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Significant associations of prostate-specific antigen nadir and time to prostate-specific antigen nadir with survival in prostate cancer patients treated with androgen-deprivation therapy

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Abstract

Objective. The influence of prostate-specific antigen (PSA) kinetics on the outcome of metastatic prostate cancer (PCa) after androgen-deprivation therapy (ADT) remains poorly characterised. We evaluated the prognostic significance of PSA nadir and time to PSA nadir as well as their interactive effect on prostate cancer-specific mortality (PCSM) and all-cause mortality (ACM) after ADT.

Methods. A total of 650 men with advanced or metastatic PCa treated with ADT were studied. The prognostic significance of PSA nadir and time to PSA nadir on PCSM and ACM were analysed using Kaplan–Meier analysis and the Cox regression model.

Results. On multivariate analysis, clinical M1 stage, Gleason Score 8–10, PSA nadir $\geq$ 0.2 ng/ml and time to PSA nadir $<$ 10 months were independent predictors of PCSM and ACM. The combined analysis showed that patient with higher PSA nadir and shorter time to PSA nadir had significantly higher risk of PCSM and ACM compared to those with lower PSA nadir and longer time to PSA nadir (hazard ratios = 6.30 and 4.79, respectively, all $P < 0.001$).

Conclusions. Our results suggest that higher PSA nadir level and faster time to reach PSA nadir after ADT were associated with shorter survival for PCa.

Keywords: *Prostate cancer, androgen-deprivation therapy, metastatic prostate cancer, prostate-specific antigen kinetics, time to prostate-specific antigen nadir, prostate-specific antigen nadir*

Abbreviations: *PCa = prostate cancer; PSA = prostate-specific antigen; ADT = androgen-deprivation therapy; HR = hazard ratios; CI = confidence interval; AR = androgen receptor; PCSM = prostate cancer-specific mortality; ACM = all-cause mortality*

Introduction

With the increase in use of prostate-specific antigen (PSA) as a screening tool, prostate cancer (PCa) can be diagnosed at an early and clinically localised stage. However, 10%–20% of men with PCa present with metastatic disease, and in many others, metastasis occurs despite surgical treatment or radiotherapy. The standard initial systematic therapy for locally advanced or metastatic PCa is androgen-deprivation therapy (ADT) [1,2]. The androgen-dependent period in patients with metastatic PCa lasts for a median of 14 to 30 months [3]. The disease then progresses to a phase when ADT alone fails to control the malignancy

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despite castrate testosterone levels. At this stage, it is termed castration-resistant prostate cancer (CRPC).

Although some patients with AIPC/CRPC respond to antiandrogen withdraw or secondary hormone manipulations [4–6], their disease eventually no longer responds to further hormone therapy. Histologically, metastatic AIPC and CRPC are highly resistant to the chemotherapy and yield poor response with median survivals of 12 to 18 months [7–10].

PSA kinetics has been used as useful prognostic indicators for disease progression or survival in different clinical setting including radical prostatectomy and external beam radiation [11–14]. However, its prognostic ability for those receiving ADT for metastatic PCa remains poorly characterized. Recently, studies have reported an association between PSA nadir and progression to AIPC and prostate cancer-specific mortality (PCSM) in patients receiving ADT [9,15, 16,17]. Hussain et al. [18] found that a PSA of $\leq$4 ng/ml after 7 months of ADT is a strong predictor of survival. However, the role of time to PSA nadir on predicting disease survival after ADT has not been well studied except one small case series study, which was conducted in 179 metastatic hormone-sensitive PCa patients and found an association between a faster time to PSA nadir after initiation of ADT and shorter overall survival [19]. Therefore, we conducted a large cohort study of PCa patients receiving ADT to investigate the prognostic ability of PSA nadir and time to PSA nadir as well as their interactive effect on disease mortality.

