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Rapidly decreasing level of prostate-specific antigen during initial androgen deprivation therapy is a risk factor for early progression to castration-resistant prostate cancer: A retrospective study

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Abstract

To build a practical model for predicting the progression to castration-resistant prostate cancer (CRPC) after androgen deprivation therapy (ADT).

In all, 185 patients with prostate cancer who had received ADT as the primary therapy at our institution, from 2003 to 2014, were retrospectively enrolled. The following clinical variables were included in the analysis: age, clinical tumor, node, metastasis stage, Gleason score, risk groups of prostate cancer, prostate-specific antigen (PSA) at the initiation of ADT, PSA nadir after ADT, velocity of PSA decline, and the time to PSA nadir. Cox proportional-hazards regression models were calculated to estimate effects of these variables on the time of progression to CRPC.

On univariate and multivariate analyses, the presence of distant metastasis before ADT (hazard ratio [HR] 6.030, 95% confidence interval (CI) 3.229–11.263, $P = .001$), higher PSA nadir (HR 1.185, 95% CI 1.080–1.301, $P = .001$), a velocity of PSA decline >11 ng/mL per month (HR 2.124, 95% CI 1.195–3.750, $P = .001$), and a time to PSA nadir ≤9 months (HR 0.276, 95% CI 0.162–0.469, $P = .004$) were significantly associated with an increased risk of progression to CRPC.

Patients with a rapidly decreasing PSA level in the initial phase of ADT are more likely to progress to CRPC. Our findings provide a practical approach to screen patients during ADT for early identification of those likely to progress to CRPC, allowing treatment to be modified to improve outcomes.

Abbreviations: ADT = androgen deprivation therapy, CRPC = castration-resistant prostate cancer, EAU = European Association of Urology, EBRT = external beam radiation therapy, HSPC = hormone-sensitive prostate cancer, J = Youden index, LHRH-A = luteinizing hormone-releasing hormone agonist, PSA = prostate-specific antigen, ROC = receiver-operating characteristic, TNM = tumor, node, metastasis staging, TTN = time to PSA nadir.

Keywords: androgen deprivation therapy, castration-resistant prostate cancer, prostate-specific antigen, prostate-specific antigen nadir

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1. Introduction

Androgen deprivation therapy (ADT) is the most important primary treatment for locally advanced or metastatic prostate cancer. However, due to the limited curative effect of a single treatment of ADT, combined therapy strategies are usually indicated.[1,2] Although nearly all prostate cancer patients initially respond to ADT, almost all patients with hormone-sensitive prostate cancer (HSPC) progress to castration-resistant prostate cancer (CRPC) after several years of ADT.[3,4] Currently, however, there is no unequivocal prediction model about the time of progression to CRPC.

Prostate-specific antigen (PSA) has widely been accepted as a critical biomarker of the progression of prostate cancer during ADT, with some studies having reported that lower PSA nadir and longer time to PSA nadir (TTN) to be independent risk factors for a shorter time of progression to CRPC.[5–8] However, more recent studies have drawn the opposite conclusion, namely that lower PSA nadir and longer TTN are associated with longer time to CRPC. Kuo et al[9] reported a significant association between a longer time to PSA rise during the first off-treatment interval and a longer time to CRPC progression in patients undergoing intermittent ADT. In addition, the presence of greater

bone metastases before ADT initiation, the earlier patients are likely to progress to CRPC.[10–12]

It would be useful to identify patients who initially responded to ADT, but are at risk of rapid disease progression, which would allow early implementation of an appropriate follow-up strategy to promptly detect a relapse, allowing optimal timing of further disease-modifying treatment, such as chemotherapy. The aim of our study was to explore risk factors, including PSA kinetics, for the prediction of CRPC, which would inform decisions regarding the follow-up and treatment of patients with prostate cancer receiving ADT.

2. Materials and methods

2.1. Study population and design

The clinical data of prostate cancer patients who received ADT as the primary therapy in the Department of Urology, Peking University First Hospital, from 2003 to 2014, were retrospectively reviewed. All patients were diagnosed with prostate cancer via prostate biopsy and followed up every 4 weeks from the initiation of ADT over the first year. All patients received ADT with luteinizing hormone-releasing hormone agonists (LHRH-A) or surgical castration accompanied with an antiandrogen (bicalutamide or flutamide, combined androgen blockade). The treating physician expected a survival of >6 months for all patients included in the analysis. Patients with brain metastasis, unstable liver diseases, or inflammatory diseases were excluded from this study. The study was approved by the Ethics Committee of the Peking University First Hospital.

