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ORIGINAL ARTICLE

Prostate Cancer

PSA time to nadir as a prognostic factor of first-line docetaxel treatment in castration-resistant prostate cancer: evidence from patients in Northwestern China

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Docetaxel-based chemotherapy remains the first-line treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) in China; however, the prognostic factors associated with effects in these patients are still controversial. In this study, we retrospectively reviewed the data from 71 eligible Chinese patients who received docetaxel chemotherapy from 2009 to 2016 in our hospital and experienced a reduction of prostate-specific antigen (PSA) level ≥50% during the treatment and investigated the potential role of time to nadir (TTN) of PSA. TTN was defined as the time from start of chemotherapy to the nadir of PSA level during the treatment. Multivariable Cox regression models and Kaplan–Meier analysis were used to predict overall survival (OS). In these patients, the median of TTN was 17 weeks. Patients with TTN ≥17 weeks had a longer response time to chemotherapy compared to TTN <17 weeks (42.83 *vs* 21.50 weeks, $P < 0.001$). The time to PSA progression in patients with TTN ≥17 weeks was 11.44 weeks compared to 5.63 weeks when TTN was <17 weeks. We found several factors to be associated with OS, including TTN (hazard ratio [HR]: 3.937, 95% confidence interval [CI]: 1.502–10.309, $P = 0.005$), PSA level at the diagnosis of cancer (HR: 4.337, 95% CI: 1.616–11.645, $P = 0.004$), duration of initial androgen deprivation therapy (HR: 2.982, 95% CI: 1.104–8.045, $P = 0.031$), neutrophil-to-lymphocyte ratio (HR: 3.963, 95% CI: 1.380–11.384, $P = 0.011$), and total PSA response (Class 1 [<0 response] compared to Class 2 [0–50% response], HR: 3.978, 95% CI: 1.278–12.387, $P = 0.017$). In conclusion, TTN of PSA remains an important prognostic marker in predicting therapeutic outcome in Chinese population who receive chemotherapy for mCRPC and have >50% PSA remission.

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Keywords: castration-resistant prostate cancer; chemotherapy; docetaxel; prostate-specific antigen; survival; time to nadir

INTRODUCTION

Prostate cancer (PCa) becomes one of the most prevalent urological malignancies in men from China.[1] Although more and more people with localized PCa are identified and cured after prostate-specific antigen (PSA) screening in the population, most patients have already developed metastatic disease at diagnosis. Androgen deprivation therapy has been the major treatment for advanced or metastatic PCa; however, most patients only respond for a few years and eventually progress to castration-resistant prostate cancer (CRPC).[2]

Docetaxel-based chemotherapy remains the first-line treatment strategy for the patients with metastatic CPRC (mCRPC) and provides a markedly survival benefit based on the data from two large randomized phase III clinical trials (TAX 327 and SWOG 99-16);[3,4] however, many patients still experience no response to this drug. Therefore, identification of several reliable prognostic factors will provide us an accurate evaluation of the disease and more suitable treatment strategies. Many prognostic factors have been reported to associate with the outcome of patients who received docetaxel for CRPC. For example, clinicopathologic parameters, including Gleason score, presence of visceral metastases, presence of pain, baseline PSA level, hemoglobin, albumin, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), cycles of chemotherapy, neutrophil-to-lymphocyte ratio (NLR), and time to castration resistance, were independent prognostic factors of overall survival (OS) in patients with CRPC after docetaxel treatment.[5–7]

The serum PSA level usually correlates with tumor stage and clinical outcome and it is commonly used to monitor the therapeutic effects.[8] Accordingly, PSA kinetics is a useful prognostic indicator of disease progression or survival in different clinical settings, including radical prostatectomy, radiation and hormonal therapies.[9] Although PSA time to nadir (TTN) has been proved as the most notable predictor of progression to castration resistance or individual survival after androgen deprivation therapy (ADT) in many studies,[10–13] few studies have examined its potential role in predicting therapeutic response to docetaxel or other novel targeted drugs (for example, abiraterone

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or enzalutamide) in CRPC. Thomas *et al*.[14] reported that the TTN of PSA could predict rapid relapse in men with mCRPC from Western countries receiving docetaxel chemotherapy; however, it is not clear if the same risk factors are equally predictive for the therapeutic response and patient survival between Caucasian and Chinese. In the present study, we performed a retrospective analysis to investigate whether the TTN of PSA was associated with OS in patients with mCRPC receiving docetaxel-based chemotherapy and found a proper threshold of nadir PSA level that may predict the outcome of chemotherapy for Chinese population.