Materials and methods

Patient selection

The study population was expanded from our hospital-based PCa case–control study, and the details of which have previously been described [20–26]. Briefly, patients with diagnosed and pathologically confirmed PCa were actively recruited from three medical centres, Kaohsiung Medical University Hospital, Kaohsiung Veterans General Hospital and National Taiwan University Hospital in Taiwan. The patients with PCa who had been treated with ADT (orchiectomy or LHRH agonist with or without antiandrogen), including those with disease recurrence after local treatment, were identified and followed up prospectively to evaluate clinical characteristics and PSA kinetics as prognostic predictors for clinical outcomes during ADT. Sixty-seven patients were excluded due to insufficient clinicopathological information, follow-up period or PSA never decline after ADT, leaving 650 cases for the final analysis. This study was approved by the institutional review board of the three hospitals, and informed consent was obtained from each participant.

Clinical data and outcome collection

Data were collected on patients and disease baseline characteristics, ADT treatment modalities and treatment outcomes. The PSA nadir was defined as the lowest PSA value achieved by the patient during treatment [15,17]. Time to PSA nadir was defined as the duration of time it took for the PSA value to reach nadir after ADT was started [19]. PSA decline was calculated from the slope of the linear regression of the PSA values from ADT start to the nadir PSA.

The outcomes measurements were PCSM and all-cause mortality (ACM). The cause of death was obtained by matching patients' personal identification number with the official cause of death registry provided by the Department of Health, Executive Yuan, Taiwan. In total, 162 deaths were identified and 114 of them died from PCa. In general, patients are followed up every month with PSA tests at 3 months intervals.

Statistical analyses

Kaplan–Meier analysis and Cox regression model were used to evaluate the associations of PSA nadir level and time to PSA nadir with PCSM and ACM, adjusting for other known prognostic factors. PSA nadir level was dichotomised at 0.2 ng/ml, a cut-off point that has been previously reported to correlate with post-ADT disease progression and PCa-specific survival [15,17]. Time to PSA nadir was dichotomized at a median of 10 months. To further explore the interactive effect of PSA nadir and time to PSA nadir on disease progression and survival, we categorised the patients into four groups: (1) PSA nadir $<$ 0.2 ng/ml and time to PSA nadir $\geq$ 10 months, (2) PSA nadir $<$0.2 ng/ml and time to PSA nadir $<$10 months, (3) PSA nadir $\geq$0.2 ng/ml and time to PSA nadir $\geq$10 months and (4) PSA nadir $\geq$0.2 ng/ml and time to PSA nadir $<$10 months. Since PSA nadir and time to PSA nadir were measured over time after ADT initiation, we conducted the analyses of PCSM and ACM from the landmark of 2-year after ADT initiation (the Landmark Method) [19,27]. All statistical operations were performed using SPSS version 16.0.1 (SPSS Inc., Chicago, IL). A two-sided P value of $<$0.05 was considered significant.

Results

Characteristics of the study population and PSA kinetics

The median age at diagnosis of those 650 patients was 73 years (range, 36–95 years) (Table I). At diagnosis, a plurality had Gleason scores 8–10 (36.4%), T stages of 3 or 4 or lymph node positive (30.8%) and metastatic disease (M1) (38.1%).

The median PSA level was 34.6 ng/ml at initiation of ADT and the median PSA nadir was 0.19 ng/ml. Almost half of patients (49.7%) reached a PSA nadir of $<$0.2 ng/ml, 20.2%, 19.1% and 9.7% had PSA nadir of 0.2–1.0, $>$1.0–10.0, and $>$10.0 ng/ml, respectively. The median time to PSA nadir was 10 months [interquartile range (IQR), 5–17 months]. The median

Table I. Characteristics of the cohort ($n = 650$).

