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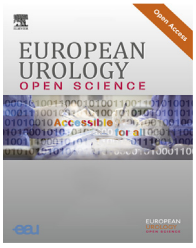

European Association of Urology

Prostate Cancer

Comparison of Survival Outcomes and Risk Factors Between Ductal Carcinoma of the Prostate and Acinar Adenocarcinoma of the Prostate: A Population-based Propensity Score–matching Study

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Abstract

Background: Ductal carcinoma of the prostate (DCP) is a rare type of prostate cancer (PCa) with a higher degree of infiltration and worse prognosis than acinar adenocarcinoma of the prostate (ACP). Previous reports comparing DCP and ACP have not been very reliable and involved small sample sizes.
Objective: To assess differences in mortality between ACP and DCP in a large-scale study.
Design, setting, and participants: Data were downloaded from the Surveillance, Epidemiology, and End Results database in June 2022. Data for 823 939 patients diagnosed with PCa from 2004 to 2019 were examined, excluding cases with survival data missing or pathological types other than DCP and ACP.
Outcome measurements and statistical analysis: Prognostic and risk factors for DCP were analyzed by generating a propensity score–matched cohort of DCP and ACP cases (1:5). Adjusted Cox models were constructed to determine hazard ratios (HRs) with 95% confidence intervals (CIs) for cancer-specific mortality (CSM) and overall mortality (OM)
Results and limitations: A total of 822 607 cases (99.8%) has ACP and 1332 (0.2%) had DCP. In comparison to ACP, age at diagnosis was significantly lower for DCP ($\leq$66 yr: 38.0% vs 50.7%; $p < 0.001$) and a higher proportion of DCP patients distant metastases (13.7% vs 5.1%; $p < 0.001$). In comparison to the ACP group, significantly higher proportions of the DCP group underwent surgery (66.1% vs 38.1%; $p < 0.001$),

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radiotherapy (13.7% vs 3.1%; $p < 0.001$), or systemic therapy (18.2% vs 3.3%; $p < 0.001$). However, the median overall survival time was significantly shorter for DCP patients (44.0 vs 73.0 mo; $p < 0.001$). DCP patients also had higher risk of CSM (HR 2.07, 95% CI 1.68–2.56; $p < 0.001$) and OM (HR 2.73 95% CI 2.42–3.08; $p < 0.001$) after propensity score matching to adjust for the influence of baseline variables. Subgroup analysis showed that DCP patients who had surgical treatment had better CSM than those without surgery, while DCP patients with regional and lower stage had better OM than those with distant stage (both $p < 0.05$ for interaction).

Conclusions: The risk of CSM and OM is significantly higher for DCP than for ACP. Earlier detection (lower stage) and surgical treatment are beneficial factors for DCP prognosis.

Patient summary: We studied survival rates for two different types of prostate cancer. We found that survival is worse for the rarer ductal carcinoma of the prostate (DCP) than for the more common acinar adenocarcinoma of the prostate. Both early diagnosis when the cancer is at a lower stage and surgical treatment are beneficial for survival in patients with DCP.

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1. Introduction

Acinar adenocarcinoma of the prostate (ACP) accounts for more than 90% of primary prostate cancer (PCa) cases, and the second most common histological PCa subtype is ductal adenocarcinoma (DCP) [1]. DCP is characterized by tall columnar cells arranged in a cribriform, papillary, solid pattern similar to prostatic intraepithelial neoplasia; microscopically, pure DCP is designated as Gleason pattern 4 [2]. However, pure DCP is extremely rare [3]. DCP is not easily distinguished from intraductal carcinoma (IDCP) or ACP. In fact, many cases diagnosed as IDCP or ACP may be DCP or ACP with a ductal component [4]. Our current understanding of DCP is increasing but is still not completely clear. A study found that patients diagnosed with IDCP had cribriform or papillary ductal morphology on biopsy specimens, but this was not associated with invasive high-grade cancer [5]. DCP cases typically have lower mean serum prostate-specific antigen (PSA) in comparison to ACP [6]. However, PSA is not considered an accurate predictor of clinical stage for DCP, as local treatment failure or metastasis frequently occurs at extremely low PSA values that do not meet the criterion for biochemical recurrence [1]. These types of failure may also be asymptomatic, leading to delays in diagnosis and subsequent treatment [2]. DCP is currently considered to be more aggressive than ACP, and is associated with a higher likelihood of extraprostatic spread and positive surgical margins, and a shorter time to recurrence or metastasis after radical prostatectomy or radical radiotherapy [2,4,7]. DCP is also more likely to metastasize more often to uncommon sites including the lungs, brain, and testes in comparison to ACP [8–10]. Thus, the 10-yr survival rate for DCP is lower than for typical ACP [2,9]. However, given the low incidence of DCP and the small sample sizes in previous studies, the risk of cancer-specific mortality (CSM) and overall mortality (OM) for patients with DCP compared to ACP, as well as factors influencing prognosis, are worth further exploration. Therefore, we used data from the Surveillance, Epidemiology and End Results (SEER) database to investigate this question to gain a deeper understanding of DCP.