PATIENTS AND METHODS

Patient treatment and ethical approval

The data from 71 Chinese patients with mCRPC who received three weekly docetaxel following diagnosis at the Department of Urology, The First Affiliated Hospital of Xi'an Jiaotong University, from January 2009 to October 2016, were retrospectively reviewed. The previous treatment and baseline characteristics of these patients were described in **Supplementary Table 1** and **2**. Docetaxel chemotherapy cycles were defined as 21-day treatment periods with docetaxel (75 mg m^{-2}) administered on day 1 of each treatment cycle, together with prednisone 5 mg twice daily. All patients were treated for ten cycles unless they could not stand the side effect of chemotherapy or gave up for individual reasons. CRPC was diagnosed according to the EAU guideline: (1) castrate serum testosterone <50 ng ml^{-1} or 1.7 nmol l^{-1}; (2) biochemical progression: three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng ml^{-1} or radiological progression: the appearance of two or more bone lesions on bone scan or enlargement of a soft-tissue lesion using the Response Evaluation Criteria in Solid Tumors (RECIST).[15]

Data were retrospectively obtained from medical records: for biochemical and radiological findings, all patients had examined PSA value at each cycle of chemotherapy and once a month after chemotherapy. Bone scan and magnetic resonance imaging (MRI) or computed tomography (CT) were examined at the beginning, after the 5th cycle, and 1 month after the end of chemotherapy. All examinations were repeated every 6 months for the follow-up. Patients without at least a 50% reduction of PSA during chemotherapy were excluded from the study.

Nadir PSA level was the lowest PSA level during chemotherapy. Thus, TTN was the time from the initiation of chemotherapy to the date that the lowest PSA value was recorded.[16] PSA progression in this study was defined as an increase in PSA of >25% from the nadir. Response to chemotherapy was defined according to the recommendations of Prostate Cancer Work Group 2 (PCWG2).[17] OS was the time between the initiation of chemotherapy to the death of any cause or the last follow-up.

Table 1: Baseline characteristics

Variable	*TTN <17-week group*	*TTN ≥17-week group*	*P*
Number of patients, *n* (%)	30 (42.3)	41 (57.7)	
Age (year, median with range in parentheses)	71.5 (53–78)	70 (55–85)	0.757
Staging, *n* (%)			
T1–T2	10 (14.1)	11 (15.5)	
T3	11 (15.5)	23 (32.4)	
T4	9 (12.7)	7 (9.9)	0.235
N0	14 (19.7)	20 (28.2)	
N1	16 (22.5)	21 (29.6)	0.860
PSA level at the beginning of cancer (ng ml^{-1}, median with range in parentheses)	263 (3.99–4437)	233.7 (0.84–5000)	0.871
Duration of initial ADT (month, median with range in parentheses)	17 (5–84)	17 (3–84)	0.323
Baseline PSA level (ng ml^{-1}, median with range in parentheses)	231.5 (22.2–3456)	167.9 (0.33–5000)	0.343
Baseline ALP level (mmol l^{-1}, median with range in parentheses)	146.2 (54.8–960)	125.8 (25.98–2050.7)	0.505
Total PSA response, *n* (%)			
Class 1: <0	12 (16.9)	4 (5.6)	
Class 2: 0%–50%	5 (7.0)	4 (5.6)	
Class 3: >50%	13 (18.3)	33 (46.5)	0.003
Cycles of chemotherapy, *n* (%)			
<10	16 (22.5)	13 (18.3)	
≥10	14 (19.7)	28 (39.4)	0.067
Total ALP response, reduction (%, mean±s.d.)	42.03±28.67	38.74±43.88	0.839
Albumin (g l^{-1}, median with range in parentheses)	41.6 (33.2–49.4)	40 (27.8–47.4)	0.053
Hemoglobin (g l^{-1}, median with range in parentheses)	122 (69–151)	111 (69–158)	0.451
Ca^{2+} (mmol l^{-1}, median with range in parentheses)	2.13 (1.69–2.42)	2.14 (1.69–2.48)	0.290
NLR, *n* (%)			
<3.3	17 (23.9)	26 (36.6)	
≥3.3	13 (18.3)	15 (21.1)	0.565
Time to PSA progression after TTN (week, mean±s.d.)	5.63±3.45	11.44±8.41	<0.001
Total time to PSA progression (week, mean±s.d.)	15.23±5.04	33.85±8.98	<0.001
Duration of response to chemotherapy, after TTN (week, mean±s.d.)	21.50±12.17	42.83±18.52	<0.001
Duration of response to chemotherapy, total (week, mean±s.d.)	31.10±15.20	65.24±21.05	<0.001
Total PSA reduction (%, mean±s.d.)	7.17±79.01	69.15±47.66	<0.001