Characteristic	N	Percentage	Median	IQR
Age at diagnosis (yr)			73	67–78
PSA at ADT initiation			34.6	11.3–128.6
Clinical stage at diagnosis				
T1/T2	201	31.1		
T3/T4/N1	199	30.8		
M1	246	38.1		
Biopsy Gleason score at diagnosis				
2–6	209	32.8		
7	196	30.8		
8–10	232	36.4		
Treatment modality				
ADT as primary treatment	364	56		
ADT for post RP PSA recurrence*	74	11.4		
ADT for post RT PSA failure†	21	3.2		
Neoadjuvant/adjuvant ADT with RT	133	20.3		
Others	58	9		
Type of ADT				
LHRH analogue with/without antiangrogen	590	90.8		
Orchiectomy	60	9.2		
PSA nadir (ng/ml)				
<0.2	323	49.7		
0.2–1.0	131	20.2	0.19	0.01–1.36
>1.0–10.0	124	19.1		
>10.0	63	9.7		
Time to PSA nadir, months			10	5–17
PSA decline (ng/ml/yr)			34	8–143

Abbreviations: PSA: prostatic-specific antigen; ADT: androgen-deprivation therapy; RP: radical prostatectomy; RT: radiotherapy; LHRH: luteinizing hormone-releasing hormone; IQR: interquartile range.

*PSA recurrence defined as two consecutive PSA measurements >0.2 ng/ml at an interval of >3 months.

†1996 ASTRO definition for PSA failure post-RT: three consecutive increases in PSA is a reasonable definition of biochemical failure after radiation therapy.

PSA decline after ADT was 34 ng/ml/yr. The PSA levels at the start of ADT were similar between the groups with short (<10 months) and the long (10 months) time to PSA nadir (median 35.3 ng/ml vs. 34.3 ng/ml, $P = 0.210$). However, the group with rapid PSA decline (34 ng/ml/yr) had much higher baseline PSA levels compared with the group with slow PSA decline (median 126.9 ng/ml vs. 13.0 ng/ml, $P < 0.001$). Patients who had a rapid PSA decline or short time to PSA nadir were less likely to achieve a PSA nadir < 0.2 ng/ml ($P < 0.001$).

Univariate and multivariate analyses of predictors for PCSM and ACM

With a mean and median follow-up of 47 and 43 months, 162 patients died and 114 of them died from PCa. In univariate analysis, clinical M1 stages, Gleason scores of 8–10, higher PSA at ADT initiation, PSA nadir ≥ 0.2 ng/ml, shorter time to PSA nadir (<10 months) and rapid PSA decline (34 ng/ml/yr) were significant predictors for PCSM and ACM. Figure 1 showed the Kaplan–Meier curves of PCa-specific survival and overall survival following ADT, stratified by PSA decline (log-rank test, all $P < 0.001$) and time to PSA nadir (log-rank test, $P = 0.010$ and 0.005, respectively).

In the multivariate analyses, clinical M1 stage, higher Gleason score (8–10), higher PSA nadir (0.2 ng/ml) and shorter time to PSA nadir (<10 months) were significant predictors for PCSM. Similarly, clinical M1 stage, higher PSA nadir and shorter time to PSA nadir were associated with worse overall survival (Table II, Model 1).

In subgroup analyses dichotomized by PSA nadir level (<0.2 vs. ≥ 0.2 ng/ml), we found that the effects of time to PSA nadir and other clinical factors on PCSM and ACM were attenuated in patients with PSA nadir <0.2 ng/ml but clinical M1 stage and higher Gleason score remained significant predictors for PCSM and ACM in patients with PSA nadir ≥ 0.2 ng/ml (Table II, Model 2).

In the combined analyses of PSA nadir and time to PSA nadir, patients with lower PSA nadir level and longer time to PSA nadir had the best survival. The group with the higher PSA nadir level and shorter time to PSA nadir had the worst survival (hazard ratios were 6.30 and 4.79 for PCSM and ACM, respectively, all $P < 0.001$; Table II, Model 3). Figure 2 showed the Kaplan–Meier curves of PCa-specific survival and overall survival following ADT, stratified by PSA nadir level and time to PSA nadir groups. Faster PSA decline was an independent predictor for PCSM and ACM (Table II, Model 4).

