Original Article

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Prognostic Impact of Intraductal Carcinoma in Patients with Metastatic Prostate Cancer Treated with Abiraterone Acetate or Enzalutamide

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Abstract

Objective: This study aimed to evaluate the prognostic impact of intraductal carcinoma of the prostate (IDC-P) in patients with metastatic prostate cancer treated with enzalutamide or abiraterone acetate.

Materials and Methods: We retrospectively analyzed data from patients with metastatic prostate cancer who received abiraterone acetate or enzalutamide. The primary outcome was overall survival (OS). Secondary outcomes were prostate-specific antigen (PSA) progression-free survival (PFS) and radiologic PFS.

Results: A total of 94 men were enrolled in the study. Among them, 30 patients (31.9%) received androgen receptor pathway inhibitors for metastatic hormone-sensitive prostate cancer (mHSPC), and 64 patients (68.1%) were treated for metastatic castration-resistant prostate cancer (mCRPC). The presence of IDC-P was associated with significantly shorter OS than in patients without IDC-P (35.38 months vs. 55.59 months, respectively; p=0.011). In mCRPC, median OS was significantly shorter in patients with IDC-P (35.38-55.59 months), while the difference was not significant in the mHSPC cohort [35.48 months vs. not reached (NR)]. Multivariate Cox regression analysis identified IDC-P as an independent adverse prognostic factor for OS (hazard ratio 3.16, 95% confidence interval 1.56-6.41; p=0.001). Similarly, median PSA-PFS was significantly shorter in patients with IDC-P than in those without IDC-P (15.87 vs. 31.11 months, p=0.020). In mCRPC, median PSA-PFS was significantly shorter in patients with IDC-P (15.9 vs. 28.4 months), whereas the difference was not significant in the mHSPC cohort (18.3 months vs. NR).

Conclusion: The presence of IDC-P is associated with poorer PSA-PFS and OS in patients with metastatic prostate cancer treated with abiraterone acetate or enzalutamide.

Keywords: Prostate cancer, intraductal carcinoma, enzalutamide, abiraterone acetate

Introduction

The most frequently observed histological type of prostate cancer is prostatic acinar adenocarcinoma. While the term "ductal spread of prostate carcinoma" has been used for several decades, intraductal carcinoma of prostate (IDC-P) was recognized as a distinct pathological entity in the 2016 edition of the World Health Organization (WHO) classification of tumors of the urinary system and male genital organs (1-3). IDC-P is considered a manifestation of advanced prostate cancer, characterized by intraductal spread of aggressive tumor cells and cancerous transformation of pre-existing ductal and acinar structures by high-grade prostatic adenocarcinoma. IDC-P is identified in approximately 15-30% of radical prostatectomy specimens and 14% of biopsies with concomitant carcinoma, whereas isolated IDC-P without invasive cancer is exceedingly rare, occurring in only 0.06-0.26% of cases (4-7). Presence of IDC-P correlates with a higher tumor grade, larger volume, and advanced stage for localized prostate cancer (8-10). Compared with conventional acinar adenocarcinoma, IDC-P is enriched for genomic alterations linked to aggressive behavior, including *PTEN* loss, *TP53* alterations, and *BRCA2* alterations, along with MYC amplification and higher levels of genomic instability (11-13). IDC-P is associated with a higher risk of biochemical recurrence, as well as shorter prostate cancer-specific survival and overall survival (OS) following definitive treatment (14,15).

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Androgen receptor pathway inhibitors (ARPIs), including abiraterone acetate, enzalutamide, apalutamide, and darolutamide, have become widely used in the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC). Several clinical and molecular factors are associated with poor outcomes in patients receiving ARPIs, including high Gleason score, presence of liver metastases, high disease volume, *de novo* metastatic presentation, elevated baseline prostate-specific antigen (PSA), low hemoglobin levels, elevated alkaline phosphatase levels, and AR-V7 positivity (16-25). Although several retrospective studies showed that presence of IDC-P was associated with shorter CRPC-free survival, PSA progression-free survival (PSA-PFS) and OS in patients who treated with ARPIs, data on the prognostic impact of uncommon histological subtypes in patients treated with ARPIs is limited (26-28). This study aimed to evaluate the prognostic impact of IDC-P in patients with metastatic prostate cancer who were treated with enzalutamide or abiraterone acetate.