T1-T2: tumor confined within prostate; T3: tumor extends through the prostatic capsule; T4: tumor fixed or invades the adjacent structures other than seminal vesicles (e.g., bladder, levator muscles, and/or pelvic wall); ADT: androgen deprivation therapy; ALP: alkaline phosphatase; NLR: neutrophil-to-lymphocyte ratio; PSA: prostate-specific antigen; TTN: time to nadir; CI: confidence interval; s.d.: standard deviation

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. Informed written consent was obtained from all patients prior to their enrollment in this study.

Statistical analysis

Data were summarized by frequency for categorical variables and by median for continuous variables. Association between categorical variables (i.e., stage T, N, or Class 1 [<0], 2 [0–50%], and 3 [>50%] for PSA response) was assessed using the Chi-square test or Fisher's exact test. The two groups were compared with the Student's *t*-test or Kruskal–Wallis test as appropriate, and variables of different groups were compared with the Chi-square test for the differences in mean time for chemotherapy response, PSA progression, total PSA reduction, or other baseline characteristics. OS was estimated using the Kaplan–Meier method and was compared with the log-rank test. All the factors were assessed in uni- and multi-variate models using Cox regression. All statistical analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of 71 eligible patients were shown in **Table 1**. At the initiation of chemotherapy, the median age was 71 years (range: 53–85 years). The number of patients staging T1–T2 (tumor confined within prostate), T3 (tumor extends through the prostatic capsule), and T4 (tumor fixed or invades the adjacent structures other than seminal vesicles) was 21 (29.6%), 34 (47.9%), and 16 (22.5%), respectively. All patients had metastatic disease, and 37 (52.1%) had lymphatic metastasis. The median baseline PSA value at the diagnosis of cancer was 239.60 ng ml^{-1} (range: 0.84–5000 ng ml^{-1}). The median duration of initial ADT was 17 months (range: 3–84 months). The median baseline PSA level before chemotherapy was 199.20 ng ml^{-1} (range: 0.33–5000 ng ml^{-1}), and the median baseline ALP level was 138 mmol l^{-1} (range: 25.98–2050.70 mmol l^{-1}). Forty-two (59.2%) patients finished chemotherapy more than ten cycles. Forty-six (64.8%) patients had a PSA value reduction ≥50%, but 16 (22.5%) patients failed. The remaining 71 patients were divided into two groups according to the TTN value during chemotherapy. We chose 17 weeks as the optimal threshold using sensitivity curve based on survival status.

