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PSA Kinetics Affect Prognosis in Patients With Castration-resistant Prostate Cancer Treated With Enzalutamide

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Abstract. *Background/Aim: There is little evidence regarding the predictive value of prostate-specific antigen (PSA) kinetics in patients with castration-resistant prostate cancer treated with an androgen receptor signaling inhibitor. This study investigated the correlation between PSA kinetics and prognosis in patients with castration-resistant prostate cancer treated with enzalutamide. Patients and Methods: We analyzed data from 103 patients who received enzalutamide as primary treatment for castration-resistant prostate cancer at our hospital, focusing on the associations between overall survival and PSA kinetics variables, such as maximal PSA response, PSA nadir, and time to PSA nadir. Results: The median PSA level at the initiation of enzalutamide was 18.1 ng/ml (interquartile range=7.9-61.2 ng/ml). The median maximal PSA response rate was 88% (interquartile range 55-98), and the median PSA nadir was 1.84 (interquartile range (IQR)=0.38-14.7) ng/ml. The median time to PSA nadir was 19 (IQR=6-28.5) weeks. Maximal PSA response rate <90% [hazard ratio (HR)=2.28, 95% confidence interval (CI)=1.03-5.03, p=0.0413], PSA nadir >2 ng/ml (HR=2.30, 95%CI=1.05-5.07, p=0.0379), time to nadir <19 weeks (HR=2.48, 95%CI=1.15-5.35, p=0.0204) were all independently predictive of shortened overall survival even after adjusting for pre-treatment factors. Conclusion: Maximal PSA response, PSA nadir, and time to PSA nadir correlated with survival in patients with castration-resistant prostate cancer receiving enzalutamide as a first-line therapy.*

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Prostate cancer (PCa) treatment is advancing rapidly, and upfront therapy with docetaxel or androgen receptor signaling inhibitors (ARSI) is now widely used for metastatic castration-sensitive PCa (mCSPC). However, in the real world, mCSPC is often treated with androgen deprivation therapy (ADT) (1).

Enzalutamide is effective for castration-resistant prostate cancer (CRPC) (2). We have previously reported that in patients receiving enzalutamide as primary treatment for CRPC, the time to castration resistance and metastases to the lymph nodes at the initiation of enzalutamide treatment are associated with the response to enzalutamide (3). However, we could not identify the independent pre-treatment factors that correlated with overall survival (OS). A biomarker for predicting OS has yet to be established.

There is accumulating evidence that PSA kinetics have prognostic value in patients treated with ADT (4). In recent years, post hoc analyses of the LATITUDE and TITAN trials found that PSA kinetics predict OS in mCSPC patients receiving ARSI as upfront therapy (5, 6). However, few reports have shown a correlation between PSA kinetics and prognosis in patients with CRPC, and there is no consensus. The biology of CSPC and CRPC treated with ARSI differs significantly from that of those treated with conventional hormone therapy, and PSA kinetics change accordingly (7, 8). Analyzing the association between PSA kinetics and prognosis during ARSI treatment is important both in terms of predicting patient prognosis and understanding the biology of CRPC treated with ARSI.

In this study, we focused on PSA kinetics after the initiation of enzalutamide treatment to explore the factors that may affect OS.

Patients and Methods

Study design and data collection. The previously analyzed cohort was updated with an increased number of cases and observation period (6). Patients who were started on enzalutamide for CRPC at Osaka University Hospital from 2014 to August 2022 and who had not yet received treatment with docetaxel and ARSI for CRPC were included in the present study. The definitions of CRPC and PSA progression are the same as in our previous reports (3, 9). The history of docetaxel administration to CSPC was acceptable. Patients with insufficient clinical data were excluded. We obtained the patients' ages, Gleason scores, laboratory and imaging data at the initiation of enzalutamide treatment, and PSA levels from their medical records. Tumors were classified as high volume if they had four or more bone metastases, with at least one outside the pelvis or spine, or if they had at least one visceral metastasis according to the criteria of the CHAARTED trial (10).

