A Surveillance, Epidemiology and End Results database analysis of the prognostic value of organ-specific metastases in patients with advanced prostatic adenocarcinoma

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Abstract. Prostate cancer (PCa) survival markedly decreases with the occurrence of distant metastasis, and treatment decisions can be influenced by metastasis site, and affect patient survival outcomes. The aim of the present study was to evaluate the potential prognostic value of metastasis to specific sites and the prognostic value of prostatectomy in patients with only bone metastasis, and to determine potential risk factors for bone metastasis in prostatic adenocarcinoma using large scale clinical data. The Surveillance, Epidemiology and End Results (SEER) database (2010-2013) was queried via the SEER*Stat (version 8.3.4) program. A total of 210,730 prostatic adenocarcinoma patients were identified from the SEER database between January 2010 and December 2013. Univariate and multivariate Cox regression analysis and Kaplan-Meier curves were used for survival comparisons with corresponding 95% confidence intervals. Patients with PCa with only liver metastatic lesions had worse overall and cancer-specific survival rates compared with those patients with only bone or lung metastasis. Multivariate Cox regression analysis revealed that age <50 years, married status, T1 and T3 tumor stage according to Tumor-Node-Metastasis (TNM) staging system from the 7th AJCC cancer staging manual, and prostatectomy were associated with better overall survival and cancer-specific survival in patients with only bone metastasis. Binary logistic regression analysis revealed that unmarried status, African descent and undifferentiated histological grade were risk factors for PCa bone metastasis. Prostatic adenocarcinoma patients with only liver metastasis had worse prognostic outcomes compared with patients with other distant organ metastases. Prostatectomy improved the 3-year survival rate in stage IV PCa patients and stage IV PCa patients with only bone metastasis. These findings were based on large-scale clinical data and can provide novel perspectives for the treatment of patients with advanced prostate adenocarcinoma.

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Introduction

Prostate, lung and colorectal cancer account for ~42% of all cancer types in men, and prostate cancer (PCa) accounts for almost one in five newly diagnosed cancer cases in the United States (1). In the United States, PCa is the most common cancer in men, and PCa-specific mortality ranks second, after that of lung cancer (2). Although four well-established risk factors have been identified, namely increased age, ethnicity, obesity and family history, other potential factors that determine the risk of developing PCa are not well known (3,4). Histologically, most cases of PCa are classified as acinar adenocarcinoma and have a poor prognosis (5).

There is increasing awareness that cancer metastasis plays an important role in the survival of PCa patients. Treatment decisions for PCa patients differ according to both patient- and disease-related factors. Radical prostatectomy (RP) is the standard treatment for clinically localized PCa, and it provides adequate local control in organ-confined disease (6). Traditionally, RP is discouraged in patients with advanced disease, owing to the increased complication rate and treatment-related morbidity (7). In recent years, it has been suggested that prostatectomy may provide a benefit for metastatic PCa patients (8); however, for advanced disease with site-specific metastasis of the bone, brain, liver or lung, there is insufficient evidence to support the efficacy of prostatectomy, particularly RP which includes including total prostatectomy and cystoprostatectomy.

To the best of our knowledge, analyses of the prognostic value of organ-specific metastasis based on large population-based data for PCa are lacking. Thus, in the present study, the data pertaining to metastatic prostate adenocarcinoma patients registered in the Surveillance, Epidemiology and End Results (SEER) database was reviewed, and the prognostic outcomes were analyzed to assess the efficacy of prostatectomy among patients with bone metastasis only.

Materials and methods

Data collection/selection and description of participants. The SEER-18 Regs Research Data released in November 2017 was retrieved using the SEER*Stat software version 8.3.5 (https://seer.cancer.gov/seerstat/software/) (National Cancer Institute; National Institutes of Health, USA). Detailed information about distant metastatic sites was updated to 2013 and was not available before the year 2010. Therefore, the current study was restricted to patients registered between January 2010 and December 2013. The survival data of PCa patients was monitored until December 2017. In order to identify patients with metastatic prostate adenocarcinoma, cases were included with the primary site stated as 'Prostate' and the following codes: ICD-O-3 Hist/behave, malignant='8140/3: Adenocarcinoma, NOS'. Patients with stage I, II and III PCa according to the 7th AJCC prostate cancer classification criteria were excluded (9). Cases with unknown race data, unknown marital status data, unknown survival data and unknown specific metastatic site data were excluded. Only data from patients with single primary PCa were extracted. Extracted data included the following: Marital status at diagnosis, age at diagnosis, sex, race (white, black or other), grade, TNM stage according to the AJCC (7th edition, 2010), RX Summ-Surg Prim Site (surgical information of primary cancer site), radiation sequence with surgery, CS mets at DX-bone (bone metastases since 2010), CS mets at DX-brain (brain metastases since 2010), CS mets at DX-liver (liver metastases since 2010), CS mets at DX-lung (lung metastases since 2010), cancer-specific factor 1 (serum PSA levels), survival and vital status record (10). At present, systemic therapy data are not available in the SEER database. Exclusion criteria were as follows: i) Patients with unclear derived M stage according to the AJCC (7th edition); ii) patients with unclear RX Summ-Surg Prim Site (1998+); iii) patients classified as clinical stage I/II or III prostate adenocarcinoma according to the AJCC 7th edition.

Study variables. Patient characteristics were extracted from the SEER database, including marital status, race, age at diagnosis, TNM stage at diagnosis, primary tumor site, grade, surgery condition, radiotherapy condition, bone metastasis, brain metastasis, liver metastasis and lung metastasis. According to the AJCC 7th edition criteria of TNM stage and clinical stage of prostate cancer, PCa patients with T4, N0, M0 any T stage, N1, M0, and any T stage, any N stage, M1 were classified as stage IV patients.

Statistical analysis. In the present study, the χ^2 test was used to compare the clinicopathological characteristics among cases with and without bone metastasis. Kaplan-Meier analysis was used to build survival curves and log-rank testing was employed for the comparison of long-term survival outcomes. The Cox proportional hazards regression model was employed to perform univariate and multivariate analyses of the hazard ratios with corresponding 95% confidence intervals (CIs) of the study variates. Associations between marital status, age at diagnosis, race, histological grade and TNM stage at diagnosis were examined by binary logistic regression. A two-tailed P-value of <0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS software 20.0 (IBM Corporation).

Table I. Baseline characteristics of patients with stage IV prostate adenocarcinoma (n=10,777) in the present study.

