Original Paper

CD133 Immunoexpression in Prostatic Acinar Adenocarcinomas

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ABSTRACT: Prostatic acinar adenocarcinomas (PAA) continue to represent a challenge in terms of incidence and efficiency of screening and targeted therapy programs. The capacity of the tumor cell population to renew itself through differentiation and activation of stem cells constitutes a mechanism of tumor protection and survival, but also of acquisition of aggressive phenotypes. In this study, we analyzed CD133 immunoexpression in 55 cases, in relation to the clinico-epidemiological and histopathological parameters of the tumors. CD133 reactions were present at the nuclear and cytoplasmic level and focally membranous in tumor and stromal cells, both from tumor areas and in the case of non-neoplastic tissue. CD133 showed significantly higher reactions in PAA diagnosed in patients in extreme age groups and with elevated serum PSA values. Immunoreactions were significantly higher in some subtypes of PAA (conventional and colloid), in advanced grading groups and with perineural and lymphovascular invasion. In addition to identifying reservoirs of cells with stem potential, CD133 can be used to identify PAA with aggressive behavior, suggesting a biological connection of the two features and the utility for stratifying patients for therapy.

KEYWORDS: *Prostate adenocarcinoma, stem cells, CD133.*

Introduction

Prostatic acinar adenocarcinomas (PAA) continue to be a public health problem due to their increasing incidence, although survival rates have improved considerably [1,2].

The widespread impact on the elderly male population, the emergence of non-responsive tumor differentiations to treatment, overdiagnosis and overtreatment of indolent forms are challenges that characterize PAA in all areas of the world, including those where incidence, mortality and treatment costs have remained high, such as Eastern Europe, including Romania, where it ranks third in incidence in men, after lung and colon cancer [1,3-5].

At the same time, the persistence of cell populations after classical hormonal, chemo-and radiotherapeutic oncological treatments demonstrates in some tumor groups mechanisms of proliferation and survival that are selected according to tumor receptors and viability [6].

These include alterations in the androgen pathway, tumor signaling and transcription, immune response, and epithelial-mesenchymal transition [7].

Also, the tumor stem-like phenotype has been demonstrated as a potential source of tumor cells capable of supporting the initial or residual tumor population after treatment and which may confer PAA an aggressive biological behavior [6-8].

There are numerous markers that have been studied to characterize stem cells in general, including at the prostate level, such as CD44, CD133, integrin α2β1, Oct4, SOX2 (Sex Determining Region Y-transcription factor), KLF4 (Krüppel-like factor 4), c-Myc (transcription factor), Nanog (homeobox protein), with variable results, some controversial [7-9].

CD133 (Prominin 1) is a transmembrane glycoprotein used as a marker of stem and progenitor cell populations, involved in tumor initiation, disease progression and treatment resistance [10].

In oncological pathology, its expression is associated with aggressive tumor phenotypes, including prostate cancer, but with varied results in relation to the histopathological parameters of PAA [10-13].

Also, the literature emphasizes that the phenomenon of the presence of stem cells in the tumor bed is contextual and variable between tumor types and between compartments of the same tumor [14].

However, the analysis of the distribution of stem cells in PAA may contribute with additional data that help to identify tumors with aggressive potential or resistance to therapy.

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Objective

The study analyzed CD133 expression in prostatic acinar adenocarcinomas, in relation to histological tumor prognostic parameters, and the results obtained may have an impact on clinical practice.

Methods

The study enrolled 55 cases of prostatic acinar adenocarcinoma (PAA), which were operated and diagnosed in the Urology and Pathology Departments of the Emergency Clinical County Hospital Craiova, over a four-year period (2020-2023).

The biological material used for diagnosis and therapy was represented by radical prostatectomy specimens (35 cases), and in the case of incidental diagnosis, fragments of transurethral resection of the prostate (TURP) were analyzed (20 cases).

This study included only surgical specimens from patients without prior oncological, anti-inflammatory or immunomodulatory treatments and without primary processing artifacts, so that only cases in which direct prostatectomy was decided after biopsy or those in which the diagnosis was incidental after TURV were selected.