Endpoints. We defined OS as the primary endpoint. We analyzed the effects of PSA kinetics, such as maximal PSA response, PSA nadir, and time to PSA nadir (TTN), on OS. We also analyzed the impact of pretreatment variables on OS. Multivariate analysis was performed using pre- and post-treatment variables that showed significant differences in the univariate analysis. We defined OS as the time from the initiation of enzalutamide administration to death. PSA progression-free survival (PSA–PFS) was the secondary endpoint. The definition of PSA-PFS is the same as in our previous study (3).

Statistical analysis. Clinical variables are presented as frequencies and percentages for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. Survival curves were constructed using the log-rank test and the Kaplan-Meier method. Cox proportional hazard models were utilized to evaluate relationships between clinical variables and endpoints. Each factor related to PSA kinetics that was a significant predictor in the univariate analysis was subjected to multivariate analysis, along with the pretreatment parameters significantly associated with prognosis in the univariate analysis. The two groups were compared using Fisher's exact test for categorical variables and the *t*-test for continuous variables. Statistical significance was set at $p<0.05$. JMP Pro 17 version (SAS Institute Inc., Cary, NC, USA) was used for all the data analyses.

Approval of the research protocol by the Institutional Reviewer Board and the approval number. This study was approved by the Institutional Review Board of Osaka University Hospital. (Ethics review number: 13397-20) This study complies with the provisions of the Declaration of Helsinki.

Results

Patient characteristics. As shown in Figure 1, 103 patients met the inclusion criteria. Table I shows the clinical characteristics of the 103 patients. The median duration of

Table I. *Patient characteristics*.

Variable	Total (N=103)
Median age, years (IQR)	74 (69-81)
Median serum PSA level at diagnosis, ng/ml (IQR)	47.4 (12.6-165)
Clinical T stage at diagnosis, n (%)	
<T3a	34 (33%)
≥T3a	60 (58%)
Not available	9 (9%)
Gleason sum at diagnosis, n (%)	
<8	21 (20%)
≥8	73 (71%)
Not available	9 (9%)
Treatment for CSPC, n (%)	
CAB	68 (66%)
ADT	28 (27%)
ADT+docetaxel	6 (6%)
CAB+docetaxel	1 (1%)
PSA nadir during the initial treatment for CSPC, ng/ml (IQR)	0.26 (0.028-1.2)
Median time to CRPC, months (IQR)	18 (9.5-35)
Lymph node metastasis at the start of enzalutamide administration, n (%)	
Presence	22 (21%)
Absence	76 (74%)
Not available	5 (5%)
Bone metastasis at the start of enzalutamide administration, n (%)	
Presence	68 (66%)
Absence	31 (30%)
Not available	4 (4%)
Visceral metastasis at the start of enzalutamide administration, n (%)	
Presence	11 (11%)
Absence	87 (84%)
Not available	5 (5%)
High-volume tumor at the start of enzalutamide administration, n (%)	
Presence	50 (49%)
Absence	49 (48%)
Not available	4 (4%)
Distant metastasis at the start of enzalutamide administration, n (%)	
Presence	79 (77%)
Absence	23 (22%)
Not available	1 (1%)
Hb at the start of enzalutamide administration, median (g/dl, IQR)	12.6 (11.3-13.5)
ALP at the start of enzalutamide administration, median (U/l, IQR)	268 (207-403)
PSA at the start of enzalutamide administration, median (ng/ml, IQR)	18.1 (7.9-61.2)
Maximal PSA response rate (%, IQR)	88 (55-98)
PSA nadir (ng/ml, IQR)	1.84 (0.38-14.7)
TTN (week, IQR)	19 (6-28.5)

IQR: Interquartile range; PSA: prostate-specific antigen; CSPC: castration-sensitive prostate cancer; CAB: combined androgen blockade; ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; Hb: hemoglobin; ALP: alkaline phosphatase; TTN: time to PSA nadir.

