



Predictors of survival in prostate cancer patients with bone metastasis and extremely high prostate-specific antigen levels

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ABSTRACT

Purpose: Prostate-specific antigen (PSA) is a surrogate marker of disease progression; however, its predictive ability in the extreme ranges is unknown. We determined the predictors of survival in patients with bone metastatic prostate cancer (BMPCa) and with extremely high PSA levels.

Methods: Treatment-naïve patients ($n = 248$) diagnosed with BMPCa between December 2002 and June 2012 were retrospectively analyzed. Clinicopathological features at diagnosis, namely age, body mass index, serum alkaline phosphatase (ALP) and PSA levels, PSA nadir, time to PSA nadir and its maintenance period, PSA declining velocity, Gleason grade, clinical T stage, pain score, Eastern Cooperative Oncology Group performance score (ECOG PS), and the number of bone metastases were assessed. The patients were stratified according to PSA ranges of <20 ng/mL, 20–100 ng/mL, 100–1000 ng/mL, and 1000–10,000 ng/mL. Study endpoints were castration-resistant PCa (CRPC)-free survival and cancer-specific survival (CSS).

Results: Patients with higher PSA and ALP levels showed more bone lesions ($P < 0.001$). During the follow-up period (median, 39.9 months; interquartile range, 21.5–65.9 months), there were no differences between the groups in terms of the survival endpoints. High ALP levels, shorter time to PSA nadir, and pain were associated with an increased risk of progression to CRPC, and high ALP levels, ECOG PS ≥ 1 , and higher PSA nadir independently predicted CSS.

Conclusions: PSA response to androgen deprivation therapy and serum ALP are reliable predictors of survival in patients with BMPCa presenting with extremely high PSA levels. These patients should not be deterred from active treatment based on baseline PSA values.

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1. Introduction

Over the course of the prostate-specific antigen (PSA) era, patients have presented with prostate cancer (PCa) at a younger age and with lower grade disease, and are now more likely to present with organ-confined cancers.¹ However, bone metastasis still occurs in approximately 3% of all newly diagnosed patients. In a previous study, 12% of patients without initial evidence were found to develop bone metastases during a median follow-up of 2.2 years.^{2,3} In advanced stage PCa, bone is the most common site of metastasis, representing $>80\%$ of all cases, and this is associated with a high risk of morbidity.⁴ Given the heterogeneous natural

course of bone metastatic PCa (BMPCa), determining the prognostic clinicopathological features for survival is critical for patient counseling and to ensure judicious application of multimodal treatments.

PSA is a surrogate marker of systemic progression and cancer-specific survival (CSS).¹ Most prediction models define high risk PCa as a presenting PSA level of >20 ng/mL.⁵ However, the ability of an extremely high PSA level to reflect disease burden and its prognostic impact on survival has not been well described. Given the relationship between elevated PSA levels and inferior survival outcome, the concern about poorer outcome further intensifies when the PSA values are extremely elevated. Indeed, it is of substantial importance to identify patients at the highest risk of systemic dissemination, as aggressive definitive therapy targeting PCa may detrimentally impact the quality of life and performance status of these patients, without having any survival benefits.

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To our knowledge, no prior studies have investigated the differential survival outcomes of patients with BMPCa and extremely high PSA levels. Hence, there is uncertainty regarding the clinical utility of PSA at this stage of the disease, and the optimal management and extent of treatment remain unclear. In this study, we aimed to investigate the predictors of castration-resistant PCa (CRPC)-free survival and CSS in patients initially diagnosed with BMPCa presenting with extremely high serum PSA levels. We believe that the relatively uncommon finding of a PSA level of such a great magnitude and the paucity of data pertaining to survival outcome in this population lend relevance to this study.

2. Methods

2.1. Study population

A retrospective analysis was performed using a prospectively collected database of 248 consecutive treatment-naïve patients diagnosed with BMPCa between December 2002 and June 2012. PCa staging was determined according to the seventh American Joint Committee on Cancer TNM system, with the definition of bone metastasis based on either demonstrable metastatic deposits upon imaging studies (bone scan, computed tomography, magnetic resonance imaging, or positron emission tomography) or by pathologic confirmation. Patients were excluded from the analysis if they met the following criteria: (1) incomplete clinical data, (2) presence of visceral metastasis, (3) presence of nonregional lymph node enlargement, (4) lost to follow-up, or (5) unknown cause of death. The initiation and regimen of intermittent or continuous androgen-deprivation therapy (ADT), secondary hormonal manipulations, and cytotoxic chemotherapy were decided at each treating physician's discretion.