2. Patients and methods

We obtained a license from SEER to download PCa data for this study in June 2022. The PCa types included in the study were ACP and DCP. Cases with invalid survival data and those with other pathological PCa types were excluded. The year of PCa diagnosis ranged from 2004 to 2019.

For convenience of analysis, baseline variables were divided into relevant categories. Age was categorized according to the median as ≤66 yr and >66 yr. Marital status (married, single, and unknown) and race (White, Black, and others) were divided into three groups. Annual household income (<$65 000, ≥$65 000, and unknown) and year of diagnosis (2004–2011 and 2012–2019) were categorized according to the median. Residential location was divided into three groups according to home location 1 (large city), location 2 (small city), and missing data. To facilitate data analysis, we used the "Combined summary stage (2004+)" record in the SEER database for disease stage, which was divided into three categories: disease stages up to regional (including in situ, localized, and regional); distant disease; and unknown or unstaged. According to radiotherapy and cancer-directed surgery received, treatment was divided into two categories: those who received radiotherapy or surgery (yes) and those who did not (no). Systemic therapy, including chemotherapy, traditional hormone therapy, and novel hormone therapy, was categorized as yes, no, and unknown. We used "SEER cause-specific death classification" and "Vital status recode" in the database to calculate CSM and OM, respectively.

Data analysis was performed using SPSS version 26.0 (IBM, Armonk, NY, USA). Nonparametric independent-sample Mann-Whitney *U* tests were used to compare categorical data between the two groups. The Kaplan-Meier method was used to analyze the differential effect of pathological type on OM and CSM as a single factor. To further reduce the influence of baseline variables on prognosis, a 1:5 propensity score (PS) matching algorithm implemented in MatchIt version 4.4.0 (MatchIt, Sao Paulo, Brazil) was applied to sample a matched ACP subset for comparison with DCP in Cox models using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). We selected patients with a survival time of at least 6 mo for PS matching. All covariates were balanced using the "nearest" neighbor matching without replacement and the generalized linear model for estimating the PS. After PS matching, we

constructed two adjusted models: adjusted model 1 (adjusted for age, year of diagnosis, race, and stage only) and adjusted model 2 (adjusted for age, year of diagnosis, race, stage, radiotherapy, surgery, and systemic therapy). The adjusted and unadjusted models were used to calculate hazard ratio (HR) values and 95% confidence intervals (CIs) before and after PS matching using multivariate Cox regression. Forest plots were generated using R statistical software (R Foundation for Statistical Computing) to compare intrafactor differences to calculate p values for interaction. A difference was considered to be statistically significant at $p < 0.05$.

3. Results

3.1. Baseline variables for DCP versus ACP

We collected data for 834 861 PCa patients from the SEER database. After screening against the inclusion and exclusion criteria, 823 939 patients were retained for the study, including 822 607 with ACP (99.8%) and 1332 with DCP (0.2%; Fig. 1). The patients excluded consisted of 13 cases with no pathological information, 1360 cases with invalid survival data, 76 cases of squamous cell carcinoma variants of PCa, 109 cases of transitional cell carcinoma of the prostate, and 9364 cases of other epithelial tumors of the prostate.

There were significant differences in baseline factors between the two groups before matching. Notably, in comparison to ACP, more DCP patients were diagnosed at a younger age (≤66 yr: 38.0% vs 50.7%; $p < 0.001$), but a greater proportion of DCP cases had distant metastases (13.7% vs 5.1%; $p < 0.001$). Greater proportions of DCP than ACP patients underwent surgery (66.1% vs 38.1%; $p < 0.001$), radiotherapy (13.7% vs 3.1%; $p < 0.001$), and systemic therapy (18.2% vs 3.3%; $p < 0.001$; Table 1).

3.2. Mortality outcomes for DCP versus ACP

The survival time in the overall cohort ranged from 0 to 191 mo. The median survival time was much shorter for DCP than for ACP (44.0 vs 73.0 mo; $p < 0.001$). In terms of mortality, the DCP group had higher CSM (18.2% vs 7.0%; $p < 0.001$) and OM (34.4% vs 24.2%; $p < 0.001$) rates than the ACP group (Table 1). Kaplan-Meier estimation of survival and log-rank tests also indicated that the DCP group had significantly worse prognosis than the ACP group in terms of both CSM ($p < 0.001$) and OM ($p < 0.001$; Supplementary Fig. 1).