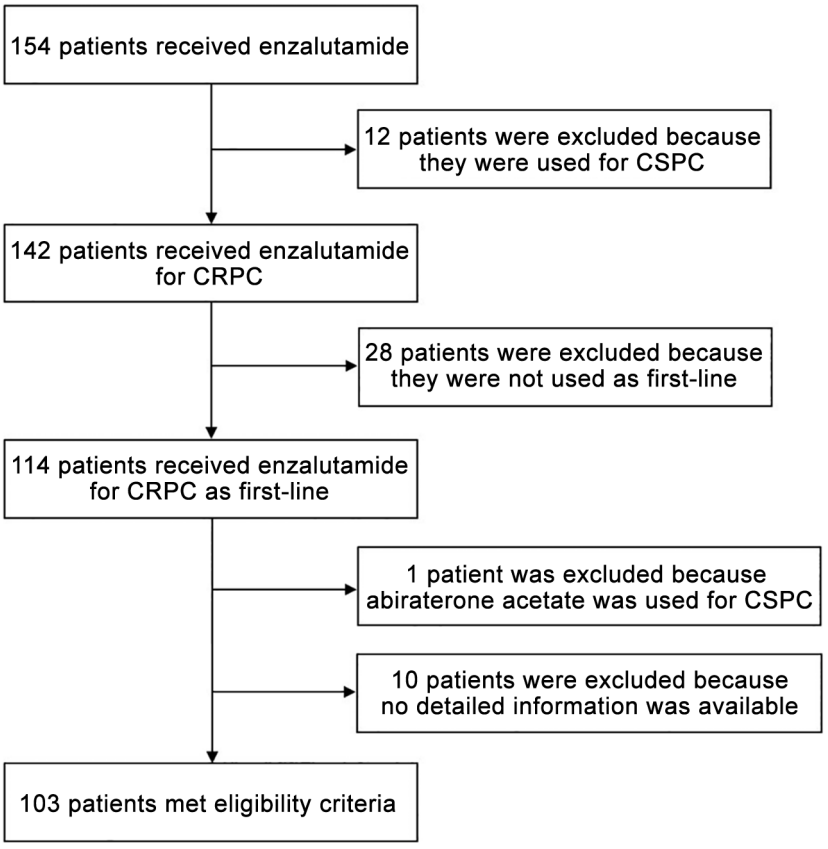

Figure 1. *Study schematic. CSPC: Castration-sensitive prostate cancer; CRPC: castration-resistant prostate cancer.*

treatment with enzalutamide and observation were 11 (IQR=6-22.5) and 23 months (IQR=11.5-44), respectively. The median PSA level at the start of enzalutamide treatment was 18.1 (IQR=7.9-61.2) ng/ml. The median maximum PSA response rate, PSA nadir, and TTN were 88% (IQR=55-98), 1.84 (IQR=0.38-14.7) ng/ml, and 19 (IQR=6-28.5) weeks, respectively. During the observation period, 35 patients died and 72 patients developed PSA exacerbations.

Factors affecting OS. In this study, we analyzed the correlation between OS and three parameters: the maximal PSA response rate, PSA nadir, and TTN. The maximal PSA response rate <90% [hazard ratio (HR)=2.84, 95% confidence interval (CI)=1.39-5.80, p=0.0040], PSA nadir >2 ng/ml (HR=3.23, 95%CI=1.61-6.47, p=0.0010), and TTN <19 weeks (HR=2.89, 95%CI=1.45-5.75, p=0.0025) were parameters that were associated with shorter survival in the univariate analysis (Table II). We previously reported that in univariate analysis, time to CRPC <18 months, high-volume tumors, alkaline phosphatase (ALP)>upper limit of normal (ULN), and PSA >20 ng/ml were correlated with worse OS (There were no significant factors in the multivariate analysis). In this cohort, time to CRPC <18 months (HR=2.5, 95%CI=1.23-5.12, p=0.0118), high-volume tumor (HR=2.45, 95%CI=1.16-5.17, p=0.0187), ALP>ULN (HR=2.89, 95%CI=1.30-6.44, p=0.0092), and PSA >20 ng/ml (HR=2.24, 95%CI=1.11-4.50, p=0.0243) were also associated with worse OS. Each of the three PSA kinetic parameters was subjected to multivariate analysis along with the pretreatment factors (Table III, Models 1-3). Maximal PSA response rate <90% (HR=2.28, 95%CI=1.03-5.03, p=0.0413), PSA nadir >2 ng/ml (HR=2.30, 95%CI=1.05-5.07, p=0.0379), TTN <19 weeks (HR=2.48, 95%CI=1.15-5.35, p=0.0204) were all independently correlated with OS regardless of pre-treatment factors.