Discussion

The present study showed that, in addition to clinical metastatic stage, higher Gleason score and higher PSA nadir (0.2 ng/ml), a more rapid PSA decline and a shorter time to PSA nadir (<10 months, dichotomized by the median value) were significantly associated with worse PCSM and ACM after ADT. Furthermore, combined analysis showed that patient with higher PSA nadir and shorter time to PSA nadir had the worst disease progression and survival, whereas those with lower PSA nadir and longer time to PSA nadir had the best ones. To the best of our knowledge, our series represents the largest cohort to demonstrate the important prognostic significance of time to PSA nadir and its interactive effect with PSA nadir level on survival in patients with PCa receiving ADT.

According to the American Society of Clinical Oncology clinical practice guidelines 2007, ADT remains the mainstay treatment for men with metastatic hormone-sensitive PCa [28]. In addition, ADT also serves as a standard care in the treatment of men with

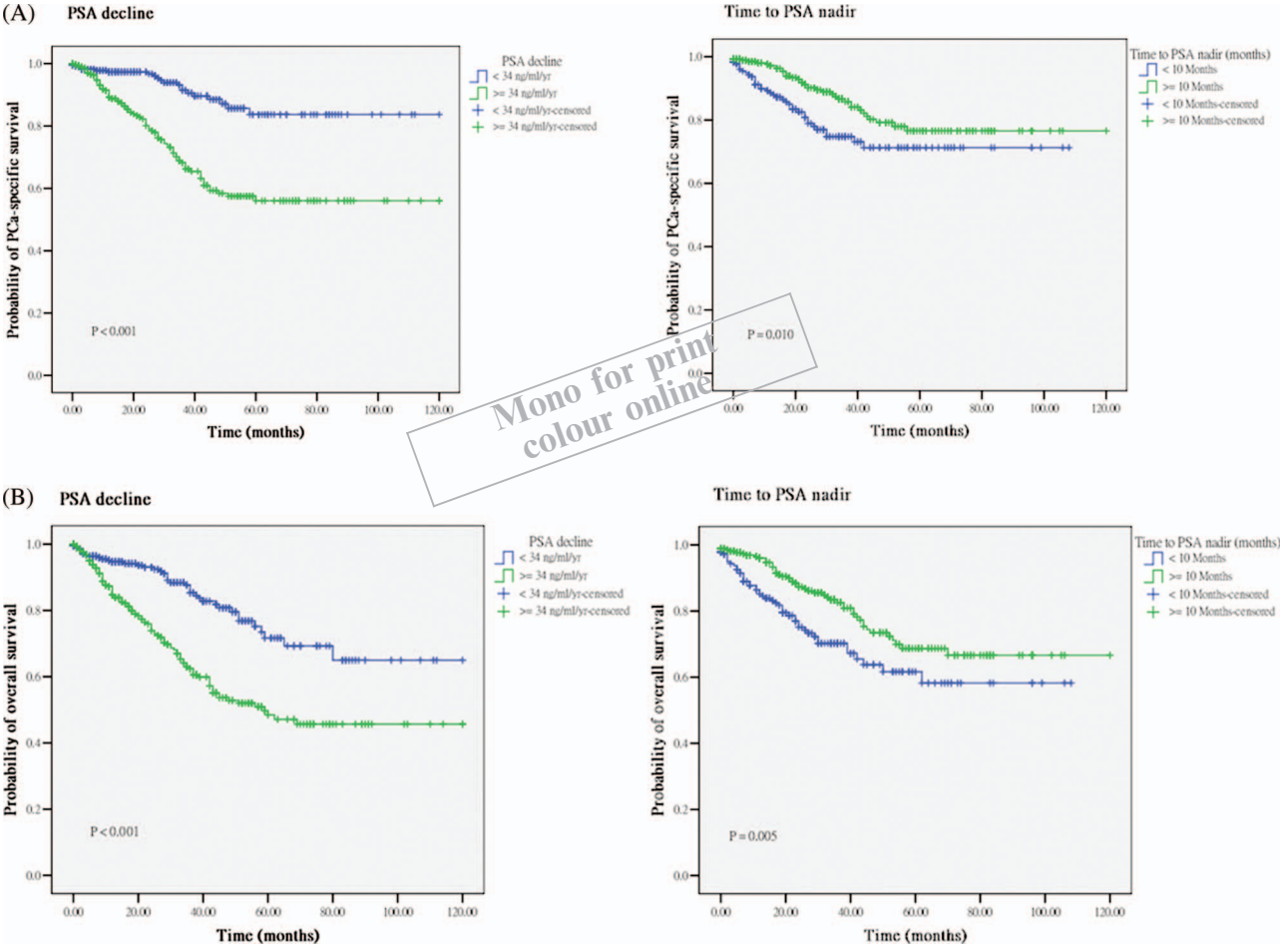

Figure 1. Kaplan–Meier curves of (A) prostate cancer-specific survival and (B) overall survival following ADT, stratified by PSA decline (left) and time to PSA nadir (right).

disease recurrence after local treatment failure (National Comprehensive Cancer Network PCa treatment guidelines 2009). It has been well established that PSA kinetics can serve as a prognostic predictor of patients' outcome before the initiation of radical prostatectomy and radiotherapy and during biochemical recurrence when these therapies failed [11–14]. However, the influence of PSA kinetics, such as PSA decline, PSA response, time to PSA nadir and PSA after 7 months induction course of ADT on disease progression and survival in patient with hormone-sensitive PCa, has not been well studied. Most studies have focussed attention on the association between PSA response and survival, trying to determine if this variable could be used as a