The endpoint of this study was the diagnosis of CRPC, which was based on the European Association of Urology (EAU) guidelines 2016,[13] and defined as follows: castrate serum testosterone <50 ng/dL or 1.7 nmol/L, in addition to either biochemical progression (3 consecutive rises in PSA 1 week apart, resulting in two 50% increases over the nadir, with a PSA >2 ng/mL), or radiological progression.[14] The following demographic and clinical variables were extracted from the medical records for analysis: age, the clinical tumor, node, and metastasis (TNM) stage, Gleason score (GS), the risk group of the prostate cancer according to EAU 2016 guideline[13] (low, intermediate, and high risk), PSA at the initiation of ADT, PSA nadir after ADT, time to PSA nadir (TTN), and velocity of PSA decline (baseline PSA − PSA nadir)/TTN). The TTN was classified as ≤9 months or >9 months, based on a previously published study in a Japanese cohort.[15] The PSA nadir and velocity of PSA decline were also dichotomized based on the Youden Index (J = sensibility + specificity − 1) calculated from the receiver-operating characteristic (ROC) curve. The new GS grading system was used to classify patients into the following 5 grades: grade group 1, GS ≤6; grade group 2, GS 3 + 4 = 7; grade group 3, GS 4 + 3 = 7; grade group 4, GS 4 + 4 = 8; and grade group 5, GS 9 and 10. The time to CRPC was defined as the duration from the initiation of ADT to progression to CRPC.

2.2. Statistical analysis

All statistical analyses were performed using SPSS (version 22.0, SPSS Inc., Chicago, IL). Comparisons of time to CRPC between different groups were evaluated using Kaplan–Meier survival curves and log-rank test. Multivariate Cox proportional-hazards models were developed to estimate the association (hazard ratio [HR]) between each risk factors and the time to CRPC.

Table 1

Baseline clinical characteristics of patients treated with androgen deprivation therapy and median time to CRPC.

Variables	No. of patients (%)	Median time to CRPC, mos
Age (mean ± SD, y)	71.02 ± 8.67	
BMI (mean ± SD, kg/m^2)	24.10 ± 4.77	
PSA on initiation of ADT (median, interquartile range, ng/mL)	30.96 (1.4, 3187.0)	
T stage		
T1	4 (2.2%)	57
T2	61 (33.0%)	56
T3	90 (48.6%)	28
T4	24 (13.0%)	13
Missing	6 (3.2%)	
N stage		
N0	143 (77.3%)	45
N1	37 (20.0%)	20
Missing	5 (2.7%)	
Distant metastasis		
Yes	69 (37.3%)	23
No	114 (61.6%)	62
Missing	2 (1.1%)	
Grade groups		
≤6	20 (10.8%)	57
3+4	37 (20.0%)	50
4+3	27 (14.6%)	50
8	33 (17.8%)	38
9-10	60 (32.4%)	24
Missing	8 (4.3%)	
Risk groups		
Low	8 (4.3%)	68
Intermediate	24 (13.0%)	56
High	150 (81.1%)	28
Missing	3 (1.6%)	
Progressed to CRPC	121 (65.4%)	
Follow-up time, mos	45	

BMI = body mass index, CRPC = castration-resistant prostate cancer, PSA = prostate-specific antigen.

Significant variables on univariate analysis were included in a multivariate analysis to detect the most significant factor for predicting progression to CRPC. All reported *P* values were 2-sided, with a *P* value <.05 considered statistically significant.

3. Results

3.1. Patient characteristics and the time to progression to CRPC

Our retrospective analysis was based on the data of 185 patients (mean age 71.02 ± 8.67 years) with prostate cancer who had received ADT as the primary therapy. The median time to progression to CRPC in this cohort was 38 months (range 4–158 months). Patients' characteristics and the time to progression to CRPC are reported in Table 1.