Factors affecting PSA-PFS. The effect of PSA kinetics on PSA-PFS was also analyzed. Maximal PSA response rate <90% (HR=5.63, 95%CI=3.13-10.1, p<0.0001), PSA nadir >2 ng/ml (HR=11.3, 95%CI=5.92-21.7, p<0.0001), TTN <19 weeks (HR=11.3, 95%CI=6.05-21.1, p<0.0001) were associated with shorter PSA-PFS in univariate analysis (Table II). We previously reported that age <75 years, time to CRPC <18 months, lymph node metastasis, high-volume tumor, ALP>ULN, and PSA >20 ng/ml were factors that were correlated with worse PSA-PFS in a univariate

Table II. *Univariate analysis for overall survival (OS) and prostate-specific antigen-progression-free survival (PSA-PFS).*

		OS		PSA-PFS	
Variable	*vs*. Referent	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Maximal PSA response rate	<90 *vs*. ≥90%	2.84 (1.39-5.80)	0.0040	5.63 (3.13-10.1)	<0.0001
PSA nadir	>2 *vs*. ≤2 ng/ml	3.23 (1.61-6.47)	0.0010	11.3 (5.92-21.7)	<0.0001
TTN	<19 *vs*. ≥19 weeks	2.89 (1.45-5.75)	0.0025	11.3 (6.05-21.1)	<0.0001

HR: Hazard ratio; CI: confidence interval; TTN: time to PSA nadir.

Table III. *Multivariate analysis of overall survival (OS).*

		Model.1		Model.2		Model.3	
Variable	*vs*. Referent	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Time to CRPC	<18 *vs*. ≥18 months	1.90 (0.824-4.37)	0.133	1.96 (0.843-4.54)	0.119	2.39 (1.04-5.45)	0.0392
High-volume tumor	Present *vs*. absent	0.909 (0.378-2.18)	0.831	0.839 (0.346-2.03)	0.697	1.06 (0.429-2.63)	0.896
ALP at the start of enzalutamide treatment	>ULN *vs*. ≤ULN	2.17 (0.868-5.42)	0.0975	2.15 (0.872-5.30)	0.0965	1.79 (0.725-4.40)	0.208
PSA at the start of enzalutamide treatment	>20 *vs*. ≤20 ng/ml	2.09 (0.864-5.04)	0.102	1.90 (0.797-4.55)	0.148	1.78 (0.737-4.29)	0.200
Maximal PSA response rate	<90 *vs*. ≥90 %	2.28 (1.03-5.03)	0.0413				
PSA nadir	>2 *vs*. ≤2 ng/ml			2.30 (1.05-5.07)	0.0379		
TTN	<19 *vs*. ≥19 weeks					2.48 (1.15-5.35)	0.0204

OS: Overall survival; HR: hazard ratio; CI: confidence interval; CRPC: castration-resistant prostate cancer; ALP: alkaline phosphatase; ULN: upper limit of normal; PSA: prostate-specific antigen; TTN: time to PSA nadir.

analysis. In this cohort, age <75 years (HR=1.66, 95%CI=1.04-2.67, p=0.0354), time to CRPC <18 months (HR=1.96, 95%CI=1.19-3.22, p=0.0078), lymph node metastasis (HR=3.05, 95%CI=1.71-5.44, p=0.0002), high-volume tumor (HR=2.06, 95%CI=1.24-3.42, p=0.0051), ALP>ULN (HR=1.89, 95%CI=1.08-3.30, p=0.0249), and PSA >20 ng/ml (HR=2.80, 95%CI=1.72-4.56, p<0.0001) were also associated with worse PSA-PFS in univariate analysis. Each parameter related to PSA kinetics was subjected to multivariate analysis along with pre-treatment factors (Table IV, Models 1-3). Maximal PSA response rate <90% (HR=4.87, 95%CI=2.32-10.2, p<0.0001), PSA nadir >2 ng/ml (HR=8.99, 95%CI=3.87-20.9, p<0.0001), TTN <19 weeks (HR=10.2, 95%CI=4.71-22.2, p<0.0001) were all independently correlated with PSA-PFS regardless of pre-treatment factors.