3.3. Comparisons after PS matching

PS matching was applied to adjust for the influence of age, year of diagnosis, race, marital status, income, residential location, stage, radiotherapy, surgery, and systemic therapy. We used a DCP:ACP ratio of 1:5 for case matching (Table 2). After PS matching, there were no significant differences in these variables between the groups (all $p > 0.05$). The differences in CSM and OM rates remained similar for the groups after PS matching. The DCP group had significantly higher CSM ($p < 0.001$) and OM ($p = 0.03$) rates than the matched ACP group (Fig. 2). Multivariable Cox proportional-hazard

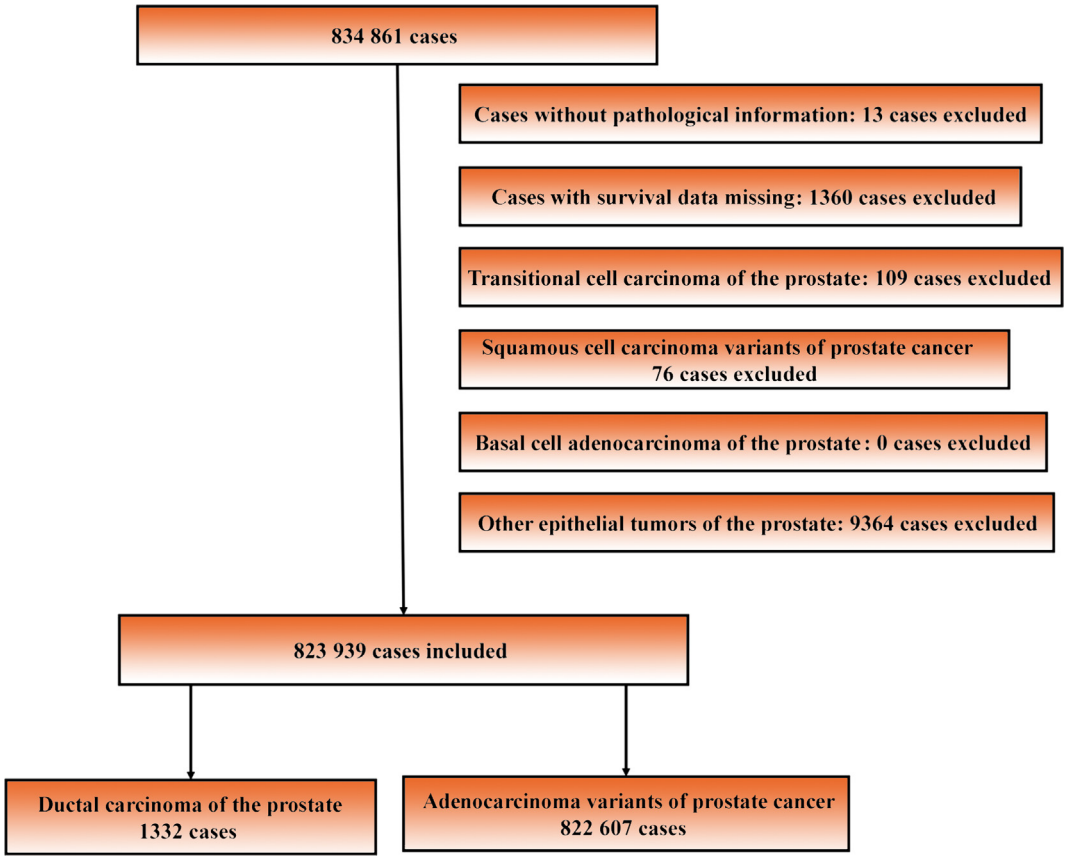

Fig. 1 – Study flowchart.

