type	No. of FTC Cases	Percentage (%)
Vascular invasion only	2	14.3

Capsular invasion only	6	42.9
Both	6	42.9

Table 2: Immunohistochemical scoring of CD56 and Galectin-3 expression in follicular adenoma and carcinoma of the thyroid

A. Summary Scoring – All Benign vs Malignant Cases

Marker	Immunohistochemical Scoring in Follicular Adenoma (n = 36)		Immunohistochemical Scoring in Follicular Carcinoma (n = 14)	
	0	**1+**	**2+**	**3+**
CD56	1	3	17	15
Galectin-3	0	2	1	0

B. Subtype-wise Scoring: CD56 and Galectin-3 Expression

Subtype	CD56 (0 / 1+ / 2+ / 3+)	Galectin-3 (0 / 1+ / 2+ / 3+)
Minimally Invasive FC (n = 9)	6 / 0 / 2 / 1	1 / 2 / 5 / 1
Widely Invasive FC (n = 4)	4 / 0 / 0 / 0	1 / 1 / 2 / 0
Hurthle Cell Carcinoma (n = 1)	1 / 0 / 0 / 0	0 / 1 / 0 / 0

The combined use of CD56 (negative marker) and Galectin-3 (positive marker) enhanced diagnostic accuracy, yielding specificity of 97% and an overall sensitivity of 86%. This confirms that the panel of both markers outperformed either marker alone in distinguishing follicular adenoma from follicular carcinoma.

ROC analysis further supported these findings:

- Area Under Curve (AUC) for CD56: 0.928 (95% CI: 0.815–0.985)
- AUC for Galectin-3: 0.872 (95% CI: 0.738–0.952)

Table 3: Comparison of benign and malignant tumours with various diagnostic metrics

Diagnostic Metric	Benign Tumours		Malignant Tumours	
	CD56	**Galectin-3**	**CD56**	**Galectin-3**
Sensitivity	94.4%	5.6%	21.4%	85.7%
Specificity	85.7%	94.4%	94.4%	85.7%
Positive Predictive Value (PPV)	91.9%	50.0%	85.7%	92.3%
Negative Predictive Value (NPV)	90.0%	72.0%	75.0%	88.0%
Positive Likelihood Ratio (PLR)	6.6	1.0	3.83	6.0
Negative Likelihood Ratio (NLR)	0.06	1.0	0.83	0.17
95% Confidence Interval (OR)	15.4–122.5	0.08–2.95	0.21–70.8	15.4–122.5
Odds Ratio (OR)	88.0	0.44	15.0	88.0
P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001

This study reinforces that CD56 is highly expressed in benign follicular adenomas but markedly reduced in follicular carcinomas, making it a highly specific negative marker for malignancy. Conversely, Galectin-3 is rarely expressed in benign tumours but frequently positive in malignant ones, thus serving as a sensitive and reliable positive marker.

Importantly, the combination of CD56 and Galectin-3 provides superior diagnostic power in differentiating benign from malignant follicular thyroid neoplasms, especially in challenging cases where conventional histology may be equivocal. These markers, when used together, may improve preoperative or intraoperative decision-making and reduce diagnostic ambiguity.

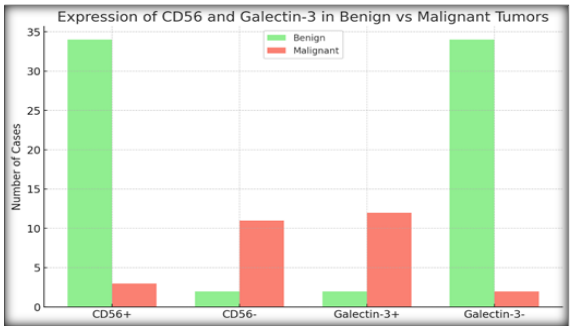

Figure 1: Shows the distribution of CD56 and Galectin-3 expression in benign vs. malignant follicular thyroid tumors

