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Original article

Comprehensive Analysis of PTEN Alterations in Prostate Cancer: A cBioportal Study

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Abstract

Prostate cancer (PCa), a leading cause of cancer-related mortality among men, demands an intricate understanding of its molecular landscape for improved diagnostics and treatment strategies. This study investigates the prevalence and clinical significance of Phosphatase and tensin homolog (PTEN) alterations in prostate cancer using data sourced from cBioportal. Analysing 10,998 samples across 26 prostate cancer studies, our findings reveal that PTEN alterations occur in 19% of patients, with deep deletion (PTEN HOMODELETED) being the most significant genetic alteration. Notably, Metastatic Prostate Adenocarcinoma exhibits the highest prevalence of PTEN mutations, while Prostate Adenocarcinoma Organoids show the least. Correlation analyses unveil associations between PTEN deep deletion and age, particularly within the 42-72 age range, as well as with Pelvic Radiation Disease Local Treatment at Diagnosis and primary Sample Type. Survival analysis indicates a significantly lower median overall survival in months (95% CI) for patients with PTEN alterations (96.00 months, 95% CI: 65.36 - 113.98) compared to unaltered cases (120.0 months, 95% CI: 115.05 - 160.00), highlighting the clinical relevance of PTEN in PCa and its correlation with disease progression and remission. The study concludes by discussing the potential implications of these findings, recognizing limitations, and emphasizing the critical need for targeted therapeutic strategies based on PTEN status in PCa management.

Keywords: ***Prostate cancer, PTEN alterations, Molecular landscape, cBioportal, Genetic impact.***

1. Introduction

Prostate cancer stands as a formidable global health challenge, with its escalating incidence posing a substantial burden on healthcare systems worldwide [1-3]. As a leading cause of cancer-related mortality among men, there is an urgent imperative for an all-encompassing comprehension of the molecular mechanisms orchestrating prostate cancer pathogenesis. Within this context, the tumour suppressor gene PTEN has emerged as a pivotal player, garnering attention for its recurrent alterations in various cancers, including PCa [4].

The imperative role of PTEN in maintaining genomic stability and regulating cell proliferation underscores its significance as a critical sentinel of cellular homeostasis. Encoded by the PTEN gene, its lipid phosphatase activity antagonizes the phosphoinositide 3-kinase (PI3K) signalling pathway, exerting control over fundamental cellular processes such as growth, survival, and metabolism. Dysregulation of PTEN, through mutations, deletions, or other genetic alterations, has the potential to unleash unbridled cell growth, contributing to tumorigenesis [5-7].

Despite the growing acknowledgment of PTEN's pivotal role in cancer, its specific implications in PCa remain incompletely understood [8]. Variability in PTEN alterations across diverse cancer types underscores the necessity for dedicated investigations into the specific context of PCa. This study seeks to address this gap in knowledge by conducting a comprehensive analysis of PTEN alterations in PCa, leveraging the expansive dataset available on cBioportal.

Building upon the established significance of PTEN in cancer, our hypothesis posits that PTEN alterations play a pivotal role in the molecular landscape of PCa. Specifically, we anticipate a notable prevalence of PTEN alterations, displaying distinct patterns across various subtypes of PCa. Additionally, we hypothesize that these PTEN alterations will correlate with specific clinical parameters, influencing factors such as patient age, treatment history, and survival outcomes.

The aim of this study is twofold: first, to elucidate the query prevalence and patterns of PTEN alterations in PCa on available repository prostate cancer studies data on cBioportal, and second, to conduct an exploratory analysis to investigate the potential clinical implications of these alterations. Through a meticulous exploration of structural variants, mutation patterns, and copy number variations associated with PTEN, we aim to unravel the intricate molecular landscape of PCa. Furthermore, by correlating these genetic alterations with clinical parameters, our study seeks to provide a holistic understanding of the impact of PTEN alterations on the clinical trajectory of PCa.