Table 1 – Comparison of baseline characteristics between the two study groups

	DCP (n = 1332)	ACP (n = 822 607)	Z value	p value
Age category, n (%)			−9.25	<0.001
≤66 yr	506 (38.0)	416 766 (50.7)		
>66 yr	826 (62.0)	405 793(49.3)		
Year of diagnosis, n (%)			−9.09	<0.001
2004–2011	525 (39.4)	426 773 (51.9)		
2012–2019	807 (60.6)	395 834 (48.1)		
Race, n (%)			−0.89	0.37
White	1,050 (78.8)	636 538 (77.4)		
Black	153 (11.5)	117 099 (14.2)		
Other/unknown	129 (9.7)	68 970 (8.4)		
Marital status, n (%)			−5.28	<0.001
Married	923 (69.3)	523 314 (63.6)		
Single	293 (22.0)	175 219 (21.3)		
Unknown	116 (8.7)	124 074 (15.1)		
Income, n (%)			−0.01	0.99
<$65 000	581 (43.6)	358 797 (43.6)		
≥$65 000	751 (56.4)	463 556 (56.4)		
Unknown	0	254 (0.0)		
Residential location, n (%)			−1.02	0.31
Large city	765 (57.4)	483 850 (58.8)		
Small city	567 (42.6)	338 503 (41.2)		
Unknown	0	254 (0.0)		
Stage, n (%)			−7.84	<0.001
In situ, localized, or regional disease	1,114 (83.6)	743 964 (90.4)		
Distant disease	182 (13.7)	41 812 (5.1)		
Unknown/unstaged	36 (2.7)	36 831 (4.5)		
Radiotherapy, n (%)			−22.39	<0.001
Yes	183 (13.7)	25 404 (3.1)		
No	1,149 (86.3)	797 203 (96.9)		
Surgery, n (%)			−20.67	<0.001
Yes	881 (66.1)	313 270 (38.1)		
No	433 (32.5)	489 296 (59.5)		
Unknown/others	18 (1.4)	20 041 (2.4)		
Systemic therapy, n (%)			−15.53	<0.001
Yes	242 (18.2)	27 106 (3.3)		
No	946 (71.0)	675 257 (82.1)		
Unknown	144 (10.8)	120 244 (14.6)		
Cancer-specific mortality, n (%)			−15.84	<0.00
Dead (attributable to this cancer diagnosis)	242 (18.2)	57 941 (7.0)		
Alive or died of other cause	1,082 (81.2)	759 832 (92.4)		
Missing/unknown	8 (0.6)	4 834 (0.6)		
Overall mortality, n (%)			−8.63	<0.001
Dead	458 (34.4)	199 397 (24.2)		
Alive	874 (65.6)	623 210 (75.8)		
Median survival, mo (interquartile range)	44.0 (21.0–87.0)	73.0 (30.0–121.0)		

ACP = acinar adenocarcinoma of the prostate; DCP = ductal carcinoma of the prostate.

modeling was performed to analyze the risk of CSM and OM for DCP versus ACP (Table 3). The HR before matching was 3.34 (95% CI 2.95–3.79; $p < 0.001$) for CSM and 1.98 (95% CI 1.81–2.17) for OM. After PS matching, we constructed two adjusted models: adjusted model 1 was adjusted for age, year of diagnosis, race, and stage; and adjusted model 2 was adjusted for age, year of diagnosis, race, stage, radiotherapy, surgery, and systemic therapy. DCP patients had much higher risk of CSM than ACP patients according to in adjusted model 1 (HR 2.12, 95%CI 1.72–2.62; $p < 0.001$) and adjusted model 2 (HR 2.07, 95% CI 1.68–2.56; $p < 0.001$). Similarly, DCP patients had a higher risk of OM according to adjusted model 1 (HR 2.98, 95% CI 2.64–3.35; $p < 0.001$) and adjusted model 2 (HR 2.729, 95% CI 2.42–3.08; $p < 0.001$).

3.4. *Subgroup comparisons for DCP*

We performed subgroup analysis for age, year of diagnosis, race, marital status, income, residential location, stage, surgery, radiotherapy, and systemic therapy for the DCP cohort and found no significant differences, except for surgery for CSM and stage for OM. These results indicate that regardless of variable category, DCP was associated with worse CSM and OM outcomes (p for interaction >0.05; Fig. 3). However, surgery had a significant effect on CSM (p for interaction 0.018), indicating that surgical treatment was a protective factor against CSM in DCP. DCP patients who underwent surgery had better CSM than those without surgery. Furthermore, stage had a significant effect on OM (p for interaction 0.024), suggesting that regional and lower stages had a significant protective effect on OM in DCP. DCP patients with regional and lower stage had better OM than those with distant disease.

4. Discussion

Our study revealed that the proportion of patients with DCP was very low, accounting for only 0.2% of the study cases. In comparison to the ACP group, a greater proportion of DCP patients were diagnosed at a younger age, but a higher

Table 2 – Comparison of baseline variables for the two groups after 1:5 DCP:ACP propensity score matching