Uni- and multi-variable Cox regression analysis of OS

Patient age, staging T and N, baseline ALP level before chemotherapy, total ALP response, albumin, hemoglobin, and PSA nadir level were not associated with OS of patients in univariable analysis (**Table 2**). In contrast, OS was associated with PSA level at the diagnosis of cancer ($P = 0.040$), during initial ADT ($P = 0.016$), TTN ($P = 0.002$), baseline PSA value ($P = 0.036$), number of chemotherapy ($P = 0.033$), NLR ($P = 0.011$), total PSA response (Class 1 *vs* Class 2, $P = 0.027$), and Ca^{2+} concentration ($P = 0.031$). According to the Kaplan–Meier analysis, median OS for TTN ≥17-week group was 41 months compared to 18 months when TTN was <17 weeks ($P < 0.001$) (**Figure 1**).

In multivariable analysis, patients with higher PSA level at the beginning of cancer (≥150.10 ng ml^{-1}) or NLR (>3.3) had a higher risk of death than others (hazard ratio [HR]: 4.337, 95% confidence interval [CI]: 1.616–11.645, $P = 0.004$ and HR: 3.963, 95% CI: 1.380–11.384, $P = 0.011$, respectively). On the other hand, patients with shorter duration of initial ADT (<18 months) or TTN (<17 weeks) may suffer worse outcome than others (HR: 2.982, 95% CI: 1.104–8.045, $P = 0.031$ and HR: 3.937, 95% CI: 1.502–10.309, $P = 0.005$, respectively). Patients with poor PSA response (<0) may suffer a shorter OS than the other group (Class 2: 0–50%) (HR: 3.978, 95% CI: 1.278–12.387, $P = 0.017$) (**Table 2**).

Effect of chemotherapy on TTN and mean time to PSA progression

We divided TTN into two groups in selecting 17 weeks as threshold and found that patient age, staging T and N, PSA value at diagnosis of cancer, duration of initial ADT, baseline of PSA, ALP level before chemotherapy, cycle of chemotherapy, albumin, total ALP reduction, NLR, hemoglobin, and Ca^{2+} concentration had no effect on TTN. However, the total mean time to PSA progression in patients with

Table 2: Uni- and multi-variable model analysis of overall survival

Variable	*Category*	*Univariable*	*P*	*Multivariable*	*P*
		HR for death (95% CI)		*HR for death (95% CI)*	
Age (year)	≥65 *vs* <65	0.956 (0.432–2.115)	0.912		
Staging T	T3 *vs* T1–T2	1.848 (0.642–5.405)	0.260		
	T4 *vs* T1–T2	1.825 (0.660–5.501)	0.246		
Staging N	N1 *vs* N0	1.190 (0.568–1.762)	0.840		
PSA level at the diagnosis of cancer (ng ml^{-1})	≥150.1 *vs* <150.1	2.201 (1.036–4.677)	0.040	4.337 (1.616–11.645)	0.004
Duration of initial ADT (months)	≥18 *vs* <18	0.354 (0.152–0.825)	0.016	2.982 (1.104–8.045)	0.031
Baseline PSA level at trial entry (ng ml^{-1})	≥110.7 *vs* <110.7	3.108 (1.077–8.970)	0.036	1.280 (0.370–4.425)	0.696
Baseline ALP level at trial entry (mmol l^{-1})	≥85.7 *vs* <85.7	1.762 (0.841–4.840)	0.134		
Number of chemotherapy cycles, (*n*)	≥10 *vs* <10	0.425 (0.193–0.933)	0.033	1.558 (0.620–3.906)	0.346
Total PSA response, reduction (%)	CL1 *vs* CL2	0.349 (0.173–0.898)	0.027	3.978 (1.278–12.387)	0.017
	CL1 *vs* CL3	0.428 (0.137–1.330)	0.143	1.888 (0.459–7.757)	0.378
Total ALP response, reduction (%)	≥39.7 *vs* <39.7	0.882 (0.420–1.852)	0.739		
NLR	>3.3 *vs* ≤3.3	2.733 (1.259–5.932)	0.011	3.963 (1.380–11.384)	0.011
Albumin (g l^{-1})	≥37 *vs* <37	0.917 (0.832–1.01)	0.077		
Hemoglobin (g l^{-1})	≥105 *vs* <105	0.531 (0.252–1.115)	0.094		
Ca^{2+} (mmol l^{-1})	≥2.11 *vs* <2.11	0.438 (0.207–0.827)	0.031	1.166 (0.397–3.420)	0.780
TTN (week)	≥17 *vs* <17	0.311 (0.149–0.650)	0.002	3.937 (1.502–10.309)	0.005
Nadir PSA (ng ml^{-1})	≥16.3 *vs* <16.3	1.251 (0.552–2.831)	0.592		