Characteristics	Number	Percentage
Age, years		
<50	426	3.95
≥50	10,351	96.05
Race		
White	8,179	75.89
Black	1,929	17.90
Others[a]	669	6.21
Marital status		
Married	6,941	64.41
Single/unmarried	3,836	35.59
Grade		
I	21	0.19
II	488	4.83
III	8,216	76.24
IV	81	0.75
Unknown	1,971	18.29
Bone metastasis		
Yes	5,963	55.33
No	4,814	44.67
Brain metastasis		
Yes	83	0.77
No	10,694	99.23
Liver metastasis		
Yes	280	2.60
No	10,497	97.40
Lung metastasis		
Yes	512	4.75
No	10,265	95.25
Lymph node metastasis		
Yes	4,258	39.51
No	5,250	48.71
Unknown	1,269	11.78
Radiation therapy		
Yes	1,085	10.07
No	9,692	89.93
Prostatectomy		
Yes	2,981	27.66
No	7,761	72.01
Unknown	35	0.32

[a]American Indian/Alaska native and Asian/Pacific Islander.

Results

Incidence of different metastatic sites among stage IV PCa patients. The selection criteria are shown in Fig. 1. Among 210,730 cases identified in the SEER database, a total of 10,777 patients with stage IV prostatic adenocarcinoma between January 2010 and December 2013 were included in the present study.

Table I summarizes the distribution of different clinical characteristics of PCa patients. The majority of patients

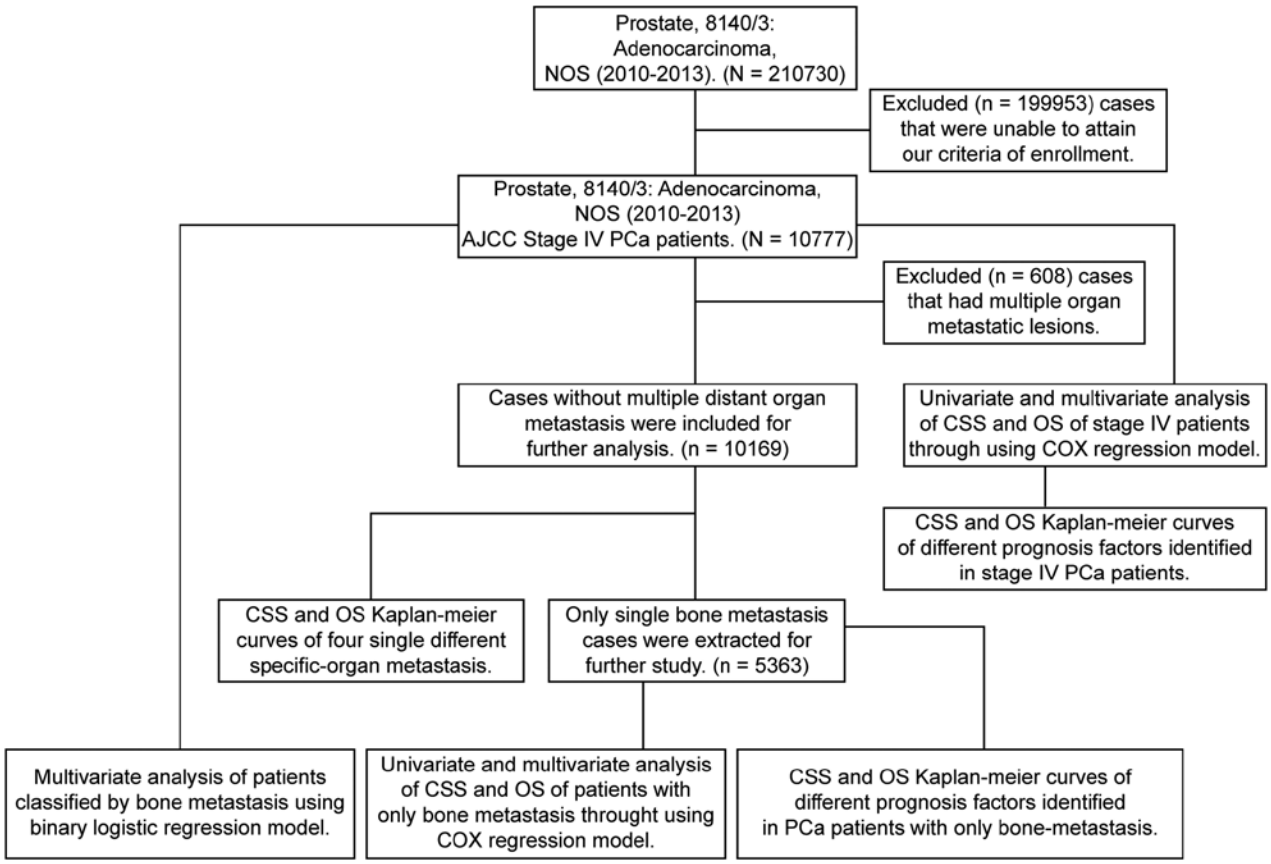

Figure 1. Flow chart of the study, including selection and exclusion criteria. NOS, not otherwise specified; AJCC, American Joint Committee on Cancer; PCa, prostate cancer; CSS, cancer-specific survival; OS, overall survival.

(n=5,963, 55.33%) presented with bone metastasis, followed by lung (n=512, 4.75%), liver (n=280, 2.60%) and brain (n=83, 0.77%) metastasis. Prostatectomy (RP, including total prostatectomy and cystoprostatectomy) was performed in 2,981 (27.66%) patients, and 1,085 (10.07%) patients received radiation therapy. There were 4,258 (39.51%) patients with lymph node metastasis.

Identification of statistically significant variates with regard to survival outcomes in patients with stage IV PCa. Several variates were identified by univariate and multivariate analysis of cancer specific-survival (CSS) and overall survival (OS) in PCa patients using Cox hazards regression models. Single/unmarried status, age ≥50 years, black race, M1 stage, bone metastasis, liver metastasis and lung metastasis were associated with worse CSS and OS. Races classified as 'other' (American Indian/Alaska native and Asian/Pacific Islander), radiation therapy and prostatectomy were associated with better CSS and OS (Tables II and III). Based on multivariate Cox regression analysis, the following factors were significantly associated with poor OS and/or CSS: Single/unmarried status [hazard ratios (HRs), 1.164 (CSS) and 1.211 (OS), P<0.001], age ≥50 years [HRs, 1.309 (CSS), P=0.034 and 1.421 (OS), P=0.003], black race vs. white race; [HR, 1.151 (CSS), P=0.009], M1 stage [HRs, 3.096 (CSS) and 2.419 (OS), P<0.001] and PSA level >20 ng/ml [HR, 1.27 (OS), P=0.035]. On the other hand, 'other' race (American Indian/Alaska native and Asian/Pacific Islander) was a significant predictor of better CSS and OS (vs. white race; HRs, 0.750, P=0.005 and 0.774, P=0.004, respectively), as was prostatectomy (HR, 0.147 and 0.143, respectively, P<0.001). Radiation therapy was a significant predictor of better OS only (HR, 0.756, P=0.003) (Table III). Next, Kaplan-Meier survival analysis was performed to calculate the differences in OS and CSS by the variates identified through multivariate Cox hazards regression analysis (Fig. 2). The 3-year CSS rate of patients who received prostatectomy was 97.3%, compared with 54.3% in patients who did not undergo prostatectomy (P<0.0001). The 3-year OS rate of patients who received prostatectomy was 96.0%, whereas that of patients who did not was only 47.4% (P<0.001) (Fig. 2E). Married status, age <50 years and radiation therapy also led to higher 3-year CSS and OS rates (Fig. 2A, B and D). By contrast, M1 stage, bone metastasis, liver metastasis, lung metastasis and black race were associated with reduced survival in stage IV PCa patients (Fig. 2C and F-I).