	DCP (n = 1223)	ACP (n = 6104)	p value
Age, n (%)			0.77
≤66 yr	476 (38.9)	2349 (38.5)	
>66 yr	747 (61.1)	3755 (61.5)	
Year of diagnosis, n (%)			0.75
2004–2011	514 (42.0)	2535 (41.5)	
2012–2019	709 (58.0)	3569 (58.5)	
Race, n (%)			0.66
White	964 (78.8)	4842 (79.3)	
Black	147 (12.0)	732 (12.0)	
Other/unknown	112 (9.2)	530 (8.7)	
Marital status, n (%)			0.82
Married	854 (69.8)	4292 (70.3)	
Single	263 (21.5)	1261 (20.7)	
Unknown	106 (8.7)	551 (9.0)	
Income, n (%)			0.81
<$65 000	543 (44.4)	2733 (44.8)	
≥$65 000	680 (55.6)	3371 (55.2)	
Unknown	0	0	
Residential location, n (%)			0.96
Large city	700 (57.2)	3489 (57.2)	
Small city	523 (42.8)	2615 (42.8)	
Unknown	0	0	
Stage, n (%)			0.12
In situ, localized, or regional disease	1037 (84.8)	5289 (86.6)	
Distant disease	157 (12.8)	615 (10.1)	
Unknown/unstaged	29 (2.4)	200 (3.3)	
Radiotherapy, n (%)			0.79
Yes	165 (13.5)	806 (13.2)	
No	1058 (86.5)	5298 (86.8)	
Surgery, n (%)			0.85
Yes	808 (66.1)	4010 (65.7)	
No	398 (32.5)	2023 (33.1)	
Unknown/other	17 (1.4)	71 (1.2)	
Systemic therapy, n (%)			0.84
Yes	217 (17.7)	1015 (16.6)	
No	866 (70.8)	4442 (72.8)	
Unknown	140 (11.4)	647 (10.6)	
Cancer-specific mortality, n (%)			<0.001
Dead (attributable to this cancer diagnosis)	224 (18.3)	252 (4.1)	
Alive or died of other cause	992 (81.1)	5166 (84.6)	
Missing/unknown	7 (0.6)	686 (11.2)	
Overall mortality, n (%)			<0.001
Dead	420 (34.3)	1357 (22.2)	
Alive	803 (65.7)	4747 (77.8)	

ACP = acinar adenocarcinoma of the prostate; DCP = ductal carcinoma of the prostate.

proportion them had distant metastases (13.7% vs 5.1%). Even though a greater proportion of DCP patients underwent surgery, radiotherapy, or systemic therapy, they had higher risk of CSM (18.3% vs 4.1%) and OM (34.3% vs 22.2%). After PS matching and model adjustment, we found that CSM and OM were 1.07 and 1.73 times more likely in the DCP group than in the ACP group, respectively. Further analysis showed that age, year of diagnosis, race, marital status, income, residential location, radiotherapy, and systemic therapy had no influence on CSM or OM in DCP when compared to ACP, while surgery was a protective factor against CSM, and lower stage (in situ, localized, or regional disease) had a protective effect on OM in the DCP group.

DCP is an extremely rare PCa. As early as 2011, Meeks et al. [9] analyzed SEER data for 693 DCP patients. They found that DCP accounted for approximately 0.1% of all PCa cases and that its incidence had increased every decade, but the percentage relative to ACP had remained stable. Another study found that pure DCP was extremely rare, while ACP with ductal carcinoma components was more common [3]. However, we found that DCP accounted for 0.2% of all our PCa cases.

DCP patients are typically younger than ACP patients. In the study by Meeks et al. [10], the median patient age was 71 yr overall and 68 yr for the DCP group. A separate small study found concordant results: patients with biopsy-confirmed DCP (n = 58) had a younger mean age of 69 yr [4]. In our study, with the largest sample to date, DCP patients were younger than those with ACP.

DCP patients have high rates of metastasis and poor outcomes. According to Meeks et al. [9], men with DCP (n = 693) were more likely to have advanced disease and had higher mortality (DCP 12% vs 4% ACP), similar to outcomes for ACP patients with Gleason 4 + 4 disease. A study by Brinker et al. [4] including 10% patients (n = 58) with metastatic DCP found a higher risk of progression after treatment. The actuarial risk of progression was 34% (patients with radical prostatectomy) and 42% (all patients) 2 yr after treatment, and the mean time to progression was shorter for DCP than for ACP. Similar results were observed in a study with a larger sample (n = 164): 37.7% of the DCP group had metastatic disease, including 112 new metastases and 52 post-treatment metastases. Metastasis occurred at median follow-up of 22 mo among patients receiving curative therapy (n = 45); notably, the proportion of lung metastases was higher in the post-treatment than the de novo metastatic DCP group [11]. Further analysis showed that in comparison to DCP alone, advanced locoregional staging, higher tumor grade, and positive surgical margin status were more predictive of worse biochemical recurrence-free survival outcomes for men with DCP components after radical prostatectomy [12]. The percentage ductal composition was an important predictor of PSA recurrence in ACP with a ductal component [13]. Another study included 581 DCP patients from the SEER database (2004–2015) to analyze CSM rates for DCP versus ACP in nonmetastatic and metastatic PCa [14]. The authors found the DCP was associated with higher CSM in the overall nonmetastatic group as well as the metastatic group. However, they did not make any OM comparisons. In comparison to the above studies, we included the largest sample of DCP patients (n = 1332) to date. We found that the proportion of patients with distant metastases on initial diagnosis was significantly higher for DCP than for ACP (13.7% vs 5.1%), similar to the report by Brinker et al. [4]. After PS matching and construction of adjusted models, we found that DCP patients had worse survival outcomes, with higher risk of both CSM and OM in comparison to patients with ACP. Furthermore, we found that lower stage was a protective factor against OM in patients with DCP.

