International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

A Study on Expression of PTEN Immunohistochemical Marker in Prostatic Carcinoma

Running Title: *PTEN immunohistochemistry in prostatic carcinoma*

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Abstract: ***Background*: Loss of the tumour suppressor PTEN activates PI3K–AKT–mTOR signalling and is linked to aggressive prostate cancer. Data from transurethral resection of the prostate (TURP) specimens are limited. *Aim*: To assess PTEN expression by immunohistochemistry (IHC) in prostatic carcinoma and correlate it with clinicopathological parameters. *Materials and Methods*: Twenty-five TURP specimens with histologically confirmed prostatic carcinoma were studied (January 2024–April 2026). Tumours were graded by the Gleason system and ISUP grade group (GG). PTEN IHC was performed on formalin-fixed paraffin-embedded sections; loss was defined as complete absence of tumour-cell staining with preserved internal controls. Associations were tested by Fisher's exact test. *Results*: Patients were aged 54–86 years (mean 71.7 ± 8.5). There were 11 low-grade (GG 1–3) and 11 high-grade (GG 4–5) adenocarcinomas, one case of high-grade prostatic intraepithelial neoplasia and two metastatic deposits (ungraded). PTEN loss was seen in 10 cases (40%). It occurred in 4 of 11 low-grade (36.4%) and 6 of 11 high-grade tumours (54.5%) ($p = 0.67$). Perineural and lymphovascular invasion were present in 28% and 8% of cases, without significant association with PTEN status. *Conclusion*: PTEN loss is common in TURP-detected prostatic carcinoma and shows a non-significant trend towards higher grade, with loss also seen in some low-grade tumours. PTEN IHC is an inexpensive adjunct worth testing in larger studies with outcome data.***

Keywords: PTEN; prostatic carcinoma; immunohistochemistry; Gleason grade; transurethral resection of prostate; PI3K–AKT pathway

1. Introduction

Prostate cancer is among the most commonly diagnosed malignancies in men worldwide, with GLOBOCAN 2020 estimating more than 1.4 million new cases and over 375,000 deaths annually.[1] Incidence is highest in North America, Western Europe and Oceania and lower in Asian and African populations, differences attributed to genetic susceptibility, environmental factors, access to healthcare and the extent of prostate-specific antigen (PSA) screening.[2,3] In India, recorded incidence is rising, which has been linked to increasing life expectancy, better diagnostic services and greater awareness.

Prostate cancer is biologically heterogeneous. Some tumours remain indolent for years, whereas others progress rapidly to metastasis.[4] Current management relies on serum PSA, Gleason grading with the ISUP/WHO grade groups, and stage.[5–7] These parameters are essential but do not fully capture tumour behaviour, particularly in intermediate-risk disease, which has prompted interest in tissue-based molecular markers that complement morphology.[8]

The PTEN (phosphatase and tensin homolog) gene, located on chromosome 10q23, is one of the most frequently altered tumour suppressor genes in prostate cancer.[9,10] PTEN encodes a lipid phosphatase that converts phosphatidylinositol 3,4,5-trisphosphate (PIP3) to PIP2 and thereby restrains PI3K–AKT–mTOR signalling.[11,12] Loss of PTEN function, through deletion, mutation, epigenetic silencing or post-translational mechanisms, results in sustained pathway activation, increased proliferation and reduced apoptosis.[13,14] PTEN loss has been associated with higher Gleason grade, advanced stage, biochemical recurrence, metastasis and castration resistance.[15–18]

Because the several mechanisms of inactivation converge on loss of protein, immunohistochemistry (IHC) offers a practical, functional read-out of PTEN status on routine formalin-fixed paraffin-embedded (FFPE) tissue, and shows good concordance with PTEN gene deletion detected by fluorescence in situ hybridization (FISH).[19,20] Most published work, however, derives from radical prostatectomy cohorts in Western populations. Data from transurethral resection of the prostate (TURP) specimens, which are the commonest tissue source for prostate cancer diagnosis in many Indian centres, remain limited.[21] The present study evaluated PTEN expression by IHC in TURP-detected prostatic carcinoma and correlated it with clinicopathological features.