CL1: Class 1, PSA response <0; CL2: Class 2, PSA response 0%–50%; CL3: Class 3, PSA response >50%; T1–T2: tumor confined within prostate; T3: tumor extends through the prostatic capsule; T4: tumor fixed or invades the adjacent structures other than seminal vesicles (e.g., bladder, levator muscles, and/or pelvic wall); ADT: androgen deprivation therapy; ALP: alkaline phosphatase; HR: hazard ratio; NLR: neutrophil-to-lymphocyte ratio; PSA: prostate-specific antigen; TTN: time to nadir; CI: confidence interval

TTN ≥17 weeks was 33.85 weeks compared to 15.23 weeks when TTN was <17 weeks ($P < 0.001$). The total mean duration of response to chemotherapy in patients with TTN ≥17 weeks was 65.24 weeks compared to 31.10 weeks when TTN was <17 weeks ($P < 0.001$). We should take into consideration that TTN would influence the above results, so we redefined the time to PSA progression and duration of response to chemotherapy without TTN. Compared with TTN <17-week group, patients with longer TTN (≥17 weeks) may have a longer mean time to PSA progression (11.44 weeks *vs* 5.63 weeks, $P < 0.001$) and duration of response to chemotherapy (42.83 weeks *vs* 21.50 weeks, $P < 0.001$) (**Figure 2** and **3**). Another factor, i.e., PSA reduction was 69.15% when TTN was ≥17 weeks, but only 7.17% when TTN was <17 weeks ($P = 0.009$) (**Table 1**).

DISCUSSION

ADT is generally performed and effective for advanced or metastatic PCa until men develop CRPC. Patients with mCRPC have a very poor prognosis, and docetaxel-based chemotherapy has been regarded as the standard treatment.[18] Many prognostic factors associated with the treatment efficacy have been reported.[5–7] In our previous study, we have also demonstrated that NLR, PSA level at the diagnosis of cancer, number of chemotherapy cycles, and total PSA response were independent prognostic factors on OS and progression-free survival (PFS) of Chinese patients with mCRPC treated with docetaxel.[19] In this study, our results further showed that TTN was a strong predictor of OS for these patients in both uni- and multi-variate Cox proportional hazards regression analyses.

Indeed, the measurement of PSA levels is useful for evaluating the therapeutic effects of ADT or chemotherapy in patients with PCa; however, there is no agreement on the prognostic importance of different PSA indexes after treatment. Among PSA indexes, PSA nadir and TTN have been reported as good predictors of disease progression, survival, and therapeutic response in metastatic PCa.[10–13] However, there were very few studies to evaluate their potential prognostic roles in docetaxel-based chemotherapy for patients with mCRPC. A retrospective study analyzed the data from 41 consecutive mCRPC patients treated with docetaxel and found that a TTN from the initiation of chemotherapy of <16 weeks was an independent predictor of shorter duration of response.[14] Another study reported that PSA kinetic parameters prior to ADT including PSA half-time, PSA level at nadir, duration of nadir, PSA doubling time, and PSA level at the start of chemotherapy were obvious surrogate markers predicting cancer-specific survival (CSS) in patients undergoing docetaxel treatment for CRPC.[20] However, the predictive role of TTN in survival of Chinese patients with mCRPC receiving docetaxel-based chemotherapy is still unknown.