All tissues were fixed in 10% buffered formalin for 24 hours, and lesions were classified according to the World Health Organization (WHO) criteria established for PAA [15].

Histopathological (HP) analysis included clinico-epidemiological data represented by age group and serum PSA (prostate-specific antigen) level and the main prognostic parameters of PAA, which referred to tumor type, grading groups (International Society of Urological Pathology), presence of perineural and lymphovascular invasion and tumor stage for cases in which prostatectomy was performed.

Subsequently, 3-4µm serial sections were made from the obtained paraffin blocks, which were used and processed for immunohistochemical (IHC) investigation, which followed the expression of CD133 in relation to the HP parameters of PAA.

After deparaffinization with xylene of the sections, hydration in alcoholic solutions of decreasing concentrations (100-70%), rinsing in distilled water and antigenic retrieval in citrate buffer pH6 for 20 minutes by microwave boiling was performed.

Peroxidase blocking (H2O2, 10%, 15 minutes) was followed by nonspecific blocking with bovine serum albumin (BSA, 1%, 30 minutes).

We used mouse anti-human CD133 monoclonal antibody (Biocare), at a dilution of 1:75, which was incubated in a humid chamber overnight at 4ºC.

The EnVision™ FLEX+Polymeric Amplification System (Dako, Agilent) was used to visualize the reactions using 3,3'-Diaminobenzidine tetrahydrochlorid (DAB), as brown chromogen.

The sections were counterstained with Hematoxylin and permanently mounted (CV Mount, Leica Biosystems).

For quantification, the CD133 positivity index (PI) was used, which resulted from counting the signals of the labeled cells at a 20x objective, on ten microscopic fields (MF)/case, in the tumor areas with the most signals, followed by obtaining the average.

For statistical analysis, the PI was considered low (1-5 positive cells), moderate (6-10 positive cells) or high (>10 positive cells). In this study, all labeled cells in the tumor areas were quantified, regardless of the cellular location of the reaction.

Comparison tests (χ2-chi square/Fisher) within SPSS12 (Statistical Package for the Social Sciences) were used for statistical analysis, in which p values <0.05 were considered significant.

Results

The study included prostatic acinar adenocarcinomas (PAA) that came from patients aged between 44-88 years, with a mean of 70.1±11.6 years, most belonging to the 8th and 9th decades of life, with 36.5% and 23.6% respectively (Table 1).

Serum PSA levels varied in PAA, most cases presenting values below 20ng/ml, observed in 61.8% of patients (Table 1).

In relation to the histopathological type, conventional PAA (CPAA) were identified in 78.2% of cases and predominated in the investigated casuistry.

These were followed in order by foamy cell PAA (FPAA) and atrophic (APAA) with 9.1% and 5.5%, respectively by pseudohyperplastic (PPAA) and colloid (CoPAA) types with 3.6% each (Table 1).

PAA in ISUP 2 and 4 predominated with 23.6% of cases each, followed by ISUP 1 and 5 with 20% and 18.2%, with the fewest cases being identified in ISUP 3 with 14.6% (Table 1).

Perineural and lymphovascular invasion were present in 49.1% and 18.2% of cases (Table 1).

For the 35 prostatectomy cases, stages II and III predominated with 21.8% and 30.9%, followed by stages I/IV with 5.5% each of the entire casuistry (Table 1).

Table 1. Distribution of cases in relation to the clinico-epidemiological and histopathological parameters investigated.

Investigated parameters	No. cases
Age (years)	<50: 5
	50-59: 7
	60-69: 10
	70-79: 20
	80-89: 13
Serum PSA (ng/ml)	≤10: 16
	11-19: 18
	20-50: 15
	>50: 6
Histological tumor types	CPAA: 43
	FPAA: 5
	APAA: 3
	PPAA: 2
	CoPAA: 2
Tumor grading groups (International Society of Urological Pathology)	ISUP 1: 11
	ISUP 2: 13
	ISUP 3: 8
	ISUP 4: 13
	ISUP 5: 10
Tumor perineural invasion (PNI)	Absent: 28
	Present: 27
Tumor lymphovascular invasion (LVI)	Absent: 45
	Present: 10
Tumor stages	I: 3
	II:12
	III: 17
	IV: 3