2. Objectives

Primary objective

- To detect loss of PTEN expression by immunohistochemistry in prostatic carcinoma.

Secondary objectives

- To study the association of PTEN loss with patient age and clinicopathological findings.
- To evaluate the relationship between PTEN loss and Gleason grade, grade group and Gleason score.
- To assess PTEN expression in cases associated with prostatic intraepithelial neoplasia.
- To analyse the association of PTEN loss with high-grade and metastatic prostate carcinoma.

3. Materials and Methods

Study design and setting

This hospital-based cross-sectional study was conducted in the Department of Pathology, Alluri Sitarama Raju Academy of Medical Sciences, Eluru, Andhra Pradesh, over 27 months (January 2024 to April 2026). The study was approved by the institutional (BHR) Ethics Committee with Approval number: ASRAMS BHR-EC/Approval No. 157/2024, and consent was documented using the study consent form.

Study population

Twenty-five cases of histopathologically confirmed prostatic carcinoma diagnosed on TURP specimens, with adequate FFPE tissue available, were included. Cases with inadequate or poorly preserved tissue or insufficient material for IHC were excluded.

Histopathological evaluation

FFPE blocks were cut at 3–4 µm onto poly-L-lysine coated slides and stained with haematoxylin and eosin (H&E). Tumours were graded by the Gleason system and assigned to ISUP/WHO grade groups (GG).[5,6,8] For analysis, GG 1–3 were designated low grade and GG 4–5 high grade. Cases that could not be graded (one case showing only high-grade prostatic intraepithelial neoplasia, HGPIN, and two metastatic deposits) were analysed separately. Presence of HGPIN, perineural invasion (PNI) and lymphovascular invasion (LVI) was recorded.

Immunohistochemistry for PTEN

Sections were deparaffinised in xylene and rehydrated through graded alcohols. Heat-induced epitope retrieval was carried out in citrate buffer (pH 6.0), and endogenous peroxidase was blocked with 3% hydrogen peroxide. Sections were incubated with a mouse monoclonal anti-PTEN primary antibody (Oncore Diagnostics, Bengaluru), followed by a horseradish peroxidase (HRP)-conjugated secondary antibody. The reaction was developed with 3,3′-diaminobenzidine (DAB) and counterstained with haematoxylin. Positive and negative controls were run with every batch.

Interpretation of PTEN expression

Cytoplasmic and nuclear staining were assessed. A binary scoring system was used, as it is the most reproducible approach.[19,20] PTEN loss was defined as complete absence of staining in tumour cells, with preserved staining in adjacent benign glands, stromal and endothelial cells serving as internal positive controls. Weak or partial staining was regarded as retained expression.

Statistical analysis

Data were tabulated in Microsoft Excel. Categorical variables are given as numbers and percentages, and age as mean ± standard deviation. The association between PTEN status and tumour grade was tested by Fisher's exact test because of the small sample and low expected cell counts; a two-sided p value <0.05 was considered significant.

4. Results

Patient and tumour characteristics

The 25 patients were aged 54–86 years (mean 71.7 ± 8.5 years; median 73 years); 17 (68%) were 70 years or older (Figure 1). The clinicopathological profile is summarised in Table 1. Of the 25 cases, 11 (44%) were low-grade (GG 1–3) and 11 (44%) were high-grade (GG 4–5) adenocarcinoma; the remaining 3 (12%) comprised one case of HGPIN and two metastatic deposits of prostatic carcinoma, which were not graded. PNI was present in 7 cases (28%) and LVI in 2 (8%) (Figure 2).

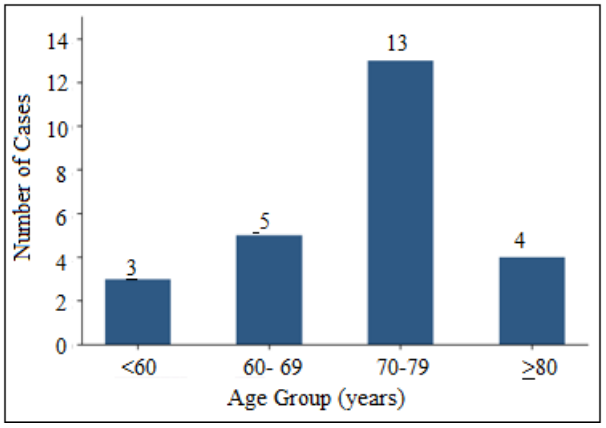


Figure 1: Age distribution of the patients (n = 25).