Higher PCa stage and rapid progression contribute to poor oncological prognosis, while lower stage may result in survival benefits from curative treatment such as radical radiotherapy and radical prostatectomy [15]. However, Bergamin et al. [2] reported that patients with DCP did not respond as well to radical radiotherapy as patients with ACP. The authors evaluated the efficacy of radical radiotherapy for 27 patients with DCP (nine pure ductal carcinoma

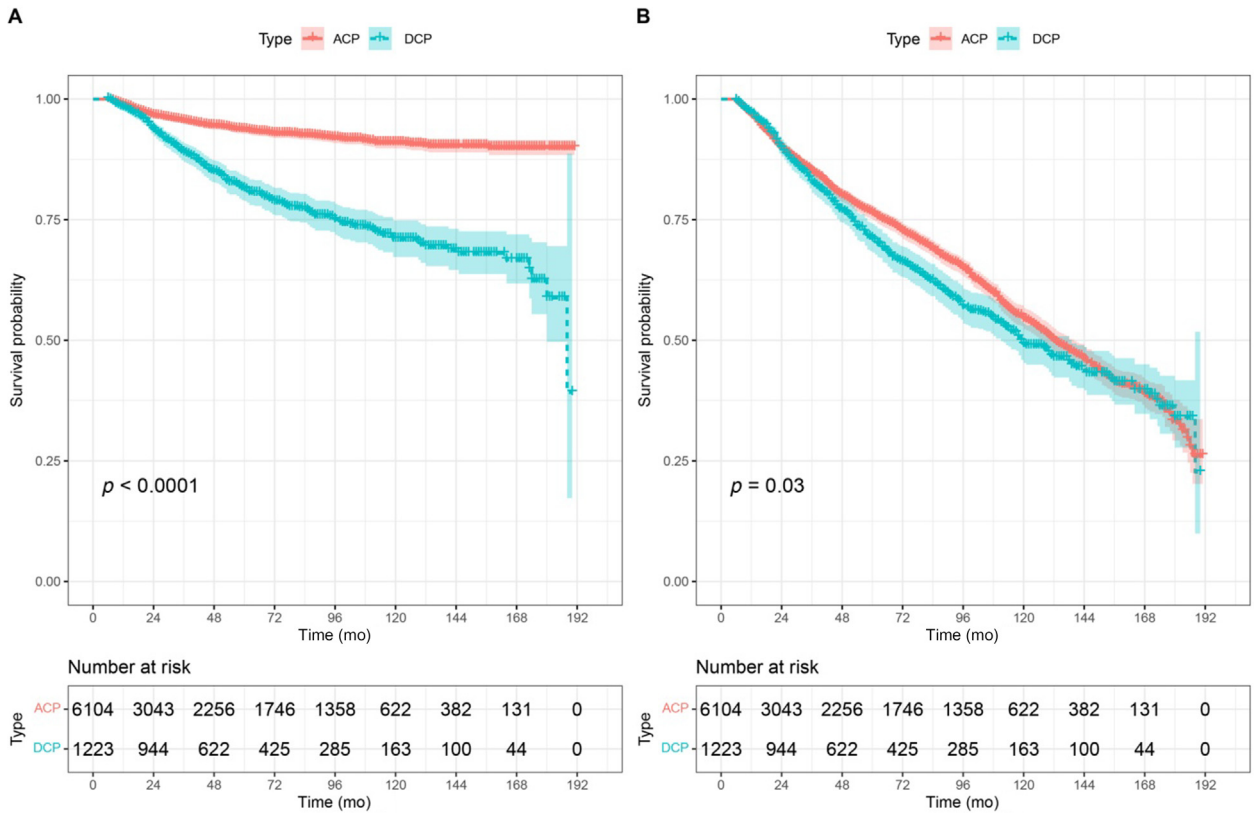

Fig. 2 – Comparison of (A) cancer-specific mortality and (B) overall mortality between the DCP and ACP groups according to the Kaplan-Meier method after propensity score matching. Cancer-specific mortality and overall mortality were significantly higher in the DCP group than in the ACP group (both $p < 0.05$). ACP = acinar adenocarcinoma of the prostate; DCP = ductal carcinoma of the prostate.

