

Research Article

Prognostic Impact of Ductal Component in Metastatic Hormone-Sensitive Prostate Cancer Treated with ARPI-Based Therapy

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Abstract

Objectives: Histological heterogeneity in metastatic hormone-sensitive prostate cancer (mHSPC) may influence treatment outcomes beyond conventional clinical risk models. The prognostic significance of ductal component-containing tumors in patients treated with androgen receptor pathway inhibitors (ARPIs) remains insufficiently defined.

Methods: This retrospective single-center cohort study included patients with mHSPC treated with androgen deprivation therapy plus an ARPI between January 2016 and June 2025. Tumors were classified as pure acinar or ductal component-containing based on pathology reports. Radiographic progression-free survival (rPFS) was the primary endpoint, and overall survival (OS) was secondary. Survival analyses were performed using Kaplan–Meier and Cox regression models.

Results: A total of 104 patients were included, of whom 18 (17.3%) had ductal component-containing tumors. Median follow-up was 30.5 months. Median rPFS was not reached in the pure acinar group and was 26.7 months in the ductal component group. Ductal component was independently associated with shorter rPFS (hazard ratio [HR] 2.29, 95% CI 1.08–4.87; $p=0.031$) and OS (HR 6.36, 95% CI 2.15–18.78; $p=0.001$). Patients with ductal component-containing tumors also showed numerically less favorable PSA response patterns, including lower rates of deep PSA decline.

Conclusion: Ductal component-containing histology is associated with inferior survival in patients with mHSPC treated with ARPI-based therapy. These findings support the role of histological subtype as a clinically meaningful factor for risk stratification in the contemporary treatment era.

Keywords: ARPI, ductal component, metastatic hormone-sensitive prostate cancer, PSA kinetics, prognosis

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Prostate cancer remains one of the most commonly diagnosed malignancies and a leading cause of cancer-related mortality among men worldwide.^[1,2] In the metastatic hormone-sensitive setting (mHSPC), treatment paradigms have evolved substantially over the past decade with the incorporation of androgen receptor pathway inhibitors (ARPIs) and

combination strategies, leading to significant improvements in survival outcomes.^[3–6] Despite these advances, considerable heterogeneity in treatment response persists, underscoring the need for reliable prognostic and predictive factors.

Traditional risk stratification models in mHSPC, such as CHAARTED and LATITUDE, have focused primarily on clinical

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variables including metastatic burden and disease distribution^[5,7] While these frameworks provide valuable prognostic information, they do not fully capture underlying tumor biology. Increasing attention has therefore been directed toward pathological and molecular features that may refine prognostic stratification beyond conventional clinical parameters.^[8]

Among these, histological subtypes of prostate cancer have emerged as potentially important but underexplored determinants of disease behavior. While the vast majority of prostate cancers are acinar adenocarcinomas, variant histologies including ductal adenocarcinoma have been associated with more aggressive clinical features and poorer outcomes^[9,10] Ductal prostate cancer, although relatively uncommon, has been reported to present with higher stage at diagnosis, increased metastatic potential, and reduced survival compared with conventional acinar tumors^[11,12]

Importantly, ductal differentiation is not limited to pure ductal adenocarcinoma but may also be present as a component within otherwise acinar tumors. Emerging evidence suggests that even partial ductal differentiation may confer adverse biological behavior^[9–14] However, the clinical significance of mixed acinar–ductal histology remains incompletely defined, particularly in the context of contemporary systemic therapies.

In parallel, prostate-specific antigen (PSA) kinetics have been widely recognized as robust prognostic markers in advanced prostate cancer. Early PSA response, depth of PSA decline, and PSA nadir have all been associated with long-term outcomes across multiple treatment settings.^[15–22] Nevertheless, the interaction between tumor histology and PSA dynamics has not been well characterized, and it remains unclear whether variant histologies exhibit distinct PSA response patterns that may influence clinical outcomes.

Despite growing recognition of the prognostic relevance of both histological subtype and PSA kinetics, data integrating these factors in patients treated with modern ARPI-based regimens remain limited. In particular, the impact of ductal component–containing histology on treatment outcomes and its interplay with PSA response dynamics have not been adequately explored in real-world mHSPC populations.

Therefore, in this study, we aimed to evaluate the prognostic significance of ductal component–containing histology in patients with mHSPC treated with ARPI-based therapy. Additionally, we sought to investigate PSA response patterns across histological subtypes.