Similar with the results from Western countries,[14,20] we also found that patients with a longer TTN had a longer response time to chemotherapy and time to PSA progression in this study. Importantly, TTN, duration of initial ADT, and total PSA response were significantly associated with OS of mCRPC patients in a single center from Northwestern China. However, there is still no consensus of both optimal threshold of PSA nadir and cutoff value of TTN after ADT or chemotherapy for predicting survival. Our study selected the median of TTN (17 weeks) as threshold, which was more than 16 weeks reported by the study from the United Kingdom.[14] The reason we supposed was that most of the patients from Northwestern China failed to be diagnosed early or treated, so some Chinese patients with mCRPC represent an extremely high level of PSA at the diagnosis of cancer. Therefore, the TTN of PSA in these patients would be longer than men from Western countries. Nevertheless, this retrospective study, based on populations from Northwestern China, demonstrated that TTN was an independent prognostic factor on OS in Chinese patients with mCRPC treated with docetaxel and had >50% PSA remission.

In addition, treatment options for patients with mCRPC following docetaxel-based chemotherapy are rapidly increasing nowadays, and more drugs, including abiraterone acetate, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T, have been shown to improve patient survival, which are available for second-line treatment of CRPC following docetaxel.[21–26] Therefore, it would be helpful to identify

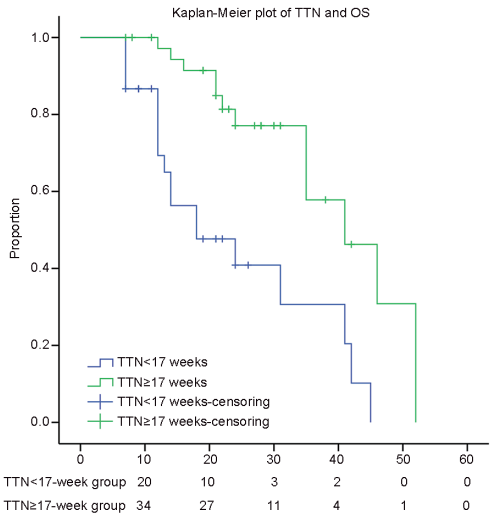

Figure 1: Survival curves for 71 mCRPC patients treated with docetaxel. mCRPC: metastatic castration-resistant prostate cancer; OS: overall survival; TTN: time to nadir.

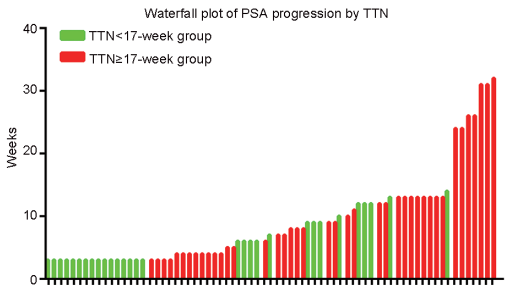

Figure 2: Waterfall plot of PSA progression for 71 mCRPC patients treated with docetaxel. mCRPC: metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; TTN: time to nadir.

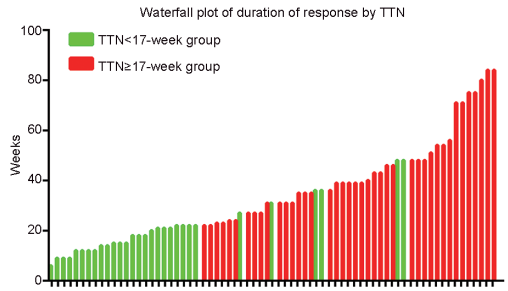

Figure 3: Waterfall plot of duration of response to chemotherapy for 71 mCRPC patients treated with docetaxel. mCRPC: metastatic castration-resistant prostate cancer; TTN: time to nadir.

patients with mCRPC who initially respond to docetaxel-based chemotherapy but are at a high risk of rapid disease relapse. Herein, our study suggests that patients with TTN <17 weeks after chemotherapy might be expected to have a shorter PFS, indicating that these patients should be re-evaluated earlier and should be considered for a new treatment strategy such as abiraterone or enzalutamide to get the maximum survival benefit.