Table 3 – Multivariable Cox proportional-hazard models for survival outcomes in ductal carcinoma of the prostate

Outcome and model	HR (95% CI)	*p* value
Cancer-specific mortality		
Unadjusted model	3.34 (2.95–3.79)	<0.001
Adjusted model 1[a]	1.79 (1.57–2.03)	<0.001
Adjusted model 2[b]	1.69 (1.49–1.93)	<0.001
PSM unadjusted model	2.59 (2.17–3.11)	<0.001
PSM adjusted model 1[a]	2.12 (1.72–2.62)	<0.001
PSM adjusted model 2[c]	2.07 (1.68–2.56)	<0.001
Overall mortality		
Unadjusted model	1.98 (1.81–2.17)	<0.001
Adjusted model 1[a]	1.44 (1.31–1.58)	<0.001
Adjusted model 2[b]	1.35 (1.22–1.47)	<0.001
PSM unadjusted model	1.13 (1.01–1.26)	0.03
PSM adjusted model 1[a]	2.97 (2.64–3.35)	<0.001
PSM adjusted model 2[c]	2.73 (2.42–3.08)	<0.00

CI = confidence interval; HR = hazard ratio; PSM = propensity score matching.
[a] Adjusted for age, year of diagnosis, race, and stage.
[b] Adjusted for age, year of diagnosis, race, stage, radiotherapy, and systemic therapy.
[c] Adjusted for age, year of diagnosis, race, stage, radiotherapy, surgery, and systemic therapy.

and 18 mixed ductal-acinar adenocarcinoma) and found that four (15%) experienced local failure and five (19%) had distant failure (four biopsy-proven lung metastases) after 38 mo of follow-up. All distant failures occurred in cases with PSA <3 ng/ml [2]. A recent study additionally found that patients with DCP had worse 5-yr metastasis-free and overall survival rates than those with high-risk ACP, regardless of radical prostatectomy or radiotherapy with or without neoadjuvant therapy. In addition, all DCP patients (15/15) who received neoadjuvant androgen deprivation therapy (ADT) before radical prostatectomy experienced some level of pathological degradation [16]. Similarly, our study showed that while 13.7% of DCP patients received radiotherapy, this did not appear to affect CSM or OM. However, we did find that surgery may be a protective factor against CSM for these patients. DCP patients who underwent surgery had better CSM than those without surgery. Thus, it may be better for DCP patients if radical surgery is prioritized over radiotherapy.

Endocrine therapy is a common treatment for patients with advanced PCa [17] but it is not as effective for DCP [9,16]. We found that 18.2% of DCP patients received systemic therapy, including ADT, but systemic therapy did not alter CSM and OM outcomes in DCP as much as in ACP. A recent genomic analysis showed that 91% of DCP patients ($n = 11$) treated with ADT exhibited intrinsic upregulation of androgen resistance pathways, which led to a decline in ADT effectiveness and may contribute to poor prognosis [16]. This may explain the poor response of DCP to ADT treatment.

Given the current poor outcomes for DCP patients, new potential treatments are needed. A recent study found that the gene mutation spectrum in DCP patients is not conducive to endocrine therapy and is more likely to benefit from immune checkpoint inhibitor (ICI) therapy in comparison to