Methods

Study design and patient population

This retrospective single-center cohort study included patients diagnosed with metastatic hormone-sensitive pros-

tate cancer (mHSPC) between January 2016 and June 2025. Patients were treated at a tertiary academic oncology center and received androgen deprivation therapy (ADT) in combination with an ARPI, including abiraterone, enzalutamide, or apalutamide. Eligible patients had histologically confirmed prostate adenocarcinoma, radiologically documented metastatic disease, and available baseline clinical and follow-up data. Patients with neuroendocrine differentiation or non-adenocarcinoma histologies were excluded. Patients with insufficient baseline clinical or follow-up data were excluded during cohort selection. Missing data among included patients were minimal; no imputation was performed, and analyses were based on available complete cases.

Histopathological assessment

Histopathological data were obtained from original pathology reports. Tumors were categorized as pure acinar adenocarcinoma or tumors containing a ductal component, defined as the presence of any ductal differentiation regardless of proportion. Given the retrospective design and variability in pathology reporting practices, a binary classification (ductal component present vs. absent) was adopted. In exploratory analyses, tumors with ductal features were further subclassified into pure ductal and mixed acinar–ductal subtypes.

Clinical variables and risk stratification

Baseline clinical variables included age, Eastern Cooperative Oncology Group (ECOG) performance status, Gleason grade group, metastatic presentation (de novo vs. metachronous), sites of metastasis, and baseline PSA levels. Baseline PSA was defined as the serum PSA level measured immediately prior to initiation of first-line systemic therapy for metastatic disease (ADT plus an androgen receptor pathway inhibitor). Disease burden was classified according to the CHARTED criteria, where high-volume disease was defined as the presence of visceral metastases and/or ≥ 4 bone metastases with at least one beyond the vertebral bodies and pelvis.^[7] Risk stratification was additionally assessed using LATITUDE criteria, with high-risk disease defined by at least two of the following: Gleason score ≥ 8 , ≥ 3 bone metastases, or measurable visceral metastasis.^[5]

PSA kinetics

PSA kinetics were evaluated using routinely collected clinical data. Early PSA response was assessed by PSA90, defined as a $\geq 90\%$ decline from baseline PSA assessed 10–14 weeks after treatment initiation. PSA nadir was defined as the lowest PSA value achieved during follow-up, and time to PSA nadir (TTN) was calculated from treatment initiation to the date of nadir PSA. A deep PSA response was defined as a nadir PSA < 0.02 ng/mL. These PSA-based parameters

were selected based on prior studies demonstrating their prognostic relevance in metastatic hormone-sensitive prostate cancer.^[4]

Outcomes

The primary endpoint was rPFS, defined as the time from treatment initiation to radiographic progression or death from any cause. Radiographic progression was determined in accordance with the Prostate Cancer Working Group 3 (PCWG3) criteria, incorporating the appearance of new lesions or progression of existing disease on imaging, with confirmation of bone progression when required.^[23]

Overall survival (OS), defined as the time from treatment initiation to death from any cause, was evaluated as a secondary endpoint. Patients without events were censored at the date of last follow-up.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the two-sided Fisher's exact test because of the small cell counts in the ductal component group. Survival outcomes were estimated using the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards regression models were used to evaluate factors associated with rPFS and OS. Univariable analyses included clinically relevant variables such as age, ECOG performance status, metastatic burden, baseline PSA and the presence of ductal component. Variables were considered for multivariable analysis based on clinical relevance, univariable findings, model parsimony, and avoidance of conceptually overlapping covariates. CHAARTED disease volume and LATITUDE risk classification were not entered simultaneously because of conceptual overlap; CHAARTED disease volume was selected as the measure of metastatic burden. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. A two-sided $p < 0.05$ was considered statistically significant. No adjustment for multiple comparisons was applied to exploratory analyses; therefore, the corresponding p values should be interpreted as nominal and hypothesis-generating.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the İstanbul University–Cerrahpaşa Non-Interventional Clinical Trials Ethics Committee (no: 2025/302; date: 14.05.2025). Due to the retrospective design, the requirement for informed consent was waived.

Results

Patient characteristics

A total of 104 patients were included in the final analysis, of whom 86 (82.7%) had pure acinar adenocarcinoma and 18 (17.3%) had tumors containing a ductal component.

The median follow-up duration for the overall cohort was 30.5 months (IQR, 16.3–43.7).

