Original Article

Diagnostic Utility of Cytokeratin 19 in Differentiating Papillary Thyroid Carcinoma from Follicular Patterned Thyroid Lesions -An Immunohistochemical Study

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Abstract

Background: Papillary thyroid carcinoma (PTC) is the most common malignant tumour of the thyroid gland, accounting for approximately 80–85% of all thyroid malignancies. Its diagnosis relies on distinctive nuclear features; however, these may be subtle or equivocal in follicular-patterned lesions, posing diagnostic challenges. Cytokeratin 19 (CK19) immunohistochemistry has been proposed as a useful adjunct in diagnostically challenging cases. The aim is to evaluate the diagnostic utility of CK19 immunohistochemistry in differentiating Papillary thyroid carcinoma and its follicular variant from other follicular-patterned thyroid lesions. **Material and Methods:** This retrospective observational study was conducted in the Department of Pathology, Dr. D. Y. Patil School of Medicine, Nerul, Navi Mumbai, over two years (January 2024 – December 2025). A total of 28 thyroidectomy specimens comprising PTC (n=4), FVPTC (n=4), follicular adenoma (FA, n=14), multinodular goitre (MNG, n=2), and non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP, n=4) were included. CK19 expression was graded semi- quantitatively from 0 to 4+. **Results:** All eight cases of PTC/FVPTC showed Strong, diffuse, membranous and cytoplasmic positivity (4+) CK19 positivity. Benign lesions demonstrated absent or focal staining. NIFTP showed heterogeneous expression without diffuse strong positivity. CK19 demonstrated 100% sensitivity, specificity, positive predictive value, and negative predictive value in this cohort (Fisher's exact test, $p<0.0001$). **Conclusion:** CK19 immunohistochemistry is a reliable adjunct tool for differentiating Papillary thyroid carcinoma and its variants from benign follicular-patterned thyroid lesions, particularly in cases with equivocal morphological features.

Keywords: Papillary thyroid carcinoma; Cytokeratin 19; Follicular-patterned thyroid lesions; Immunohistochemistry; NIFTP.

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Introduction

Papillary thyroid carcinoma (PTC) is the most common malignant tumour of the thyroid gland, accounting for approximately 80–85% of all thyroid malignancies.[1] It predominantly affects adults with a female predilection and generally carries a favourable prognosis when detected early. Histologically, PTC is characterised by distinctive nuclear features including nuclear enlargement, overlapping, clearing ("Orphan Annie eye" nuclei), irregular nuclear contours, grooves, and intranuclear cytoplasmic inclusions.[2] However, diagnosis becomes challenging when nuclear features are subtle, focal, or present within lesions exhibiting a predominantly follicular growth pattern. Follicular-patterned thyroid lesions span a wide spectrum, from benign entities such as follicular adenoma (FA) and multinodular goitre (MNG) to borderline entities such as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and malignant lesions including FVPTC.[3] Several benign lesions may occasionally exhibit focal nuclear clearing, grooves, or overlapping, thereby mimicking PTC. Conversely, FVPTC may lack well-formed papillae and demonstrate a purely follicular architecture. Interobserver variability in the diagnosis of FVPTC and borderline follicular lesions has been well documented.[4]

Among various immunohistochemical markers, CK19 — a low-molecular-weight cytokeratin of the cytoskeletal intermediate filament family — has emerged as one of the most diagnostically useful IHC in thyroid pathology.[5] CK19 demonstrates strong and diffuse cytoplasmic staining in most cases of PTC including FVPTC, while benign follicular lesions typically show absent or focal staining.[6,7]

Several studies have demonstrated the diagnostic value of CK19 in identifying PTC, especially in lesions with equivocal morphology.[8,9] However, occasional overlap in staining patterns has been reported, emphasising the need for interpretation in conjunction with routine histopathology.[10,11]

The present study aims to evaluate the diagnostic utility of CK19

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immunohistochemistry in differentiating PTC from other follicular-patterned thyroid lesions exhibiting focal papillary-like nuclear features.