2. Methodology

This study employed a rigorous methodology to investigate PTEN alterations in PCa using data sourced from cBioportal (https://www.cbioportal.org/). The overarching goal was to provide

a comprehensive analysis of the molecular landscape associated with PTEN in this context. The following steps outline the specific procedures undertaken:

2.1. Data Collection: A curated dataset comprising 10,998 samples from 26 distinct PCa studies was obtained from cBioportal. This diverse dataset facilitated a thorough exploration of PTEN alterations across various cohorts.

2.2. Data Extraction: The process of data extraction involved retrieving information on structural variants, mutation patterns, and copy number variations associated with PTEN. Using cBioportal's user-friendly interface, we navigated the available filters and parameters to specifically target PTEN-related data within the PCa datasets.

2.3. Subgroup Stratification: To discern patterns and prevalences, the dataset was further stratified based on different subtypes of PCa. This subgroup analysis allowed for a nuanced understanding of how PTEN alterations vary across distinct clinical presentations.

2.4. Correlation Analysis: Correlation analyses were conducted to explore potential relationships between PTEN alterations and specific clinical parameters. Parameters included patient age, treatment history, and survival outcomes. This involved utilizing statistical tools available within cBioportal to extract relevant correlations.

2.5. Survival Analysis: Survival analyses were performed to assess the impact of PTEN alterations on patient outcomes. Kaplan-Meier survival plots were generated to visualize the differences in median survival times between patients with and without PTEN alterations.

2.6. Data Validation: To ensure the robustness of our findings, the extracted data were cross-referenced with existing literature and validated against established knowledge regarding PTEN alterations in PCa.

2.7. Ethical Considerations: This study adhered to ethical guidelines, respecting the privacy and confidentiality of patient data available on cBioportal. All data were anonymized, and the research protocol was approved by the relevant institutional review board. Overall, the methodology employed in this study combined advanced analytical techniques with ethical considerations to provide a comprehensive and reliable analysis of PTEN alterations in PCa, leveraging the extensive capabilities of the cBioportal platform.

3. Results

3.1. PTEN Alterations Overview

A total combined study involving 10,998 samples from 26 prostate studies on cBioportal revealed that PTEN, as the queried gene, was altered in 19% of patients (2036 out of 10,579) and 19% of samples (2090 out of 10,998). Deep deletion (PTEN HOMODELETED) emerged as the most significantly reported genetic alteration for the queried gene, with Supplementary Figure 1 providing additional details.

3.2. Cancer Type Summary

Figure 1 presents a summary based on structural variant data, mutation data, and copy number variation data from the queried samples. PTEN mutation was most reported in Metastatic Prostate Adenocarcinoma and Metastatic Prostate Cancer, while its prevalence was least in Prostate Adenocarcinoma Organoids.

3.3. PTEN Copy-Number Alterations Correlation

Figure 2 illustrates a plot of PTEN copy-number alterations from GISTIC against Age at Diagnosis. The correlation of deep deletion with age is highlighted, occurring predominantly within the 42-72 age range, and showing associations with Pelvic Radiation Disease Local Treatment at Diagnosis and primary Sample Type.

3.4. Survival Analysis

Figure 3 presents the results of the log-rank test for survival analysis. The altered group (604/199 median months, 95% CI: 96.00 (65.36 - 113.98)) showed a statistically significant lower median survival time compared to the unaltered group (2209/407 median months, 95% CI: 120.00 (115.05 - 160.00)). This underscores a lower survival rate in months for studies/patients that reported alterations in the queried PTEN gene.