CONCLUSIONS

This study provided a potential association between TTN and the outcome of patients with mCRPC who received docetaxel-based chemotherapy; however, we should not neglect the limitation of this study. It was only an open-labeled, nonrandomized or historically controlled study with limited sample size. In addition, extremely high level of PSA at the diagnosis of PCa was one of the characteristics of CRPC population in Northwestern China, which might bring some deviation to our results. Hence, we need to further continue our study with a larger sample of population.

AUTHOR CONTRIBUTIONS

KJW and XQP designed the study, analyzed and interpreted the clinical data, wrote and revised the manuscript. KJW, XQP, GT, DPW, JHF, and YMJ collected the clinical data and engaged in patient follow-up. DLH supervised the project and revised the manuscript. All the listed authors have participated actively in the study. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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Supplementary Table 1: Previous treatment of 71 metastatic castration-resistant prostate cancer patients

Treatment	*TTN ≥17-week group (n)*	*TTN <17-week group (n)*	*Total (n)*
ADT	29	23	52
ADT + radiotherapy	10	5	15
ADT + surgery	2	2	4

ADT: androgen deprivation therapy; mCRPC: metastatic castration-resistant prostate cancer; TTN: time to nadir

Supplementary Table 2: Baseline characteristics of 71 metastatic castration-resistant prostate cancer patients

	TTN <17-week group	*TTN ≥17-week group*	*Total*
Number of patients, *n* (%)	30 (42.3)	41 (57.7)	71
Age (year, median with range in parentheses)	71.5 (53–78)	70 (55–85)	71 (53–85)
Staging, *n* (%)			
T1–T2	10 (14.1)	11 (15.5)	21 (29.6)
T3	11 (15.5)	23 (32.4)	34 (47.9)
T4	9 (12.7)	7 (9.9)	16 (22.5)
N0	14 (19.7)	20 (28.2)	34 (47.9)
N1	16 (22.5)	21 (29.6)	37 (52.1)
PSA level at the beginning of cancer (ng ml^{-1}, median with range in parentheses)	263 (3.99–4437)	233.7 (0.84–5000)	239.6 (0.84–5000)
Duration of initial ADT (months, median with range in parentheses)	17 (5–84)	17 (3–84)	17 (3–84)
Baseline PSA level (ng ml^{-1}, median with range in parentheses)	231.5 (22.2–3456)	167.9 (0.33–5000)	199.2 (0.33–5000)
Baseline ALP level (mmol l^{-1}, median with range in parentheses)	146.2 (54.8–960)	125.8 (25.98–2050.7)	138 (25.98–2050.7)
Total PSA response, *n* (%)			
Class 1: <0	12 (16.9)	4 (5.6)	16 (22.5)
Class 2: 0%–50%	5 (7.0)	4 (5.6)	9 (12.7)
Class 3: >50%	13 (18.3)	33 (46.5)	46 (64.8)
Cycles of chemotherapy, *n* (%)			
<10	16 (22.5)	13 (18.3)	29 (40.8)
≥10	14 (19.7)	28 (39.4)	42 (51.2)
Total ALP response, reduction (%, mean±s.d.)	42.03±28.67	38.74±43.88	0.839
Albumin (g l^{-1}, median with range in parentheses)	41.6 (33.2–49.4)	40 (27.8–47.4)	0.053
Hemoglobin (g l^{-1}, median with range in parentheses)	122 (69–151)	111 (69–158)	0.451
Ca^{2+} (mmol l^{-1}, median with range in parentheses)	2.13 (1.69–2.42)	2.14 (1.69–2.48)	0.290
NLR, *n* (%)			
<3.3	17 (23.9)	26 (36.6)	43 (60.6)
≥3.3	13 (18.3)	15 (21.1)	28 (39.4)

T1–T2: tumor confined within prostate; T3: tumor extends through the prostatic capsule; T4: tumor fixed or invades the adjacent structures other than seminal vesicles (e.g., bladder, levator muscles, and/or pelvic wall); ADT: androgen deprivation therapy; ALP: alkaline phosphatase; NLR: neutrophil-to-lymphocyte ratio; PSA: prostate-specific antigen; TTN: time to nadir; s.d.: standard deviation