Baseline clinicopathological characteristics are summarized in Table 1. Patients with ductal component-containing tumors showed numerically higher rates of adverse clinical features, including ECOG performance status ≥ 1 (66.7% vs. 44.2%), CHAARTED high-volume disease (77.8% vs. 60.5%), and Gleason score ≥ 8 (66.7% vs. 57.0%), although these differences were not statistically significant (all $p > 0.05$).

Baseline PSA was numerically higher in the ductal component group, but the difference was not statistically significant (114.5 vs. 74.0 ng/mL, $p = 0.38$). Detailed baseline characteristics across three histological subtypes are provided in Supplementary Table S1.

Radiographic progression-free survival

A total of 38 radiographic progression events occurred during follow-up, including 28 (32.6%) in the pure acinar group and 10 (55.6%) in the ductal component group.

Median rPFS was not reached in the pure acinar group, whereas it was 26.7 months in patients with ductal component-containing tumors. Kaplan–Meier curves for rPFS according to histology are shown in Figure 1.

In univariable Cox regression analysis, ductal component-containing histology was associated with inferior rPFS (HR 2.26, 95% CI 1.09–4.67; $p = 0.028$). This association remained independently significant in multivariable analysis (HR 2.29, 95% CI 1.08–4.87; $p = 0.031$) after adjustment for ECOG performance status, CHAARTED disease volume, and baseline PSA (Table 2).

Log-transformed baseline PSA was also independently associated with shorter rPFS (HR 1.20, 95% CI 1.02–1.41; $p = 0.026$). Forest plot visualization of univariable and multivariable Cox regression analyses for rPFS is presented in Figure 2.

Overall survival

A total of 22 deaths were recorded during follow-up, including 14 in the pure acinar group and 8 in the ductal component group. Median OS was not reached in the overall cohort or in the pure acinar group, whereas it was 33.1 months in patients with ductal component-containing tumors. Kaplan–Meier curves for OS according to histology are shown in Figure 3.

Table 1. Baseline clinicopathological characteristics according to histology

Variable	Total (n=104)	Pure acinar (n=86)	Ductal component (n=18)	p
Age, years (mean±SD)	70.1±8.5	69.8±8.3	71.5±9.1	0.41
Age ≥65 years, n (%)	78 (75.0)	63 (73.3)	15 (83.3)	0.55
ECOG performance status, n (%)				0.11
0	54 (51.9)	48 (55.8)	6 (33.3)	
≥1	50 (48.1)	38 (44.2)	12 (66.7)	
De novo metastatic disease, n (%)	79 (76.0)	64 (74.4)	15 (83.3)	0.55
Bone metastasis, n (%)	92 (88.5)	77 (89.5)	15 (83.3)	0.43
Visceral metastasis, n (%)	28 (26.9)	22 (25.6)	6 (33.3)	0.56
Prior local treatment, n (%)	34 (32.7)	30 (34.9)	4 (22.2)	0.41
Gleason score ≥8, n (%)	61 (58.7)	49 (57.0)	12 (66.7)	0.60
CHAARTED high-volume disease, n (%)	66 (63.5)	52 (60.5)	14 (77.8)	0.19
LATITUDE high-risk disease, n (%)	58 (55.8)	46 (53.5)	12 (66.7)	0.43
Treatment, n (%)				0.59
Abiraterone	36 (34.6)	31 (36.0)	5 (27.8)	
Enzalutamide/Apalutamide	68 (65.4)	55 (64.0)	13 (72.2)	
Baseline PSA, median (IQR)	83.5 (19.1–272)	74 (12–282)	114.5 (38–220)	0.38
Median follow-up, months (IQR)	30.5 (16.3–43.7)			

ECOG: Eastern Cooperative Oncology Group; PSA: prostate-specific antigen; IQR: interquartile range. Comparison of baseline characteristics between patients with pure acinar adenocarcinoma and those with ductal component-containing tumors. Categorical p values were calculated using the two-sided Fisher's exact test.

In univariable analysis, ductal component-containing histology was associated with inferior OS (HR 3.96, 95% CI 1.63–9.60; $p=0.002$). In multivariable analysis, this association remained

significant (HR 6.36, 95% CI 2.15–18.78; $p=0.001$) (Table 3). ECOG performance status ≥1 and CHAARTED high-volume disease were also independently associated with shorter OS.