surrogate for survival [18,29–32]. In general, the efficacy of ADT has been correlated with more profound PSA declines, lower PSA after 7 months of ADT that reflect improved survival subsequently. Among the parameters for PSA response or PSA doubling time, some of them need to be calculated using linear regression that may be time consuming and not suitable for routine clinical practice. In accordance with previous reports [15–17,19], we also demonstrated that a lower PSA nadir (<0.2 ng/ml) was independently associated with longer survival in our data-set.

In contrast to our general thinking, patient having a rapid PSA response (faster PSA decline) might have a longer survival, our results showed that a more rapid PSA decline and a shorter time to PSA nadir were associated with shorter PCa-specific survival and overall survival; moreover, time to PSA nadir was independently associated with survival even after adjusting for other co-variants. However, after careful literature review, our result is not the only one that showed this phenomenon. In a small series of 179 metastatic hormone-sensitive PCa patients, Choueiri et al. [19] found that a faster time to reach a PSA nadir after initiation of ADT was associated with shorter overall survival duration, notably, time to PSA nadir was independently associated with overall survival even after adjusting for other variables. However, they did not investigate the influence of time to PSA nadir on PCa-specific survival. In our study, we found that time to PSA nadir was an independent predictor for both PCSM and ACM, thus, our finding strongly confirmed that the shorter time to PSA nadir was significantly associated with shorter survival for PCa after ADT. So far, the exact mechanism responsible for this clinical observation remains unknown. PSA nadir level and time to PSA nadir may represent for 'capacity' and

Table II. Cox proportional hazard regression analyses of clinicopathological factors predicting PCSM and ACM following ADT.