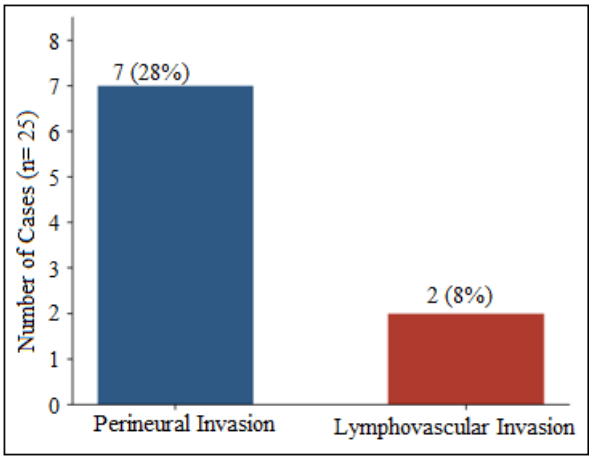


Figure 2: Frequency of perineural and lymphovascular invasion (n = 25)

Table 1: Clinicopathological profile of the study cohort (n = 25)

Parameter	Category	n (%)
Age (years)	<60	3 (12)
	60–69	5 (20)
	70–79	13 (52)
	≥80	4 (16)
Histological category	Low-grade adenocarcinoma (GG 1–3)	11 (44)
	High-grade adenocarcinoma (GG 4–5)	11 (44)
	HGPIN (not graded)	1 (4)
	Metastatic carcinoma (not graded)	2 (8)
ISUP grade group (n = 22)	GG 1 (3+3=6)	2 (9.1)
	GG 2 (3+4=7)	4 (18.2)
	GG 3 (4+3=7)	5 (22.7)
	GG 4 (8)	7 (31.8)
	GG 5 (9)	4 (18.2)
Perineural invasion	Present	7 (28)
Lymphovascular invasion	Present	2 (8)
PTEN status	Loss	10 (40)
	Retained	15 (60)

GG, ISUP/WHO grade group; HGPIN, high-grade prostatic intraepithelial neoplasia. Percentages for grade group are of the 22 gradable cases.

PTEN expression

PTEN loss was seen in 10 of 25 cases (40%), while 15 (60%) retained expression. Internal controls (benign glands, stroma, endothelium) stained appropriately in all cases. Representative PTEN-retained and PTEN-lost tumours are shown in Figure 3.