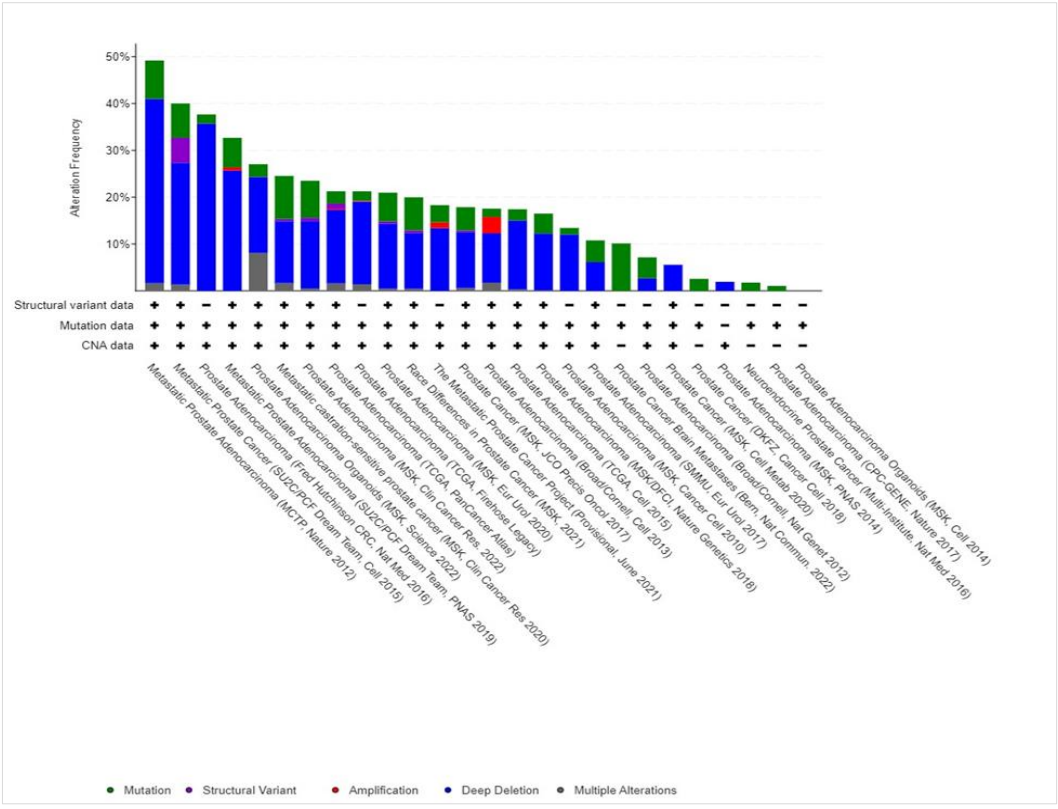

Figure 1: Summary of Prostate Cancer Types.

