North Clin Istanb 2024;11(6):534–540
doi: 10.14744/nci.2023.79735

Original Article MEDICAL ONCOLOGY

The evaluation of cyclin D1 expression in prostate carcinoma cases

Asude Aksoy,[1] Selcen Vicdanli,[2] Gokhan Artas[3]

[1]Department of Medical Oncology, University of Health Sciences, Fethi Sekin City Hospital, Elazig, Turkiye
[2]Department of Internal Medicine, Fethi Sekin City Hospital, Elazig, Turkiye
[3]Department of Pathology, Firat University Faculty of Medicine, Elazig, Turkiye

ABSTRACT

OBJECTIVE: Cyclin D1 (CDDN1) is an important protein for mitotic cell cycle advancement through the G1 phase and contributes to the control of the cyclin-dependent kinases CDK4 and CDK6. We evaluated the relationship between CDDN1 expression and clinicopathological features in prostate cancer (PCa) cases and whether CDDN1 could be used as a prognostic biomarker for PCa cases in this study.

METHODS: This study comprised ninety cases; seventy-five had PCa and fifteen had benign prostatic hypertrophy (BPH) diagnoses (as the control group). The pathological specimens were stained immunohistochemically and categorized as a 'low' (L) or a 'high' (H) group for CDDN1 expression. The cases' clinicopathological features and survival rates were evaluated statistically, within a 95% confidence interval, $p<0.05$, retrospectively.

RESULTS: The median follow-up time was 75 (17–96) months, and the median overall survival (OS) was 87 months (CI 95%: 74.74–99.25). While the OS was 66 months (CI 95%: 49.61–82.38) in the H-CDDN1 group, the OS of the L-CDDN1 group was not yet reached. The OS of the L-CDDN1 group was longer in statistical significance ($p=0.011$). A Cox regression analysis revealed that the levels of CDDN1 expression, the values of lactate dehydrogenase, and post-treatment prostate specific antigen were found to be prognostic factors for OS in PCa cases ($p<0.05$).

CONCLUSION: Our results suggest the overexpression of CDDN1 is a potentially useful but poor prognostic biomarker for PCa cases.

Keywords: Biomarker; cyclin D1; prognosis; prostate carcinoma; survival.

Cite this article as: *Aksoy A, Vicdanli S, Artas G. The evaluation of cyclin D1 expression in prostate carcinoma cases. North Clin Istanb 2024;11(6):534–540.*

One of the most prevalent malignancies in men, prostate cancer (PCa), is typically a disease of older men, with hormonal variables involved in its pathogenesis [1]. In 2020, PCa accounted for 10.6% of all cancers. Less than 25% of the cases are in the advanced stage, with two-thirds in the localized stage. The disease's stage and potential risk factors affect how it is treated. While radical prostatectomy, brachytherapy alone, external beam radiation therapy (RT) with or without brachytherapy, or active surveillance are the basic options for treating PCa in its localized stages, androgen deprivation therapy (ADT) is the cornerstone treatment for PCa with advanced stage. The disease's prognosis depends on the case's sensitivity to ADT. Among the current treatment options are procedures that target androgen pathways in cases of castration-sensitive or androgen-dependent prostate cancer, alternative hormone treatment options such as

Received: May 13, 2023 *Revised:* October 02, 2023 *Accepted:* November 02, 2023 *Online:* November 13, 2024

Correspondence: Asude AKSOY, MD. Saglik Bilimleri Universitesi, Fethi Sekin Sehir Hastanesi, Tibbi Onkoloji Klinigi, Elazig, Turkiye.
Tel: +90 424 606 60 00 - 6669 e-mail: asudeaksoy@hotmail.com