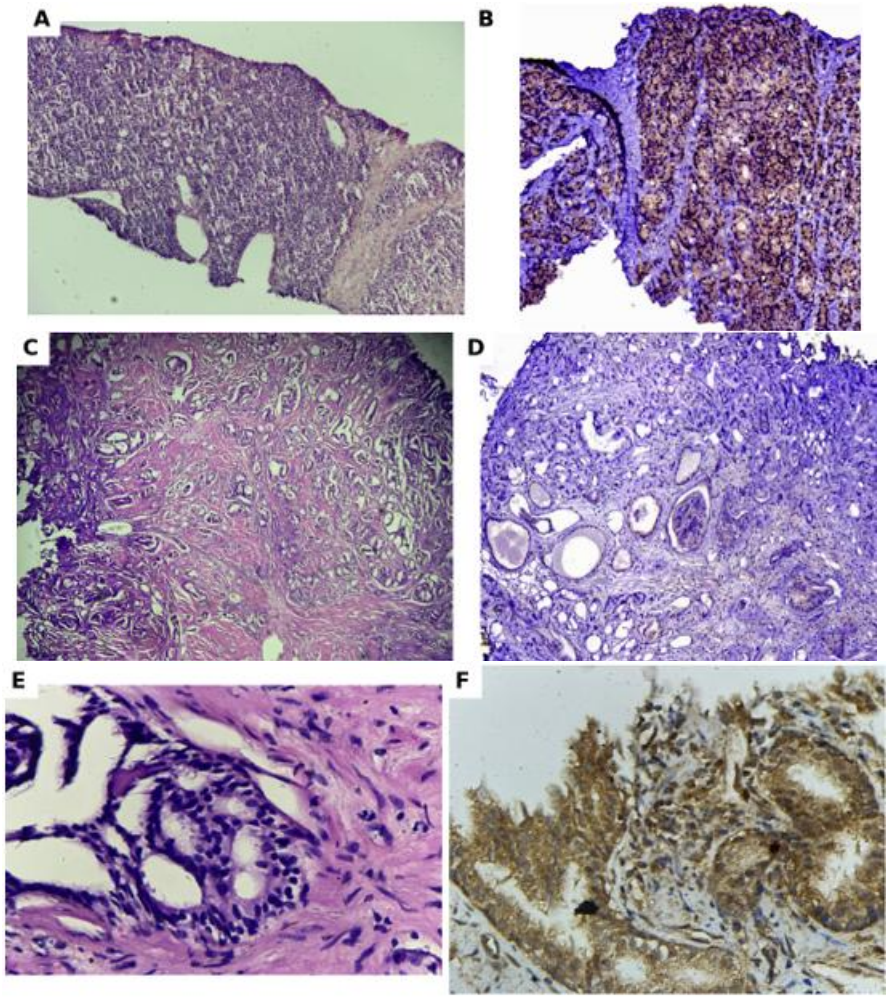


Figure 3: Representative H&E and PTEN immunostaining. (A, B) Prostatic adenocarcinoma with retained (positive) PTEN expression, ×10. (C, D) Cribriform adenocarcinoma with complete loss of PTEN in tumour cells, ×10. (E, F) Acinar adenocarcinoma with retained PTEN expression, ×40. A, C, E: H&E; B, D, F: PTEN IHC.

PTEN expression and tumour grade

PTEN loss was present in 4 of 11 low-grade tumours (36.4%) and in 6 of 11 high-grade tumours (54.5%) (Table 2, Figure 4). The difference was not statistically significant (Fisher's exact test, p = 0.67). The odds of PTEN loss in high-grade tumours were 2.1 times those in low-grade tumours, but the confidence interval is wide given the sample size. The HGPIN case and both metastatic cases retained PTEN.

Table 2: PTEN expression in relation to tumour grade

Tumour grade	PTEN loss n (%)	PTEN retained n (%)	Total
Low grade (GG 1–3)	4 (36.4)	7 (63.6)	11
High grade (GG 4–5)	6 (54.5)	5 (45.5)	11
Not graded (HGPIN / metastatic)	0 (0)	3 (100)	3
Total	10 (40.0)	15 (60.0)	25

Low versus high grade: Fisher's exact test, p = 0.67 (not significant).

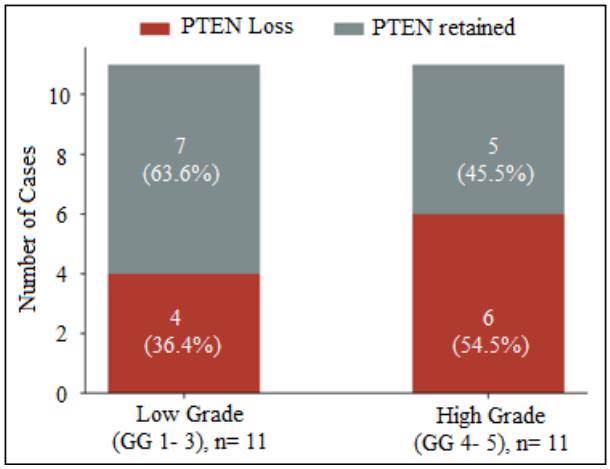


Figure 4: PTEN expression (loss versus retained) in low-grade and high-grade prostatic adenocarcinoma.

