Prognostic Significance Of PTEN Loss In Prostatic Adenocarcinoma: An Immunohistochemical Study

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KEYWORDS

PTEN, Immunohistochemistry, Prostatic Adenocarcinoma

ABSTRACT

Introduction: Phosphatase and Tensin Homolog on chromosome 10 (PTEN) is a tumour suppressor gene that is essential for chromosome integrity, cell cycle regulation and DNA repair. Loss of PTEN expression has been implicated in prostate cancer progression and poor prognosis. However, very few studies have been done in the Indian population concerning the use of PTEN as a prognostic marker in prostatic carcinoma.
Aim: The aim of the study was to evaluate PTEN expression in prostatic adenocarcinoma and its association with known clinicopathological prognostic factors.
Materials and Methods: A cross-sectional study was conducted on 50 cases of prostatic adenocarcinoma diagnosed at the Department of Pathology in a tertiary care health centre in South India. PTEN expression was assessed using immunohistochemistry and correlated with known clinicopathological variables, including age, preoperative serum PSA levels, Gleason score and grade, and perineural invasion.
Results: Loss of PTEN expression was observed in 23 cases (46%) and was more frequent in tumours exhibiting higher grade. A statistically significant correlation was found between PTEN loss and aggressive histopathological features like higher Gleason scores (p-value = 0.046) and Gleason grade (p-value = 0.019). No significant association was found with age (p-value = 0.106), preoperative serum PSA levels (p-value = 0.113) and perineural invasion (p-value = 0.209).
Conclusion: PTEN loss is significantly associated with aggressive histopathological features, suggesting its potential as a prognostic marker in prostatic adenocarcinoma. Incorporating PTEN status in routine diagnostic workup may help in the identification of high-risk patients. Further large-scale studies are warranted to validate PTEN as a reliable prognostic biomarker.

1. Introduction:

One of the most frequent cancers in men to be diagnosed is prostate cancer. With 14,67,854 cases reported worldwide in 2022, it is on the rise globally and is a significant contributor to male cancer-related mortality (3,97,430 deaths worldwide) (1). From slow-growing, indolent tumours to extremely aggressive, metastatic forms, it is a diverse disease. For both pathologists and clinicians, this variability poses serious difficulties, underscoring the need for a more thorough comprehension of its aetiology, diagnosis, and progression. Consequently, there has been an increased emphasis on the identification of prognostic markers in order to facilitate the early detection of cases that are considered to be high-risk.

On chromosome 10q23 is the tumour suppressor gene PTEN (Phosphatase and Tensin Homolog on chromosome 10). It is essential for chromosome integrity, cell cycle regulation and DNA repair. Additionally, it regulates lipid, carbohydrate and mitochondrial metabolism. By inhibiting phosphoinositide (PI) 3-kinase-dependent signalling, PTEN suppresses the proliferation and growth of cells (2). It is one of the most frequently inactivated tumour suppressors in human cancers. In normal tissues, the localisation of PTEN varies across different cell types. Some studies show homogenous cytosolic localization while others show predominantly nuclear staining (3).

PTEN is the most commonly inactivated tumour suppressor seen in approximately 20% of primary prostatic cancer and 50% of castration-resistant cancers, primarily through mutation and deletion. Some studies have suggested that PTEN loss is associated with aggressive features and poor patient outcomes (4–6).

Despite its potential, there are currently very few studies that examine the clinicopathological significance of PTEN expression in prostatic carcinoma, particularly in India. This highlights the necessity for additional research to determine the prognostic relevance of PTEN. This study aimed to assess PTEN expression in prostatic carcinoma and its correlation with established clinicopathological prognostic factors, including age, preoperative serum PSA level, Gleason score and grade, and perineural invasion.

2. Materials And Methods

This cross-sectional study was done in a tertiary care health centre in South India. The study included 50 cases of prostatic adenocarcinoma received in the Department of Pathology. The cases comprised of core needle biopsy of the prostate (Transrectal ultrasound (TRUS) biopsy) and Transurethral resection of prostate (TURP) specimens. Cases lacking sufficient material or tissue blocks for assessment and immunohistochemical (IHC) analysis were excluded. Instances of metastasis to the prostate were likewise excluded.