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abiraterone, enzalutamide, darolutamide, and apalutamide, chemotherapy, immunotherapy strategies, poly (ADP-ribose) polymerase inhibitors for metastatic castration-resistant prostate cancer (mCRPC) cases with homologous recombination. Metastatic CRPC cases are typically treated by microtubule-targeting drugs. The mitotic spindle cannot form, and the cell cycle stops if microtubule development and assembly are absent. Taxanes cause mitotic arrest and subsequent cell death because they slow tubulin depolymerization during the mitotic cycle [2]. Docetaxel has a well-established role in chemotherapy-naive patients, and cabazitaxel, a second-generation taxane, is active in individuals who had previously taken docetaxel. In recent years, tissue-agnostic therapy has been designed according to the molecular structure of solid tumors, resulting in more promising results. Up to 23% of mCRPCs have homologous recombination repair (HRR) gene alterations such as breast cancer susceptibility gene (BRCA)2, ataxia-telangiectasia mutated (ATM), checkpoint kinase 2 (CHEK2), and BRCA1 genes. These tumors have also been shown to be sensitive to poly ADP-ribose phosphate (PARP) inhibitors. Pembrolizumab or dostarlimab are options for cases with deficient mismatch repair/high levels of microsatellite instability. Pembrolizumab has been observed to prolong survival in metastatic PCA cases with a high tumor mutational burden [3–8].

Today, different molecular pathways for tissue agnostic therapy, which is shaped according to the molecular structure of the tumor, and the functions of these points in carcinogenesis should be defined.

When a mutation occurs for any cause, the genetic structure becomes unstable, and normal cellular processes shift, causing oncogenesis to start happening. CDDN1 encourages cell division by building complexes (CDK-4 or CKD-6) with cyclin-dependent kinase in cells. Retinoblastoma protein (Rb) phosphorylation and the subsequent activation of E2 factor (E2F)-sensitive genes are promoted by the CDK4/CDK6 complex, which is activated by the CDDN1 [8]. CDDN1 is overexpressed in various epithelial malignancies, particularly mantle cell lymphoma, breast cancer (BC), and a subset of multiple myelomas [9–11]. Recent evidence also obviously suggests that CDDN1 performs a role in cancer progression and resistance to therapy. This study focuses on the new gains regarding CDDN1 dysregulation in cell cycle control emerging from current research during PCa development and progression.

Highlight key points

- The overexpression of CDDN1 is significantly correlated with prostate cancer cases who had benign prostatic hypertrophy tissue.
- The overexpression of CDDN1 was correlated with high grade in advanced-stage prostate cancer cases.
- Prostate cancer cases with low-CDDN1 expression had longer overall survival.
- The expression of CDDN1 can serve as a prognostic biomarker in prostate cancer cases.

MATERIALS AND METHODS

Cases Selection

Biopsy samples were taken from seventy-five cases, sixty of whom had been diagnosed with PCa, and, as a control group, fifteen had benign prostatic hypertrophy (BPH). The Firat University Non-interventional Research Ethics Committee granted approval for this study (date: 26.04.2016, number: 08/01). and allowed to use recording data from cases, treated in the medical oncology department of the medical faculty hospital between 2009 and 2017. For all situations, written informed consent was provided, which was in the Statement of Helsinki. The pathology department of the medical faculty provided prostate tissue paraffin blocks collected after transurethral resection (TUR), radical prostatectomy, and core needle biopsy. The World Health Organization (WHO) revised the Gleason score (GS) in 2016. Based on the GS, the patients were divided into prognostic groups: Group 1 (GS: 3+3); Group 2 (GS: 3+4); Group 3 (GS: 4+3); Group 4 (GS: 3+5; 4+4; 5+3); and Group 5 (GS: 5+4; 4+5; 5+5) [12].

Pathological Evaluation

For immunohistochemical examination, 5-µm-thick sections from paraffinized tumor tissues were used. CDDN1 (anti-Cyclin D1 (SP4-R) Rabbit Monoclonal, 1/150, VENTANA) was processed in an automated stainer (Ventana MedicalSystem, SN: 712299, REF: 750-700, Arizona, USA) for staining. Under a Leica DM500 microscope, the preparations were examined, assessed, and photographed. Histoscoring was calculated according to the degree of frequency (0.1: <25%, 0.4:26–50%, 0.6:51–75%, 0.9:76–100%) and degree of density (0: no, +0.5: only a little, +1: little, +2: middle, +3: strong) (Fig. 1A–D). The histoscore value was calculated according to the result of "Frequency X density" [13].