When analysed by grade group (Table 3), PTEN loss occurred in both GG 1 cases, in 1 of 4 GG 2 and 1 of 5 GG 3 cases, in 3 of 7 GG 4 cases and in 3 of 4 GG 5 cases. These numbers are too small for inference.

Table 3: PTEN loss across ISUP grade groups (n = 22 gradable cases)

Grade group	Gleason score	Cases	PTEN loss n (%)
GG 1	3+3 = 6	2	2 (100)
GG 2	3+4 = 7	4	1 (25.0)
GG 3	4+3 = 7	5	1 (20.0)
GG 4	4+4 / 5+3 = 8	7	3 (42.9)
GG 5	4+5 / 5+4 = 9	4	3 (75.0)

Case numbers per group are small; percentages are descriptive only.

PTEN expression and other parameters

Patients with PTEN loss were slightly older (mean 73.8 years) than those with retained expression (mean 70.3 years). PNI was present in 3 of 10 PTEN-lost cases (30%) and 4 of 15 PTEN-retained cases (26.7%; p = 1.00). LVI was seen only in PTEN-retained cases (2 of 15; p = 0.52) (Table 4). None of these associations was significant.

Table 4: PTEN status in relation to age, perineural and lymphovascular invasion

Parameter	PTEN loss (n = 10)	PTEN retained (n = 15)	p value
Mean age, years	73.8	70.3	–
Perineural invasion, n (%)	3 (30.0)	4 (26.7)	1
Lymphovascular invasion, n (%)	0 (0)	2 (13.3)	0.52

p values by Fisher's exact test.

5. Discussion

PTEN is a central regulator of PI3K–AKT–mTOR signalling, and its loss removes a key brake on proliferation, survival and metabolism.[13,22] In this TURP-based series, PTEN loss was found in 40% of prostatic carcinomas. This lies within the broad range reported in the literature, in which PTEN protein or gene loss is found in roughly one-fifth to one-half of primary prostate cancers depending on cohort, specimen type, assay and cut-off.[17,19] Table 5 places our findings alongside published data.

Table 5: Present findings compared with the published literature

Feature	Present study	Published observations
Specimen and method	TURP; PTEN IHC (binary scoring)	Mostly prostatectomy or biopsy cohorts; IHC with or without FISH[15,19,23]
Overall PTEN loss	40% (10/25)	About 20–50% in primary tumours, varying with cohort and method[17,19]
Relation to grade	36.4% (low) vs 54.5% (high); p = 0.67	Loss more frequent with higher grade and in aggressive patterns[15,17,24]
Loss in low-grade tumours	Present (4/11)	Heterogeneous, subclonal loss described; associated with upgrading[23,25]
HGPIN	1 case, PTEN retained	PTEN loss reported in HGPIN, especially adjacent to carcinoma[26,27]
Perineural invasion	28%; no association with PTEN	Invasive behaviour reported in PTEN-deficient tumours[17,18]
Lymphovascular invasion	8%; no association with PTEN	Not consistently quantified; PTEN loss linked to metastasis[18,28]

IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; HGPIN, high-grade prostatic intraepithelial neoplasia; TURP, transurethral resection of the prostate.

PTEN loss and tumour grade

PTEN loss was more frequent in high-grade (54.5%) than low-grade (36.4%) tumours, and the proportion was highest in GG 5 (3 of 4). The difference did not reach significance (p = 0.67), which is unsurprising with 22 gradable cases; the study had little power to detect a moderate difference. The direction of the trend agrees with larger studies showing that PTEN loss increases with Gleason grade and is enriched in aggressive histology such as cribriform and intraductal carcinoma.[15,17,24] Mechanistically, constitutive AKT activation after PTEN loss promotes dedifferentiation, loss of

glandular architecture and resistance to apoptosis, providing a plausible link between molecular and morphological progression.[12,13,29]

PTEN loss in low-grade tumours and heterogeneity

Four of the 11 low-grade tumours, including both GG 1 tumours, showed PTEN loss. This indicates that Gleason grading, which is based purely on architecture, does not capture all molecular risk.[5,6,8] PTEN loss is often subclonal, so that PTEN-deficient clones may arise within morphologically lower-grade tumours and drive later progression.[17,30] Studies of needle biopsies have shown that PTEN loss in biopsy tissue is associated with upgrading at prostatectomy.[23,25] Our observation of PTEN loss in low-grade disease is consistent with this and, if confirmed in larger series, suggests that PTEN IHC could identify tumours whose apparent indolence is misleading. The finding in the two GG 1 cases must be read cautiously, as it rests on two patients.