Impact of site-specific metastasis on survival outcomes. As it was found that metastasis to different organs may induce different survival outcomes in stage IV PCa patients, Kaplan-Meier survival analysis was performed to compare OS in advanced PCa patients with metastasis to the bone, brain, liver and lung. A total of 608 patients with metastatic lesions in multiple organs were excluded, and 10,169 patients were included in the analysis. Of these patients, 52.74% had bone metastasis, 0.22% had brain metastasis, 0.42% had liver

Table II. Univariate analysis of CSS and OS in 10,777 patients with advanced prostate cancer.

	CSS				OS			
Variable	P-value	HR	95% CI		P-value	HR	95% CI	
Marital status								
Married		1.000				1.000		
Single	<0.001	1.608	1.479	1.748	<0.001	1.647	1.528	1.776
Age, years								
<50		1.000				1.000		
≥50	<0.001	1.620	1.263	2.077	<0.001	1.775	1.404	2.243
Race								
White		1.000				1.000		
Black	0.016	1.137	1.024	1.262	0.003	1.152	1.048	1.265
Other[a]	0.005	0.754	0.618	0.920	0.01	0.795	0.667	0.947
Grade								
Well differentiated		1.000				1.000		
Moderately differentiated	0.168	0.440	0.136	1.416	0.006	0.305	0.132	0.707
Poorly differentiated	0.934	0.953	0.307	2.961	0.198	0.591	0.265	1.316
Undifferentiated	0.144	2.418	0.740	7.897	0.486	1.360	0.573	3.228
Tumor stage								
T0		1.000				1.000		
T1	<0.001	0.434	0.274	0.686	0.004	0.519	0.332	0.811
T2	<0.001	0.411	0.26	0.648	0.002	0.488	0.313	0.761
T3	<0.001	0.152	0.095	0.244	<0.001	0.175	0.111	0.276
T4	<0.001	0.272	0.172	0.430	<0.001	0.32	0.205	0.501
Node stage								
N0		1.000				1.000		
N1	<0.001	0.627	0.569	0.692	0.340	0.956	0.872	1.048
Metastasis stage								
M0		1.000				1.000		
M1	<0.001	11.147	9.472	13.121	<0.001	2.419	1.979	2.957
Radiation therapy								
No		1.000				1.000		
Yes	<0.001	0.361	0.297	0.439	<0.001	0.337	0.281	0.405
Prostatectomy surgery								
No		1.000				1.000		
Yes	<0.001	0.041	0.031	0.055	<0.001	0.049	0.038	0.0620
PSA level, ng/ml								
≤20		1.000				1.000		
>20	0.056	1.241	0.994	1.569	0.019	1.271	1.032	1.565
Distant lymph node metastasis								
Yes		1.000				1.000		
No	<0.001	0.627	0.569	0.692	<0.001	0.61	0.558	0.666
Bone metastasis								
Yes		1.000				1.000		
No	<0.001	0.167	0.149	0.188	<0.001	0.192	0.173	0.212
Brain metastasis								
Yes		1.000				1.000		
No	<0.001	0.303	0.223	0.413	<0.001	0.327	0.245	0.437
Liver metastasis								
Yes		1.000				1.000		
No	<0.001	0.233	0.197	0.276	<0.001	0.256	0.219	0.300

Table II. Continued.

	CSS				OS			
Variable	P-value	HR	95% CI		P-value	HR	95% CI	
Lung metastasis								
Yes		1.000				1.000		
No	<0.001	0.360	0.312	0.416	<0.001	0.384	0.336	0.438

[a]American Indian/Alaska native and Asian/Pacific Islander. CSS, cancer-specific survival; OS, overall survival; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval.

metastasis, and 0.78% had lung metastasis (Fig. 3A). It was demonstrated that PCa patients with only liver metastasis had the worst 3-year CSS and OS rates (31.9 and 22.8%, respectively). The 3-year CSS and OS rates of patients with only bone metastasis were 49.6 and 41.6%, respectively. Patients with only lung metastasis (3-year CSS and OS, 79.9 and 63.7%) had improved OS compared with those with only bone or liver metastasis (Fig. 3B and C).

Identification of risk factors for bone metastasis in patients with stage IV PCa. As the present results indicated that stage IV PCa was most prone to distant metastasis to the bone, multivariate binary logistic regression analysis was performed to identify risk factors of bone metastasis in 10,777 patients with advanced PCa. The results suggested that single/unmarried status, black race, NX stage and grade IV (undifferentiated adenocarcinoma) were risk factors for bone metastasis. T3 and T4 stage patients, as well as N1 stage patients, were less likely to have bone metastasis (Table IV).

Identification of 'risk' factors and 'protective' factors for CSS and OS in patients with advanced PCa with only bone metastasis. Univariate and multivariate COX hazards regression analyses were conducted in 5,363 patients with stage IV PCa with only bone metastasis to identify the contribution of different variates to CSS and OS. According to the results, single/unmarried status was deemed as risk factor for CSS and OS; age ≥50 years was deemed as risk factor for OS (Tables V and VI). On the other hand, 'other' race (American Indian/Alaska native and Asian/Pacific Islander), T1 stage, T3 stage and prostatectomy were regarded as 'protective' factors in stage IV patients with only bone metastasis, moreover, T2 stage was additionally regarded as a 'protective' factor for CSS in stage IV PCa patients but not OS (Tables V and VI).

Prostatectomy is effective in improving survival outcomes in patients with advanced PCa with only bone metastasis. Kaplan-Meier analysis was conducted using significant factors from Cox regression analysis to determine their impact on survival in patients with stage IV PCa with only bone metastasis. According to the results, married patients had better 3-year survival rates than single/unmarried patients (CSS, 51.9 vs. 46.2%; OS, 45.6 vs. 38.5%; Fig. 4A). 'Other' race patients (American Indian/Alaska native and Asian/Pacific Islander) also had better CSS and OS than white patients (Fig. 4B). T1 and T3 stage patients had better CSS and OS than T0 stage patients, although this difference was not statistically significant (Fig. 4C). Radiation therapy did not significantly improve patient's survival (Fig. 4D). Moreover, it was found that prostatectomy could potently improve the 3-year CSS and OS rates (vs. no prostatectomy; CSS, 85.1 vs. 49.0%; OS, 81.5 vs. 42.1%; Fig. 4E). The HR of CSS in patients with T2 stage bone metastases was 0.523; suggesting that patients with stage T2 cancer had improved specific survival outcomes compared with T0 patients (Table VI). However, as the effect of T2 stage did not significantly affect OS, it is possible that T2 stage would be a protective factor for survival outcomes in single bone metastasis PCa patients.