Materials and Methods

We conducted a retrospective single-center cohort study in the Department of Medical Oncology at Ankara University. The study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ankara University Faculty of Medicine Ethics Committee (decision no: İ06-428-24, date: 13.06.2024). The study included patients with metastatic prostate adenocarcinoma who received abiraterone acetate or enzalutamide from January 1, 2014, to December 2024. Patients who received androgen deprivation therapy (ADT) or a single line of docetaxel treatment were eligible for the study. Patients who received more than one line of docetaxel or who received treatment other than ADT or docetaxel prior to ARPI treatment were excluded from the study. We excluded patients who received triplet therapy, which included ADT, an ARPI, and docetaxel. Patients whose pathology results were unavailable or who were diagnosed based solely on non-prostatic tissue samples were excluded from the study. Additionally, patients with incomplete data that prevented us from conducting survival analyses for secondary malignancy and for pure neuroendocrine pathology were excluded from the study.

Patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory findings, and timelines for diagnosis, treatment, progression, and death were retrospectively extracted. High volume disease was defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis. The primary outcome of the study was OS. OS was defined as the time from the start of the ARPI (abiraterone acetate or enzalutamide) to death. Secondary outcomes were PSA-PFS, radiologic PFS (rPFS), and PSA50 response rate. PSA-PFS was defined as the interval between the initiation of ARPI (abiraterone acetate or enzalutamide) and PSA progression or death. PSA progression was characterized by a ≥25% increase in PSA levels, reaching at least 2 ng/mL, and confirmed by a subsequent measurement taken at least 3 weeks later, in accordance with the PCWG3 criteria (29). rPFS was defined as the interval between the initiation of the ARPI (abiraterone acetate or enzalutamide) and the time at radiologic progression according to PCWG3 criteria or death (29). PSA50 response rate was defined as the proportion of participants with a PSA reduction of 50% or more from baseline.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 24.0. Continuous variables were presented as medians with interquartile ranges (IQR), while categorical variables were expressed as frequencies and percentages. Comparisons between categorical variables were performed using the chi-square test. For continuous variables, the Mann-Whitney U test or Student's t-test was applied, depending on the distribution of the data. Survival outcomes were estimated using the Kaplan-Meier method. Variables with a p-value ≤0.10 in univariate analyses were included in multivariate models. Cox proportional hazards regression (backward likelihood ratio method) was used for multivariable analysis to estimate hazard ratios (HR) with 95% confidence intervals (CI). All p-values were two-sided, and values <0.05 were considered statistically significant.

Results

A total of 254 patients with metastatic prostate cancer who were treated with abiraterone acetate or enzalutamide were screened. Ninety-four men who met the inclusion criteria, whose median age was 68.9 years (IQR=12.8), were included in the study. Of these patients, 79 (84%) have ECOG 0 or 1 performance status. A total of 69 patients (73.4%) had a Gleason grade group >7, and IDC-P was identified in 19 patients (20.2%). While 39 patients (41.5%) were treated with abiraterone acetate, 55 patients (58.5%) received enzalutamide. ARPIs were administered for mHSPC in 30 patients (31.9%) and for mCRPC in 64 patients (68.1%). The most common metastatic site was the bone (85.1%), followed by the lymph node (64.9%) and the lung (16%). All baseline characteristics are shown in Table 1. Patients with and without IDC-P had similar characteristics overall, except for the disease setting at initiation of ARPI therapy and the presence of bone and lung metastases (Table 1).

The median follow-up time was 54.14 months (95% CI 43.30-64.99). Median OS was 49.18 months (95% CI 36.39-61.96). Median OS was significantly shorter in patients with IDC-P [35.38 months (95% CI 19.58-51.19)] compared to patients without IDC-P [55.59 months (95% CI 45.05-66.13)] (p=0.011) (Figure 1A). In the mHSPC cohort, the median OS was not reached in patients without IDC-P, whereas it was 35.48 months (95% CI 12.31-58.65) in those with IDC-P (p=0.073) (Figure 1B). In the mCRPC cohort, the median OS was 49.93 months (95% CI 37.78-62.09) in patients without IDC-P and 35.38 months (95% CI 10.37-60.40) in patients with IDC-P (p=0.035) (Figure 1C). In the mCRPC cohort, among patients previously treated with docetaxel, median OS was 25.13 months (95% CI 3.23-47.03) in those with IDC-P versus 45.96 months (95% CI 33.41-58.52) in those without IDC-P (p=0.035). Multivariate Cox regression analysis showed that the presence of IDC-P was an independent predictor of poor OS (HR 3.16, 95% CI 1.56-6.41; p=0.001) after adjusting for confounding factors, such as ECOG performance status, Gleason grade group, presence of high grade prostatic intraepithelial neoplasia (HGPIN), type of ARPI, and disease volume (Table 2).