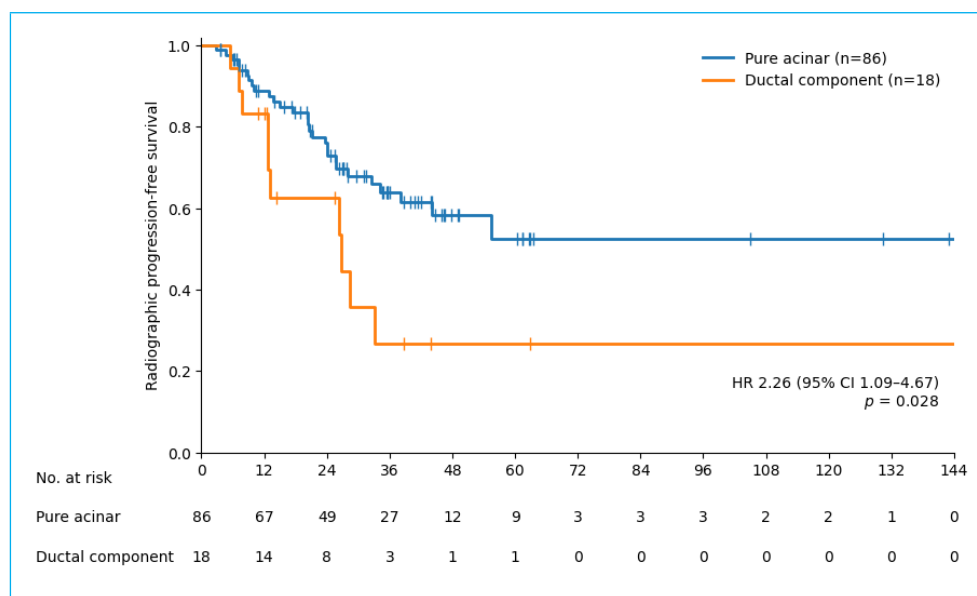


Figure 1. Kaplan–Meier curves for radiographic progression-free survival according to histology. HR: Hazard ratio; CI: Confidence interval. Kaplan–Meier estimates of rPFS comparing pure acinar adenocarcinoma versus ductal component-containing tumors. Estimates at later time points should be interpreted cautiously because of the small number of patients remaining at risk in the ductal component group. Hazard ratios were estimated using Cox proportional hazards models.

Table 2. Univariable and multivariable Cox regression analyses for radiographic progression-free survival

Variable	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Ductal component (yes vs. no)	2.26 (1.09–4.67)	0.028	2.29 (1.08–4.87)	0.031
ECOG performance status ≥ 1	1.73 (0.90–3.33)	0.102	1.85 (0.94–3.66)	0.076
De novo metastatic disease	2.44 (0.86–6.89)	0.093	—	—
Bone metastasis	1.41 (0.34–5.88)	0.640	—	—
Visceral metastasis	1.02 (0.45–2.33)	0.954	—	—
Prior local treatment	0.51 (0.18–1.45)	0.207	—	—
Gleason score ≥ 8	1.32 (0.63–2.80)	0.464	—	—
CHAARTED high-volume disease	3.35 (1.40–8.01)	0.007	2.34 (0.91–6.02)	0.077
LATITUDE high-risk disease	2.05 (0.97–4.34)	0.059	—	—
Treatment (abiraterone vs. enzalutamide/apalutamide)	0.88 (0.46–1.67)	0.688	—	—
Log-transformed baseline PSA	1.29 (1.12–1.49)	<0.001	1.20 (1.02–1.41)	0.026

HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; PSA: Prostate-specific antigen. Multivariable model included ductal component (yes vs. no), ECOG performance status ≥ 1 , CHAARTED high-volume disease, and log-transformed baseline PSA. Baseline PSA was log-transformed due to its skewed distribution.

PSA response and kinetics

Numerical differences in PSA response patterns were observed between histological subtypes. Patients with ductal component-containing tumors had lower rates of PSA90 response (50.0% vs. 65.1%, $p=0.21$) and deep PSA response (22.2% vs. 39.5%, $p=0.18$). Time to PSA nadir was numerically longer in the ductal component group (median 6.8 vs. 5.6 months, $p=0.27$). These differ-

ences were not statistically significant (Supplementary Table S2).