Discussion

The main findings of the present study were: i) Prostate adenocarcinoma patients with only liver metastasis had worse prognostic outcomes than those with only bone or only lung metastasis; ii) prostatectomy potently improved the CSS and OS of stage IV PCa patients with only bone metastasis; and iii) unmarried status, age ≥50 years, M1 stage, bone metastasis, liver metastasis and lung metastasis were risk factors for survival in patients with stage IV PCa.

The Cox regression model is widely used in survival analysis with censoring data and different covariates (11). When analyzing survival data of the patients, the HR generated by Cox regression model represents the probability of death at a particular time. The Kaplan-Meier curve can efficiently use all data, including the censored data, to estimate the time-to-event curve. Comparisons of different groups is assessed by log-rank test, which is able to estimate the long-term prognosis of patients (11). Therefore, survival analysis of stage IV PCa patients and single bone metastasis advanced PCa patients was performed using the Cox regression model and Kaplan-Meier analysis methods.

Using COX regression models, M1 stage, bone metastasis, liver metastasis and lung metastasis were first identified to be significantly associated with impaired CSS and OS (Tables II and III) among stage IV PCa patients. Radiation therapy and prostatectomy were also identified to be effective therapeutic methods to improve patient CSS and OS in advanced PCa.

The bone was revealed to be the most common metastatic site for stage IV PCa, and patients with bone metastases had

Table III. Multivariate analysis of CSS and OS in 10,777 patients with advanced prostate cancer.

	CSS				OS			
Variable	P-value	HR	95% CI		P-value	HR	95% CI	
Marital status								
Married		1.000				1.000		
Single	<0.001	1.164	1.069	1.269	<0.001	1.211	1.121	1.309
Age, years								
<50		1.000				1.000		
≥50	0.034	1.309	1.021	1.682	0.003	1.421	1.124	1.798
Race								
White		1.000				1.000		
Black	0.009	1.151	1.024	1.262	0.527	0.971	0.881	1.067
Other[a]	0.005	0.750	0.618	0.921	0.004	0.774	0.649	0.922
Grade								
Well differentiated		1.000				1.000		
Moderately differentiated	0.146	0.419	0.111	1.352	0.004	0.296	0.128	0.685
Poor differentiated	0.653	0.771	0.248	2.397	0.084	0.493	0.221	1.101
Undifferentiated	0.477	1.537	0.470	5.031	0.801	0.895	0.376	2.127
Tumor stage								
T0		1.000				1.000		
T1	0.065	0.643	0.402	1.028	0.266	0.773	0.491	1.217
T2	0.072	0.653	0.410	1.039	0.279	0.780	0.497	1.224
T3	0.071	0.641	0.396	1.037	0.179	0.727	0.456	1.158
T4	0.742	1.081	0.678	1.725	0.358	1.236	0.786	1.944
Node stage								
N0		1.000				1.000		
N1	0.950	1.003	0.906	1.111	0.340	0.956	0.872	1.048
Metastasis stage								
M0		1.000				1.000		
M1	<0.001	3.096	2.443	3.923	<0.001	2.419	1.979	2.957
Radiation therapy								
No		1.000				1.000		
Yes	0.066	0.829	0.679	1.012	0.003	0.756	0.628	0.911
Prostatectomy surgery								
No		1.000				1.000		
Yes	<0.001	0.147	0.105	0.206	<0.001	0.143	0.108	0.189
PSA level, ng/ml								
≤20		1.000				1.000		
>20	0.069	1.236	0.984	1.553	0.035	1.251	1.016	1.541
Distant lymph node metastasis								
Yes		1.000				1.000		
No	0.722	1.019	0.92	1.128	0.384	0.96	0.875	1.053
Bone metastasis								
Yes		1.000				1.000		
No	<0.001	0.739	0.633	0.863	<0.001	0.775	0.674	0.891
Brain metastasis								
Yes		1.000				1.000		
No	0.115	0.774	0.562	1.064	0.102	0.779	0.579	1.049
Liver metastasis								
Yes		1.000				1.000		
No	<0.001	0.472	0.396	0.563	<0.001	0.501	0.424	0.589

Table III. Continued.

Variable	CSS			OS		
	P-value	HR	95% CI	P-value	HR	95% CI
Lung metastasis						
Yes		1.000			1.000	
No	<0.001	0.776	0.667 0.902	0.001	0.794	0.691 0.912

[a]American Indian/Alaska native and Asian/Pacific Islander. CSS, cancer-specific survival; OS, overall survival; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval.