Median PSA-PFS was 28.42 months (95% CI 22.28-34.56). The median PSA-PFS was 15.87 months (95% CI 6.55-25.19) for patients with IDC-P and 31.11 months (95% CI 23.43-40.77) for patients without IDC-P (p=0.020) (Figure 2A). In the mHSPC cohort, the median PSA-PFS was not reached in patients without IDC-P, whereas it was 18.33 months (95% CI 6.71-29.96) in those with IDC-P (p=0.073) (Figure 2B). In the mCRPC cohort, the median PSA-PFS was 28.42 months (95% CI 21.32-35.51) in patients without IDC-P and 15.87 months (95% CI 1.48-30.27) in patients with IDC-P (p=0.011) (Figure 2C). In the mCRPC cohort, among patients previously treated with docetaxel, the median PSA-PFS was 28.38 months (95% CI 22.28-34.49) in patients without IDC-P and 15.87 months (95% CI 0.07-31.66) in patients with IDC-P (p=0.032). Multivariate Cox regression analysis showed that the presence of IDC-P was an independent predictor of poor PSA-PFS (HR 2.14, 95% CI 1.15-3.99; p=0.017) after adjusting for confounding factors, such as Gleason grade group, presence of HGPIN, type of ARPI, and disease volume (Table 3).

The median rPFS for the entire population was 33.18 months (95% CI 27.57-38.79). Although patients with IDC-P had numerically longer rPFS, the difference was not statistically significant [23.62 months (95% CI 13.53-33.71) for patients with IDC-P versus 34.20 months (95% CI 26.37-42.03) for those without IDC-P; p=0.091] (Figure 3A). In the mHSPC cohort, the median rPFS was not reached in patients without IDC-P, whereas median rPFS was 23.62 months (95% CI, NE-NE) in those with IDC-P (p=0.395) (Figure 3B). In the mCRPC cohort, the median rPFS was 33.18 months (95% CI 27.21-39.15) in patients without IDC-P and 21.49 months (95% CI 3.63-39.34) in patients with IDC-P (p=0.030) (Figure 3C). In the mCRPC cohort, among patients previously treated with

Table 1. General characteristic of the patients

		All patients (n=94)	IDC-P (-) (n=75)	IDC-P (+) (n=19)	p
Age	**Median (IQR)**	68.96 (12.8)	68.89 (14.2)	68.06 (7.5)	0.204
	<65	33 (35.1)	24 (32)	9 (47.4)	0.282
	≥65	61 (64.9)	51 (68)	10 (52.6)	
ECOG performance status	**0-1**	79 (84)	65 (86.7)	14 (73.7)	0.206
	2	12 (12.8)	8 (10.7)	4 (21)	
	Unknown	3 (3.2)	2 (2.7)	1 (5.3)	
Grade group	**≤7**	25 (26.6)	23 (30.7)	2 (10.5)	0.089
	>7	69 (73.4)	52 (69.3)	17 (89.5)	
Cribriform pattern		4 (4.3)	3 (4)	1 (5.3)	0.807
HGPIN		13 (13.8)	12 (16)	1 (5.3)	0.226
Neuroendocrine differentiation		3 (3.2)	1 (1.3)	2 (10.5)	0.042
***De novo* metastatic disease**		64 (68.1)	49 (65.3)	15 (78.9)	0.242
Disease setting at initiation of ARPIs	**mHSPC**	30 (31.9)	20 (26.7)	10 (52.6)	**0.030**
	mCRPC	64 (68.1)	55 (73.3)	9 (47.4)	
Prior treatment for mPCa (among mCRPC patients)	**ADT**	16 (25)	15 (27.3)	1 (11.1)	0.229
	ADT + docetaxel	48 (75)	40 (72.7)	8 (88.9)	
ARPI type	**Abiraterone**	39 (41.5)	34 (45.3)	5 (26.3)	0.193
	Enzalutamide	55 (58.5)	41 (54.7)	14 (73.7)	
Bone metastasis		80 (85.1)	61 (81.3)	19 (100)	**0.041**
≤4		18 (19.1)	14 (18.7)	4 (21.1)	0.099
5-10		13 (13.8)	8 (10.7)	5 (26.3)	
>10		49 (52.1)	39 (52)	10 (52.6)	
Lymph node metastasis		61 (64.9)	48 (64)	13 (68.4)	0.793
Lung metastasis		15 (16)	15 (20)	0	**0.033**
Liver metastasis		5 (5.3)	5 (6.7)	0	0.247
Disease volume	**Low**	32 (34)	25 (33.3)	7 (36.8)	0.791
	High	62 (66)	50 (66.7)	12 (63.2)	
Bone modifying agent		57 (60.6)	45 (60)	12 (63.2)	0.801