CPAA: conventional prostate acinar adenocarcinoma; FPAA: foamy prostate acinar adenocarcinoma; APAA: atrophic prostate acinar adenocarcinoma; PPAA: pseudohyperplastic prostate acinar adenocarcinoma; CoPAA: colloid prostate acinar adenocarcinoma

CD133 immunoexpression was identified in all cases, especially at the nuclear and cytoplasmic and focal membrane levels at the level of some cells present in the tumor stroma or stromal cells associated with the tumor epithelium or at the level of some tumor cells. CD133 reactions were also present at the level of non-tumor areas, in rare stromal cells.

For the entire analyzed group, the number of labeled cells at the tumor level varied, ranging from 1-40 cells, with a mean value of 14.8±10, most of the positivity indices (PI), being moderate and high.

Depending on the age groups, the highest mean values of PI CD133 were identified in the case of patients at the extremes of the range, in those aged 80-89 and <50 years, with 20.4±10.7 and 19.4±7.7 labeled cells (Table 2).

These were followed by patients aged 60-69 years with 17.3±12.7 positive cells and those aged 50-59 years and 70-79 years with values close to 10.5±6.5 and 10.3±7.4 (Table 2).

Regarding PSA values, PI CD133 presented the richest immunostaining in patients with 20-50 ng/ml and >50ng/ml, with 21.3±10.5 and 20±8.3 labeled cells (Table 2).

While cases with PSA values of 11-19ng/ml had PI CD133 of 14.4±9.4, those with values ≤10ng/ml presented an average PI of 7.3±5 stained cells (Table 2).

Table 2. Distribution of CD133 immunostaining in relation to the analyzed parameters.

Investigated parameters		CD133 (range of positive cells)
Age (years)	<50	12-30
	50-59	7-25
	60-69	1-40
	70-79	1-30
	80-89	7-35
	p value (χ2 test)	0.006
Serum PSA (ng/ml)	≤10	1-20
	11-19	5-35
	20-50	5-40
	>50	10-30
	p value (χ2 test)	0.005
Histological tumor types	CPAA	5-40
	FPAA	5-15
	APAA	1-5
	PPAA	1-2
	CoPAA	7-15
	p value (χ2 test)	0.009
Tumor grading groups (International Society of Urological Pathology)	ISUP 1	1-15
	ISUP 2	5-12
	ISUP 3	7-15
	ISUP 4	10-30
	ISUP 5	15-40
	p value (χ2 test)	<0.001
Tumor perineural invasion (PNI)	Absent	1-25
	Present	1-40
	p value (Fisher test)	0.036
Tumor lymphovascular invasion (LVI)	Absent	1-30
	Present	15-40
	p value (Fisher test)	0.004
Tumor stages	I	5-8
	II	5-40
	III	7-30
	IV	25-35
	p value (χ2 test)	0.196

CPAA: conventional prostate acinar adenocarcinoma; FPAA: foamy prostate acinar adenocarcinoma; APAA: atrophic prostate acinar adenocarcinoma; PPAA: pseudohyperplastic prostate acinar adenocarcinoma; CoPAA: colloid prostate acinar adenocarcinoma

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In relation to PAA type, the highest PI CD133 values were present by far in CPAA, with 17.2±9.9 cells, followed by CoPAA with an average of 11 cells and FPAA with 8.6±3 cells; the lowest PI CD133 values were observed in APAA and PPAA, with averages of 3±2 cells and 1.5 cells (Table 2, Figure 1A-D).