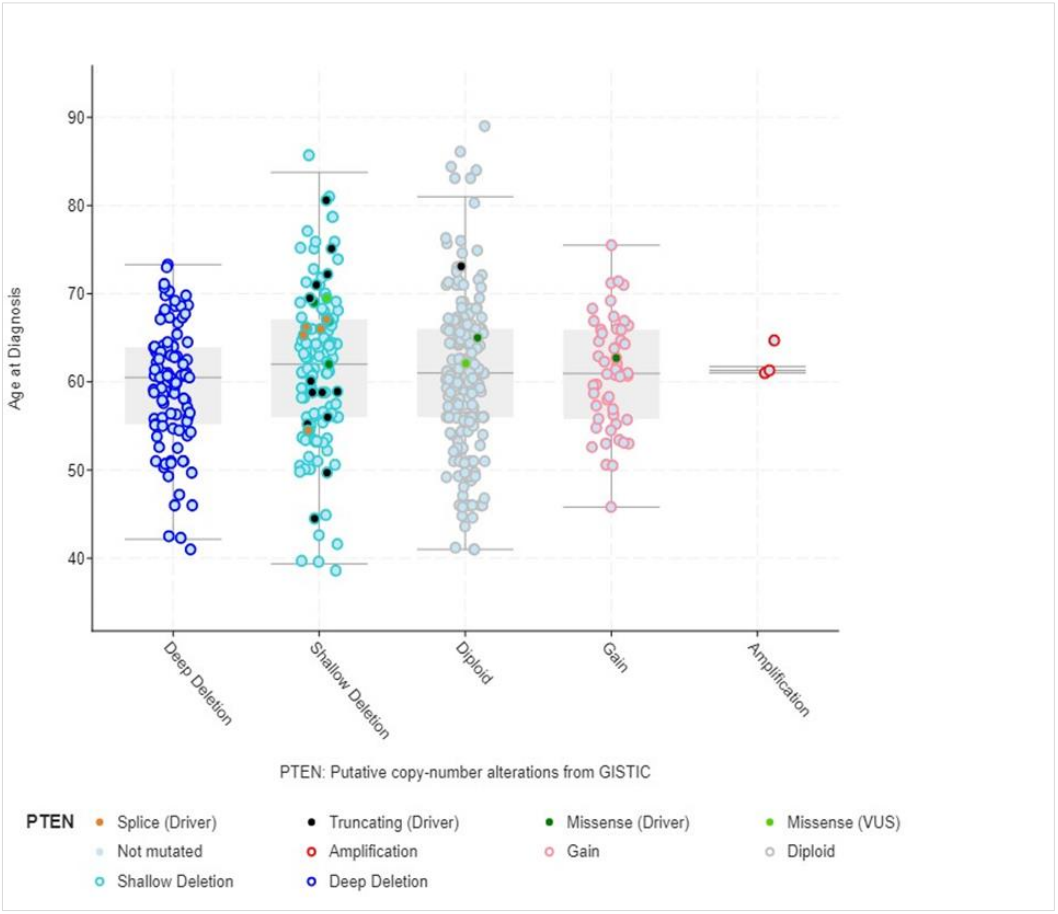

Figure 2: Plot of PTEN Copy-Number Alterations Correlation.

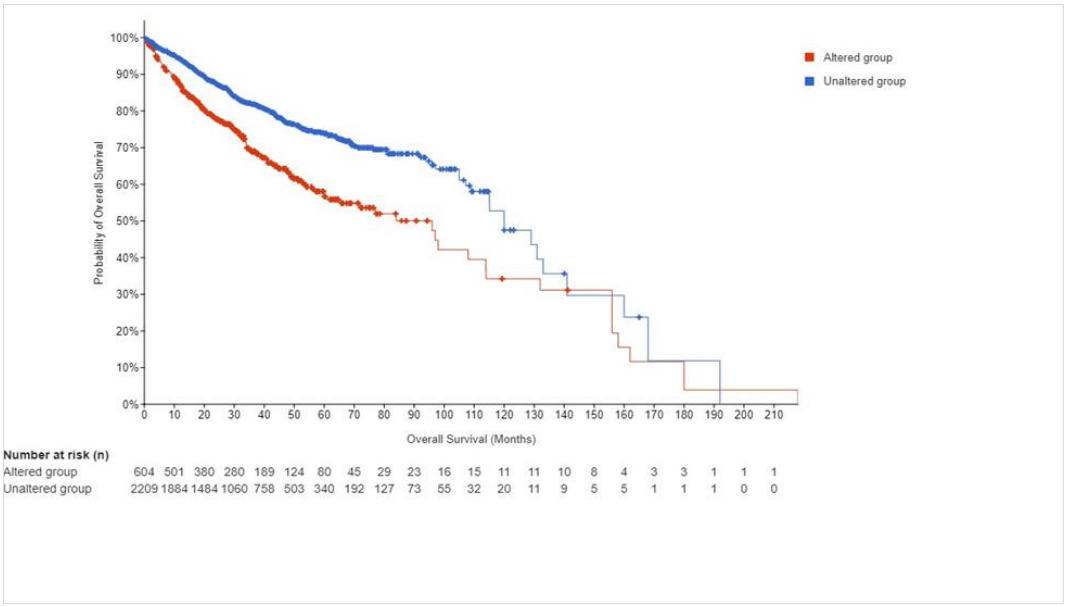

Figure 3: Overall Survival Analysis

4. Discussion

The discussion of our findings delves into the multifaceted implications of PTEN alterations in PCa offering a nuanced interpretation of the comprehensive analysis conducted in this study. The integration of molecular insights with clinical correlates enriches our understanding of PTEN's role in disease progression, paving the way for potential clinical applications [9].