All these specimens were received in 10% neutral-buffered formalin. After adequate fixation and grossing, sections were prepared and stained with Haematoxylin and Eosin (H&E) for histopathological examination. The tumour was evaluated using the Gleason grading system (7,8). Gleason score of a total of 6 was classified as grade 1; a score of 3+4=7 was classified as grade 2, while 4+3=7 was classified as grade 3. A total score of 8 was designated as grade 4, and a total score of 9 or higher was classified as grade 5. Perineural invasion was identified by the presence of nerve fibres exhibiting complete circumferential involvement by malignant cells (9).

PTEN immunohistochemistry: The peroxidase and anti-peroxidase (PAP) method was employed for this purpose. Primary antibody against PTEN (clone: 6H2.1; mouse monoclonal antibody from DSS) was used. PTEN cytoplasmic and nuclear staining was determined quantitatively. Tumour cells were classified as exhibiting PTEN loss if the intensity of nuclear and cytoplasmic staining was markedly diminished or entirely absent in more than 10% of the tumour. Heterogenous PTEN loss was designated for cases where over 10% to under 100% of tumour cells exhibited PTEN loss, while homogeneous PTEN loss was assigned to cases with complete (100%) PTEN loss. PTEN was considered intact for cases with more than 90% of tumour cells showing cytoplasmic or nuclear staining (10).

Statistical analysis: The data was imported into a Microsoft Excel spreadsheet and analysed using SPSS Statistics version 24.0. The Chi-square test by Pearson was employed to evaluate correlations among different parameters. A p-value below 0.05 was deemed statistically significant.

3. Result

A total of 50 cases of prostatic carcinoma were included in this study. The age group of these cases ranged from 43 years to 88 years, with the mean and median being 70.2 years and 72 years, respectively. Preoperative serum PSA levels of these patients ranged from 4ng/mL to 154ng/mL (mean- 57.6ng/mL; median- 51.25ng/mL). Among the various Gleason grades, most of the cases belonged to Gleason grade group 5 (13 cases; 26%). Out of the 50 cases, perineural invasion was noted in 18 cases (36%).

Of the 50 cases that were examined, 27 cases (54%) showed intact PTEN and 23 cases (46%) showed loss of PTEN. Among the 23 cases of PTEN loss, 13 cases (57%) showed heterogenous PTEN loss (Figure 1) and 10 cases (43%) showed homogenous PTEN loss (Figure 2).

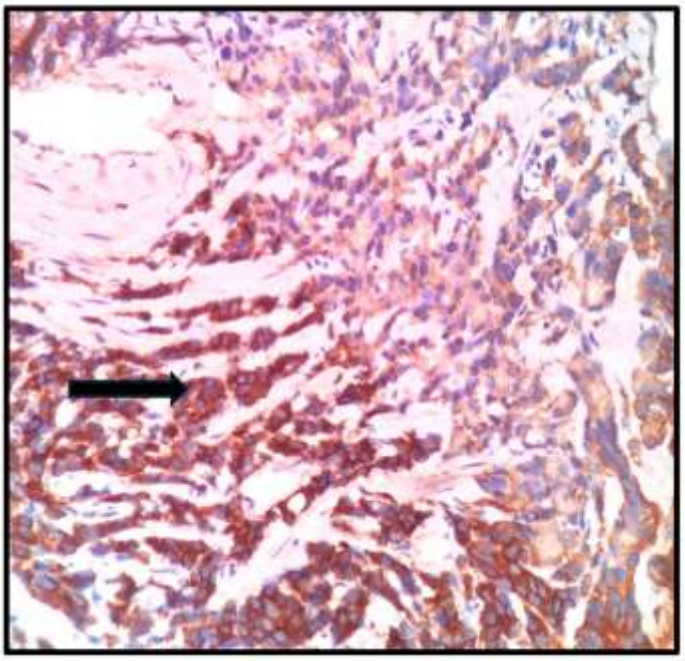

Figure 1: Tumour showing heterogenous PTEN loss. Few tumour cells show positive cytoplasmic and nuclear PTEN staining (arrow) (IHC x400)