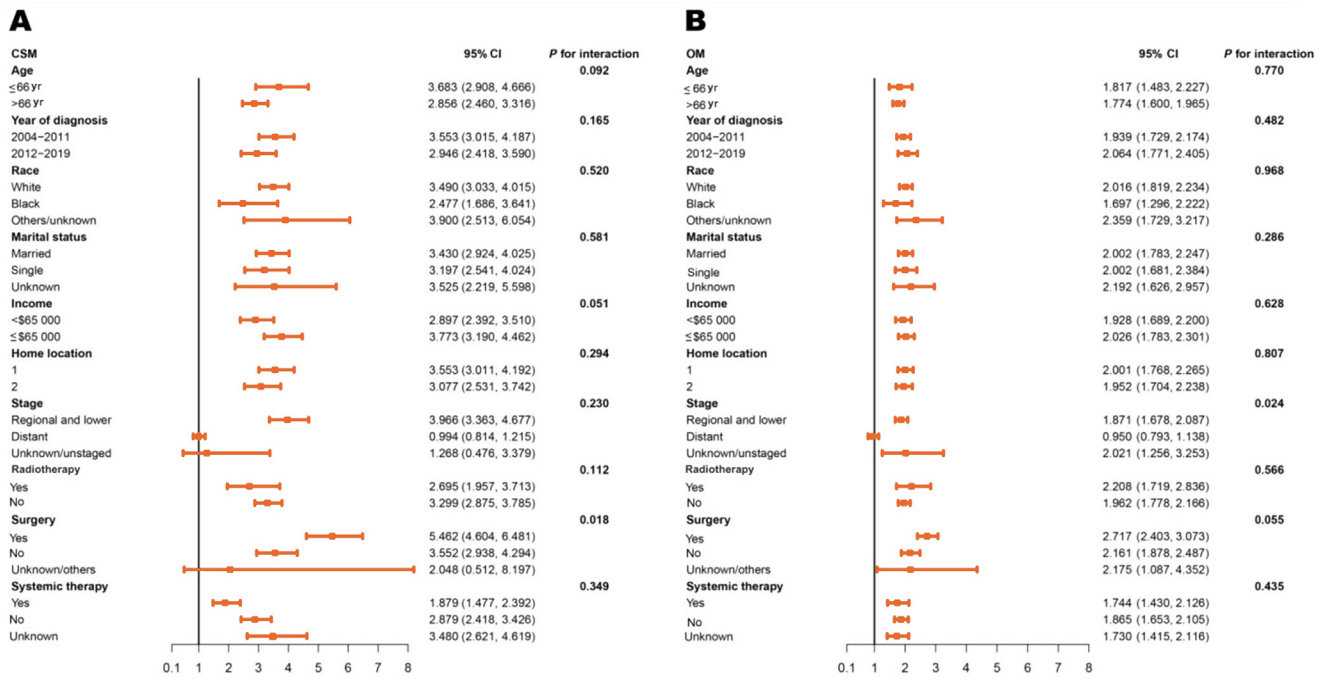

Fig. 3 – Subgroup comparisons for multiple variables for the association between ductal carcinoma of the prostate and (A) cancer-specific mortality (CSM) and (B) overall mortality (OM). Receipt of surgery was a protective factor against CSM (*p* for interaction 0.02), while regional and lower stage had a significant protective effect against OM (*p* for interaction 0.02). HR = hazard ratio; CI = confidence interval.

ACP [18]. Next-generation sequencing (NGS) revealed that the DCP group was enriched in mutations in several important pathways, including approximately 50% (25/51) with alterations in DNA damage repair pathways, 14% (seven of 51) with mismatch repair gene mutations, and 31% (16/51) with homology repair mutations. In addition, mutations activating the PI3K (37%, 19/51), WNT (31%, 16/51), and MAPK (16%, eight of 51) pathways were all common in the DCP group, suggesting that these patients would not benefit from conventional ADT therapy and need NGS-based ICI or other guided therapy [18]. Immunohistochemical PD-L1 assessment is used clinically as a predictive biomarker for multiple solid tumors (eg, non–small-cell lung cancer), although the predictive power of PD-L1 positivity varies by drug and histology [19,20]. One study defined positive expression as detection of PD-L1 in at least 1% of the cells of a lesion, and found PD-L1 positivity in 7.7% (39/508) of primary PCa, 16.7% (four of 24) of DCP, and 42.9% (three of seven) of small-cell carcinoma cases [21], indicating that ICI-based treatment may be a potential option for DCP patients. Similarly, another study found that even though deficient mismatch repair and PD-L1 in tumor cells were uncommon (<5%) in both DCP and ACP, PD-L1 expression was observed more commonly in tumor-infiltrating immune cells, with PD-L1 positivity in 29% (10/34) of DCP patients and 14% (six of 42) of ACP patients [22]. These results suggest that DCP patients may derive more benefit from PD-L1-targeted therapies than ACP patients.

Our study has some limitations. First, data on PSA and Gleason score were not included. Second, we did not subdivide stage information into T, N, and M stages. We were also unable to distinguish whether DCP was pure or mixed. Finally, this was a retrospective study in which the data only cover part of the population from North America, and clinical status may contribute to treatment choice and impact clinical outcomes. However, we could not include more clinically relevant information for further analyses because of database limitations. Nevertheless, as the proportion of patients with DCP is generally very low, the large sample size for the present study means that our conclusions may be more valuable.

5. Conclusions

Although our study has some limitations, this is the largest sample used to date to analyze prognostic outcomes and risk factors for DCP. In comparison to ACP, patients with DCP had significantly higher risk of CSM and OM. Lower stage and surgical treatment were protective factors and brought survival benefits. While these patients may not respond well to some current treatments, such as endocrine therapy and radiotherapy, immune checkpoint inhibitors may have potential therapeutic benefits. It is recommended that the clinical value of this strategy be further studied.

Author contributions: Yongbao Wei had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wei, Kobayashi, Horie, Wang, Li.
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Analysis and interpretation of data: Lu, Zhang, Wu, Gao, Lin, Zhu, Ye.
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Administrative, technical, or material support: Horie, Wang, Li.
Supervision: Wei, Li.
Other: None.

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Data sharing statement: The data can be accessed in the Surveillance, Epidemiology and End Results database.

***Ethics considerations*:** Approval for this study was obtained from Fujian Provincial Hospital. The study was performed in accordance with the relevant guidelines and regulations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.10.013.

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