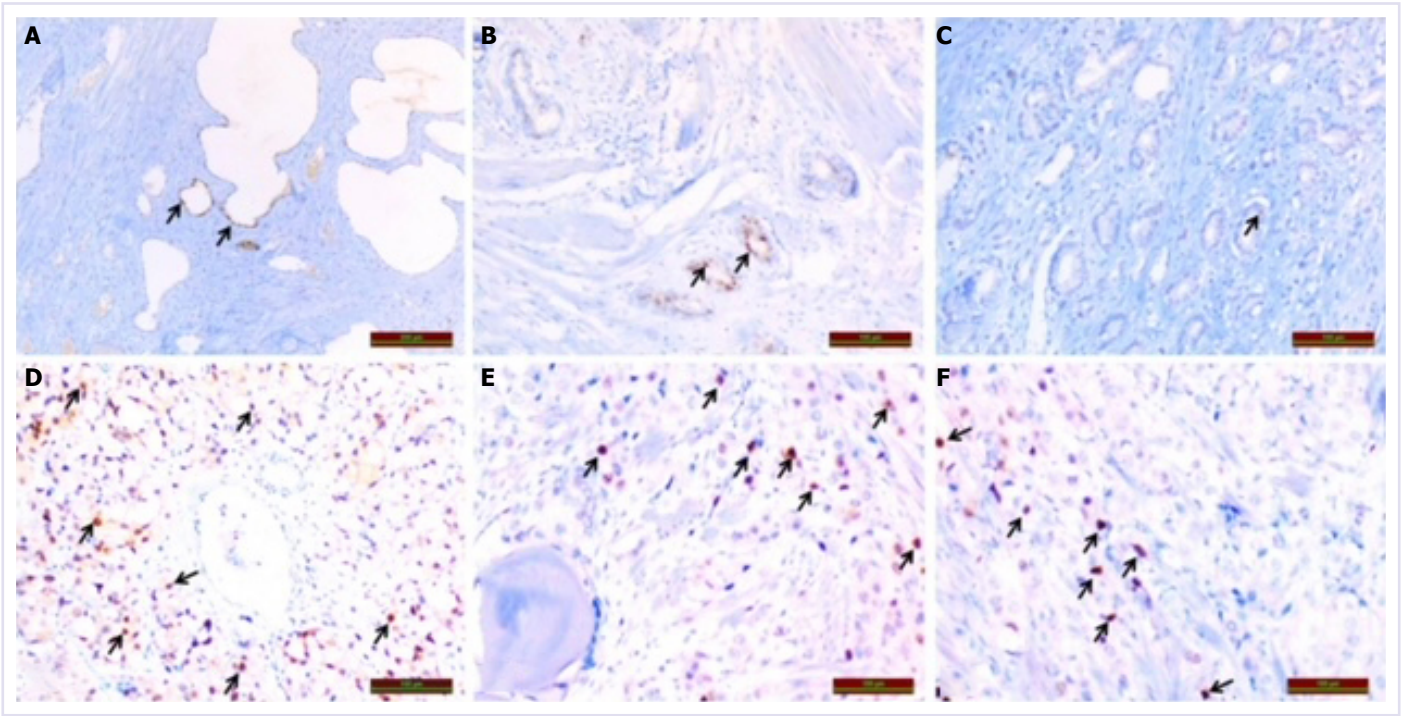

Figure 1. Histopathological evaluation for cyclin D1 (CDDN1) – in the prostate acinar adenocarcinoma (PCa) tissue. **(A)** CDDN1 (+) expression evaluation in the control group (Haematoxylin & Eosin (HE) X100), Immunoperoxidase X 100). **(B)** CDDN1 immunoreactivity in Group 1 - PCa tissue (Haematoxylin & Eosin (HE) X 100), Immunoperoxidase X 100). **(C)** CDDN1 immunoreactivity in Group 2 - PCa tissue (Haematoxylin & Eosin (HE) X 100), Immunoperoxidase X 100). **(D)** CDDN1 immunoreactivity in Group 3 – PCa tissue (Haematoxylin & Eosin (HE) X 100), Immunoperoxidase X 100). **(E)** CDDN1 immunoreactivity in Group 4 - PCa tissue (Haematoxylin & Eosin (HE) X 100), Immunoperoxidase X 100). **(F)** CDDN1 immunoreactivity in Group 5 - PCa tissue (Haematoxylin & Eosin (HE) X 100), Immunoperoxidase X 100).

The cut-off value of CDDN1 was determined as 0.45 was chosen (sensitivity 64% and specificity 80%) with the ROC (Receiver Operating Characteristics) curve (Fig. 2A). AUC (area under the curve)=0.659±0.054 (CI 95%: 0.55–0.76) (p=0.053). The low (L-CDDN1) group was classified as those with a CDDN1 value <0.45, and the high (H-CDDN1) group was classified as those with a CDDN1 value ≥0.45.

The mean prostate-specific antigen (PSA) values of the cases were evaluated separately before and after treatment. Pre-PSA: It was evaluated as the mean of PSA value before treatment and last- PSA: It was evaluated as the mean of PSA value after treatment.

Statistical Analysis

For statistical analysis, IBM Corp. Armonk, NY, USA, version 25 of the Statistical Package for Social Sciences was used. The duration from diagnosis to death or final follow-up was used to determine the median overall survival (OS). Descriptive statistics are presented as "n" and % for categorical variables, mean±SD median (IQR) for continuous variables. When the data of the study were analyzed in terms of normality assumptions (Shapiro-Wilk test), in comparison of CDDN1 expression values according to control and case groups, the independent t-test from parametric tests (Shapiro-Wilk test p>0.05), Mann-Whitney U test, one of the nonparametric tests (Shapiro-Wilk test p<0.05), was used to compare CDDN1 scores according to the case and control groups. Bonferroni test, one of the post-hoc tests, was used for comparisons between groups. Chi-Square test or Fisher's Exact test was used to compare categorical variables. Kaplan-Meier method was used to compare survival times between various clinical parameter groups. Finally, multivariate Cox Regression results are given on the risk of death from various clinical factors.

The cut-off value for CDDN1 expression determined by ROC analysis results was deemed. The findings were regarded as statistically significant when they were within the 95% confidence level (CI) (p<0.05).