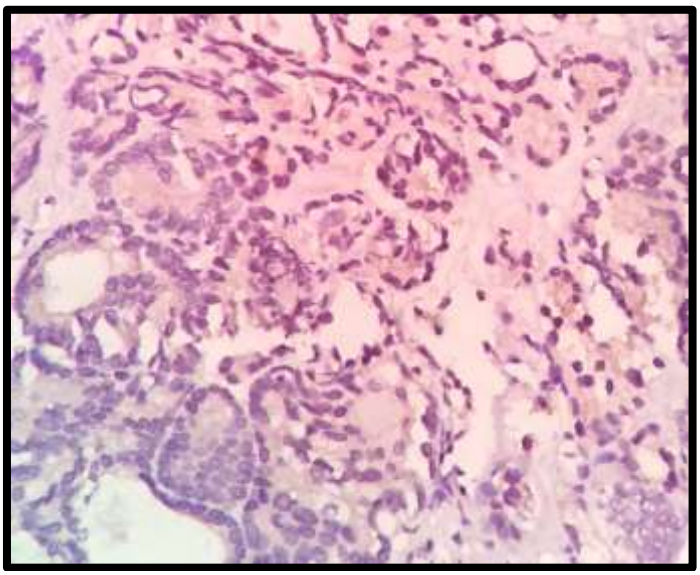

Figure 2: Tumour cells showing homogenous PTEN loss (IHC x400)

On analysing the association of PTEN expression with age, it was found to be statistically insignificant (p-value = 0.106). It was also noted that there was no significant association between PTEN expression and preoperative serum PSA levels (p-value = 0.113). On analysis of the association between PTEN loss and histopathological features, a significant correlation was noted with Gleason score (p-value = 0.046) and Gleason grade group (p-value = 0.019). PTEN loss was predominantly noted in cases with higher Gleason score and Gleason grade group (Table 1). Among the cases with PTEN loss, homogenous loss of PTEN was noted in cases with higher Gleason score and Gleason grade group as compared to the cases with heterogenous PTEN loss. However, there was no significant association between PTEN expression and perineural invasion (p-value = 0.209).

Table 1: Association of PTEN immunohistochemistry status with histopathological parameters

Histopathological parameters	PTEN status, *n (%)*			p-value
	Intact	Heterogenous loss	Homogenous loss	
Gleason score				
3+3 = 6	10 (90%)	1 (10%)	0	
3+4 = 7	7 (78%)	2 (22%)	0	
4+3 = 7	4 (50%)	2 (25%)	2 (25%)	
3+5 = 8	3 (60%)	1 (20%)	1 (20%)	
4+4 = 8	1 (25%)	2 (50%)	1 (25%)	0.046
4+5 = 9	1 (50%)	1 (50%)	0	
5+4 = 9	1 (20%)	2 (40%)	2 (40%)	
5+5 = 10	0	2 (34%)	4 (66%)	
Gleason Grade Group				
1	10 (90%)	1 (10%)	0	
2	7 (78%)	2 (22%)	0	
3	4 (50%)	2 (25%)	2 (25%)	0.019
4	4 (44.5%)	3 (33.5%)	2 (22%)	
5	2 (15%)	5 (39%)	6 (46%)	
Perineural Invasion				
Present	8 (44.5%)	4 (22%)	6 (33.5%)	0.209
Absent	19 (60%)	9 (28%)	4 (12%)	

On summarizing the results, PTEN loss showed a statistically significant correlation with high Gleason score and Gleason grade group. Thus, we can imply that loss of PTEN is associated with aggressive histopathological features in prostatic carcinoma. However, no association was noted between loss of PTEN and age, preoperative serum PSA levels and perineural invasion.