Comparison of outcomes and characteristics between TTN ≥19 weeks and <19 weeks groups. Figure 2 shows how long it takes for PSA nadir. In many cases, a longer time was required to reach the nadir. As noted above, OS and PSA-PFS are significantly prolonged in cases with TTN ≥19 weeks. Therefore, we divided the patients into two groups according to TTN ≥19 weeks or not and compared outcomes (Figure 3). The median OS for the TTN ≥19 weeks group was 82 (IQR=38-not reached) months, which was significantly longer than the median OS of 43 (IQR=17-76) months for the <19 weeks group (p=0.0016). The median PSA-PFS for the TTN ≥19 weeks group was 27 (IQR=13-56) months, which was significantly longer than the median PSA-PFS of 5 (IQR=3-7) months for the <19 weeks group (p<0.0001). Finally, the background factors between the two groups were compared (Table V). The TTN <19 weeks group had more patients with a high T stage, lymph node metastasis, distant metastasis, and low hemoglobin levels.

Discussion

In the present study, the analysis of patients treated with enzalutamide as the primary therapy for CRPC revealed that PSA kinetics after enzalutamide initiation were correlated with OS. Maximal PSA response rate <90%, PSA nadir >2 ng/ml,

Table IV. *Multivariate analysis of prostate-specific antigen (PSA)-progression-free survival (PFS).*

		Model.1		Model.2		Model.3	
Variable	*vs.* Referent	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age	<75 *vs.* ≥75 Years	1.31 (0.749-2.27)	0.347	1.30 (0.741-2.29)	0.359	1.96 (1.09-3.51)	0.0238
Time to CRPC	<18 *vs.* ≥18 Months	1.51 (0.848-2.69)	0.162	1.19 (0.649-2.18)	0.575	1.60 (0.921-2.80)	0.0952
Lymph node metastasis	Present *vs.* absent	1.46 (0.679-3.15)	0.332	1.24 (0.569-2.71)	0.586	2.22 (1.06-4.66)	0.0345
High-volume tumor	Present *vs.* absent	1.34 (0.718-2.49)	0.360	1.29 (0.693-2.39)	0.424	1.96 (0.994-3.86)	0.0521
ALP at the start of enzalutamide treatment	>ULN *vs.* ≤ULN	1.71 (0.832-3.51)	0.145	1.89 (0.920-3.89)	0.0831	1.29 (0.640-2.59)	0.478
PSA at the start of enzalutamide treatment	>20 *vs.* ≤20 ng/ml	1.69 (0.807-3.52)	0.165	1.16 (0.556-2.44)	0.688	1.07 (0.478-2.38)	0.875
Maximal PSA response rate	<90 *vs.* ≥90 %	4.87 (2.32-10.2)	<0.0001				
PSA nadir	>2 *vs.* ≤2 ng/ml			8.99 (3.87-20.9)	<0.0001		
TTN	<19 *vs.* ≥19 Weeks					10.2 (4.71-22.2)	<0.0001

HR: Hazard ratio; CI: confidence interval; CRPC: castration-resistant prostate cancer; ALP: alkaline phosphatase; ULN: upper limit of normal; TTN: time to PSA nadir.

and TTN <19 weeks were all factors that shortened OS independent of pre-treatment factors.