Subgroup analyses

Subgroup analyses demonstrated a consistent direction of effect across all evaluated subgroups. The adverse impact of ductal component appeared more pronounced in patients with ECOG 0 (HR 4.77, $p=0.004$), high-volume disease

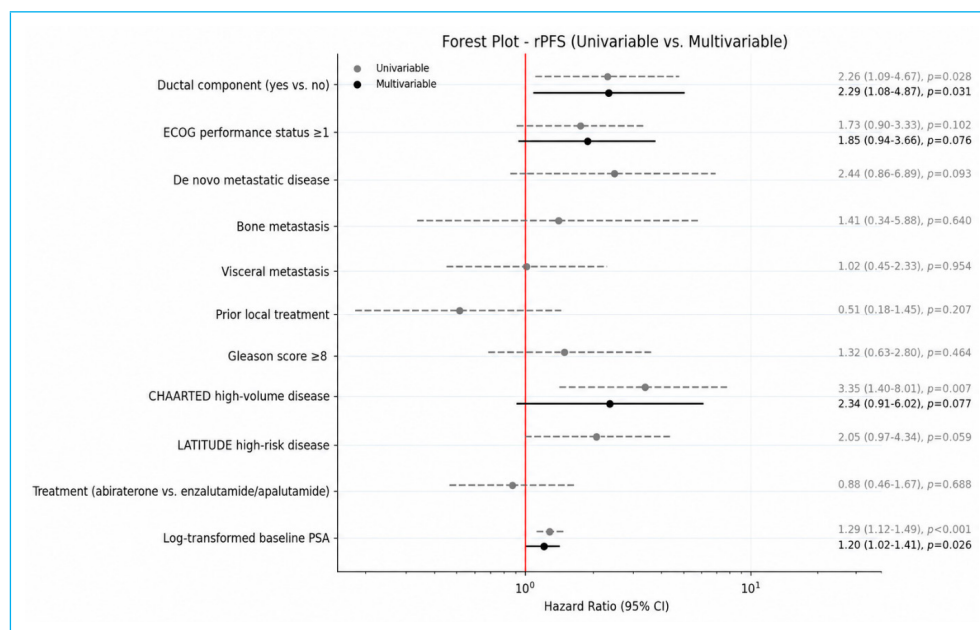


Figure 2. Forest plot of univariable and multivariable Cox regression analyses for radiographic progression-free survival.

HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; PSA: Prostate-specific antigen. Forest plots showing hazard ratios from univariable and multivariable Cox regression analyses for rPFS. Dashed lines represent univariable analyses; solid lines represent multivariable analyses.

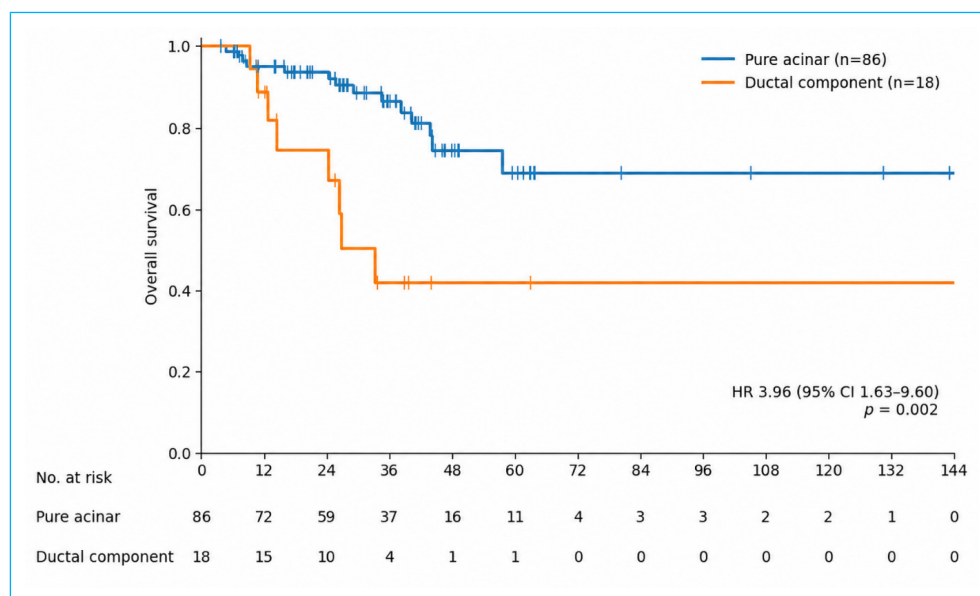


Figure 3. Kaplan–Meier curves for overall survival according to histology.

HR: Hazard ratio; CI: Confidence interval. Kaplan–Meier estimates of OS comparing pure acinar adenocarcinoma versus ductal component-containing tumors. Estimates at later time points should be interpreted cautiously because of the small number of patients remaining at risk in the ductal component group. Hazard ratios were estimated using Cox proportional hazards models.