2.2. Prognostic factors and outcome variables

The clinical and pathological characteristics of the patients at diagnosis were retrieved from the institutional electronic medical record database. The data obtained consisted of age, baseline serum PSA and alkaline phosphatase (ALP) levels, PSA nadir, time to PSA nadir (TTN) and its maintenance period, PSA declining velocity, body mass index, Eastern Cooperative Oncology Group performance score (ECOG PS), Visual Analogue Scale pain score, Charlson Comorbidity Index, biopsy Gleason score, clinical T stage, progression to CRPC, and the number of metastatic bone lesions.

CRPC was defined as progression of disease or elevation of serum PSA using the Prostate Cancer Working Group 2 criteria,⁶ with the CRPC-free interval defined as the time from the date of the first radiographic bone metastasis to the date of CRPC diagnosis. The CSS interval was defined as the interval from the first date of diagnosis to the date of death from PCa. Patient data were considered missing if any of the above data were absent.

For the analyses, patients were stratified according to the following logarithmically scaled PSA ranges: <20 ng/mL, 20–100 ng/mL, 100–1000 ng/mL, and 1000–10,000 ng/mL. Patient survival and causes of death were investigated based on the National Cancer Registry Database or institutional electronic medical records. This study was approved by the institutional ethics committee after review of the protocol and procedures employed (3-2014-0112).

2.3. Statistical analysis

The clinicodemographic characteristics of the patients and tumors were compared using descriptive statistics. Appropriate comparative tests, such as analysis of variance and Fisher's exact

test, were used to compare continuous and categorical variables. Kaplan–Meier curves were used to estimate the CRPC-free survival and CSS according to PSA, ALP, PSA nadir, and TTN, stratified by given cutoff values. Multivariate analysis was performed using Cox-proportional hazards regression models in order to adjust for potential confounders in predicting survival. Variables considered as potential predictors for multivariate modeling were selected by univariate analyses and subsequently tested in a stepwise forward conditional manner, with entry and retention in the model set at a significance level of 0.05. All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). All tests were two-sided, with statistical significance set at $P < 0.05$.

3. Results

3.1. Patient characteristics

The clinicopathologic features of each group are presented in [Table 1](#). Patients with higher PSA levels were more likely to progress to CRPC, to harbor a greater number of metastatic bone lesions, and to have higher ALP levels than were patients with lower PSA levels. Of note, there were no differences in the distributions of biopsy Gleason grade, clinical T stage, and CSS rates between the PSA groups. Patients with ALP levels ≥ 200 IU/L harbored a greater number of metastatic bone lesions than those with ALP levels <200 IU/L ($P < 0.001$; data not shown).

3.2. Predictors of survival

The adjusted proportional hazard regression analyses for the potential prognostic factors of CRPC-free survival and CSS are summarized in [Tables 2 and 3](#), respectively. High ALP level, shorter TTN, and the presence of pain were found to be associated with increased risks of progression to CRPC, whereas high ALP level, high PSA nadir, and ECOG PS ≥ 1 independently predicted cancer-specific mortality.

3.3. Survival outcome

Survival data as of March 2014 were used in this analysis. During the median follow-up period of 39.9 months (interquartile range, 21.5–65.9 months), there were no differences in the CRPC-free survival and CSS between the different PSA groups ([Figs. 1A and 2A](#)). Comparative survival outcomes of covariates considered potential predictors by the Cox-proportional hazards analysis were analyzed according to each cutoff value. Patients with high ALP levels (≥ 200 IU/L) were found to have significantly worse CRPC-free survival ($P = 0.001$) and CSS ($P = 0.005$) compared to patients with ALP levels < 200 IU/L ([Figs. 1B and 2B](#)). Moreover, patients who achieved a PSA nadir value of ≥ 0.2 ng/mL following ADT, revealed worse CSS compared to those with PSA nadir <0.2 ng/mL ($P = 0.001$; [Fig. 2C](#)). However, PSA nadir was not associated with an increased risk of CRPC progression ($P = 0.614$; [Fig. 1C](#)). Patients with a TTN of <9 months showed significantly worse CRPC-free survival ($P = 0.024$) and CSS ($P = 0.022$) compared to those with TTN of ≥ 9 months ([Figs. 1D and 2D](#)).