ADT: Androgen deprivation treatment, ARPI: Androgen receptor pathway inhibitor, ECOG: Eastern Cooperative Oncology Group, HGPIN: High grade prostatic intraepithelial neoplasia, IDC-P: Intraductal carcinoma of prostate, IQR: Interquartile range, mCRPC: Metastatic castration-resistant prostate cancer, mHSPC: Metastatic hormone-sensitive prostate cancer, mPCa: Metastatic prostate cancer

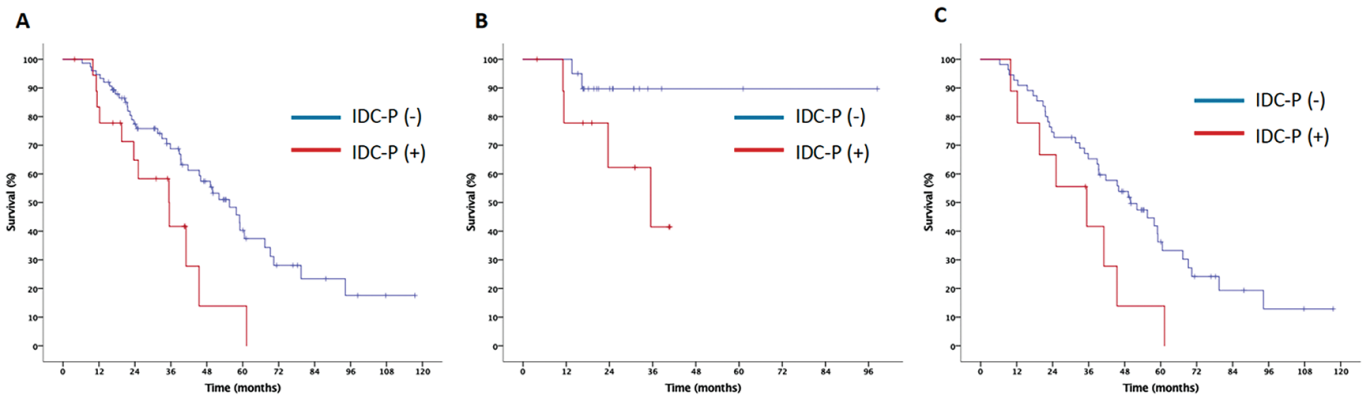

Figure 1. Kaplan-Meier curves for overall survival in the entire cohort (A), mHSPC subgroup (B) and mCRPC subgroup (C)

IDC-P: Intraductal carcinoma of the prostate, mHSPC: Metastatic hormone-sensitive prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer

Table 2. Univariate and multivariate analysis for predictors of overall survival

Variable		Univariate HR (95% CI)	p	Multivariate* HR (95% CI)	p	Multivariate** HR (95% CI)	p
Age	<65	1		-		-	
	≥65	0.83 (0.47-1.46)	0.518	-	-	-	-
ECOG-PS	0-1	1		1		1	
	2	2.41 (1.16-5.00)	0.018	2.05 (0.89-4.71)	0.089	2.26 (1.02-5.00)	0.044
Grade group	≤7	1		1		-	
	>7	1.97 (1.01-3.85)	0.047	1.20 (0.56-2.58)	0.643	-	-
IDC-P	No	1		1		1	
	Yes	2.33 (1.19-4.57)	0.014	2.78 (1.34-5.75)	0.006	3.16 (1.56-6.41)	0.001
HGPIN	No	1		1		-	
	Yes	0.37 (0.13-1.03)	0.057	0.46 (0.13-1.62)	0.227	-	-
De novo metastasis	No	1		-		-	
	Yes	0.85 (0.48-1.51)	0.578	-	-	-	-
Disease setting at initiation of ARPIs	mHSPC	1		-		-	
	mCRPC	1.78 (0.75-4.23)	0.140	-	-	-	-
ARPI	Abiraterone	1		1		1	
	Enzalutamide	0.58 (0.33-0.99)	0.050	0.58 (0.31-1.09)	0.092	0.05 (0.27-0.91)	0.023
Prior treatment	ADT	1		-		-	
	ADT + docetaxel	1.82 (0.84-3.94)	0.128	-	-	-	-
Bone metastasis	No	1		-		-	
	Yes	1.74 (0.69-4.40)	0.238	-	-	-	-
Lymph node metastasis	No	1		-		-	
	Yes	1.63 (0.91-2.94)	0.101	-	-	-	-
Lung metastasis	No	1		-		-	
	Yes	1.22 (0.64-2.33)	0.551	-	-	-	-
Liver metastasis	No	1		-		-	
	Yes	0.72 (0.22-2.33)	0.589	-	-	-	-
Disease volume	Low	1		1		1	
	High	2.47 (1.20-5.07)	0.014	2.42 (1.13-5.19)	0.023	2.44 (1.14-5.19)	0.023

*: First step in cox regression analysis, **: Final step in cox regression analysis, ADT: Androgen deprivation treatment, ARPI: Androgen receptor pathway inhibitor, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, HGPIN: High grade prostatic intraepithelial neoplasia, HR: Hazard ratio, IDC-P: Intraductal carcinoma of prostate, mCRPC: Metastatic castration-resistant prostate cancer, mHSPC: Metastatic hormone-sensitive prostate cancer, PS: Performance status

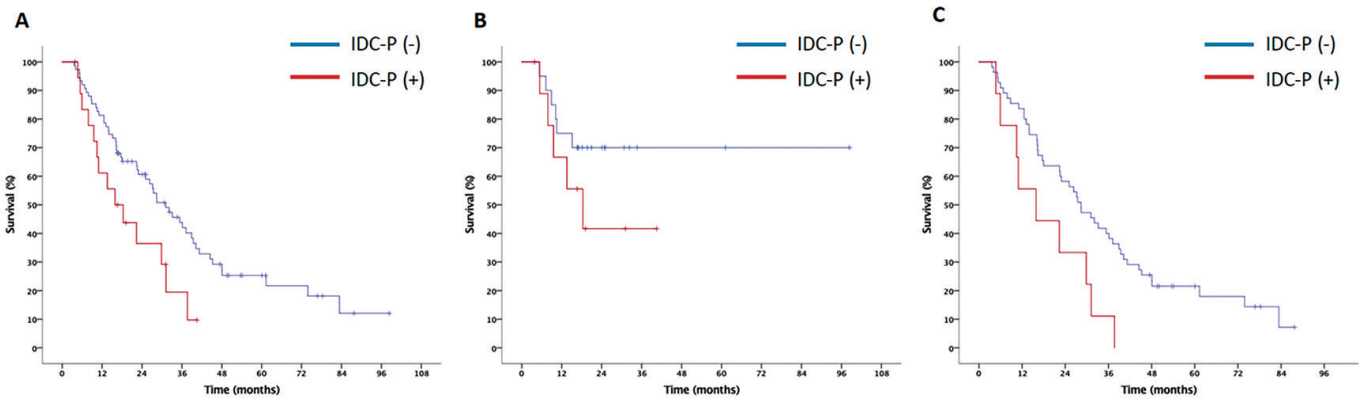

Figure 2. Kaplan-Meier curves for PSA-PFS in the entire cohort (A), mHSPC subgroup (B) and mCRPC subgroup (C)

IDC-P: Intraductal carcinoma of the prostate, mHSPC: Metastatic hormone-sensitive prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer, PSA-PFS: Prostate specific antigen-progression free survival

Table 3. Univariate and multivariate analysis for predictors of PSA progression free survival