Variables	PCSM		ACM	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1				
Age (yr)	1.04 (0.98–1.03)	0.771	1.02 (1.00–1.05)	0.079
Clinical stage at diagnosis				
T1/T2	1 (Ref.)	–	1 (Ref.)	–
T3/T4/N1	1.97 (0.83–4.68)	0.126	1.05 (0.54–2.04)	0.882
M1	**3.55 (1.56–8.10)**	**<0.001**	**2.16 (1.18–3.93)**	**0.012**
Gleason score at diagnosis				
2–6	1 (Ref.)	–	1 (Ref.)	–
7	0.78 (0.38–1.58)	0.483	0.91 (0.52–1.61)	0.754
8–10	**2.07 (1.15–3.75)**	**0.016**	1.65 (1.00–2.73)	0.051
PSA at ADT initiation (ng/ml)*	1.12 (0.98–1.29)	0.088	1.12 (0.99–1.26)	0.064
PSA nadir (ng/ml)				
<0.2	1 (Ref.)	–	1 (Ref.)	–
≥0.2	**3.64 (2.08–6.37)**	**<0.001**	**2.83 (1.80–4.45)**	**<0.001**
Time to PSA nadir (mo)†				
≥10	1 (Ref.)	–	1 (Ref.)	–
<10	**1.68 (1.03–2.75)**	**0.039**	**1.66 (1.09–2.53)**	**0.019**
Model 2				
PSA nadir < 0.2 ng/ml				
Age (yr)	0.97 (0.92–1.02)	0.276	1.00 (0.96–1.05)	0.891
Clinical stage at diagnosis				
T1/T2	1 (Ref.)	–	1 (Ref.)	–
T3/T4/N1	1.06 (0.27–4.22)	0.931	0.75 (0.27–2.11)	0.585
M1	2.23 (0.54–9.31)	0.271	1.55 (0.56–4.25)	0.397
Gleason score at diagnosis				
2–6	1 (Ref.)	–	1 (Ref.)	–
7	0.72 (0.18–2.98)	0.651	0.93 (0.37–2.34)	0.878
8–10	2.04 (0.66–6.30)	0.214	1.21 (0.49–2.94)	0.683
PSA at ADT initiation (ng/ml)*	1.07 (0.81–1.40)	0.648	1.14 (0.91–1.43)	0.253
Time to PSA nadir (mo)†				
≥10	1 (Ref.)	–	1 (Ref.)	–
<10	1.57 (0.60–4.14)	0.358	1.75 (0.83–3.68)	0.139
PSA nadir ≥ 0.2 ng/ml				
Age (yr)	1.02 (0.98–1.05)	0.313	1.03 (1.00–1.06)	0.084
Clinical stage at diagnosis				
T1/T2	1 (Ref.)	–	1 (Ref.)	–
T3/T4/N1	2.76 (0.86–8.85)	0.088	1.34 (0.55–3.26)	0.518
M1	**4.56 (1.52–13.69)**	**0.007**	**2.68 (1.22–5.89)**	**0.014**
Gleason score at diagnosis				
2–6	1 (Ref.)	–	1 (Ref.)	–
7	0.92 (0.40–2.13)	0.849	1.03 (0.50–2.13)	0.929
8–10	**2.22 (1.09–4.51)**	**0.028**	**2.06 (1.10–3.87)**	**0.024**
PSA at ADT initiation (ng/ml)*	1.15 (0.98–1.34)	0.085	1.10 (0.96–1.27)	0.181
Time to PSA nadir (mo)				
≥10	1 (Ref.)	–	1 (Ref.)	–
<10	1.68 (0.95–2.99)	0.077	1.58 (0.94–2.65)	0.083
Model 3				
Combined analysis of PSA nadir and time to PSA nadir				
Age (yr)	1.00 (0.98–1.03)	0.765	1.02 (1.00–1.05)	0.08
Clinical stage at diagnosis				
T1/T2	1 (Ref.)	–	1 (Ref.)	–
T3/T4/N1	1.97 (0.83–1.03)	0.127	1.05 (0.54–2.04)	0.882
M1	**3.56 (1.56–8.12)**	**0.003**	**2.16 (1.18–3.92)**	**0.012**
Gleason score at diagnosis				
2–6	1 (Ref.)	–	1 (Ref.)	–
7	0.78 (0.38–1.59)	0.495	0.92 (0.52–1.62)	0.775
8–10	**2.08 (1.05–3.75)**	**0.016**	**1.65 (1.00–2.73)**	**0.050**
PSA at ADT initiation (ng/ml)*	1.12 (0.98–1.28)	0.09	1.12 (0.99–1.26)	0.066
PSA nadir/time to PSA nadir				
<0.2 ng/ml/ ≥ 10 mo	1 (Ref.)	–	1 (Ref.)	–
<0.2 ng/ml/ < 10 mo	1.89 (0.73–4.85)	0.188	1.85 (0.89–3.85)	0.098
≥0.2 ng/ml/ ≥ 10 mo	**3.90 (1.84–8.27)**	**<0.001**	**3.04 (1.66–5.57)**	**<0.001**
≥0.2 ng/ml/ < 10 mo	**6.30 (3.00–13.23)**	**<0.001**	**4.79 (2.63–8.73)**	**<0.001**