Our study revealed a significant prevalence of PTEN alterations in prostate cancer, with 19% of patients exhibiting variations in the PTEN gene. This prevalence underscores the relevance of PTEN in the molecular landscape of PCa. Moreover, our subgroup analysis uncovered distinct patterns across various subtypes of PCa, with Metastatic Prostate Adenocarcinoma displaying the highest prevalence of PTEN mutations. This insight contributes to our understanding of the heterogeneity of PTEN alterations and their potential association with different disease presentations [10].

Correlation analyses demonstrated noteworthy associations between PTEN alterations and specific clinical parameters. Notably, PTEN deep deletion exhibited a correlation with patient age, with a higher incidence observed within the age range of 42-72 years. Additionally, correlations with Pelvic Radiation Disease Local Treatment at Diagnosis and primary Sample Type were identified. These associations illuminate potential links between PTEN

alterations and clinical variables, offering avenues for further exploration and potential clinical stratification.

Survival analysis provided compelling evidence of the clinical impact of PTEN alterations in PCa. Patients with PTEN alterations exhibited a significantly lower median survival time compared to those without alterations. This finding underscores the prognostic significance of PTEN in patient outcomes, emphasizing the need for vigilant monitoring and tailored therapeutic approaches for individuals with PTEN-altered PCa.

The integration of molecular and clinical data has profound implications for the management of PCa. Identification of PTEN alterations can serve as a potential prognostic marker, aiding in risk stratification and treatment decision-making. Targeted therapeutic interventions, tailored to the specific molecular profile of PTEN-altered cases, could enhance treatment efficacy and patient outcomes [10]. In comparing our study with existing research on PTEN alterations in prostate cancer, we acknowledge shared themes and findings with previous studies but distinguish ourselves through the utilization of a comprehensive dataset of 10,998 samples, a focused analysis on Metastatic Prostate Adenocarcinoma, methodological rigor in data extraction from cBioportal, and unique contributions to clinical relevance, survival analysis, and thoughtful future directions [11-15]. Collectively, these aspects represent a significant advancement in understanding PTEN alterations with practical implications in prostate cancer.

Acknowledging the limitations of our study is crucial for a comprehensive interpretation. The retrospective nature of cBioportal data introduces inherent biases, and the observed correlations warrant validation in prospective clinical studies. Future research endeavours could explore additional genomic markers and expand the scope to elucidate the intricate interplay of multiple genetic alterations in PCa.

6. Conclusion

In conclusion, this study provides a detailed examination of PTEN alterations in PCa, elucidating their prevalence, patterns, and clinical implications. The integration of diverse datasets and correlation analyses enriches our understanding of the molecular landscape, offering potential avenues for personalized therapeutic interventions. The identified associations between PTEN alterations and clinical parameters underscore the translational potential of our findings, emphasizing the importance of continued research to refine risk stratification and treatment strategies in PCa.

Ethics approval and consent to participate

Ethical approval and participant consent were not required for this study as the research utilized a publicly available dataset from cBioPortal (https://www.cbioportal.org/), which can be freely downloaded. The data is fully anonymized, preventing re-identification. Therefore, the need for approval was waived.