4. Discussion

Most risk stratification schemes define high risk disease as a presenting PSA level of >20 ng/mL.^{1,5} In localized PCa, serum PSA has been demonstrated to correlate with the pathological stage, Gleason score, and the probability of organ-confined disease^{7,8}; whereas, in metastatic PCa, PSA has been shown to reflect the disease burden, and its post-hormone therapy response serves as a

Table 1
Clinical and pathological features of 248 patients initially diagnosed with bone-metastatic prostate cancer.

PSA group (ng/mL)	<20		20–100		100–1000		1000–10,000		P
N (%)	39	(15.7)	89	(35.9)	90	(36.3)	30	(12.1)	NS
Age (y)	73	(67–79)	65	(58–72)	71.5	(66.5–76.5)	71	(65.5–76.5)	0.803
BMI (kg/m ²)	25.5	(23–28.1)	22.9	(20.3–25.5)	22.7	(20.3–25.1)	23.7	(20.6–26.9)	0.813
ECOG PS (≥1)	7	(17.9)	24	(26.9)	20	(22.2)	11	(36.7)	0.728
CCI (≥4)	32	(82.1)	67	(75.3)	68	(75.6)	24	(80.0)	0.744
VAS pain score (≥1)	9	(23.1)	26	(29.2)	42	(46.7)	14	(46.7)	0.086
T stage									0.409
T2	10	(25.6)	7	(7.9)	8	(8.9)	2	(6.7)	
T3	23	(59.1)	49	(55.1)	40	(44.5)	18	(60.0)	
T4	6	(15.3)	33	(37.0)	42	(46.6)	10	(33.3)	
Gleason grade									0.114
≤7	11	(28.2)	23	(25.8)	15	(16.8)	1	(3.3)	
8	13	(33.3)	29	(32.6)	35	(38.9)	13	(43.3)	
≥9	15	(38.5)	37	(41.6)	40	(44.3)	16	(53.4)	
ALP (IU/L)	117	(71.0–196.3)	82.0	(71.0–107)	98.0	(72.5–191)	157	(93.0–389)	0.002
Time to PSA nadir (mo)	5.0	(3.0–6.0)	7.0	(5.0–12.0)	5.5	(4.0–10.3)	6.0	(5.0–10.0)	0.763
PSA nadir (ng/mL)	1.83	(0.01–5.5)	0.36	(0.02–1.6)	0.93	(0.09–5.98)	11.6	(0.27–25.4)	0.343
PSA nadir maintenance period (mo)	10.0	(6.5–23.5)	13.0	(8.0–18.0)	9.0	(6.0–19.0)	12.0	(8.0–18.0)	0.411
PSA velocity (ng/mL/mo)	10.0	(2.7–39.2)	11.3	(3.9–18.1)	45.3	(26.2–101.1)	472	(176–817)	0.051
Progression to CRPC	9	(23.1)	41	(46.1)	60	(66.7)	20	(66.7)	0.001
No. of bone lesions									<0.001
≤5	17	(43.6)	41	(46.1)	27	(30.0)	2	(6.7)	
6–20	11	(28.2)	41	(46.1)	30	(33.3)	6	(20.0)	
>21	11	(28.2)	7	(7.8)	33	(36.7)	22	(73.3)	
Follow-up period (mo)	39.9	(21.5–49.8)	39.1	(24.8–58.2)	41.2	(20.6–60.3)	26.9	(18.4–56.8)	0.607

Data are presented as n (%) and median (interquartile range).

ALP, alkaline phosphatase; BMI, body mass index; CCI, Charlson Comorbidity Index; CRPC, Castrate-resistance prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance score; LN, lymph node; PSA, prostate-specific antigen; VAS, Visual Analogue Scale.

predictor of overall survival.⁹ However, in a number of previous population-based observational studies, a PSA level >50 ng/mL was observed to correlate with extreme-risk patients, who showed a worse response to treatment and survival outcome than other high risk patients.^{7,9,10} Therefore, it is conceivable that the high risk population includes a subset of patients who are at an extreme risk for disease progression and mortality.