(*continued*)

Table II. (*Continued*).

Variables	PCSM		ACM	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 4				
PSA decline				
Age (yr)	1.01 (0.99–1.03)	0.422	**1.03 (1.01–1.05)**	**0.003**
Clinical stage at diagnosis				
T1/T2	1 (Ref.)	–	1 (Ref.)	–
T3/T4/N1	1.78 (0.85–3.73)	0.124	1.32 (0.77–2.26)	0.312
M1	**3.48 (1.75–6.92)**	**<0.001**	**2.50 (1.52–4.11)**	**<0.001**
Gleason score at diagnosis				
2–6	1 (Ref.)	–	1 (Ref.)	–
7	0.86 (0.46–1.59)	0.624	0.92 (0.57–1.48)	0.726
8–10	**2.33 (1.40–3.87)**	**0.001**	**1.93 (1.28–2.91)**	**0.002**
PSA decline (ng/ml/yr)‡				
<34	1 (Ref.)	–	1 (Ref.)	–
≥34	**2.20 (1.29–3.77)**	**0.004**	**1.56 (1.04–2.34)**	**0.032**

Abbreviations: ADT, androgen-deprivation therapy; PCSM, prostate cancer-specific mortality; ACM, all-cause mortality; PSA, prostate-specific antigen; HR, hazard ratio.
*As continues variable with log transformed.
†Divided by a median of 10 months.
‡Divided by a median of 34 ng/ml/year.
$P \leq 0.05$ are given in boldface.