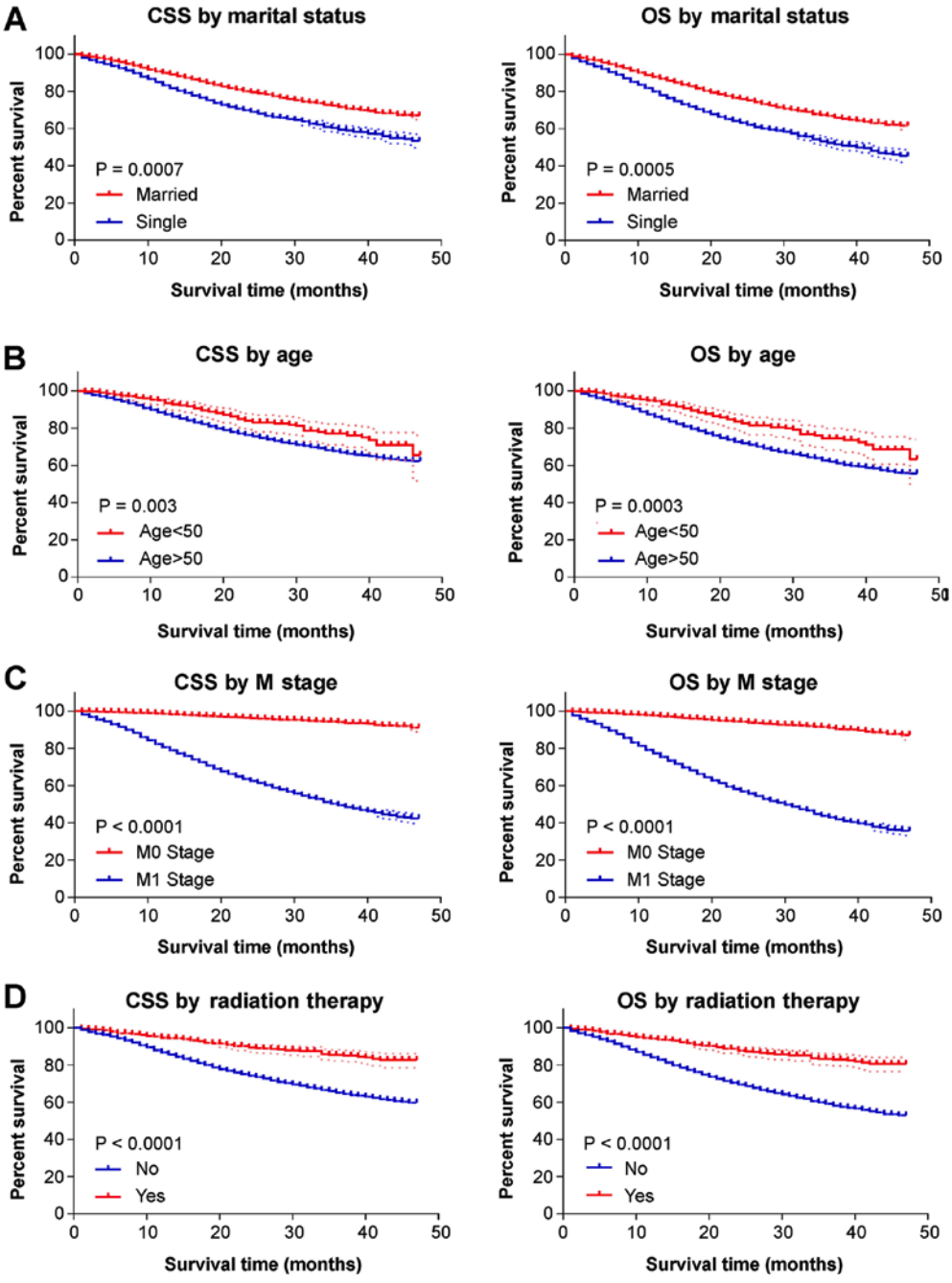

Figure 2. Kaplan-Meier curves for CSS and OS by different study variates. (A-D) The dotted lines reveal the 95% confidence interval of each points on the Kaplan-Meier curve. The marital status 'single' includes divorced, single (never married), separated and widowed. Prostatectomy includes: Radical prostatectomy, NOS; total prostatectomy, NOS; excised prostate, prostatic capsule, ejaculatory ducts, seminal vesicle and including a narrow cuff of bladder neck; Prostatectomy, NOS. CSS, cancer-specific survival; OS, overall survival; NOS, not otherwise specified.

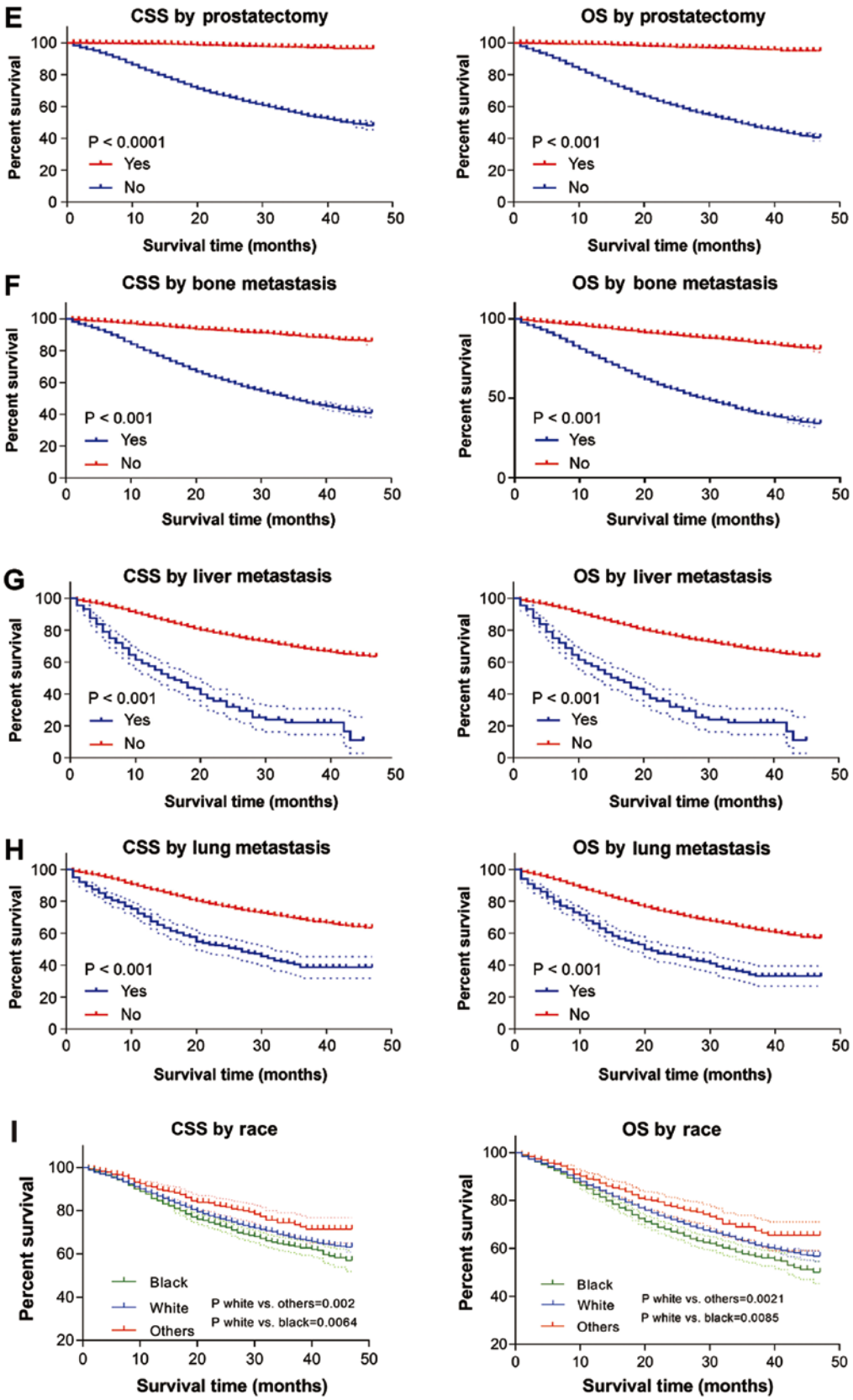

Figure 2. Continued. Kaplan-Meier curves for CSS and OS by different study variates. (E-I) The dotted lines reveal the 95% confidence interval of each points on the Kaplan-Meier curve. The marital status 'single' includes divorced, single (never married), separated and widowed. Prostatectomy includes: Radical prostatectomy, NOS; total prostatectomy, NOS; excised prostate, prostatic capsule, ejaculatory ducts, seminal vesicle and including a narrow cuff of bladder neck; Prostatectomy, NOS. CSS, cancer-specific survival; OS, overall survival; NOS, not otherwise specified.