Post hoc analyses of several large clinical trials have demonstrated that PSA kinetics predict prognosis in mCSPC patients treated with ARSI. The post hoc analysis of the LATITUDE trial revealed that PSA response rate, reduction of PSA to <0.1 ng/ml within six months, and longer TTN were predictive of OS and radiographic PFS (rPFS) in patients with mCSPC treated with abiraterone acetate (5). In addition, post hoc analysis of the TITAN trial revealed that deep PSA decline improved OS and rPFS in patients with mCSPC treated with apalutamide (6). Even regarding patients with mCSPC treated with ADT, there are many reports that PSA kinetics, such as PSA doubling time, PSA nadir, and TTN predict prognosis (4).

However, few studies have shown an association between PSA kinetics and prognosis in patients with CRPC treated with ARSI. Tseng *et al*. reported that PSA nadir ≤2 was a factor in prolonging OS in a group of patients treated with ARSI as the primary therapy for CRPC (11). A post-hoc analysis of the PROSPER study revealed that the PSA nadir and PSA decline rate affected metastatic free survival and OS in patients with non-metastatic CRPC treated with enzalutamide (12). España *et al*. analyzed a group of patients with metastatic CRPC (mCRPC) who received abiraterone after progression on docetaxel and reported that early PSA response and TTN were independent predictors of OS (13). Miyazawa *et al*. reported that PSA velocity and PSA doubling time during PSA progression predicted OS in patients with metastatic CRPC treated with enzalutamide (14). Thus, although there are few reports, PSA kinetics is

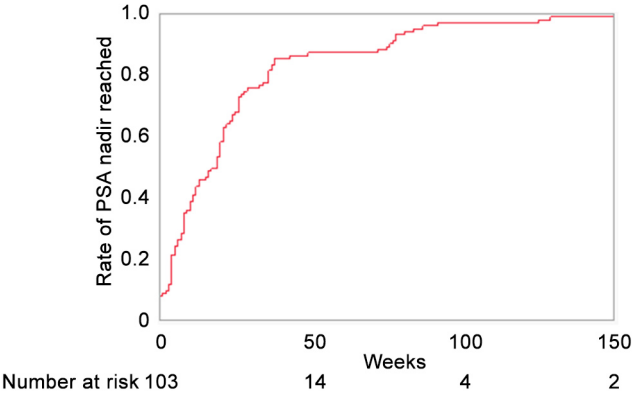

Figure 2. *Kaplan-Meier analysis showing time from the start of enzalutamide to reach PSA nadir.*

expected to be a prognostic tool for patients with CRPC treated with ARSI. PSA kinetics also predict prognosis in patients with CRPC treated with docetaxel. We have previously demonstrated in a multicenter study that a 50% or greater reduction in PSA levels prolongs OS in patients treated with docetaxel as the primary therapy for CRPC (15).

This study showed that TTN at <19 weeks is a factor that shortens OS and PSA-PFS. To the best of our knowledge, this is the first report to demonstrate an association between TTN and prognosis in patients treated with enzalutamide as the primary therapy for CRPC. Tseng *et al*. reported that longer TTN prolongs OS in patients with mCRPC treated with ARSI as the primary therapy (11). Miyake *et al*. reported that longer TTN prolonged PSA-PFS in patients