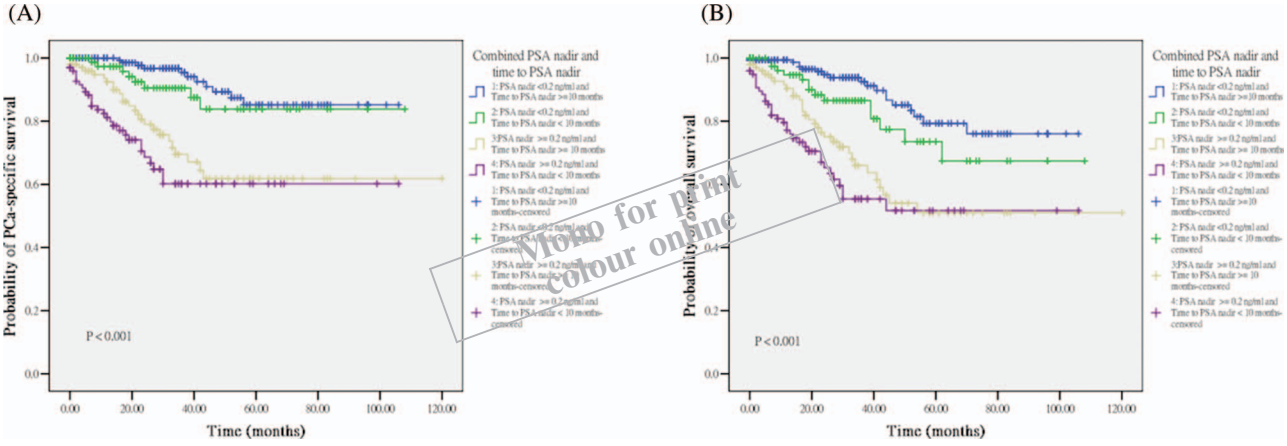

Figure 2. Kaplan–Meier curves of (A) prostate cancer-specific survival and (B) overall survival following ADT, stratified by PSA nadir level and time to PSA nadir groups: group 1: PSA nadir < 0.2 ng/ml and time to PSA nadir ≥ 10 months, group 2: PSA nadir < 0.2 ng/ml and time to PSA nadir < 10 months, group 3: PSA nadir ≥ 0.2 ng/ml and time to PSA nadir ≥ 10 months, groups 4: PSA nadir ≥ 0.2 ng/ml and time to PSA nadir < 10 months. Log-rank test: $P < 0.001$.

'adapting ability', respectively, for PCa to become androgen independent (or castration resistant). In fact, the rapid decrease in PSA after ADT may be due to ablation of androgen receptor (AR) function that causes the cell-cycle arrest rather than cell death of PCa cells [33]. In addition, instead of its classic proliferation role of AR, the AR can also act as a tumour suppressor for PCa [34]. Thus, the quick suppression of androgen/AR during ADT may have a negative impact on disease progression and survival. Our findings also partly reflect the complicated role of androgen/AR signals in the progression of PCa [35,36], although further *in vivo* and *in vitro* experiments are needed to confirm this hypothesis. Other possibilities such as a significant heterogeneity in metastatic PCa may cause the striking viability in survival. The severity of disease characteristics in our cohort was no worse than those reported by other series [19,37], thus, in this study, it was improbable that we selected a subset of patients with aggressive PCa that quickly becomes resistant to ADT.

We found that the effect of time to PSA nadir on PCSM and ACM was attenuated when we performed subgroup analyses dichotomized by PSA nadir level (<0.2 vs. ≥0.2 ng/ml), this may be due to insufficient case numbers for subgroup analysis or may be indicated that PSA nadir is a more powerful predictor than time to PSA nadir. Interestingly, the significant associations of clinical stage and Gleason score with survival were also decreased in patients who had a PSA nadir < 0.2 ng/ml, suggesting that PSA nadir < 0.2 ng/ml might play a critical role to determine survival after ADT. We also recognised that there were fewer death events in the

group of patients with PSA nadir < 0.2 ng/ml, further study with more cases in that group is necessary for investigating the relationship between time to PSA nadir and survival.

The most interesting finding in this study was probably that we demonstrated an interactive effect of PSA nadir and time to PSA nadir. By Kaplan–Meier and multivariate Cox regression analyses, we found that those with higher PSA nadir and shorter time to PSA nadir had significant higher risk for disease mortality compared to those with lower PSA nadir and longer time to PSA nadir (Table II, Figure 2). However, the detailed mechanism of interaction between these two variables deserves further investigation.

Our study has strengths and limitations. The study was conducted using a valid large cohort ($n = 650$), adequate follow-up period and detailed clinical information allowing stable and reliable statistical analyses when stratified by PSA nadir and time to PSA nadir on disease mortality for PCa after ADT. One limitation is that we did not include some important factors, such as lactate dehydrogenase and performance status in this study, because they are not measured routinely in patients who received ADT at our institutions. Second, heterogeneous clinical backgrounds did exist between our series and other studies. In addition, our homogeneous Chinese Han population might make our findings less generalisable to other ethnic groups. Finally, although several PSA kinetic parameters such as PSA response and PSA doubling time were already reported, our finding regarding the PSA decline and time to PSA nadir could enrich the predictive information for PCa prognosis and survival.

Conclusions

Both PSA nadir and time to PSA nadir can independently predict survival in PCa patients who have received ADT. It might be possible to combine time to PSA nadir with PSA nadir level to identify PCa patients at higher risk after ADT and such patients might benefit from more aggressive treatment or novel therapeutic agents. Further large-scale prospective studies and external validation in other ethnic groups are needed to confirm our findings.

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