significantly impaired CSS and OS rates. Therefore, it was necessary to find risk factors that were associated with bone metastasis in stage IV PCa. Multivariate binary logistic regression analysis suggested that single/unmarried patients, black

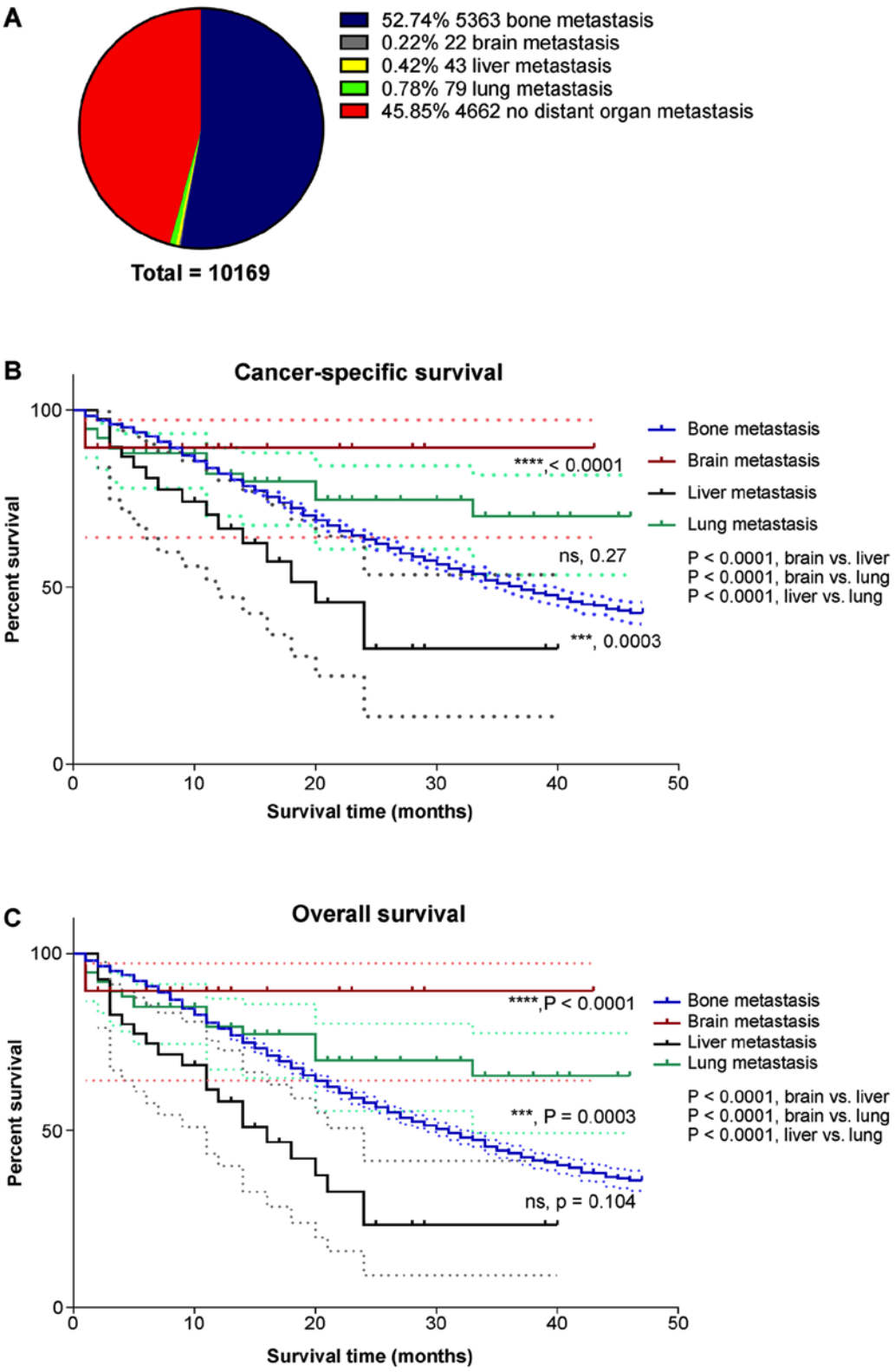

Figure 3. (A) Pie-chart of single organ metastasis percentage distribution. (B) Kaplan-Meier curves for cancer-specific survival of patients with or without specific organ metastasis. (C) Kaplan-Meier curves for overall survival of patients with or without specific organ metastasis. The dotted lines indicate the 95% confidence intervals of each point on the Kaplan-Meier curve. ns, not significant.

patients and patients with grade IV (undifferentiated adenocarcinoma) were more likely to have bone metastasis (Table VI). However, T3 stage, T4 stage and N1 stage were 'protective' factors. One possible explanation for this result is that certain groups of patients were included that were diagnosed as having stage IV PCa according to the AJCC 7th edition, but did not have metastatic disease: Patients with i) any T stage, N1, M0; ii) T4,any N stage, M0; and iii) T3, N1, M0.

As bone metastasis may potently impair survival outcomes for patients with stage IV PCa, finding effective treatment

Table IV. Multivariate binary logistic regression analysis of patient characteristics classified by bone metastasis at diagnosis (n=10,777).

Variable	Bone metastasis		Pearson χ^2	Multivariate analysis			
	No	Yes	P-value	Odds ratio	95% CI		P-value
Total patients	4,814 (44.7)	5,963 (55.3)					
Marital status			<0.001				
Married	3,457 (49.8)	3,484 (50.2)		1.000			
Single	1,357 (35.4)	2,479 (64.6)		1.671	1.505	1.856	<0.001
Age, years			0.001				
<50	224 (52.6)	202 (47.4)		1.000			
≥50	4,590 (44.3)	5761 (55.7)		1.044	0.818	1.334	0.729
Race			<0.001				
White	3,783 (46.3)	4396 (53.7)		1.000			
Black	735 (38.1)	1194 (61.9)		1.155	1.013	1.317	0.032
Other[a]	296 (44.2)	373 (55.8)		1.093	0.893	1.338	0.387
Grade			<0.001				
Well differentiated	10 (47.6)	11 (52.4)		1.000			
Moderately differentiated	306 (62.7)	182 (37.3)		0.488	0.168	1.411	0.907
Poorly differentiated	4,122 (50.2)	4094 (49.8)		1.064	0.376	3.01	0.581
Undifferentiated	32 (39.5)	49 (60.5)		1.391	1.01	8.26	0.048
Unknown	344 (17.5)	1627 (82.5)		4.301	1.812	10.204	<0.001
Tumor stage			<0.001				
T0	10 (18.9)	43 (81.1)		1.000			
T1	422 (21.4)	1,550 (78.6)		1.11	0.523	2.357	0.758
T2	750 (29.4)	1,804 (70.6)		0.815	0.385	1.723	0.59
T3	1,445 (72.5)	548 (27.5)		0.211	0.1	0.448	<0.001
T4	1,996 (73.9)	705 (26.1)		0.069	0.033	0.146	<0.001
TX	191 (12.7)	1313 (87.3)		1.499	0.790	3.233	0.192
Node stage			<0.001				
N0	1,817 (34.6)	3,433 (65.4)		1.000			
N1	2,868 (67.4)	1,390 (32.6)		0.166	0.148	0.186	<0.001
NX	129 (10.2)	1,140 (89.8)		2.342	1.882	2.914	<0.001