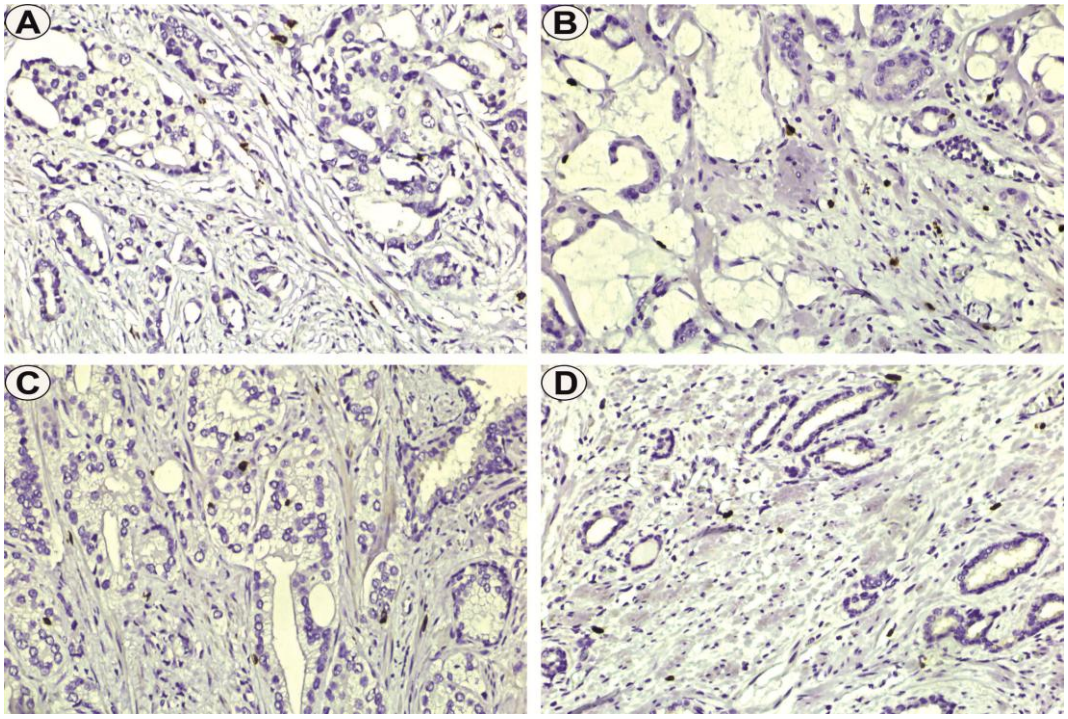

Figure 1. Prostate acinar adenocarcinoma (PAA), CD133 immunostaining, x200. A. CPAA type; B. CoPAA type; C. FPAA type; D. APAA type.

We found an increase in PI CD133 in relation to the ISUP grading groups, as the grade advanced, so that the highest values were present in the case of PAA located in ISUP 5 and ISUP 4 with 28.5±8.1 cells and 21.9±5.2 cells (Table 2, Figure 2A).

In comparison, ISUP groups 1, 2 and 3 had mean values of 10.1±3.4, 7.7±2.4 and 5.9.±4.4 positive cells, respectively (Table 2, Figure 2B-D).