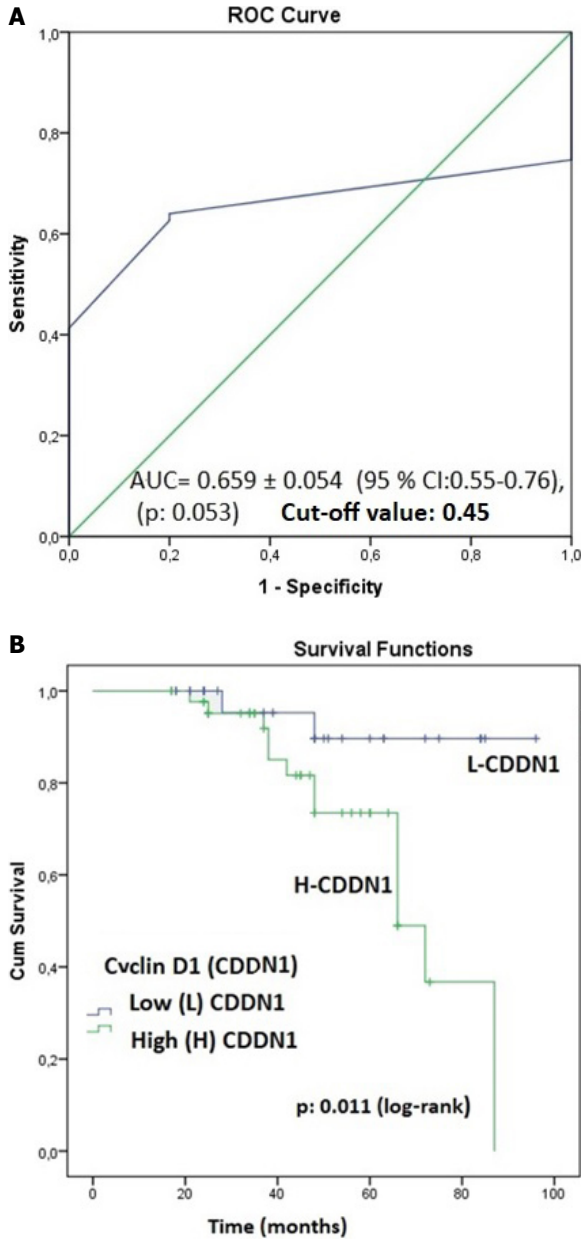

Figure 2. **(A)** The receiver operating characteristic curve (ROC) for cyclin D1 (CDDN1) expression. **(B)** Kaplan-Meier survival curves stratified by cyclin D1 (CDDN1) groups.

RESULTS

Immunohistochemically, H-grade PCa tumors expressed a higher level of CDDN1 in their cytoplasm than the control BPH tissue (Table 1 and Fig. 1). The overexpression of CDDN1 was observed to have a significant positive relationship with high-grade Gleason scores, lactic dehydrogenase enzyme (LDH) value, high values of pre-PSA to last-PSA, advanced age, and the presence of lymphovascular invasion (LVI) and per-neural invasion (PNI). There was a negative correlation between CDDN1 expression and disease-free survival (DFS) (Table 2, 3).

Table 1. The relationship cyclin D1 (CDDN1) immunoreactivity histoscore of paraffin block prostate tissue specimens for each group compared with a control group

Group	CDDN1*	p^{β}
Control (15)	0.40±0.11	**0.001**
Case (75)	77±0.59	
Group 1 (GS: <6)	0.27±0.10	**0.05**
Group 2 (GS:3+4)	0.38±0.20	1
Group 3 (GS: 4+3)	1.07±0.70	**0.036**
Group 4 (GS: 8)	0.96±0.44	**0.003**
Group 5 (GS: 9–10)	1.17±0.64	**0.006**

*: Histoscore (Frequency X Density) Mean value±SD (Standard deviation); β: Versus to control group; One-way ANOVA test used.

In all instances, OS was 87 months (CI 95%: 74.74–99.25), and the median follow-up time was 75 (17–96) months. The OS was 66 months in the H-CDDN1 group (CI 95%: 49.61–82.38), and the OS of the L-CDDN1 group was not yet reached. There was a statistically significant difference between the two groups (p=0.011), (Fig. 2B). L-CDDN1, the high values of LDH, and the last value of PSA were prognostic factors for OS in PCa cases according to Cox regression analysis (Table 3). In the current study, the value of CDDN1 expression was found to be a prognostic factor for OS, in PCa cases ($p<0.05$).

The multivariate Cox regression model revealed that the high values of LDH, last-PSA, and the overexpression of CDDN1 raised the likelihood of mortality, in Table 3.

DISCUSSION

PCa is the world's second major malignancy and the sixth leading cause of cancer-related mortality rates in males [1]. Approximately one-third of patients demonstrate primary resistance to ADT, which is observable. Following ADT therapy, most patients will ultimately develop CRPC, which has mostly responded inadequately to treatment strategies. In these cases, the disease will be managed with next-generation anti-hormonal medications, such as apalutamide, darolutamide, enzulatamide, abiraterona acetate, and cytotoxic chemotherapies including taxane and cabazitaxel [2]. Tumor burden is also an important factor for therapy selection since the CHAARTED re-