Variable		Univariate HR (95% CI)	p	Multivariate* HR (95% CI)	p	Multivariate** HR (95% CI)	p
Age	<65	1		-		-	
	≥65	0.95 (0.56-1.59)	0.834	-	-	-	-
ECOG-PS	0-1	1		-		-	
	2	1.72 (0.87-3.41)	0.118	-	-	-	-
Grade group	≤7	1		1		-	
	>7	1.28 (1.03-1.59)	0.028	1.10 (0.61-2.01)	0.746	-	-
IDC-P	No	1		1		1	
	Yes	2.04 (1.10-3.75)	0.023	2.09 (1.11-3.95)	0.023	2.14 (1.15-3.99)	0.017
HGPIN	No	1		1		1	
	Yes	0.27 (0.09-0.75)	0.012	0.35 (0.12-1.02)	0.054	0.34 (0.12-0.96)	0.042
De novo metastasis	No	1		-		-	
	Yes	0.71 (0.42-1.18)	0.184	-	-	-	-
Disease setting at initiation of ARPIs	mHSPC	1		-		-	
	mCRPC	1.52 (0.79-2.93)	0.212	-	-	-	-
ARPI	Abiraterone	1		1		1	
	Enzalutamide	0.59 (0.36-0.96)	0.035	0.66 (0.39-1.08)	0.097	0.65 (0.40-1.08)	0.095
Prior treatment	ADT	1		-		-	
	ADT + docetaxel	0.89 (0.48-1.68)	0.737	-	-	-	-
Bone metastasis	No	1		-		-	
	Yes	1.78 (0.81-3.91)	0.150	-	-	-	-
Lymph node metastasis	No	1		-		-	
	Yes	1.51 (0.89-2.58)	0.128	-	-	-	-
Lung metastasis	No	1		-		-	
	Yes	1.18 (0.64-2.19)	0.590	-	-	-	-
Liver metastasis	No	1		-		-	
	Yes	0.97 (0.35-2.68)	0.949	-	-	-	-
Disease volume	Low	1		1		1	
	High	1.79 (1.06-3.15)	0.044	1.94 (1.09-3.47)	0.025	1.96 (1.10-3.49)	0.022

*: First step in cox regression analysis, **: Final step in cox regression analysis, ADT: Androgen deprivation treatment, ARPI: Androgen receptor pathway inhibitor, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, HGPIN: High grade prostatic intraepithelial neoplasia, HR: Hazard ratio, IDC-P: Intraductal carcinoma of prostate, mCRPC: Metastatic castration-resistant prostate cancer, mHSPC: Metastatic hormone-sensitive prostate cancer, PS: Performance status, PSA: Prostate specific antigen

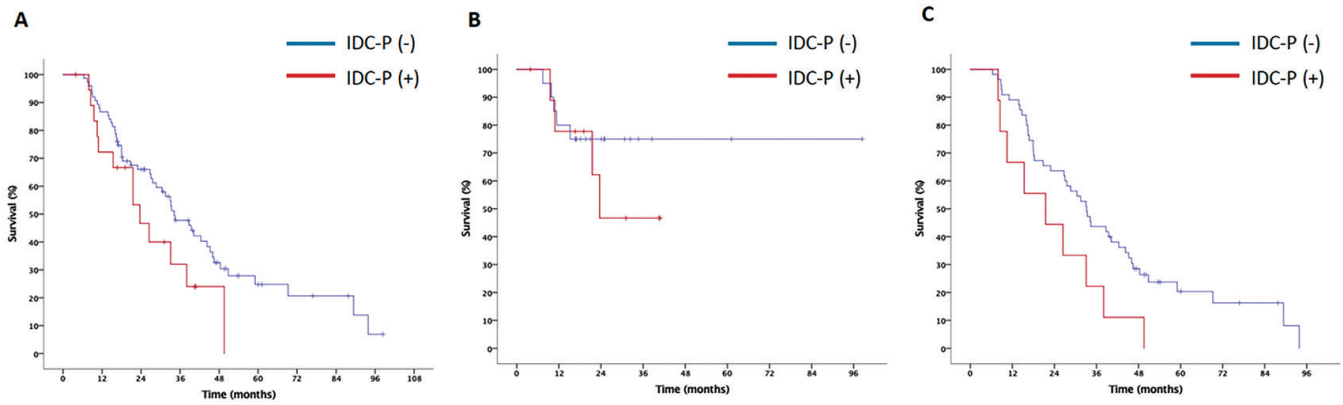

Figure 3. Kaplan-Meier curves for rPFS in the entire cohort (A), mHSPC subgroup (B) and mCRPC subgroup (C)