(HR 2.28, $p=0.039$), and lower baseline PSA levels (HR 4.43, $p=0.018$), while no statistically significant association was observed in other subgroups (Supplementary Table S3 and Supplementary Figure S1).

Exploratory analysis by histological subtype

Exploratory analyses across three histological subtypes

demonstrated a gradient in outcomes. Event rates were 32.6% in pure acinar tumors, 62.5% in mixed acinar–ductal tumors, and 50.0% in pure ductal tumors. Corresponding 24-month rPFS rates were 72%, 60%, and 64%, respectively. Detailed survival outcomes across histological subtypes are presented in Supplementary Table S4 and Supplementary Figure S2.

Table 3. Univariable and multivariable Cox regression analyses for overall survival

Variable	Univariable HR (95% CI)	<i>p</i>	Multivariable HR (95% CI)	<i>p</i>
Ductal component (yes vs. no)	3.96 (1.63–9.60)	0.002	6.36 (2.15–18.78)	0.001
Age ≥ 65 years	2.78 (0.82–9.39)	0.100	—	—
ECOG performance status ≥ 1	2.30 (0.94–5.67)	0.070	3.87 (1.31–11.47)	0.014
De novo metastatic disease	6.07 (0.81–45.31)	0.079	—	—
Bone metastasis	1.52 (0.20–11.31)	0.685	—	—
Visceral metastasis	1.88 (0.73–4.81)	0.188	—	—
Prior local treatment	0.21 (0.03–1.59)	0.131	—	—
Gleason score ≥ 8	1.56 (0.57–4.26)	0.387	—	—
CHAARTED high-volume disease	12.37 (1.66–92.02)	0.014	10.95 (1.35–88.62)	0.025
LATITUDE high-risk disease	2.81 (0.95–8.31)	0.062	—	—
Treatment (abiraterone vs. enzalutamide/apalutamide)	1.01 (0.43–2.38)	0.977	—	—
Log-transformed baseline PSA	1.33 (1.11–1.59)	0.002	1.22 (0.98–1.50)	0.069

HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; PSA: Prostate-specific antigen. Multivariable model included ductal component (yes vs. no), ECOG performance status ≥ 1 , CHAARTED high-volume disease, and log-transformed baseline PSA. Baseline PSA was log-transformed due to its skewed distribution.

Discussion

In this single-center real-world cohort of patients with metastatic hormone-sensitive prostate cancer treated with ADT plus ARPI, the presence of a ductal component was independently associated with significantly shorter rPFS and OS. These findings indicate that histological subtype reflects clinically relevant biological heterogeneity that is not fully captured by conventional clinical risk models such as CHAARTED or LATITUDE.^[5–7]

Ductal adenocarcinoma of the prostate has long been recognized as a more aggressive histologic variant, frequently associated with advanced stage at diagnosis, higher metastatic potential, and inferior survival outcomes compared with conventional acinar adenocarcinoma.^[9–11] Previous studies have also suggested that even partial ductal differentiation may confer adverse biological behavior, supporting the concept that mixed histologies should not be considered clinically equivalent to pure acinar tumors.^[13,14]

However, the prognostic significance of ductal features in the contemporary ARPI era remains uncertain. While some studies have reported comparable outcomes between ductal and acinar tumors in selected treatment settings^[24], our findings demonstrate a clear and independent adverse association of ductal component with both rPFS and OS. This discrepancy may be explained by differences in cohort composition, real-world treatment heterogeneity, and the inclusion of mixed histologies, which likely represent a biologically distinct subgroup.

In addition to survival outcomes, patients with ductal component-containing tumors in our study showed numerically less favorable PSA kinetics, including lower rates of deep PSA response. PSA dynamics have consistently been shown to be strong prognostic markers in mHSPC.^[15,16,25] Notably, baseline PSA levels were not significantly different between groups, supporting the notion that disease burden alone is insufficient to explain the observed outcome differences.