[a]American Indian/Alaska native and Asian/Pacific Islander. CSS, cancer-specific survival; OS, overall survival; CI, confidence interval.

methods to improve the CSS and OS of patients with bone metastasis is necessary. Historically, RP has not been recommended for patients with advanced PCa presumed to have extra-prostatic disease; instead, patients with advanced PCa were counseled to undergo radiation therapy or hormonal therapy (12). However, local resection of the primary site for metastatic solid tumors has been demonstrated to be helpful in various cancer types, including metastatic renal cell carcinoma, hepatocellular carcinoma, pancreatic cancer and metastatic breast cancer (13-21). Culp *et al* (8) demonstrated that metastatic PCa patients undergoing definitive local treatment had higher 5-year OS and CSS rates than those not undergoing local therapy. For patients with PCa, there is still no consensus about the benefit of primary site surgery in the presence of metastatic disease. The current findings demonstrate that, for patients with bone metastasis, prostatectomy may significantly improve both CSS and OS (Fig. 4). Although radiation therapy provided obvious improvements in both CSS and OS in stage IV PCa patients (Fig. 2), the present results indicated that there was no significant improvement in CSS and OS with the administration of radiation therapy to patients with only bone metastasis (Fig. 4).

Mechanisms underlying the survival benefit of primary tumor resection remain unknown. According to the 'self-seeding' hypothesis, cancer cells may seed distant sites, as well as the primary tumor site (22,23). Eliminating the primary source of the metastatic tumor cells by removing the prostate may reduce the number of circulating tumor cells (24). Therefore, it is reasonable to believe that prostatectomy may be beneficial for patients with metastatic PCa.

Cooperberg *et al* (25) showed that PCa patients aged ≥50 years may show higher CAPRA scores (the CAPRA score was developed using the Cancer of the Prostate Strategic Urologic Research Endeavor registry data) (26), implying

Table V. Univariate COX analysis of CSS and OS in patients with advanced prostate cancer and only bone metastasis.

	CSS			OS		
Variable	P-value	HR	95% CI	P-value	HR	95% CI
Marital status						
Married		1.000			1.000	
Single	<0.001	1.244	1.128 1.373	<0.001	1.29	1.182 1.410
Age, years						
<50		1.000			1.000	
≥50	0.089	1.277	0.963 1.692	0.016	1.386	1.062 1.808
Race						
White		1.000			1.000	
Black	0.779	1.018	0.901 1.15	0.551	1.034	0.926 1.155
Others[a]	0.001	0.675	0.532 0.856	0.003	0.731	0.593 0.9
Grade						
Well differentiated		1.000			1.000	
Moderately differentiated	0.228	0.410	0.096 1.746	0.027	0.310	0.110 0.876
Poorly differentiated	0.889	1.103	0.276 4.419	0.427	0.672	0.252 1.793
Undifferentiated	0.465	1.727	0.399 7.477	0.878	0.918	0.311 2.714
Tumor stage						
T0		1.000			1.000	
T1	<0.001	0.332	0.194 0.566	<0.001	0.393	0.235 0.657
T2	<0.001	0.374	0.219 0.636	0.002		0.262 0.730
T3	<0.001	0.320	0.184 0.556	<0.001	0.357	0.210 0.608
T4	0.052	0.585	0.341 1.004	0.076		0.371 1.051
Node stage						
N0		1.000			1.000	
N1	0.004	1.196	1.059 1.351	0.086	1.103	0.986 1.234
Radiation therapy						
No		1.000			1.000	
Yes	0.918	0.987	0.772 1.263	0.725	0.960	0.765 1.204
Prostatectomy surgery						
No		1.000			1.000	
Yes	<0.001	0.216	0.103 0.454	<0.001	0.255	0.137 0.475

[a]American Indian/Alaska native and Asian/Pacific Islander. CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

that older age increases the risk of metastasis in PCa patients. Similarly, in the present study, it was demonstrated that age ≥50 years was a risk factor for both CSS and OS in patients with only bone metastasis (Tables V and VI). The current study also revealed that patients with grade IV PCa (undifferentiated) had a higher risk of bone metastases than grade I patients (Table IV). Moreover, Brawley *et al* (27) suggested that mortality rates for patients with PCa are higher for black Americans than for white Americans. The findings of the current study also suggested that black patients with stage IV PCa had worse CSS and OS compared with white patients (Fig. 2). A recent study by Guo *et al* (28) suggested that liver, lung or brain metastasis resulted in a poorer prognosis in prostate cancer patients diagnosed with bone metastasis (28). By contrast, the present study assessed the effects of four specific single metastasis sites on the survival of patients with advanced PCa. Moreover, prostatectomy was identified as an effective treatment for PCa patients with single bone metastases instead of radiation therapy.

Analysis of the association between disease prognosis and metastatic site may help in optimizing disease management and devising systemic therapy strategies for PCa. The current findings suggested that patients with only liver metastasis had worse CSS and OS rates compared with those with only bone or liver metastasis (Fig. 3).

The following limitations of the present study should be considered. First, information about smoking, obesity, Gleason scores and other risk factors for PCa were not registered in the SEER database. The current analysis only evaluated prostatectomy (RP; total prostatectomy

Table VI. Multivariate COX analysis of CSS and OS in patients with stage IV prostate cancer with only bone metastasis.

	CSS			OS		
Variable	P-value	HR	95% CI	P-value	HR	95% CI
Marital status						
Married		1.000			1.000	
Single	0.002	1.172	1.058 1.293	<0.001	1.221	1.114 1.336
Age, years						
<50		1.000			1.000	
≥50	0.104	1.265	0.953 1.678	0.025	1.357	1.039 1.772
Race						
White		1.000			1.000	
Black	0.909	0.993	0.877 1.124	0.991	0.999	0.893 1.118
Other[a]	0.002	0.685	0.540 0.869	0.006	0.746	0.605 0.919
Grade						
Well differentiated		1.000			1.000	
Moderately differentiated	0.171	0.363	0.085 1.546	0.016	0.279	0.099 0.791
Poorly differentiated	0.933	0.942	0.235 3.781	0.295	0.591	0.221 1.581
Undifferentiated	0.599	1.483	0.342 6.438	0.736	0.829	0.280 2.459
T stage						
T0		1.000			1.000	
T1	0.011	0.495	0.287 0.854	0.044	0.584	0.346 0.986
T2	0.019	0.523	0.305 0.897	0.063	0.611	0.363 1.027
T3	0.011	0.480	0.273 0.844	0.025	0.539	0.314 0.926
T4	0.349	0.771	0.445 1.331	0.493	0.831	0.491 1.409
N stage						
N0		1.000			1.000	
N1	0.099	1.111	0.98 1.258	0.498	1.041	0.928 1.167
Radiation therapy						
No		1.000			1.000	
Yes	0.641	0.942	0.735 1.209	0.484	0.922	0.733 1.159
Prostatectomy surgery						
No		1.000			1.000	
Yes	0.001	0.291	0.138 0.614	0.001	0.346	0.185 0.648