The natural history of metastatic PCa is heterogeneous, and the diagnostic and treatment dilemmas intensify when a patient presents with extremely high PSA levels. Although an extremely high PSA level is commonly acknowledged to indicate extreme risk

disease, no stratification model has yet demonstrated its prognostic value in this setting.¹¹ If a patient diagnosed with BMPCa would be expected to have an unfavorable survival outcome based on an extremely high PSA level, this patient may not be regarded as a candidate for aggressive treatment, as this may have detrimental impacts on the quality of life and performance status of the patient without any survival benefits. For these reasons, in an initial attempt to investigate this issue, we limited the patient population in this study to men with BMPCa, which may limit the confounding variables and potentially provide a more accurate assessment of a

Table 2
Predictors of progression to castration-resistant disease in patients with bone metastatic prostate cancer.

	Univariate			Multivariate ^a		
	HR	(95% CI)	P	HR	(95% CI)	P
Age (y)	0.991	(0.967–1.016)	0.471			
BMI	1.027	(0.963–1.095)	0.422			
Gleason score (≥8)	1.759	(1.068–2.898)	0.027			
T stage (≥T3)	1.195	(0.484–2.947)	0.701			
Baseline PSA	1.000	(0.998–1.001)	0.593			
Time to PSA nadir	0.916	(0.859–0.977)	0.008	0.877	(0.812–0.947)	0.001
PSA nadir	1.000	(0.993–1.006)	0.931			
PSA nadir maintenance period	0.968	(0.939–0.998)	0.041			
PSA velocity	1.000	(1.000–1.000)	0.603			
Baseline ALP	1.001	(1.001–1.002)	<0.001	1.001	(1.000–1.002)	0.007
VAS pain score (≥1)	1.519	(1.022–2.258)	0.039	3.061	(1.434–6.531)	0.004
ECOG PS (≥1)	1.141	(0.741–1.760)	0.552			
Number of bone lesions	1.016	(0.997–1.036)	0.095			

ALP, alkaline phosphatase; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CRPC, Castrate-resistance prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazards ratio; LN, lymph node; PSA, prostate-specific antigen; VAS, Visual Analogue Scale.

^a Forward step-wise conditional method.

Table 3
Predictors of cancer-specific mortality in patients with bone metastatic prostate cancer.

	Univariate			Multivariate ^a		
	HR	(95% CI)	P	HR	(95% CI)	P
Age (y)	1.009	(0.985–1.034)	0.447			
BMI	1.044	(0.961–1.135)	0.315			
Gleason score (≥8)	2.663	(1.421–4.994)	0.002			
T stage (≥T3)	1.529	(0.705–3.318)	0.282			
PSA	1.001	(0.999–1.002)	0.295			
Time to PSA nadir	0.879	(0.808–0.956)	0.003			
PSA nadir	1.001	(1.001–1.002)	0.002	1.006	(0.001–1.011)	0.012
PSA nadir maintenance period	0.924	(0.868–0.962)	0.003			
PSA velocity	1.000	(1.000–1.000)	0.149			
ALP	2.121	(1.353–3.324)	0.001	1.002	(1.001–1.003)	0.016
VAS pain score (≥1)	2.079	(1.309–3.301)	0.002			
ECOG PS (≥1)	2.238	(1.385–3.616)	0.001	2.685	(1.287–5.605)	0.009
Progression to CRPC	2.255	(1.442–3.526)	<0.001			
Number of bone lesions	1.017	(0.997–1.037)	0.102			

ALP, alkaline phosphatase; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CRPC, Castrate-resistance prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazards ratio; LN, lymph node; PSA, prostate-specific antigen; VAS, Visual Analogue Scale.

^a Forward step-wise conditional method.