This study has several limitations. Its retrospective single-center design may introduce selection bias and limit generalizability. The relatively small number of patients with ductal component reduces statistical power, particularly for subgroup analyses. In addition, only 22 deaths occurred, resulting in a relatively low events-per-variable ratio in the multivariable OS model. Therefore, model overfitting and instability of the adjusted OS estimates cannot be excluded, and these findings should be interpreted cautiously. The exploratory analyses also involved multiple comparisons without adjustment for multiplicity; accordingly, the corresponding findings should be interpreted cautiously and regarded as hypothesis-generating. Histopathological classification was based on original pathology reports

without central or secondary pathology review, which may have introduced interobserver variability in the recognition of ductal differentiation, particularly when present as a minor component. The extent of ductal differentiation could also not be consistently quantified. Finally, the lack of molecular data precludes further insight into the biological mechanisms underlying these findings.

Conclusion

In conclusion, the presence of a ductal component was independently associated with inferior rPFS and OS in patients with metastatic hormone-sensitive prostate cancer treated with ARPI-based therapy. These findings suggest that histological subtype may provide additional prognostic information beyond conventional clinical risk models. Further prospective studies are warranted to validate these observations.

Disclosures

Ethics Committee Approval: The study was approved by the İstanbul University–Cerrahpaşa Non-Interventional Clinical Trials Ethics Committee (no: 2025/302; date: 14.05.2025).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived by the institutional ethics committee.

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Authorship Contributions: Concept – VA, ÖA; Design – VA, ZB; Supervision – ÖA, NSD; Materials – VA, SC, MG; Data Collection or Processing: VA, ZB, SC; Analysis or Interpretation: VA, NSD; Literature Search: VA, ZB; Writing: VA; Critical Review: NSD, ÖA.

Peer-review: Externally peer-reviewed.

Abbreviations

ECOG	Eastern Cooperative Oncology Group
PSA	Prostate-specific antigen
PSA90	≥90% decline in PSA from baseline
TTN	Time to PSA nadir
SD	Standard deviation
IQR	Interquartile range
rPFS	Radiographic progression-free survival
OS	Overall survival
HR	Hazard ratio
CI	Confidence interval
NR	Not reached

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This supplementary file provides additional analyses supporting the main findings, including detailed baseline characteristics, subgroup analyses, and PSA kinetics.

Supplementary Table S1. Baseline characteristics according to detailed histological subtype

Variable	Pure acinar (n=86)	Mixed acinar–ductal (n=8)	Pure ductal (n=10)
Age, years, mean±SD	69.8±8.3	69.1±7.9	73.4±9.9
Age ≥65 years, n (%)	63 (73.3%)	6 (75.0%)	9 (90.0%)
ECOG ≥1, n (%)	38 (44.2%)	4 (50.0%)	8 (80.0%)
De novo metastatic disease, n (%)	64 (74.4%)	7 (87.5%)	8 (80.0%)
CHAARTED high-volume disease, n (%)	52 (60.5%)	5 (62.5%)	9 (90.0%)
Visceral metastasis, n (%)	22 (25.6%)	2 (25.0%)	4 (40.0%)
Gleason score ≥8, n (%)	49 (57.0%)	6 (75.0%)	6 (60.0%)
Baseline PSA, median (IQR), ng/mL	74.0 (12–282)	100.0 (41.8–135.0)	180.5 (33.4–293)

Baseline characteristics across three histological subtypes

Supplementary Table S2. PSA response and kinetics according to histology

Variable	Pure acinar (n=86)	Ductal component (n=18)	p
PSA90 achieved, n (%)	56 (65.1)	9 (50.0)	0.21
PSA nadir <0.02 ng/mL, n (%)	34 (39.5)	4 (22.2)	0.18
Time to PSA nadir, months (median, IQR)	5.6 (3.2–8.9)	6.8 (4.1–10.5)	0.27

Comparison of PSA90 response, PSA nadir, and time to PSA nadir between pure acinar and ductal component–containing tumors. PSA90 was defined as a ≥90% decline from baseline PSA assessed 10–14 weeks after treatment initiation.