[a]American Indian/Alaska native and Asian/Pacific Islander. CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

and cystoprostatectomy were included) for metastatic PCa patients, but specific surgical information was not included (e.g., the use of laparoscopic or robotic-assisted surgeries). Resection of metastatic lesions can also affect the survival outcomes of patients with metastatic PCa, but such information cannot be retrieved from the SEER database. In addition, information on androgen deprivation therapy and neoadjuvant chemotherapy, are not included. The dataset used was representative only of the United States, so the applicability of the results to a wider population is uncertain. As the current study was based on patient data from 2010-2013, 5-year survival rate, which is deemed as an effective indicator for predicting the long-term prognosis of patients, was not available. Instead, 3-year survival rate was used as an indicator to estimate the prognosis of patients with advanced PCa. Studies based on updated SEER PCa data that include >5 years of records of 'specific site metastases' can provide 5 year-survival rate, as a long-term prognosis indicator, to further validate the current results. Although the prognosis of PCa patients can be changed with improvements of treatment, we still hypothesize that prostatectomy is beneficial for prognosis outcomes of patients with stage IV PCa.

In conclusion, based on the results of SEER analysis, patients with advanced prostatic adenocarcinoma with only liver metastasis have worse outcomes than those with only bone or lung metastasis. Despite the limitations of the SEER database, the current results suggest that prostatectomy confers a survival advantage in PCa patients with only bone metastasis.

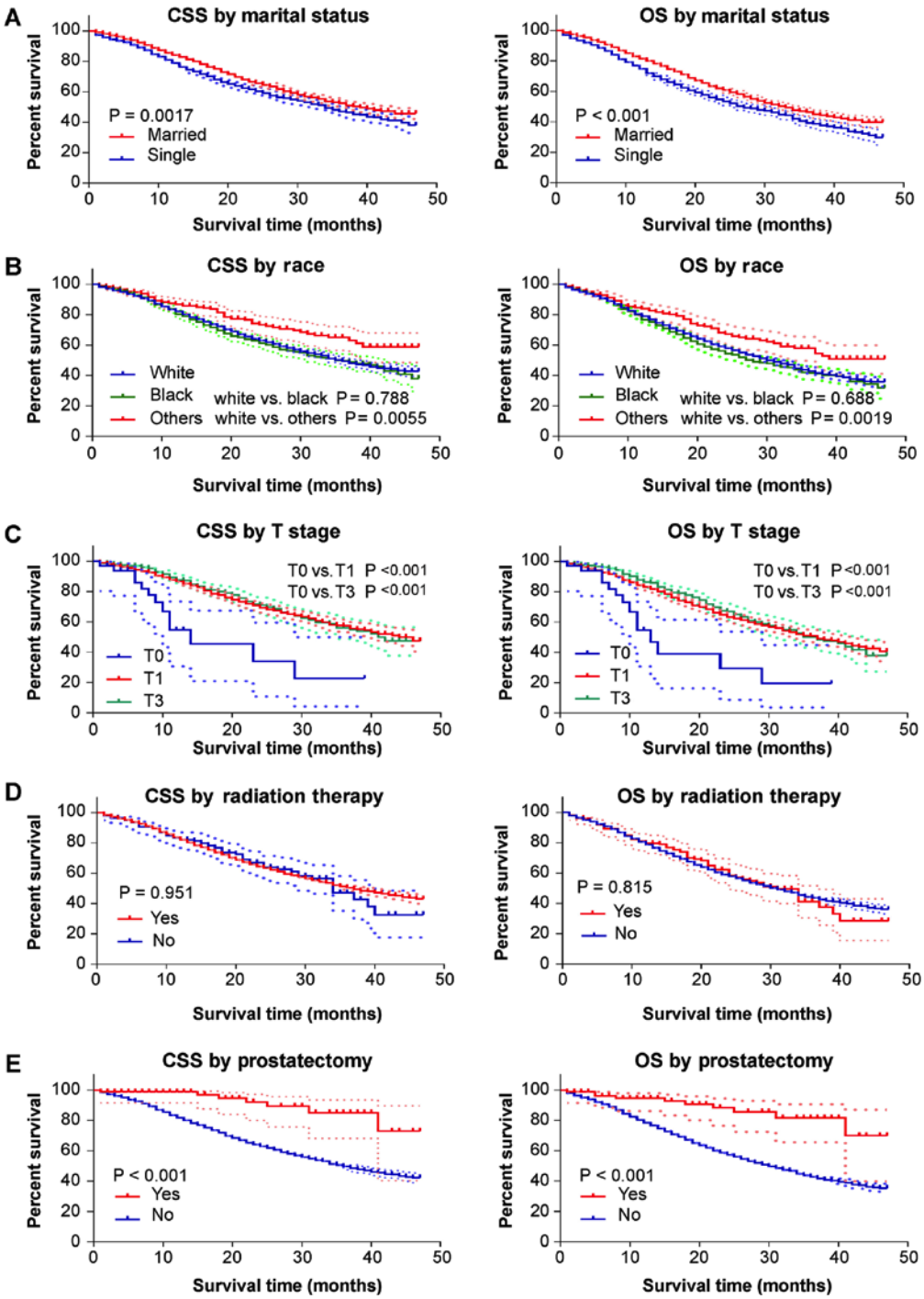

Figure 4. Kaplan-Meier curves for CSS and OS by different study variates. The dotted lines indicate the 95% confidence interval of each point on the Kaplan-Meier curve. The marital status 'single' includes divorced, single (never married), separated and widowed. 'Others' race includes American Indian/Alaska native and Asian/Pacific Islander. Prostatectomy includes: Radical prostatectomy, NOS; total prostatectomy, NOS; Excised prostate, prostatic capsule, ejaculatory ducts, seminal vesicle and including a narrow cuff of bladder neck; Prostatectomy, NOS. NOS, no other specification; CSS, cancer-specific survival; OS, overall survival.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the SEER repository (https://seer.cancer.gov/).

Authors' contributions

YD, RB and CW designed the study. YD and ZZ extracted the data. ZZ, BX, SL and WAR assisted with the data processing

and statistical analysis. YD and WAR wrote the article. CW funded the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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