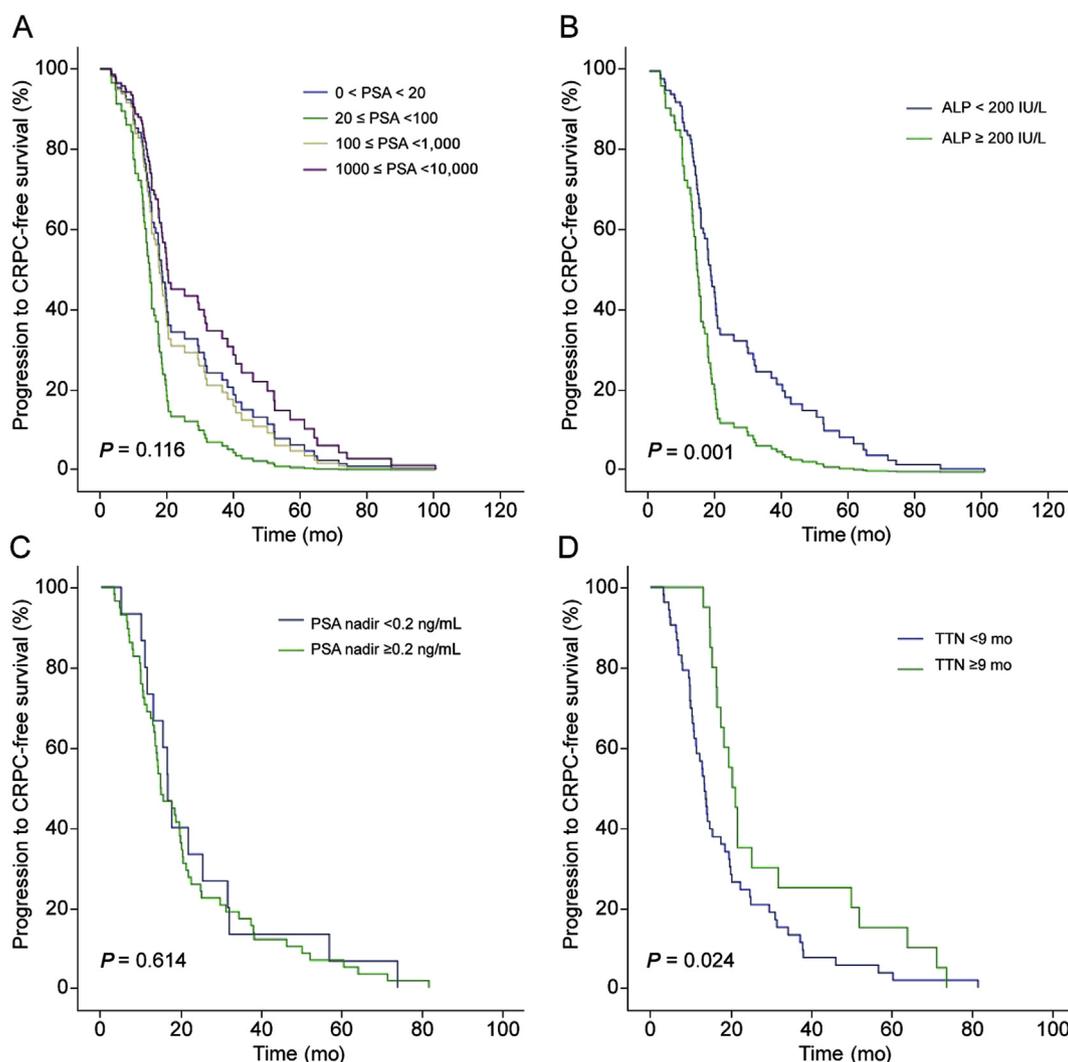


Fig. 1. Comparative survival curves of patients with bone metastatic prostate cancer for progression to castration-resistant prostate cancer (CRPC)-free survival. (A) Survival curve stratified according to serum prostate-specific antigen (PSA) levels. (B) Survival curve stratified according to serum alkaline phosphatase (ALP) levels dichotomized at 200 IU/L. (C) Survival curve stratified according to PSA nadir levels dichotomized at 0.2 ng/mL. (D) Survival curve stratified according to time to PSA nadir (TTN) dichotomized at 9 months.

specific population in which a prediction model would be clinically useful.