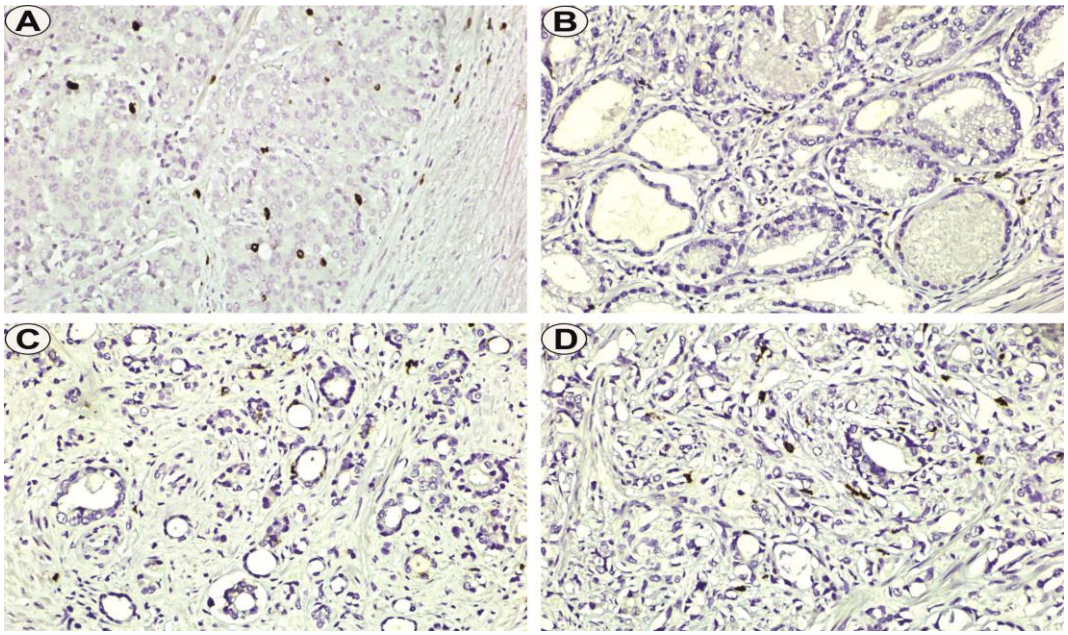

Figure 2. Prostate acinar adenocarcinoma (PAA), CD133 immunostaining, x200. A. ISUP 5; B. ISUP 1; C. ISUP 2; D. ISUP 3.

In both the case of perineural invasion (PNI) and lymphovascular invasion (LVI), the mean PI CD133 values were higher compared to PAA that did not present these aggressive features, respectively 20.1±11 versus 9.7±5.6 for PNI and 29±7.3 versus 11.7±7.6 for LVI (Table 2).

For tumor stage, PAA in stage IV presented the highest PI CD133 values, respectively 31.6±5.7 cells, followed by stage II with 20±11 cells, stage III with 17±7.7 and stage I with 6±1.7 (Table 2).

In this study, non-tumor areas showed rare CD133 positive cells (1-5 cells/200x), which increased to 7-10 cells in the case of high-grade conventional PAA and in advanced stages.

Statistical analysis indicated statistically significant differences in relation to the clinico-epidemiological parameters, PI CD133 values being significantly higher in the case of extreme ages (p=0.006, $\chi 2$ test) and in patients with PSA values ≥20ng/ml (p=0.005, $\chi 2$ test) (Table 2, Figure 3A).

We also found statistically significant differences in relation to most of the histopathological parameters investigated, PI CD133 values being significantly higher in the case of CPAA and FPAA (p=0.009, $\chi 2$ test), ISUP groups 4 and 5 (p<0.001, $\chi 2$ test), PAA with perineural (p=0.036, Fisher test) and lymphovascular (p=0.004, Fisher test) invasion (Table 2, Figure 3B-D).