Supplementary Table S3. Subgroup analyses for rPFS

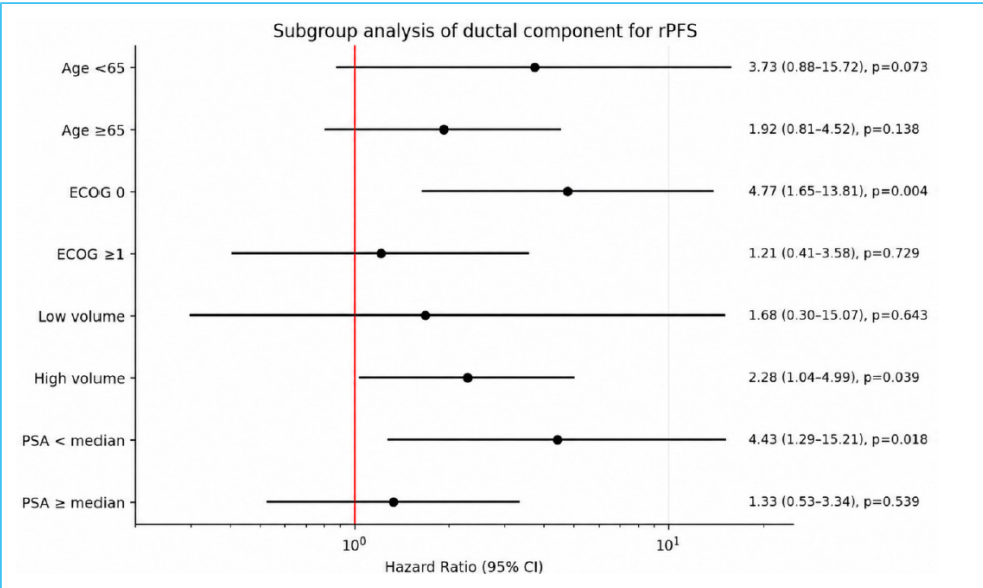
Subgroup	HR (95% CI)	p
Age <65	3.73 (0.88–15.72)	0.073
Age ≥65	1.92 (0.81–4.52)	0.138
ECOG 0	4.77 (1.65–13.81)	0.004
ECOG ≥1	1.21 (0.41–3.58)	0.729
Low volume	1.68 (0.19–15.07)	0.643
High volume	2.28 (1.04–4.99)	0.039
PSA < median	4.43 (1.29–15.21)	0.018
PSA ≥ median	1.33 (0.53–3.34)	0.539

Subgroup analyses evaluating the impact of ductal component on rPFS. Hazard ratios represent ductal component versus pure acinar within each subgroup.

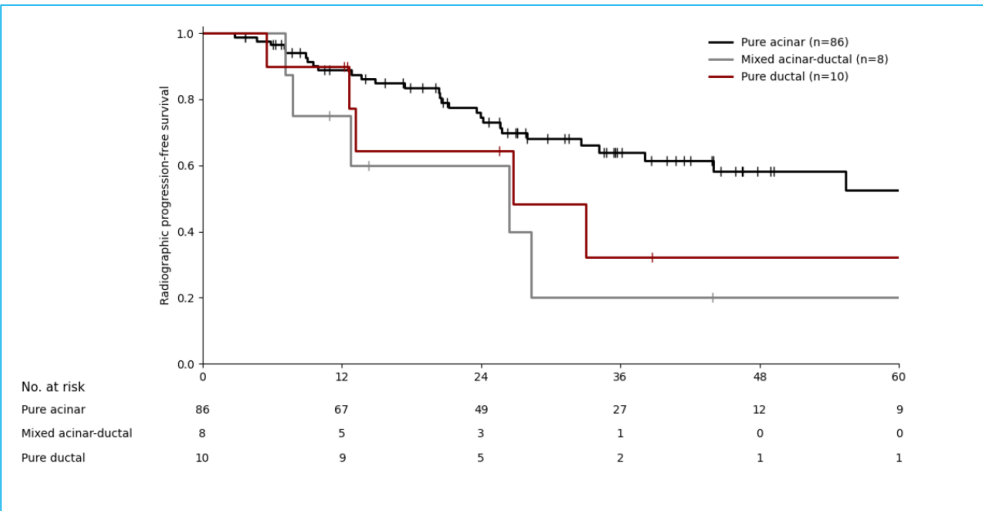
Supplementary Table S4. Radiographic progression-free survival according to detailed histological subtype

Variable	Pure acinar (n=86)	Mixed acinar–ductal (n=8)	Pure ductal (n=10)
Events, n (%)	28 (32.6%)	5 (62.5%)	5 (50.0%)
Median rPFS, months (95% CI)	Not reached	26.8 (12.0–NR)	32.1 (14.5–NR)
12-month rPFS, %	88%	75%	77%
24-month rPFS, %	72%	60%	64%

Survival outcomes according to histological subtype.



Supplementary Figure S1. Subgroup analysis forest plot for rPFS.
Forest plot showing subgroup analyses of the impact of ductal component on rPFS.



Supplementary Figure S2. Kaplan–Meier curves for rPFS across three histological subtypes.
Kaplan–Meier estimates of rPFS according to detailed histological subtype.