3.2. Results of univariate analyses

On univariate analyses, age and BMI were not relevant to the time developing to CRPC, whereas our previous study demonstrated that age is related to prostate cancer grade groups.[16] The velocity of PSA decline and the PSA nadir were significantly associated with the time developing to CRPC

(P=.001). Patients with a faster velocity of PSA decline (>11 ng/mL per month) progressed to CRPC earlier than those with a velocity ≤11 ng/mL per month (24 vs 44 months, respectively; P=.002). But there was no difference in the median time to CRPC progression between patients with a PSA nadir ≤0.03 ng/L and those with a PSA nadir >0.03 ng/mL (48 vs 28 months; P=.156).

For further analysis, patients were dichotomized into 2 groups based on the time of PSA decline to a nadir of ≤9 months (n=65, 45.8%) or >9 months (n=77, 54.2%) after the initiation of ADT. The time to CRPC was significantly shorter for the ≤9-month group (23 months) than for >9-month group (57 months; P=.001). Similarly, the time to CRPC decreased with increasing EAU risk classification (P=.001), from 68 months for the low-risk group, 56 months for the intermediate-risk group, and 28 months for the high-risk group. Patients with distant metastasis before the initiation of ADT had a significantly higher risk of developing CRPC than those without metastasis (23 vs 62 months, respectively; P=.001). The clinical tumor (T) stage, node (N) stage, and grade groups were significantly associated with time to CRPC (P=.001, P=.002, P=.001, respectively). A detailed summary of measured variables is provided in Table 2. Kaplan–Meier CRPC-free survival curves, using time to PSA nadir, presence of metastasis, and risk groups, are shown in Fig. 1.

3.3. Results of multivariate analyses

In the multivariate analyses, the presence of distant metastasis before ADT (HR 6.03, 95% CI 3.22–11.26, P=.001), higher PSA nadir (HR 1.19, 95% CI 1.08–1.30, P=.001), a velocity of PSA decline >11 ng/mL per month (HR 2.12, 95% CI 1.19–3.75, P=.001), and time to a PSA nadir ≤9 months (HR 0.28, 95% CI 0.16–0.47, P=.004) were significantly associated with an increased risk of progression to CRPC (Table 2).

4. Discussion

The presence of distant metastases at the initiation of ADT, a higher PSA nadir after ADT, a higher velocity of PSA decline, and a time to reach PSA nadir of <9 months are associated with an increased risk of progression to CRPC. To the best of our knowledge, few markers can predict the time of progression to CRPC, with PSA kinetics being the most commonly used parameters. It is generally considered that a rapid decline in PSA is indicative of a higher proportion of prostate cancer cell death

and, therefore, higher survival.[8,17] However, Yu et al[18] reported that the duration of the first off-treatment interval was predictive of both time to CRPC and death among patients with biochemical relapse of prostate cancer treated with intermittent ADT. Furthermore, a significant association was also demonstrated between a longer time to PSA rise during the first off-treatment interval and a longer time to progression to CRPC among patients with intermittent ADT.[9] Recently, Kim et al[19] reported a fluctuation in PSA levels after achievement of PSA nadir among patients receiving intermittent treatment, and that the patients whose PSA declined twice by ≥0.048 ng/mL per month after nadir were less likely to develop CRPC. These articles indicated that PSA kinetics could predict the risk of progression to CRPC.

Prostate-specific antigen nadir has been considered to be 1 of the most important predictors of survival after ADT. Svatek et al[20] established a nomogram including PSA at ADT initiation, PSA doubling time, nadir PSA on ADT, and time from ADT to androgen insensitive prostate cancer (AIPC) to predict AIPC-specific survival. Other researchers have similarly reported the PSA nadir and velocity of PSA decline velocity for predicting survival of patients after radiation, with or without ADT.[21] In our study, we identified the presence of distant metastasis before ADT, higher PSA nadir, higher PSA decline velocity, and a time to reach PSA nadir ≤9 months to be significantly associated with an increased risk of progression to CRPC. In other words, patients with a rapid decline in PSA had a greater risk to develop CRPC compared with patients with slow PSA decline. However, the mechanisms underlying our finding remain to be clarified. It is possible that a rapid decrease in PSA level may be related to a transcriptional outcome of ADT rather than prostate cancer cell death. Moreover, heterogeneous prostate cancer cells are often present in the same patient, including HSPC cells and hormone-resistant prostate cancer cells. The rapid reduction of PSA, therefore, might reflect a down-regulation of PSA expression of HSPC cells, which are regulated by androgen via the androgen receptor pathway.[15] Another possibility is that a rapid removal of HSPC cells might induce an environment that is adequate to the growth of hormone-resistant prostate cancer cells, which prompted the progression of CRPC.[15]