Materials and Methods

Study Design and Setting: This retrospective observational study was conducted in the Department of Pathology, Dr. D. Y. Patil School of Medicine, Nerul, Navi Mumbai, over a two-year period from January 2024 to December 2025. All thyroidectomy specimens diagnosed as follicular-patterned thyroid lesions were retrieved from departmental archives.

Inclusion and Exclusion Criteria

Thyroidectomy specimens with histopathological diagnoses of PTC, FVPTC, FA, NIFTP, and MNG were included. Cases with inadequate or poorly preserved paraffin blocks were excluded.

Sample Size: All eligible cases available during the study period were included by consecutive sampling. The final sample comprised 28 cases with adequate formalin-fixed paraffin-embedded (FFPE) tissue blocks.

Histopathological Evaluation: FFPE tissue sections of 3–4 µm thickness were stained with haematoxylin and eosin (H&E). All slides were reviewed to confirm diagnosis, with attention to nuclear enlargement, overlapping, clearing, grooves, and intranuclear cytoplasmic inclusions.

Immunohistochemistry: CK19 immunohistochemical staining was performed on representative FFPE sections using standard protocols. Sections were deparaffinised, rehydrated, and subjected to antigen retrieval, followed by incubation with primary monoclonal antibodies against CK19, secondary antibody system, and DAB chromogen visualisation. Positive and negative controls were included in each run.

Semi-Quantitative Scoring: CK19 expression was scored according to Bose et al.12 as follows: Nil (0%); 1+ (<5% positive cells); 2+ (5–25% % positive cell*); 3+ (25–75% % positive cell*); 4+ (>75% % positive cell*). Scores ≥3+ were considered diffuse positivity; 1+ and 2+ were focal; 0 was negative.

Statistical Analysis: Data were analysed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Fisher's exact test was used to assess associations between CK19 expression and lesion type. Sensitivity, specificity, PPV, and NPV were calculated. A p-value <0.05 was considered statistically significant.

Results

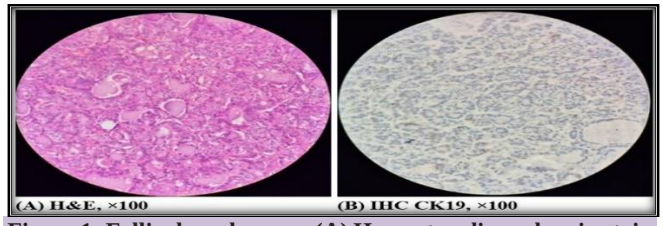

Figure 1: Follicular adenoma. (A) Haematoxylin and eosin stain showing follicular architecture with colloid-filled follicles lined by bland follicular epithelial cells (H&E, ×100). (B) CK19 immunohistochemistry demonstrating complete absence of staining in follicular epithelial cells, consistent with a benign lesion (IHC, CK19, ×100).

Demographic Characteristics: The age of patients ranged from 18 to 62 years. The majority of cases occurred in the fourth decade (31–40 years, 28.6%), followed by the fifth decade (41–50 years, 25.0%). A clear female predominance was noted with a female-to-male ratio of approximately 3.6:1 [Table 1 and 2].

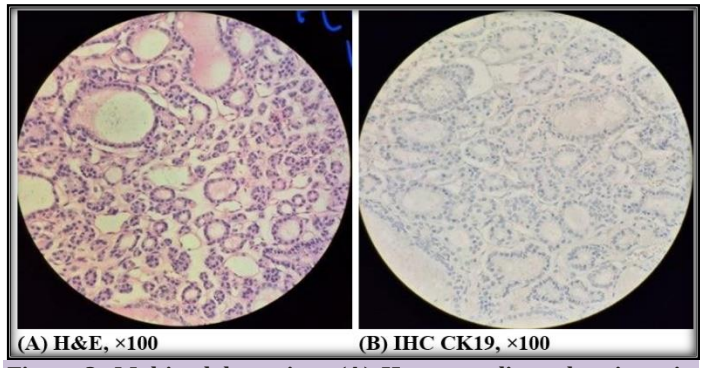

Figure 2: Multinodular goitre. (A) Haematoxylin and eosin stain showing variably sized follicles distended with colloid and lined by flattened follicular epithelium (H&E, ×100). (B) CK19 immunohistochemistry demonstrating negative expression in thyroid follicles, confirming benign nature of the lesion (IHC, CK19, ×100).