IDC-P: Intraductal carcinoma of the prostate, mHSPC: Metastatic hormone-sensitive prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer, rPFS: Radiologic progression free survival

Table 4. Univariate and multivariate analysis for predictors of radiologic progression free survival

Variable		Univariate HR (95% CI)	p	Multivariate* HR (95% CI)	p	Multivariate** HR (95% CI)	p
Age	<65	1		-		-	-
	≥65	0.77 (0.46-1.29)	0.316	-		-	-
ECOG-PS	0-1	1		1		-	
	2	1.79 (0.90-3.54)	0.097	1.31 (0.63-2.72)	0.468	-	-
Grade group	≤7	1		1		-	
	>7	1.85 (1.02-3.37)	0.044	1.16 (0.58-2.30)	0.673	-	-
IDC-P	No	1		1		-	
	Yes	1.70 (0.91-3.18)	0.095	1.92 (0.93-3.96)	0.078	-	-
HGPIN	No	1		1		1	
	Yes	0.27 (0.10-0.74)	0.011	0.29 (0.08-1.01)	0.051	0.21 (0.06-0.68)	0.010
De novo metastasis	No	1		-		-	
	Yes	0.71 (0.42-1.19)	0.199	-	-	-	-
Disease setting at initiation of ARPIs	mHSPC	1		1		-	
	mCRPC	1.96 (0.96-3.99)	0.066	1.50 (0.68-3.31)	0.314	-	-
ARPI	Abiraterone	1		-		-	
	Enzalutamide	0.72 (0.43-1.18)	0.192	-	-	-	-
Prior treatment	ADT	1		-		-	
	ADT + docetaxel	1.23 (0.63-2.41)	0.544	-	-	-	-
Bone metastasis	No	1		-		-	
	Yes	1.46 (0.67-3.22)	0.342	-	-	-	-
Lymph node metastasis	No	1		-		-	
	Yes	1.23 (0.73-2.07)	0.444	-	-	-	-
Lung metastasis	No	1		-		-	
	Yes	1.59 (0.87-2.89)	0.132	-	-	-	-
Liver metastasis	No	1		1		-	
	Yes	2.23 (0.87-5.69)	0.094	1.74 (0.64-4.75)	0.227	-	-
Disease volume	Low	1		1		1	
	High	2.19 (1.21-3.97)	0.010	2.22 (1.12-4.38)	0.022	2.44 (1.31-4.55)	0.005

*: First step in cox regression analysis, **: Final step in cox regression analysis, ADT: Androgen deprivation treatment, ARPI: Androgen receptor pathway inhibitor, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, HGPIN: High grade prostatic intraepithelial neoplasia, HR: Hazard ratio, IDC-P: Intraductal carcinoma of prostate, mCRPC: Metastatic castration-resistant prostate cancer, mHSPC: Metastatic hormone-sensitive prostate cancer, PS: Performance status

docetaxel, the median rPFS was 33.08 months (95% CI 28.54-37.49) for patients without IDC-P and 21.49 months (95% CI 6.14-36.83) for patients with IDC-P (p=0.086). Multivariate Cox regression analysis for rPFS is presented in Table 4. The PSA50 response rate was assessed in 93 patients. The PSA50 response was 43% for the entire population. There was no difference in PSA50 response rate between groups (50% for patients with IDC-P and 41.3% for patients without IDC-P; p=0.599).

Discussion

IDC-P is acknowledged as an adverse prognostic factor in nonmetastatic prostate cancer (14,15,30,31). However, the impact of IDC-P on the prognosis of metastatic prostate cancer is limited. Our findings suggest that the presence of IDC-P on pathological examination is a poor prognostic factor for patients with metastatic prostate cancer who are treated with enzalutamide or abiraterone acetate. OS (35.38-55.59) and PSA-PFS (15.87-31.11 months) were significantly shorter in patients with IDC-P.

While conventional acinar adenocarcinoma constitutes the vast majority of prostate cancer cases (95%), approximately 5% exhibit unconventional histological subtypes (32). Considering the high global incidence of prostate cancer, the second most common malignancy in men, this minority still represents a clinically significant number of patients (33). New entities, including IDC-P, were introduced in the 2016 WHO classification (3). Cribriform growth pattern and IDC-P are now recommended to be routinely reported in prostate cancer pathology (34,35). Although the recognition of unconventional histologies in prostate cancer has markedly increased over the past decade, substantial inter-center variability in pathological reporting suggests a lack of standardization, and prostate biopsy procedures likely underestimate the true incidence of these unconventional histological subtypes (31,36).