Thomas et al[22] reported similar results in patients with metastatic CRPC receiving chemotherapy in whom a time to PSA nadir from initial chemotherapy <16 weeks was an independent predictor of a shorter duration of response and shorter progression-free survival. A rapid removal of chemosensitive

Table 2				
Univariable and multivariable analyses of risk factors of progression to CRPC after androgen deprivation therapy.				
Factors	Univariable analysis HR (95% CI)	Multivariable analysis P	HR (95% CI)	P
Age	0.979 (0.958, 1.001)	.053		
BMI	0.983 (0.909, 1.064)	.675		
T stage	2.025 (1.513, 2.710)	.001		
N stage	1.937 (1.279, 2.933)	.002		
Distant metastasis	4.325 (2.827, 6.616)	.001	6.030 (3.229, 11.263)	.001
Grade groups	1.293 (1.104, 1.513)	.001		
The risk groups	1.779 (1.276, 2.479)	.002		
PSA on initiation of ADT	1.000 (1.000, 1.001)	.133		
PSA Nadir (ng/mL)	1.103 (1.042, 1.169)	.001	1.185 (1.080, 1.301)	.001
Time to PSA nadir (≤9 months vs >9 months)	0.384 (0.254, 0.581)	.001	0.276 (0.162, 0.469)	.004
PSA decline velocity >11 ng/mL per mo	2.685 (1.815, 3.973)	.002	2.124 (1.195,3.750)	.001

ADT=androgen deprivation therapy, CI=confidence interval, CRPC=castration-resistant prostate cancer, HR=hazard ratio, PSA=prostate-specific antigen.
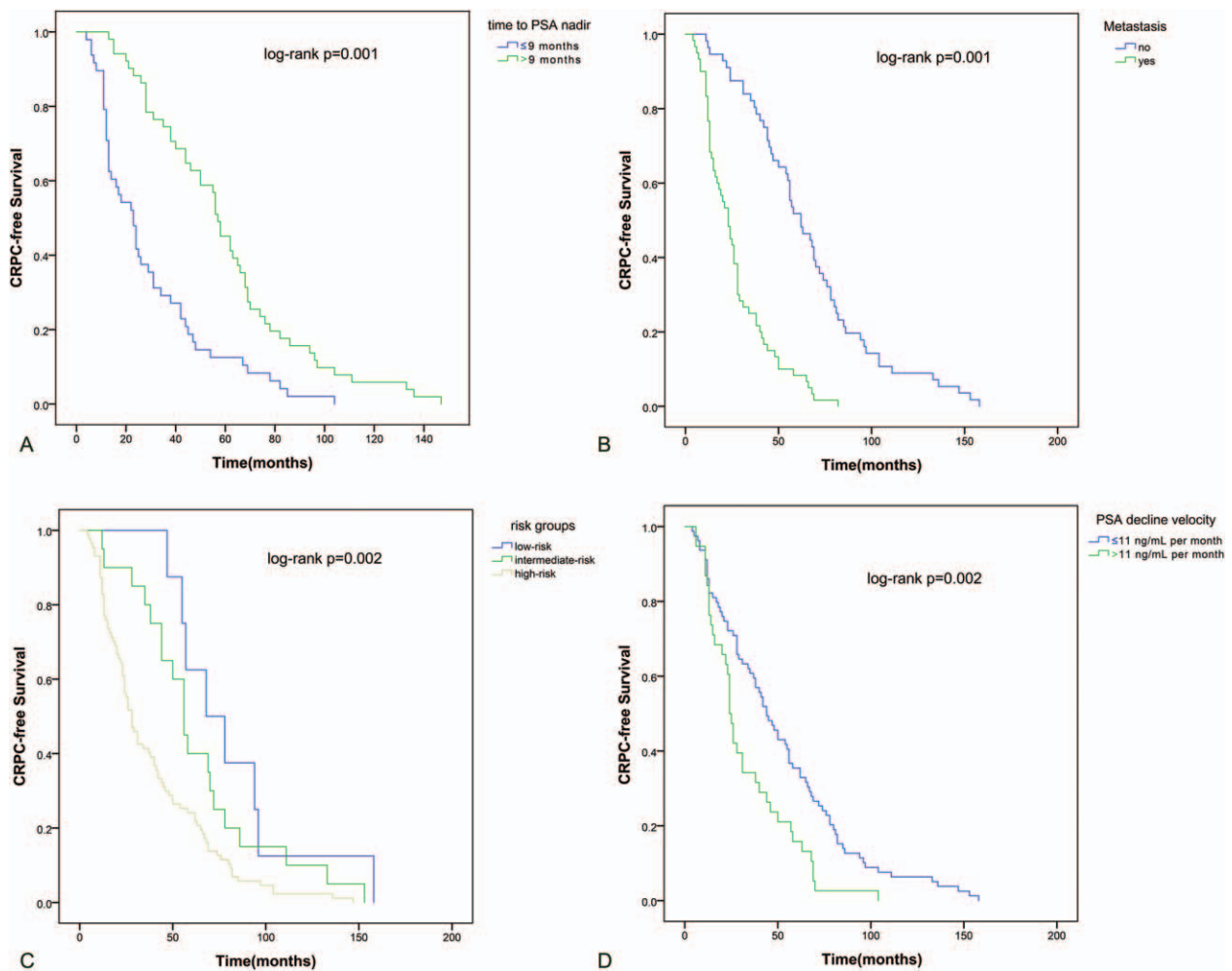
Figure 1. Kaplan–Meier CRPC-free survival in various groups. (A) Time to PSA nadir (≤9 vs >9 months); (B) with or without metastasis; (C) risk groups (low-risk, intermediate-risk, and high-risk); (D) PSA decline velocity (≤11 vs >11 ng/mL per month). CRPC=castration-resistant prostate cancer.