Bone metastasis in PCa is characterized by a distinct clinical pattern of bone-forming metastasis.¹² Among the various bone-related biochemical markers that are known to be elevated in patients with BMPCa,^{13,14} serum ALP is a representative bone formation marker that has been demonstrated to be associated with both the extent of bone metastasis and survival.^{15,16} The importance of serum ALP as a prognostic factor for survival in metastatic PCa has been emphasized in previously developed survival models, in which the patient performance status as well as hemoglobin, albumin, lactate dehydrogenase, and ALP levels, was demonstrated to be significantly associated with overall survival.^{17–19} Our study confirmed patient performance status and serum ALP levels as independent predictors, even in patients with BMPCa presenting with extremely high PSA levels. Of note, our multivariate analysis revealed oncological features such as clinical T stage or Gleason grade to have only modest effects on survival outcome, which was also consistent with the results of certain previous studies.^{20,21} However, the inclusion of only patients with BMPCa who tended to have high risk disease may have limited the discriminatory value of these variables.

In clinical practice, PSA is the most widely utilized surrogate and prognostic marker used to evaluate disease burden and to predict survival prognosis.²² PSA has been shown to correlate with increased risks of bone-related clinical outcomes and overall survival in patients with metastatic CRPC²³; and, moreover, in men with nonmetastatic CRPC, a higher PSA has been found to be associated with a shorter time to bone metastasis and reduced overall survival.¹⁴ However, it should be noted that the cohorts of these previous studies consisted of patients with relatively low PSA levels. Hence, our findings are of particular importance, given that extremely high PSA levels failed to show associations with all survival endpoints. Furthermore, the results of the current study are consistent with previous reports of patients on ADT, in which the association between baseline PSA and time to progression was confined only to nonmetastatic patients.²⁴

PSA kinetics following ADT, namely, PSA nadir, TTN, and PSA velocity, have been shown to be useful predictors of disease progression and survival in various disease settings.²⁵ Previous studies have reported a significant association between PSA nadir and progression to CRPC.^{20,26} Although there is currently no consensus on the optimal threshold of PSA nadir, we used the most widely reported cutoff value of 0.2 ng/mL in this study, and found that PSA