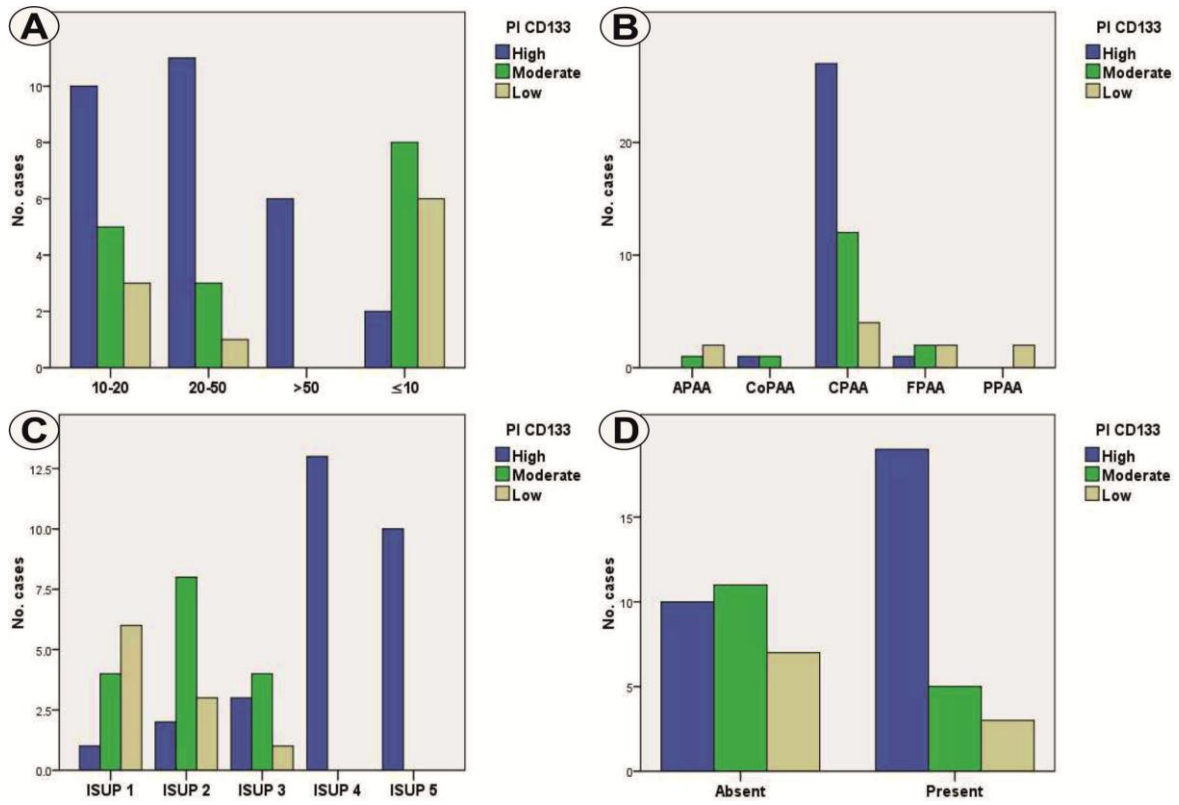

Figure 3. CD133 PI values distribution depending on serum PSA level (A), tumor type (B), ISUP groups (C) and perineural invasion (D).

Although PAA in stage IV had the highest PI CD133 values, and those in stage I the lowest, the differences were not statistically significant (p=0.196, $\chi 2$ test) (Table 2).

Discussion

The stem-like phenotype represents a mechanism that explains the maintenance of proliferative capacity in the PAA tumor population, and although the majority of tumor cells contribute to the growth of the tumor mass, a subpopulation of cells retains the ability to regenerate the tumor [14].

For this reason, contemporary therapeutic strategies focus either on the direct elimination of these cells with tumor-initiating potential, or on the disruption of the signals and microenvironment conditions that support their regenerative functions [14,16].

Also, both the epithelial-mesenchymal transition and the mesenchymal stem cell population, through communication between the tumor, fibroblasts and associated macrophages and the extracellular matrix, perform complex

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signaling that maintains a constant stem cell population, which, however, has a variable activity [6,17-20].

In our study, CD133 immunostainings were present both at the stromal level, where they predominated, and associated with the tumor prostate epithelium.

We also found the presence of CD133 cells in non-tumorous prostate areas, aspects also observed in other studies [6,10].

CD133 has been designated as a tumor stem cell marker in breast, colon, pancreatic, brain, and prostate cancers, associated with tumor aggressiveness [7,21,22].

Similarly, mesenchymal stem cells can transform into tumor-associated stem cells or even tumor cells, as occurs in gliomas, gastric, or ovarian cancers, thus constituting a reservoir of cells that can ensure tumor survival [23].

In this context, in the study conducted, although we did not perform a separate quantification of stromal and epithelial signals, this was performed in both tumor compartments.

The data in the literature are unclear both regarding the localization of CD133 expression in tumor areas and at the cellular level, as well as their significance.

Some authors have indicated the predominant membrane/cytoplasmic and rarely nuclear expression in prostate cancers of CD133, a marker that seems to have no value for tumor initiation, being more expressed in normal areas, compared to CD166 [24].

On the contrary, other authors who investigated the expression of CD133 in a panel with other stem markers in PAA and precancerous and noncancerous areas, quantified the reactions at the nuclear level and indicated an increase in the intensity of the reactions in tumor areas [25].

By comparison, in our study the reactions were predominant at the nuclear and cytoplasmic level, focally membranous and we found statistically significant differences in relation to most of the clinico-epidemiological and histological parameters of PAA analyzed.

Although CD133 is a transmembrane protein, its nuclear and cytoplasmic expression may suggest internalization and translocation of the protein, which could be involved in cellular transcription as a cofactor, as suggested by some studies [24].