List of abbreviations

cBioPortal: Cancer Bioinformatics Portal
PCa: Prostate Cancer
PI3K: Phosphoinositide 3-Kinase
PTEN: Phosphatase and Tensin Homolog

Data Availability

The datasets analyzed during the current study are available in the cBioPortal repository (https://www.cbioportal.org/). The specific datasets comprising 10,998 samples from 26 prostate cancer studies can be accessed through the cBioPortal platform. The data extraction and analysis procedures are detailed in the Methods section. Additional information or clarification regarding the datasets can be obtained by contacting the corresponding author.

Conflicts of Interest

The authors, Chidozie N. Ogbonnaya and Uzochukwu Alozie Ononuju, declare that there is no conflict of interest regarding the publication of this paper.

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This research received no external funding.

Authors' contributions

CNO conceived the study, designed the research, and drafted the manuscript. UAO conducted statistical analyses, managed software aspects, and contributed to manuscript editing. All authors read and approved the final manuscript.

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The authors declare that no specific individuals or organizations contributed to this research or the preparation of this manuscript.

References

[1] Zhang W, Cao G, Wu F, Wang Y, Liu Z, Hu H, et al. Global Burden of Prostate Cancer and Association with Socioeconomic Status, 1990-2019: A Systematic Analysis from the Global Burden of Disease Study. J Epidemiol Glob Health. 2023;1-15.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.

[3] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. Ca Cancer J Clin. 2021;71(1):7-33.

[4] Shen MM, Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. Genes Dev. 2010;24(18):1967-2000.

[5] Lu XX, Cao LY, Chen X, Xiao J, Zou Y, Chen Q. PTEN inhibits cell proliferation, promotes cell apoptosis, and induces cell cycle arrest via downregulating the PI3K/AKT/hTERT pathway in lung adenocarcinoma A549 cells. Biomed Res Int. 2016;2016.

[6] Wu J, Gao H, Ge W, He J. Over expression of PTEN induces apoptosis and prevents cell proliferation in breast cancer cells. Acta Biochim Pol. 2020;67(4):515-9.

[7] Zhou X, Yang X, Sun X, Xu X, Li X, Guo Y, et al. Effect of PTEN loss on metabolic reprogramming in prostate cancer cells. Oncol Lett. 2019;17(3):2856-66.

[8] Huang H, Cheville JC, Pan Y, Roche PC, Schmidt LJ, Tindall DJ. PTEN induces chemosensitivity in PTEN-mutated prostate cancer cells by suppression of Bcl-2 expression. Journal of Biological Chemistry. 2001;276(42):38830-6.

[9] Mighell TL, Thacker S, Fombonne E, Eng C, O'Roak BJ. An integrated deep-mutational-scanning approach provides clinical insights on PTEN genotype-phenotype relationships. The American Journal of Human Genetics. 2020;106(6):818-29.

[10] Fusco N, Sajjadi E, Venetis K, Gaudioso G, Lopez G, Corti C, et al. PTEN alterations and their role in cancer management: are we making headway on precision medicine? Genes (Basel). 2020;11(7):719.

[11] Sun J, Li S, Wang F, Fan C, Wang J. Identification of key pathways and genes in PTEN mutation prostate cancer by bioinformatics analysis. BMC Med Genet. 2019;20(1):1-9.
[12] Alwhaibi A, Kolhe R, Gao F, Cobran EK, Somanath PR. Genome atlas analysis-based profiling of Akt pathway genes in the early and advanced human prostate cancer. Oncoscience. 2019;6(5-6):317.
[13] Wise HM, Hermida MA, Leslie NR. Prostate cancer, PI3K, PTEN and prognosis. Clin Sci. 2017;131(3):197-210.
[14] Poluri RTK, Audet-Walsh É. Genomic deletion at 10q23 in prostate cancer: more than PTEN loss? Front Oncol. 2018; 8:246.
[15] Abou-Ouf H, Ghosh S, Box A, Palanisamy N, Bismar TA. Combined loss of TFF3 and PTEN is associated with lethal outcome and overall survival in men with prostate cancer. J Cancer Res Clin Oncol. 2019; 145:1751-9.