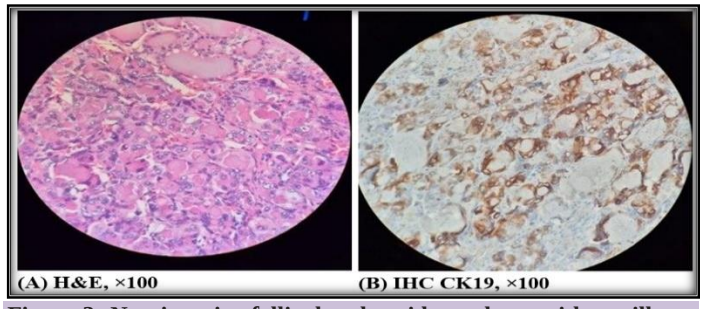

Figure 3: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). (A) Haematoxylin and eosin stain showing a follicular growth pattern with papillary-like nuclear features including nuclear enlargement and pale chromatin (H&E, ×100). (B) CK19 immunohistochemistry demonstrating focal and patchy cytoplasmic positivity, reflecting the borderline biological behaviour of NIFTP (IHC, CK19, ×100).

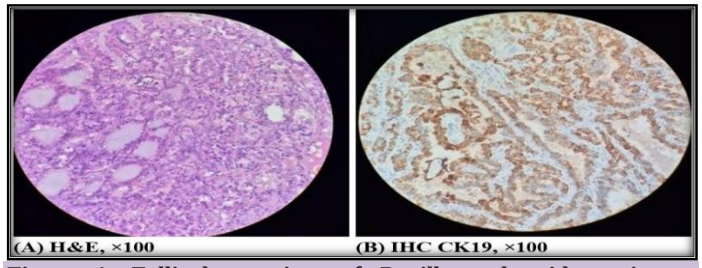

Figure 4: Follicular variant of Papillary thyroid carcinoma (FVPTC). (A) Haematoxylin and eosin stain demonstrating a follicular growth pattern with characteristic nuclear features of papillary carcinoma including nuclear clearing, grooves, and overlapping (H&E, ×100). (B) CK19 immunohistochemistry showing strong and diffuse cytoplasmic positivity (4+) in tumour cells, supporting the diagnosis of malignancy (IHC, CK19, ×100).

Table 1: Age distribution of patients with follicular-patterned thyroid lesions (n=28)

Age Group (Years)	Number of Cases	Percentage
≤20	02	7.1%
21–30	06	21.4%
31–40	08	28.6%
41–50	07	25.0%
51–60	04	14.3%
>60	01	3.6%
Total	28	100%

Table 2: Gender distribution of patients with follicular-patterned thyroid lesions (n=28)

Gender	Number of Cases	Percentage
Female	22	78.6%
Male	06	21.4%
Total	28	100%

Histopathological Spectrum and CK19 Expression: Of the 28 cases, 8 (28.6%) were malignant (4 classic PTC and 4 FVPTC), 14 (50.0%) were follicular adenoma, 2 (7.1%) were multinodular goitre, and 4 (14.3%) were NIFTP. The distribution of CK19 staining grades across all diagnoses is shown in [Table 3].

Table 3: Distribution of CK19 immunohistochemical staining grades across different histopathological thyroid lesions

Histopathological Diagnosis	Total	0	1+	2+	3+	4+	Concordance
Classic PTC	04	0	0	0	0	4 (100%)	100%
FVPTC	04	0	0	0	0	4 (100%)	100%
Follicular Adenoma	14	3 (21%)	1 (7%)	1 (7%)	2 (14%)	7 (50%)	28%
Multinodular Goitre	02	2 (100%)	0	0	0	0	100% negative
NIFTP	04	2 (50%)	1 (25%)	0	1 (25%)	0	75%
Total	28	7	2	1	3	15	—

All 8 cases of PTC/FVPTC (100%) showed diffuse strong (4+) cytoplasmic CK19 positivity. In the FA group (n=14), staining was variable: 3 cases (21%) negative, 1 (7%) 1+, 1 (7%) 2+, 2 (14%) 3+, and 7 (50%) 4+. Both MNG cases were negative. Among NIFTP (n=4), 2 cases (50%) were negative, 1 (25%) showed 1+, and 1 (25%) showed 3+; no case demonstrated diffuse strong (4+) expression.