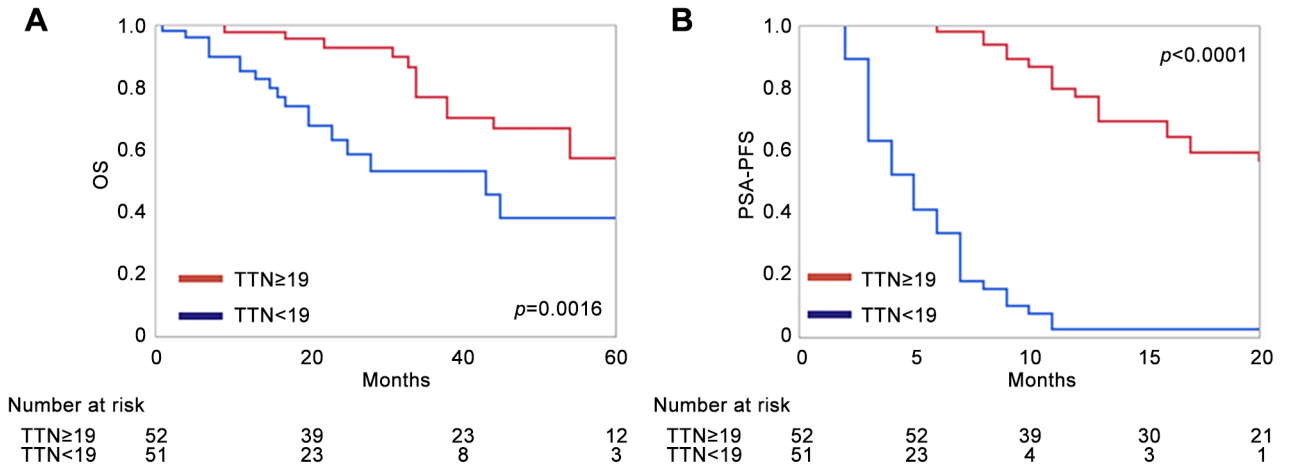

Figure 3. *Kaplan-Meier analysis showing (A) overall survival and (B) prostate-specific antigen-progression-free survival of two groups defined by time to PSA nadir (TTN).*

Table V. *Comparison of patient background when divided into two groups by time to PSA nadir (TTN).*

Variable	TTN <19 (N=51)	TTN ≥19 (N=52)	*p*-Value
Median age, years (IQR)	74 (69-82)	75.5 (69.3-81)	0.823
Median serum PSA level at diagnosis, ng/ml (IQR)	48.6 (12.7-219)	44.4 (11.6-160)	0.974
Clinical T stage at diagnosis, n (%)			0.019
<T3a	11 (22%)	23 (44%)	
≥T3a	35 (69%)	25 (48%)	
Not available	5 (10%)	4 (8%)	
Gleason sum at diagnosis, n (%)			0.0820
<8	6 (12%)	15 (29%)	
≥8	38 (75%)	35 (67%)	
Not available	7 (14%)	2 (4%)	
PSA nadir during the initial treatment for CSPC, ng/ml (IQR)	0292 (0.07-0.95)	0.12 (0.005-1.38)	0.568
Median time to CRPC, months (IQR)	14 (8-27)	27 (10.3-45.8)	0.0972
Lymph node metastasis at the start of enzalutamide administration, n (%)			0.0288
Presence	16 (31%)	6 (12%)	
Absence	34 (67%)	42 (81%)	
Not available	1 (2%)	4 (8%)	
Bone metastasis at the start of enzalutamide administration, n (%)			0.133
Presence	38 (75%)	30 (58%)	
Absence	12 (24%)	19 (37%)	
Not available	1 (2%)	3 (6%)	
High volume tumor at the start of enzalutamide administration, n (%)			0.161
Presence	29 (57%)	21 (40%)	
Absence	21 (41%)	28 (54%)	
Not available	1 (2%)	3 (6%)	
Distant metastasis at the start of enzalutamide administration, n (%)			0.0166
Presence	45 (88%)	34 (65%)	
Absence	6 (12%)	17 (33%)	
Not available	0 (0%)	1 (2%)	
Hb at the start of enzalutamide administration, median (g/dl, IQR)	12.2 (10.7-13.2)	13.2 (12-13.8)	0.0008
ALP at the start of enzalutamide administration, median (U/l, IQR)	280 (230-556)	242 (201-322)	0.526
PSA at the start of enzalutamide administration, median (ng/ml, IQR)	31.6 (11.0-109)	11.6 (7.75-23.7)	0.0796

IQR: Interquartile range; PSA: prostate-specific antigen; CSPC: castration-sensitive prostate cancer; CRPC: castration-resistant prostate cancer; Hb: hemoglobin; ALP: alkaline phosphatase.

treated with abiraterone acetate (16). However, no correlation was found between TTN and PSA-PFS in a cohort treated with enzalutamide. It has been reported that longer TTN correlates with better OS of patients with CRPC treated not only with ARSI but also with docetaxel (17).