A retrospective study that evaluated the prognostic impact of ductal features in patients with *de novo* metastatic prostate carcinoma who were treated only with ADT found no significant difference in outcomes between patients with ductal adenocarcinoma and those with pure acinar adenocarcinoma. However, the presence of IDC-P was identified as an independent adverse prognostic factor for both CRPC-free survival (HR 1.84, 95% CI 1.48-2.30) and OS (HR 1.56; 95% CI 1.05-2.31) (37). Several additional studies showed that IDC-P was associated with shorter castration-resistant prostate cancer-free survival and OS (26-28,38,39). In a retrospective study including patients with mCRPC, IDC-P positivity was associated with a poorer PSA response to docetaxel than to abiraterone acetate (21.7% vs. 52.4%). Median PSA-PFS was also significantly longer with abiraterone acetate in patients with IDC-P (13.5 vs. 6.0 months; p=0.012), whereas no such difference was seen in patients without IDC-P. Although not statistically significant, a trend toward longer OS with abiraterone acetate was observed in the IDC-P positive group (26). In another study of mCRPC patients treated with abiraterone acetate or enzalutamide, the presence of IDC-P was associated with a significantly shorter OS (57.9 vs. 38.0 months). Although PFS was numerically lower in patients with IDC-P (10.6 vs. 6.2 months), the difference did not reach statistical significance (28). These findings are largely consistent with our results, although the median PFS and OS in our study were longer, likely due to the inclusion of both mHSPC and mCRPC patients. Not only is the presence of IDC-P important for prognosis, but also its proportion and histological pattern may have prognostic significance (27). Enzalutamide use was associated with longer OS compared to abiraterone acetate. No head-to-head clinical trials have compared enzalutamide and abiraterone acetate. Although clinical trials of abiraterone acetate and enzalutamide differed in inclusion criteria and excluded patients with certain comorbidities, several meta-analyses and retrospective studies have shown enzalutamide to provide superior rPFS, PSA-PFS, and PSA response rates compared to abiraterone acetate (40-45). The superior efficacy of enzalutamide may relate to its distinct mechanism of action. Enzalutamide blocks downstream AR signaling, including nuclear translocation and transcription, and may thereby overcome resistance due to AR overactivity or mutation.

Study Limitations

This study has several limitations. First, as a retrospective analysis, it is subject to inherent biases, including selection bias, unmeasured confounding, and missing data, all of which may have influenced the outcomes. Second, the relatively small sample size, especially for patients with mHSPC, may have limited the power to detect a difference in rPFS. Nevertheless, the cohort remains one of the largest evaluating the prognostic impact of IDC-P in patients treated with ARPIs. In addition, combining mHSPC and mCRPC patients within a single survival model constitutes a methodological limitation, as differing baseline hazards between these disease settings may have influenced the observed outcomes. Although the study was conducted at a single institution, pathological evaluations were performed by different pathologists. Thus, inter-observer variability remains a potential source of heterogeneity. In addition, the patient population and prior treatments were heterogeneous, which may have further influenced the outcomes. Lastly, the relatively long inclusion period may have introduced variability in diagnostic awareness and reporting standards over time.

Conclusion

This study demonstrates that the presence of IDC-P is a poor prognostic factor for PSA-PFS and OS in patients with metastatic prostate cancer treated with abiraterone acetate or enzalutamide. Although there is growing evidence supporting the aggressive behavior of IDC-P, nearly all available data are retrospective. Therefore, prospective studies with larger cohorts are needed to establish the reliability and clinical applicability of these findings. Despite growing molecular insights into IDC-P, much of the data derive from retrospective histological analyses of prostate cancer cases. Comprehensive studies are required to better elucidate the behavior of these unconventional prostate cancer subtypes.

Ethics

Ethics Committee Approval: The study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ankara University Faculty of Medicine Ethics Committee (decision no: İ06-428-24, date: 13.06.2024).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: H.B., S.C.Y., E.Y., Y.Ü., Concept: H.B., Design: H.B., E.Y., Y.Ü., Data Collection or Processing: H.B., S.C.Y., Analysis or Interpretation: H.B., Literature Search: H.B., Writing: H.B., S.C.Y., E.Y., Y.Ü.

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