Benign vs. Malignant/Borderline Lesion Comparison

All benign lesions (FA and MNG, n=16) showed absent or weak CK19 expression (0–1+). All malignant/borderline lesions (PTC, FVPTC, NIFTP, n=12) showed expression ≥2+. This difference was statistically significant (Fisher's exact test, $p<0.0001$; [Table 4]).

Table 4: Semiquantitative CK19 expression in benign versus malignant/borderline thyroid lesions

CK19 Expression Grade	Benign Lesions (FA + MNG)	Malignant/Borderline Lesions (PTC + FVPTC + NIFTP)
Nil (0)	7	0
Weak (1+)	2	0
Moderate (2+)	0	1
Strong (3+)	0	3
Diffuse Strong (4+)	0	15

FA = follicular adenoma; MNG = multinodular goitre; PTC = Papillary thyroid carcinoma; FVPTC = follicular variant PTC; NIFTP = non-invasive follicular thyroid neoplasm with papillary-like nuclear features. $p<0.0001$, Fisher's exact test.

Diagnostic Performance of CK19: Using diffuse CK19 expression (≥2+) as the diagnostic threshold, CK19 demonstrated sensitivity, specificity, PPV, and NPV of 100%, with an overall diagnostic accuracy of 100% in this cohort [Table 5].

Table 5: Diagnostic performance of CK19 immunohistochemistry in differentiating benign from malignant/borderline thyroid lesions

Diagnostic Parameter	CK19 Immunohistochemistry
Sensitivity	100%
Specificity	100%
Positive Predictive Value (PPV)	100%
Negative Predictive Value (NPV)	100%
Overall Diagnostic Accuracy	100%

Overall CK19 Staining Pattern: Diffuse strong (4+) CK19 expression was the most frequent pattern, observed in 16/28 cases (57.1%). Strong (3+) expression was noted in 3 cases (10.7%), moderate (2+) in 1 case (3.6%), weak (1+) in 1 case (3.6%), and 7 cases (25.0%) showed no staining [Table 6].

Table 6: Overall CK19 immunohistochemical expression pattern in all 28 cases

CK19 Expression Grade	Number of Cases	Percentage
Nil (0)	07	25.0%
Weak (1+)	01	3.6%
Moderate (2+)	01	3.6%
Strong (3+)	03	10.7%
Diffuse Strong (4+)	16	57.1%
Total	28	100%

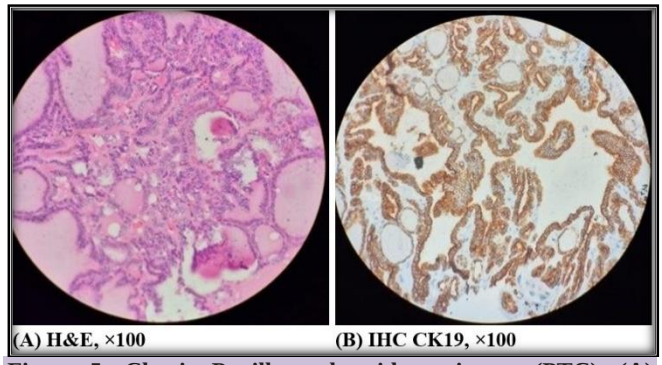

Figure 5: Classic Papillary thyroid carcinoma (PTC). (A) Haematoxylin and eosin stain showing papillary architecture with fibrovascular cores lined by tumour cells exhibiting Orphan Annie eye nuclei, intranuclear grooves, and cytoplasmic inclusions (H&E, ×100). (B) CK19 immunohistochemistry demonstrating diffuse strong cytoplasmic expression (4+) in tumour cells, confirming Papillary thyroid carcinoma (IHC, CK19, ×100).