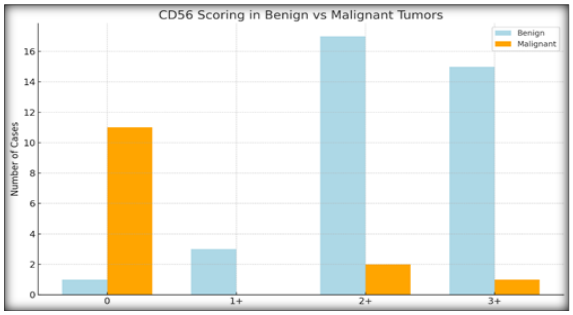

Figure 2: Displays the immunohistochemical scoring of CD56 (0 to 3+) across benign and malignant cases

DISCUSSION

In this study, we investigated the immunohistochemical expression of CD56 and Galectin-3 in follicular neoplasms of the thyroid, aiming to differentiate follicular adenoma (FA) from follicular carcinoma (FTC) using a panel of markers. The total sample comprised 50 cases, of which 36 were benign (35 FA and 1 HTA) and 14 were malignant (9 minimally invasive follicular carcinoma [MIFC], 4 widely invasive follicular carcinoma [WIFC], and 1 Hurthle cell carcinoma [HCC]).

CD56: Diagnostic Role and Literature Support

CD56, also known as neural cell adhesion molecule (NCAM), is typically expressed in normal thyroid follicular epithelium and benign lesions, such as follicular adenomas and nodular hyperplasia. It plays a role in cell adhesion, tissue architecture, and differentiation. Several studies have shown that loss or reduction in CD56 expression is associated with tumor progression and is frequently observed in malignant thyroid neoplasms, including papillary carcinoma, follicular carcinoma, and anaplastic carcinoma.

Our study findings are consistent with the literature. CD56 expression was observed in 34 out of 36 benign cases (94.4%), whereas it was absent or reduced in 11 out of 14 malignant cases (78.6%). Only three malignant cases showed any positivity, and even those were weak to moderate. This highlights the strong negative predictive value (NPV) and specificity of CD56 as a negative marker for malignancy.

These findings are in line with those reported by Scarpino et al., who observed CD56 positivity in 100% of follicular adenomas and 58.3% of Hurthle cell adenomas.[9] Similarly, Park et al. demonstrated that 93.3% of follicular adenomas and 90.5% of Hurthle cell adenomas were positive for CD56.[10] El-Atti and Shash also reported CD56 expression in 91.7% of follicular adenomas and 87.5% of Hurthle cell adenomas,[11] and El-Demellawy et al. confirmed 100% CD56 positivity in their series of benign follicular lesions.[12]

The variation in sensitivity and specificity among studies may be attributed to differences in cutoff thresholds, antibody clones, and staining protocols.[10,11,13] However, the common trend remains that CD56 expression is well-retained in benign lesions and significantly lost in malignancies, supporting its utility in ruling out carcinoma when positive.

Galectin-3: A Marker for Malignancy and Its Complexities

Galectin-3 is a β-galactoside-binding lectin with a molecular weight of 31 kDa. It plays a crucial role in multiple biological functions, including cell adhesion, proliferation, apoptosis regulation, malignant transformation, and metastasis. The cytoplasmic expression of Galectin-3 is frequently observed in malignant thyroid neoplasms and is considered a reliable positive marker for malignancy. In our study, Galectin-3 showed cytoplasmic positivity in 12 out of 14 FTC cases (85.7%), while only 2 of 36 benign lesions (5.6%) showed weak positivity. This translated into a sensitivity of 85.7%, specificity of 94.4%, positive predictive value of 92.3%, and negative predictive value of 88.0% for diagnosing malignancy. These values reinforce the diagnostic reliability of Galectin-3 in distinguishing benign from malignant follicular lesions.