Table 2. Analysis based on cyclin D1 (CDDN1) staining results

	CDDN1			
	Case (%)	L-CDDN1 (%)	H-CDDN1 (%)	p
BPH (as a control group) (n)	15	80	20	**0.001**¥
Case (n)	75	41.3	58 .7	**0.001**¥
		0.31±0.22*	1.09±0.52*	
Age* (n=75)	71.53±6.83*	71.36±6.61*	71.69±7.09*	**0.26**ë
<65 years	18.9	9 (12%)	8 (10.7%)	
≥65 years	81.1	34 (79.1%)	39 (83%)	
Stage				**0.001**ë
Local advanced	46.7	77.4	25	
Advanced	53.3	22.6	75	
Gleason score n				**0.001**ë
≥7	60	29	81.8	
<7	40	71	18.2	
Progression				**0.001**ë
Present	30.7	–	52.3	
Absent	69.3	31 (59.6%)	47.7	
Perineurol invasion				**0.0.10**ë
Positive	46.7	29	59.1	
Negative	53.3	71	40.9	
Angiolymphatic invasion				**0.022**ë
Positive	41.3	25.8	52.3	
Negative	58.7	74.2	47.7	

BPH: Benign prostatic hypertrophy; ¥: T test used; #: Mann–Whitney U Test used; *: Mean Values; ë: Pearson Chi-Square; L: Low; H: High; n: According to AJCC 8:<7 Gleason score: Very low, low and favorable intermediate risk group; ≥7 Gleason score: Very high, high, and unfavorable intermediate risk group Gleason score.

Table 3. Cox proportional hazards for the predictor of survival

	Multivariate analysis		
Variable	p	HR	CI
Age (ref: ≤65 y)	0.635	1.63	0.21–12.82
LDH value	**0.044**	1.004	1.000–1.008
Progression (+/-) (Ref: +)	0.201	4.448	0.451–43.81
Gleason Score n (Ref: Low)	0.596	1.261	0.535–2.971
CDDN1 (L/H) (Ref: Low)	**0.026**	87.774	1.693–4551
Pre-PSA	0.081	0.996	0.992–1.000
Last-PSA	**0.048**	1.003	1.000–1.006

HR: Hazard ratio; CI: Confidence interval; LDH: Lactic dehydrogenase enzyme; Pre-PSA: The mean of PSA value before treatment; Last-PSA: The mean of PSA value of after treatment; CDDN1: Cyclin D1; n: According to AJCC 8; <7 Gleason Score : Very low, low and favorable intermediate risk group; ≥7 Gleason score: Very high, high, and unfavorable intermediate risk group Gleason score; +: The present of progression; -; The absent of progression.

search found that low-volume M1 disease did not benefit as much from large-volume illness in PCa cases [14].

The CCND1 gene is located at 11q13 and is also called BCL1 or PRAD1. CDDN1 overexpression may develop from a clonal somatic mutation, amplification, or rearrangement of the CDDN1 gene. CDDN1 acts as an oncogene with its relatively early overexpression during neogenesis [15]. Cell cycle migration from G1 to the S phase and multiplication are both supported by CDDN1 expression. CDDN1 is a cyclin-dependent kinase (CDK) activating regulatory subunit. Retinoblastoma protein (Rb), a powerful inhibitor of the transition from the G1 to the S phase, is phosphorylated and turned inactive by activated cyclin D-CDK complexes. It has the potential to cause cancer by promoting anchorage-independent growth and angiogenesis via VEGF synthesis. For cell migration, angiogenesis, and the Warburg effect to occur, the cell cycle must go through the G1 phase, which depends on CDDN1 [16]. CDDN1 also regulates cellular