4. Discussion

Prostatic carcinoma became the 3rd most common cancer in men aged 60 and above by 2022, with an incidence of 6.8 per 100,000 and a risk of 1 in 125 men. 1 in 350 males under 50, 1 in 52 between 50 and 59, and over 60% of men over 65 are at risk, and the risk rises sharply with age (11,12). It is a varied disease with a wide range of manifestations, from benign, slow-growing to aggressive tumours. Nevertheless, the overwhelming majority of patients diagnosed with prostate cancer will not succumb to the illness. This dilemma necessitates the enhancement of clinical risk stratification to ascertain which patients may be safely managed through active surveillance, which can be effectively treated with prostate-targeted therapies, and which necessitate the incorporation of systemic therapy (6). There have been a plethora of prognostic indicators studied for prostate cancer. Several factors associated with progression include age, serum PSA levels, Gleason score, capsular invasion, perineural invasion and surgical margins (13). While clinicopathological variables aid in risk stratification, approximately 30% of men deemed suitable for active surveillance based on these variables are discovered to either already possess or progress to advanced disease necessitating intervention, emphasizing the necessity for more informative prognostic determinants (14).

The PTEN (phosphatase and tensin homolog on chromosome 10) tumour suppressor and the PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase) signalling pathway it regulates are frequently altered in primary prostate cancer (6). PTEN genomic deletion in prostate cancer was first identified almost two decades ago, and subsequent sequencing studies have shown that PTEN is the most commonly lost tumour suppressor gene in primary disease . The rate of prostate cancer PTEN gene deletions varies by cohort and assay. This variation may be due to the fact that PTEN deletion frequency increases with Gleason score and tumour stage (6,15,16).

Lotan T et al.(10) and Morais C et al. (17), in their investigations, did not report a significant correlation with age (p-value = 0.34 and 0.86, respectively). This is in concordance with our study, where age and PTEN expression have no significant association (p-value = 0.106). Similar to our study (p-value = 0.113), Lotan T et al.(10), also reported an insignificant association of PTEN expression with preoperative serum PSA levels (p-

value = 0.6).

Previous studies have proposed Gleason score and Gleason grade to be efficient prognostic markers in prostatic carcinoma. Few studies conducted before have demonstrated a strong correlation between PTEN loss and high Gleason scores and Gleason grade groups (4,18). McMenamin et al. (5), have reported a positive correlation between PTEN loss and a total Gleason score >7 (p-value = 0.0081). According to Lotan et al. (10), homogenous PTEN loss was associated with a total Gleason score of 8–10 (p-value <0.0001). These conclusions are comparable to this present study, where a statistically significant association is noted between loss of PTEN expression and Gleason score (p-value = 0.046) and Gleason grade group (p-value = 0.019). Additionally, the present study also noted homogenous PTEN loss to be more predominant in cases with higher Gleason score and Gleason grade group. Only Morais C et al. (17), have reported findings contrary to the above.

According to the findings of this particular study, there is no correlation between the loss of PTEN and perineural invasion (p-value = 0.209). The direct relationship between PTEN expression and perineural invasion in prostatic carcinoma has not been investigated. Any possible association between the two has to be confirmed by further investigation.

Few other studies have also noted that PTEN loss in prostatic carcinoma is associated with metastatic disease, higher tumour staging and biochemical recurrence (10,19,20). These factors could not be assessed in the study as we did not have long-term follow-up.

Thus, with the overall data, it can be said that PTEN loss in prostatic carcinoma can be correlated with aggressive histological characteristics.

This study was done without long-term follow-up. Hence, data regarding disease-free survival and overall survival are not available. Therefore, further studies with larger cohorts investigating the correlation between PTEN expression and other known clinicopathological features along with survival data are essential for a definitive assessment of the prognostic relevance of PTEN loss in prostatic carcinoma.

5. Conclusion

The present investigation emphasises a significant correlation between PTEN loss and prognostically unfavourable histopathological characteristics, including high Gleason scores and grades in prostatic adenocarcinoma. These findings highlight the significance of PTEN as a prognostic marker, facilitating the risk stratification of patients. Integrating PTEN immunohistochemical assessment into standard diagnostic procedures could improve prognostic accuracy and guide treatment strategies, especially in recognising patients who might require more intensive intervention. Comprehensive multicentric studies with extended follow-up and survival data are crucial to validate PTEN as a reliable and clinically relevant prognostic marker in prostate cancer.

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