Saleh et al. reported Galectin-3 positivity in 85.1% of malignant thyroid nodules, compared to 27.5% of benign lesions, with a specificity of 72.4% (16). In contrast, our study shows higher specificity (94.4%), possibly due to stricter positivity criteria. Kovacs et al. also found Galectin-3 to be particularly helpful in identifying minimally invasive follicular carcinoma, where histological features may be subtle.[17]

However, it is important to recognize the pitfalls in Galectin-3 interpretation. Studies have noted false positives in benign lesions, particularly in Hurthle cell changes, inflammatory settings, or cytokine-induced reactivity, which may lead to overdiagnosis.[19] Park et al. suggested that such discrepancies may arise due to variations in antibody clones, detection systems, and staining cutoffs.[18] Therefore, reliance on Galectin-3 alone is cautioned against, and combining it with a negative marker like CD56 enhances diagnostic precision.

Individually, both markers performed well in our study—CD56 as a specific marker for benign lesions and Galectin-3 as a sensitive marker for malignancy. However, when used in combination, their diagnostic accuracy improved further. The combination yielded a sensitivity of 86% and specificity of 97%, which was higher than either marker alone. This combined panel showed strong statistical significance ($p < 0.0001$), supporting its clinical utility in distinguishing follicular carcinoma from follicular adenoma, especially in ambiguous or borderline cases.

These findings are supported by previous studies suggesting that marker panels—such as CD56 + Galectin-3, CK19 + HBME1, or Galectin-3 + HBME1—are superior to single markers.[20] In our setting, the CD56 and Galectin-3 panel was cost-effective, reproducible, and provided high discriminatory power.

To conclude, our study underscores the importance of immunohistochemistry in the differential diagnosis of follicular thyroid neoplasms. CD56 emerged as a highly specific negative marker, while Galectin-3 showed high sensitivity for malignancy. Their combined use significantly improved diagnostic performance. These markers may be particularly valuable in minimally invasive or histologically equivocal cases, aiding pathologists in establishing a definitive diagnosis and guiding appropriate clinical management.

CONCLUSION

In this study of 50 cases of follicular thyroid neoplasms, we evaluated the diagnostic utility of CD56 and Galectin-3 as immunohistochemical markers in differentiating follicular adenoma (FA) from follicular thyroid carcinoma (FTC). Our findings confirmed that these markers, especially when used in combination, serve as valuable ancillary tools in resolving diagnostic ambiguity.

Galectin-3, a β-galactoside-binding lectin, showed high cytoplasmic expression in 85.7% of follicular carcinomas and minimal expression (5.6%) in benign lesions, making it a sensitive marker for detecting malignancy. The calculated sensitivity and specificity of Galectin-3 in diagnosing FTC were 85.7% and 94.4%, respectively, with a positive predictive value (PPV) of 92.3% and a negative predictive value (NPV) of 88.0%.

On the other hand, CD56, a neural cell adhesion molecule normally expressed in benign follicular epithelium, was positively expressed in 94.4% of follicular adenomas and absent or significantly reduced in 78.6% of follicular carcinomas. Its specificity in detecting malignancy as a negative marker reached 94.4%, with a sensitivity of 21.4%, reinforcing its role as a specific marker for benignity. Although neither marker alone reached absolute diagnostic accuracy, their combined application improved both sensitivity (86%) and specificity (97%) in distinguishing benign from malignant follicular thyroid neoplasms. This combination also achieved statistically significant separation between tumour categories ($p < 0.0001$).

While these immunohistochemical tests do not replace conventional histopathological examination, they offer valuable adjunctive insight, particularly in borderline or minimally invasive cases where capsular or vascular invasion may be equivocal.

In conclusion, the combined panel of CD56 (negative marker) and Galectin-3 (positive marker) is a reliable, cost-effective, and diagnostically meaningful approach to improve the diagnostic accuracy of follicular thyroid carcinoma. Incorporating this panel into routine diagnostic workflows may assist pathologists in reaching more definitive conclusions and reducing interobserver variability.

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