cells might result in a more favorable environment for the growth of chemoresistant cells.

In this study, patients with metastatic prostate cancer were more likely to progress to CRPC after ADT than patients with nonmetastatic prostate cancer, with a median progression time to CRPC of 23 and 62 months, respectively. Sureka et al[11] have previously reported a time to CRPC of 10 to 16 months from the initiation of ADT among patients with metastatic prostate cancer in an Indian cohort. Furthermore, Koo et al[12] reported a stronger correlation between progression to CRPC and bone metastasis complicated with pain, compared with the correlation between progression to CRPC and bone metastasis. The association between metastasis and progression to CRPC might be related to aggressive prostate cancer cells escaping from the primary sites to metastatic sites. At the same time, some inflammatory factors, such as interleukin (IL)-8, tumor necrosis factor-alpha (TNF)-α, IGF, and MMP-11,[23] in the microenvironment of metastatic tumors, might promote the progression to CRPC. For patients with metastatic prostate cancer, a multidisciplinary team therapy targeting the primary sites and metastatic lesions might help to prolong patient survival.

We did identify a significant difference in the time to CRPC according to risk, T stage, N stage, and grade groups on

univariate analysis. On multivariate analysis, risk, T stage, N stage, and grade were not retained as predictive factors of progression to CRPC, with PSA kinetics having a stronger association with progression to CRPC during hormonal therapy.

Radiotherapy was associated with favorable outcomes for HSPC. Shi et al[21] reported that an early rapid rate of PSA decline after external beam radiation therapy (EBRT) was associated with an increased risk of mortality from prostate cancer, as we identified among patients receiving ADT. However, the number of patients in our study who received additional radiotherapy and chemotherapy treatment was limited, and, therefore, the specific effect of additional therapy on the progression to CRPC could not be evaluated.

The present study had certain limitations which constrain the application and generalizability of our findings. The most important limitation is the retrospective nature of our study design, which includes bias associated with selection of patients and from unknown confounding variables. Second, it is known that ADT or radiotherapy might induce the expression of variant androgen receptors. However, we did not evaluate other biomarkers of androgen receptors, such as AR-V7. Third, the sample size in this study was limited and further research with larger sample sizes are required to confirm our findings.

5. Conclusions

In conclusion, patients with a rapidly decreasing PSA level in the initial phase of ADT are more likely to progress to CRPC. Our findings provide a practical approach to screen patients during ADT for early identification of those likely to progress to CRPC, allowing treatment to be modified to improve outcomes.

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