There are several reports about longer TTN being correlated with better prognosis in patients with mCSPC treated with ADT (18). Tomioka *et al*. reported that TTN <6 months during initial hormone therapy was associated with shorter OS and time to CRPC (19). Hamano *et al*. reported that shorter TTN correlated with worse prognosis after progression to mCRPC (20). Kitagawa *et al*. reported that PSA nadir <0.5 ng/ml and TTN ≥9 months correlated with favorable OS and PFS in a prospective cohort study of 10958 patients (21). The rapid decline in PSA during ADT is thought to mean that hormone-sensitive cells make up most of the tumor; in other words, there are relatively few hormone-resistant cells (22). This suggests that a rapid PSA decline is associated with improved prognosis. However, the effect of TTN on the prognosis contradicts this hypothesis. The reason a longer TTN correlates with a better prognosis is not well understood; however, several considerations have been made. First, the rapid decline in PSA levels may not reflect an antitumor effect but simply a transcriptional repressive effect of ADT on PSA (23). Second, the rapid decline in PSA levels after ADT may result in the loss of androgen receptor (AR) function as a tumor suppressor, which may promote disease progression (24). Another hypothesis is that rapid PSA decline implies rapid elimination of hormone-sensitive prostate cancer cells, which leads to the selection of a subset of hormone-resistant cells (23). Sasaki *et al*. have shown in animal studies that AR-independent fibroblasts can prevent rapid loss of AR function and contribute to longer TTN and better ADT therapeutic efficacy (25).

We need to be careful when interpreting PSA values in patients with PCa treated with ARSI. Although most patients with mCRPC have strong AR activity (26), those who have progressed with ARSI tend to have AR-null tumors compared to those who have progressed with ADT (7), and PSA levels may not reflect the disease status. Furthermore, among patients with mCSPC, more patients who received ARSI or docetaxel in the upfront setting had imaging progression without an increase in PSA than patients who received conventional hormone therapy (8). ARSI treatment induces transformation of AR-positive cells into highly invasive neuroendocrine cancer and double-negative PC (negative for both AR and neuroendocrine markers), causing disease progression that deviates from the PSA level (27). Despite this, the previous reports and the current study demonstrate that PSA kinetics correlate with prognosis in patients with CRPC treated with ARSI (11-14). PSA kinetics can be an effective tool for predicting prognosis when regular imaging studies are performed to avoid missing progression without PSA elevation.

In this study, a low hemoglobin (Hb) level was associated with a shorter TTN, although no laboratory data were found to independently predict OS. Hakozaki *et al*. reported low Hb levels as a poor prognostic factor in patients with mCRPC (28). They suggest that low Hb levels reflect the replacement of cancer cells with bone marrow, chronic inflammation, and cytokine-mediated disorders, which may result in a worsening of OS.

One limitation of this study is that it was a single-center retrospective study. It is expected that more data will be accumulated in the future and that solid evidence will be provided for the prognostic effect of PSA kinetics in patients with CRPC.

Conclusion

This study revealed that the maximal PSA response rate, PSA nadir, and TTN were associated with prognosis in patients with CRPC treated with enzalutamide as a first-line therapy.

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None.

Conflicts of Interest

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Authors' Contributions

Toshiki Oka: Methodology; data curation; formal analysis; writing—original draft; investigation; visualization. Koji Hatano: Conceptualization; data curation; project administration; writing—review & editing; investigation. Masaru Tani: Investigation. Akihiro Yoshimura: Investigation. Yuki Horibe: Data curation. Yutong Liu: Investigation. Nesrine Sassi: Investigation. Yohei Okuda: Writing—review & editing. Akinaru Yamamoto: Writing—review & editing. Toshihiro Uemura: Writing—review & editing. Gaku Yamamichi: Writing—review & editing. Yu Ishizuya: Writing—review & editing. Yoshiyuki Yamamoto: Writing—review & editing. Taigo Kato: Writing—review & editing; supervision. Atsunari Kawashima: Writing—review & editing; supervision. Kazutoshi Fujita: writing—review & editing; supervision. Norio Nonomura: Writing—review & editing; supervision.

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