proliferation, survival, and transformation independently of CDK via binding to nuclear receptors (including the estrogen receptor, thyroid hormone receptor, proliferator-activated receptor gamma-mediated (PPAR), and androgen receptors (AR) [17]. Overexpression of CDDN1 can also suppress Fas expression, resulting in improved chemotherapeutic resistance and protection against apoptosis [18]. We considered why the cytotoxic chemotherapies used are ineffective and why resistance to taxane treatments and ADTs developed rapidly, and we designed the present study based on this. It has been demonstrated that CDDN1 overexpression is linked to decreased survival and increased metastasis in many cancers [18]. The CDDN1 gene is shown to be amplified in many cancers, such as non-small cell lung cancers, head, and neck squamous cell carcinomas [19–21]. Chromosomal translocation of the CDDN1 gene has been observed in cancers such as mantle cell lymphoma and multiple myeloma, and histone deacetylase inhibitors have been used as a therapeutic target in the treatment of these cancers [22]. Similarly, pharmacological CDK4/6 inhibitors, such as p16INK4A, palbociclib, ribociclib, and abemaciclib, reduce CDK4/6 kinase activity and are currently used in the treatment of hormone receptors (+), Her-2/neu (-) BC cases with advanced-stage [23]. Although Nakamura et al. [24] identified a CDDN1 immune reactivity rate of 70% of the cases in their study exploring the association between CDDN1 expression and clinicopathological variables in PCa cases, in this investigation, we concluded that CDDN1 expressions were immune reactive in all of the cases. Nakamura et al. [24] concluded in this study that estrogen receptor beta (ER-β) is the second most significant steroid receptor after androgens in PCa pathogenesis and that estrogen influences the cell cycle by increasing CDDN1 expression via this receptor.

Pereira et al. [25] evaluated the expression of CDDN1 in PCa tissue and normal prostate tissue obtained from the autopsy series. Although they utilized normal prostate tissues as a control group in their study and reported that CDDN1 expression was not present in these tissues, we used all prostate biopsy tissues from BPH patients as a control group in this study and found that all of them were immuno-expressed for CDDN1. However, 80% of them had low CDDN1 expression. In their work, Musgrove et al. [26] demonstrated that the cyclin D1b/Slug axis contributes significantly to pro-tumorogenic events due to a decrease in CDDN1 and an increase in the androgen-dependent pathway. We may conclude that CDDN1 overexpression is a sign of malignancy and aggressiveness. Many researchers have demonstrated in their investigations that intratumoral CDDN1 overexpression is related to a poor prognosis in various cancers [27]. Similar to Pereira and colleagues in our study, a significant correlation was found between PNI, increased GS, and the degree of CDDN1 expression. While there was no correlation between PSA levels and CDDN1 in their study, there was a significant correlation in our investigation [28]. The most common signs of bone metastases in PCa are new bone growth and osteoblastic activation. The relationship between CDDN1 overexpression and blastic bone metastases was also observed in osteosarcoma, mantle cell lymphoma, and metastatic BC cases. A favorable and significant correlation was identified in this study between the number of metastases, the presence of bone metastases, and the CDDN1 expression rate. In contrast to the literature and our findings, Shiraishi et al. [28] investigated the association between the clinicopathological characteristics of PCa cases and p53, p21, GS, and CDDN1 expression and found no relationship between GS and CDDN1 expression. Some studies have also demonstrated that cell cycle arrest and cancer cell growth may be achieved by suppressing CDDN1 and androgen receptors in vivo and in vitro [29, 30]. Our study has limitations, including a retrospective design, a diverse patient group with different treatment histories, tumor burdens, and biologies.

Conclusion

A better comprehension of new drug resistance mechanisms, PCa molecular pathways, and prognostic and predictive biomarkers may help enhance mCRPC treatment. Our findings indicate that CDDN1 is a marker of aggressiveness and plays a critical role in the formation of mCRPC. Future efforts must now aim to bridge PCa biology to treatment.

Ethics Committee Approval: The Firat University Non-interventional Research Ethics Committee granted approval for this study (date: 26.04.2016, number: 08/02).

Authorship Contributions: Concept – AA; Design – AA, GA; Supervision – AA, SV; Fundings – SV; Materials – SV; Data collection and/or processing – SV; Analysis and/or interpretation – AA, GA; Literature review – AA, SV; Writing – AA, SV; Critical review – AA.

Conflict of Interest: No conflict of interest was declared by the authors.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: This study has received financial support from the Scientific Research Project of Firat University University (no: TF.17.48, February, 19.2017).

Peer-review: Externally peer-reviewed.

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