Perineural and lymphovascular invasion

PNI (28%) and LVI (8%) mark aggressive local behaviour and are associated with extraprostatic extension and recurrence.[4] PTEN loss promotes cell motility, epithelial–mesenchymal transition and angiogenesis through AKT signalling,[14,31] and PTEN-deficient tumours are enriched in metastatic disease.[18] We found no association of PTEN loss with PNI or LVI, but with 3 and 2 events respectively the study could not have detected one. The two metastatic deposits and the HGPIN case retained PTEN. This does not contradict the literature: PTEN loss is common but not universal in advanced disease, many tumours progress through other routes such as androgen receptor or DNA-repair pathway alterations,[32,33] and PTEN loss in HGPIN is more typical when HGPIN lies next to invasive carcinoma.[26,27]

Specimen type and role of immunohistochemistry

TURP samples mainly the transitional zone, whereas most prostate cancers arise in the peripheral zone, and chips are fragmented.[4,27] Because PTEN loss is frequently focal, the true frequency of loss may be under-estimated in TURP material. Nevertheless, TURP represents the specimen on which many patients are actually diagnosed in routine Indian practice, so data from this material are directly applicable. IHC evaluates the protein within preserved architecture, can reveal heterogeneity that bulk genomic assays may miss, captures loss by deletion as well as by non-genomic mechanisms, and shows good concordance with FISH.[19,20] It is cheaper and more widely available than FISH or sequencing.[34] Reproducibility depends on pre-analytical factors, antibody choice, a binary cut-off and the use of internal controls.[19]

6. Clinical Implications

First, PTEN IHC is feasible on routine TURP material and can be added at low cost to the pathology work-up of prostate cancer, including in laboratories without access to FISH or sequencing.[19,21] Second, PTEN loss in an apparently low-grade tumour may flag a lesion with higher progression potential, which could influence selection of patients for active surveillance and the intensity of follow-up.[23,25] Third, adding PTEN status to Gleason grade, stage and PSA improves prognostic models in larger series, and may be most useful in intermediate-risk disease.[16,17] Fourth, PTEN-deficient tumours depend on PI3K–AKT–mTOR signalling and show cross-talk with androgen receptor signalling, giving a rationale for combination trials of pathway inhibitors with androgen receptor-directed therapy.[35–38] These implications derive mainly from the wider literature; the present data are hypothesis-generating and do not by themselves justify a change in practice.

7. Limitations

The sample was small (25 cases, 22 gradable), giving limited statistical power; the lack of significance should not be read as absence of association. The study was single-centre and cross-sectional, with no follow-up data on recurrence, progression or survival, and no clinical stage, PSA or treatment data were analysed. TURP chips may under-sample tumour and miss focal PTEN loss; heterogeneous or partial loss was not separately categorised. One HGPIN case without invasive carcinoma and two metastatic deposits were included in the series, which limits the generalisability of the findings. PTEN IHC was not validated against FISH or sequencing, and inter-observer agreement was not measured. Larger multicentre studies with prostatectomy or biopsy material, standardised scoring and clinical follow-up are required.

8. Conclusion

PTEN loss was identified in 40% of TURP-detected prostatic carcinomas and was more frequent in high-grade (54.5%) than low-grade (36.4%) tumours, although the difference was not statistically significant in this small series. PTEN loss in a subset of low-grade tumours highlights the molecular heterogeneity that Gleason grading alone cannot capture. PTEN IHC is an inexpensive, accessible adjunct that merits evaluation in larger, outcome-linked studies as a means of refining risk stratification in prostate cancer.

Ethical approval and consent

The study was approved by the ASRAMS BHR Ethics Committee, Alluri Sitarama Raju Academy of Medical Sciences, Eluru. Patient consent was documented using the study consent form.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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