Analyses by Trerotola M et al. revealed the presence of CD133 in restricted cell subpopulations in the prostate epithelium, both in benign structures and in prostate carcinoma, suggesting the existence of a distinct cell compartment involved in the maintenance of tissue stem populations [10].

Subsequent studies confirmed the detection of CD133 in prostatic intraepithelial neoplasia and in prostate carcinoma, with a focal distribution and expression limited to distinct cell subpopulations, interpreted as belonging to the tumor stem compartment [11,12].

Analysis of the correlation between CD133 immunoexpression and tumor histological grade generated inhomogeneous results.

The study by Kalantari E et al. did not identify significant associations between the level of CD133 expression and Gleason score or tumor differentiation grade, suggesting a relatively independent behavior of this marker with respect to histopathological parameters of aggressiveness [13].

From the perspective of tumor stage, clinicopathological data are also inconsistent.

Some studies have not shown significant correlations between CD133 expression and local stage of the disease [13], while other investigations have suggested an involvement of CD133 in tumor progression and systemic dissemination, especially in the context of advanced and metastatic disease [11,12].

In our study, CD133 immunoexpression showed significantly higher differences in patients with extreme ages and high PSA values, as well as in relation to histological type, with high values in CPAA and CoPAA, but also in PAA in advanced ISUP groups, with perineural and lymphovascular invasion.

Glumac PM et al. demonstrated a significant overexpression of CD133 in androgen-independent prostatic carcinoma forms with neuroendocrine differentiation, compared to conventional prostatic adenocarcinomas [12].

Thus, CD133 immunostaining was absent in AR-positive adenocarcinomas and highly expressed in most neuroendocrine forms, suggesting a direct association with the aggressive and therapy-resistant tumor phenotype [12].

In a metastatic context, CD133 is correlated with the capacity to disseminate and adapt to the tumor microenvironment.

One study indicated increased expression of CD133 in metastases, especially in bone, as well as its association with epithelial-mesenchymal transition phenomena and prostatic cellular plasticity [11].

Also, the presence of CD133-positive cells in the circulation was associated with disease progression and poor prognosis in advanced forms of prostate cancer [11].

The biomolecular connections of stem cell-markers proteins with the cell cycle, tumor proliferation rate, and epithelial-mesenchymal transition are incompletely understood, and research in this direction is of great interest.

Understanding how the stem-like fraction is selected becomes crucial to clarify tumor longevity, even when the main mass of the carcinoma has been significantly eliminated [16].

Future studies are needed to more accurately characterize the stem cells present in PAA, as well as their source, which can be epithelial or stromal or of mesenchymal-epithelial induction, in the context in which we already know that epithelial-mesenchymal transition is associated with aggressive prostate tumors, some of these aspects being limitations of this study.

Current concepts promote proliferation from PAA as a result of the interplay between the stem-like fraction and the tumor niches that support it, which explains the variability in the biological behavior of tumors with apparent histological similarity [14,16].

Conclusions

Increased CD133 immunoexpression has been associated with extreme age, elevated PSA, and high-grade conventional PAA with vascular and perineural invasion.

The epithelial and stromal reactions indicate the presence of stem cells from different sources, but also suggest possible communication through biomolecular signals of the two cellular reservoirs.

CD133 may contribute to the identification of aggressive AAP and the stratification of patients for therapy, and the internalization of expression designates the protein as having a potential role as a transcriptional cofactor.

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None to declare.

Author Contributions

Conceptualization, A.E.S. and A.M.S.; Methodology, A.M.S., O.I.C and B.C.A.; Investigation, A.M.S. and O.I.C; Data analysis, A.E.S., A.M.S. and B.C.A.; Manuscript writing and initial draft preparation, A.M.S.; Manuscript review and editing, A.M.S., O.I.C and B.C.A.; Supervision, A.E.S.

All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki; the study and the protocols utilized therein were approved by the Ethics Committee of University of Medicine and Pharmacy of Craiova (223/28.09.2023).

Consent Statement

Not applicable for a retrospective descriptive study.

Data availability

All data presented in the manuscript are available from the authors upon request.

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