Discussion

Among the various immunohistochemical markers investigated in thyroid pathology, CK19 has emerged as one of the most useful for distinguishing PTC from benign follicular-patterned lesions.[7,8] CK19 demonstrates strong and diffuse cytoplasmic expression in more than 25% of tumour cells in most PTC cases, whereas benign lesions generally show absent or focal staining.[9]

In the present study, CK19 immunohistochemistry demonstrated strong and diffuse positivity (3+/4+) in all cases of classic PTC and FVPTC [Figure 4 and 5], while benign lesions such as FA and MNG predominantly showed negative or focal staining [Figure 1 and 2]. NIFTP demonstrated intermediate heterogeneous expression [Figure 3], consistent with its borderline biological behaviour. These findings are in keeping with the current understanding of CK19 as a marker of follicular epithelial malignant transformation.

Abouhashem and Talaat (2017) evaluated CK19 and CD56 expression in 80 thyroid lesions and reported CK19 sensitivity of 87.8% for PTC; combined use of CK19 with CD56 significantly improved diagnostic accuracy.8 Their findings support a panel approach for challenging cases, as echoed by the present study.

Kayani et al. (2009) reported that all 16 cases of FA were negative for CK19, while FVPTC demonstrated predominantly high-grade positivity (3+/4+), with a statistically significant difference ($p<0.001$).[13] These findings closely parallel our observations.

Cvejić et al. (2013) analysed CK19 expression in 351 thyroid tissue samples and demonstrated the highest diagnostic accuracy for classic PTC (91.07%), with CK19 also helpful in distinguishing FVPTC from FA.[14] The results of the present study are consistent with these findings.

Bose et al. (2012), using the same semi-quantitative scoring system employed in the present study, demonstrated that all 22 PTC cases exhibited diffuse strong CK19 expression (3+/4+), while FA (75%) and MNG (50%) showed only focal or weak staining.[12] This is consistent with our results.

Notably, 50% of FA cases in the present study demonstrated 4+ CK19 expression, representing an important potential source of false-positive results. This highlights a known limitation of CK19 as a sole diagnostic marker,[10,11] and reinforces the need to interpret IHC results in conjunction with histomorphological features and, where necessary, additional markers such as HBME-1, Galectin- 3, and CD56.[15]

Interpretation of CK19 should always be performed in conjunction with morphology, particularly in lesions showing focal staining or borderline nuclear features.

A comparative summary of key published studies is presented in [Table 7].

Table 7: Comparative summary of key studies on CK19 in follicular-patterned thyroid lesions

Study (Year)	Sample & Lesions	Key CK19 Findings	Comparison
Present Study (2026)	28 cases: PTC, FVPTC, FA, NIFTP, MNG	Diffuse strong (3+/4+) in all PTC/FVPTC; absent/focal in benign lesions	100% concordance in malignant group
Abouhashem & Talaat (2017)8	80 thyroid lesions; CK19 + CD56	CK19 sensitivity 87.8%; combined panel improves accuracy	Supports panel approach
Kayani et al. (2009)13	16 FA, 35 WDT-UMP, 60 FVPTC	All FA negative; FVPTC 4+ in majority ($p<0.001$)	Strongly supports differentiation
Cvejić et al. (2013)14	351 thyroid tumours: PTC, FVPTC, FA, FTC	Highest accuracy for classic PTC (91.07%); useful in FVPTC vs FA	Consistent with present findings
Bose et al. (2012)12	22 PTC, 8 FA, 8 MNG	100% diffuse strong CK19 in PTC; focal/weak only in FA and MNG	Consistent semi- quantitative findings

Conclusion

CK19 immunohistochemistry is a useful adjunctive marker in differentiating Papillary thyroid carcinoma and FVPTC from benign follicular-patterned thyroid lesions. Diffuse strong CK19 expression strongly favors malignancy, whereas benign lesions usually show absent or focal staining.

Limitations

The principal limitations include: (1) small sample size (n=28), limiting generalisability; (2) single-centre retrospective design; (3) evaluation of CK19 alone without a panel approach; and (4) reliance on archived material. The 100% diagnostic accuracy should be interpreted cautiously given the small and selected cohort.

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Conflicts of interest

There are no conflicts of interest.

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