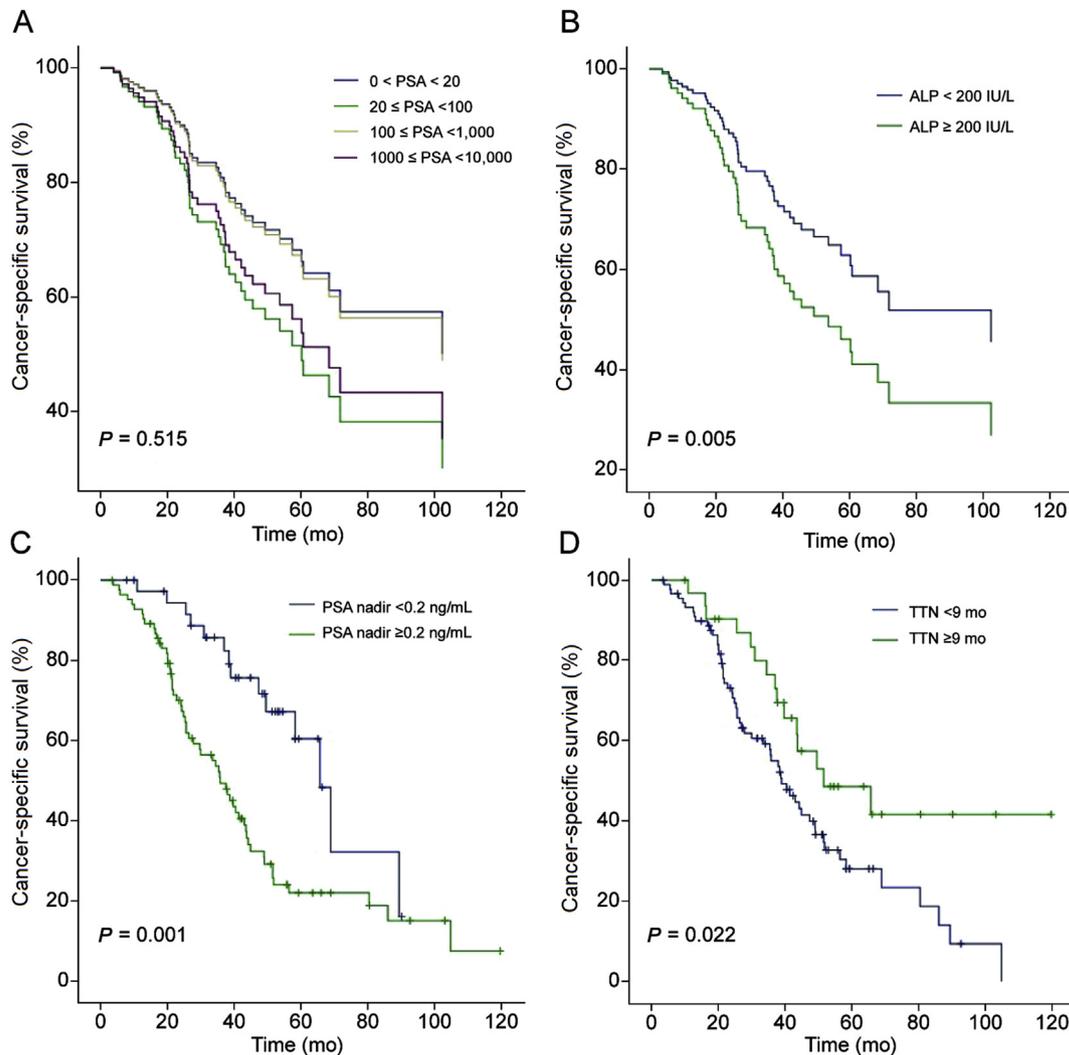


Fig. 2. Comparative survival curves of patients with bone metastatic prostate cancer for cancer-specific survival. (A) Survival curve stratified according to serum prostate-specific antigen (PSA) levels. (B) Survival curve stratified according to serum alkaline phosphatase (ALP) levels dichotomized at 200 IU/L. (C) Survival curve stratified according to PSA nadir levels dichotomized at 0.2 ng/mL. (D) Survival curve stratified according to time to PSA nadir (TTN) dichotomized at 9 months.

nadir ≥ 0.2 ng/mL was an independent predictor of CSS.^{26,27} Likewise, there is also no consensus regarding the optimal threshold of TTN for predicting survival outcomes, and various studies have reported conflicting cutoff values, varying according to each study setting.^{27,28} Herein, we showed that a cutoff period of 9 months was capable of distinguishing patients with favorable CRPC-free survival and CSS rates; these findings are consistent with those of recent studies, which have reported that a longer TTN is associated with longer remission and survival.^{29,30} Although the exact mechanism underlying the association between PSA kinetics and survival prognosis is unclear, our results highlight the fact that the prognosis of patients diagnosed with BMPCa with extremely high PSA levels depends on multiple patient factors. Based on our results, we support the use of PSA kinetics following ADT and baseline serum ALP as alternative prognostic markers to PSA for risk stratification at this stage of the disease.

The main strength of the current study was the incorporation of detailed clinicopathological data, including information on treatment, comorbidities other than cancer, and performance status, available from each patient. Moreover, the use of a single institutional cohort may ensure uniformity of the data. However, at the same time, there were several potential limitations worth

mentioning. The first is the retrospective nature of the study. This design is associated with a lack of a standard therapeutic approach, and strong patient and physician preferences existed regarding the implementation of specific treatments. As such, the indication to initiate therapy, choice of treatment modality, administration intervals, and type of agents lacked standardization. Nevertheless, we believe that this effect is inherent in any retrospective study and may reflect the real-world clinical practice in which the application of sequential therapies for metastatic PCa is not standardized. Secondly, our study cohort was limited to patients with BMPCa, and the prognostic factors identified were not determined until metastasis had developed. Thus, the results may not be generalizable to evaluating the risk for patients diagnosed with other metastases or after a certain treatment. However, despite these limitations, the current study provided information regarding the long-term survival outcomes in a unique cohort of potentially extreme-risk patients, for whom risk stratification is controversial.

An extreme serum PSA level reflects the disease burden of BMPCa; however, it is not prognostic for CRPC-free survival or CSS. Patients with BMPCa initially presenting with extremely high PSA levels should not be deterred from active treatment and should be given a definitive therapeutic goal, as these patients may show

comparable survival outcomes to that of men with relatively low PSA levels. Moreover, our observations support the use of the PSA response to ADT and serum ALP levels as alternative predictors of survival in these patients.

Conflict of interest

None of the contributing authors have any conflicts of interest, including specific financial interests, relationships, and affiliations relevant to the subject matter or materials discussed in the manuscript.

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