Impact of Prostate-Specific Antigen (PSA) Nadir and Time to PSA Nadir on Disease Progression in Prostate Cancer Treated With Androgen-Deprivation Therapy

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BACKGROUND. The influence of PSA kinetics on the outcome of metastatic prostate cancer after androgen deprivation therapy (ADT) is not well understood. We evaluated the prognostic significance of PSA nadir and time to PSA nadir as well as their potential interactive effect on the progression of disease after ADT.

METHODS. A total of 650 men with advanced or metastatic prostate cancer treated with ADT were studied. The prognostic significance of PSA nadir and time to PSA nadir on disease progression were analyzed using Kaplan–Meier analysis and the Cox regression model.

RESULTS. We found that both PSA nadir and time to PSA nadir were independent and significant predictors of disease progression. Patients with higher PSA nadir ($\geq$0.2 ng/ml) and shorter time to PSA nadir (<10 months) had significant shorter time to disease progression after adjusting for other covariates. The combined analyses showed a potential synergistic effect of these two variables on disease progression. Patient with higher PSA nadir and shorter time to PSA nadir had significantly higher risk for disease progression compared to those with lower PSA nadir and longer time to PSA nadir (Hazard Ratios (HR) = 3.11, $P < 0.001$).

CONCLUSIONS. We concluded that both PSA nadir and time to PSA nadir are significant predictors of disease progression for prostate cancer patients receiving ADT. *Prostate 71: 1189–1197, 2011.* © 2011 Wiley-Liss, Inc.

Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen; ADT, androgen-deprivation therapy; HR, hazard ratios; CI, confidence interval; AR, androgen receptor.

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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 localized 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 prostate cancer is androgen deprivation therapy (ADT) [1,2]. The androgen-dependent period in patients with metastatic prostate cancer lasts a median of 14–30 months [3]. The disease then progresses to a phase when ADT alone fails to control the malignancy despite castrate testosterone levels. At this stage, it is termed androgen-independent prostate cancer (AIPC) or 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. At this stage, it is referred to as hormone refractory prostate cancer (HRPC). Histologically, metastatic AIPC and HRPC are highly resistant to the chemotherapy and yield poor response with median survivals of 12–18 months [7–10]. An accurate prediction for patients at higher risk for disease progression after ADT is of paramount important because these patients might benefit from more aggressive treatment or novel therapeutic agents.

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 is not well understood. Recently, studies have reported an association between PSA nadir and progression to AIPC and prostate cancer specific mortality (PCSM) in patients receiving ADT [9,15–17]. The role of time-to-PSA nadir on predicting disease progression or PCSM after ADT has not been well studied except one small case series study which was conducted in 179 metastatic hormone-sensitive prostate cancer patients and found an association between a faster time to PSA nadir after initiation of ADT and shorter survival [18]. 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 potential interactive effect on disease progression.

MATERIALS AND METHODS

Patient Selection

The study population was expanded from our hospital-based PCa case-control study the details of which have previously been described [19–25]. Briefly, patients with diagnosed and pathologically confirmed PCa were actively recruited from three medical centers, Kaohsiung Medical University Hospital, Kaohsiung Veterans General Hospital, and National Taiwan University Hospital in Taiwan. For the present study, we selected the patients those who had been treated with ADT (orchiectomy or LHRH agonist with or without antiandrogen) for advanced or metastatic prostate cancer. Sixty-seven patients were excluded due to insufficient clinicopathological information or follow-up period or PSA never decline 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 [18]. The primary outcome was disease progression during treatment with ADT. Progression was defined as serial rise in PSA, at least two rises in PSA (>1 week apart) greater than the PSA nadir were needed [26]. Initiation of secondary hormone treatment for rising PSA was also considered as a progression event. The date of progression was defined as the date of first rise. All patients are followed every month with PSA tests at 3 months intervals according to consensus guidelines of Taiwan Urological Association.

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 time to disease progression, adjusting for other known prognostic factors. PSA nadir level was first categorized into <0.2, 0.2–1.0, 1.0–10, and >10 ng/ml and then dichotomized at

0.2 ng/ml, a cut-off point that has been previously reported to correlate with post-ADT disease progression and prostate cancer 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 categorized the patients into four groups: (1) PSA nadir <0.2 ng/ml and time to PSA nadir ≥10 months, (2) PSA nadir <0.2 ng/ml and time to PSA nadir <10 months, (3) PSA nadir ≥0.2 ng/ml and time to PSA nadir ≥10 months and (4) PSA nadir ≥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, those who took longer time to reach PSA nadir will live longer than those with shorter time to reach PSA nadir. In order to eliminate this ''guarantee time'' or ''lead time'' effect, we conducted the analyses of disease progression from the landmarks of PSA nadir on ADT (post-PSA nadir survival) [18]. 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

The median age at diagnosis of those 650 cases patients was 73 years old (range, 36–95 years) (Table I). At diagnosis, a plurality had Gleason scores 8–10 (36.4%), local advanced stages of T3/T4/N1 (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). Patients who had a short time to PSA nadir were less likely to achieve a PSA nadir <0.2 ng/ml, $P < 0.001$.

About seventy percent (68.9%, n = 448) of patients had disease progression during the course of the study with mean and median times of 23.3 and 17 months.

PSA Nadir Level and Disease Progression

The mean progression-free survival in patients with PSA nadir <0.2 ng/ml (28.1 months) was significantly longer than those in patients with PSA nadir 0.2–1.0 ng/ml (9.8 months), >1.0–10 ng/ml (6.8 months) and >10.0 ng/ml (4.7 months) (Log Rank Test, $P < 0.001$). The effect of dichotomizing the PSA nadir at 0.2 ng/ml on disease progression was shown in Figure 1A.

Time to PSA Nadir and Disease Progression

When time to PSA nadir was dichotomized at 10 months, significant associations were found between time to PSA nadir and progression-free survival (Fig. 1B). Patients with a longer time to PSA nadir (≥10 months) had a longer mean progression free survival compared to shorter time to PSA nadir (<10 months) (22.6 months vs. 13.9 months, log-rank test, $P < 0.001$).

Combined Analyses of PSA Nadir and Time to PSA Nadir on Disease Progression

As can be seen in Figure 2, patients in the group with lower PSA nadir level (<0.2 ng/ml) and longer time to PSA nadir (≥10 months) had the best disease progression-free survival. In contrast, patients in the group with the higher PSA nadir level (≥0.2 ng/ml) and shorter time to PSA nadir (<10 months) had the worst progression-free survival.

Univariate and Multivariate Analyses of Predictors for Disease Progression

In univariate analysis, M1 stage at diagnosis, Gleason Scores of 8–10, PSA at ADT initiation, PSA nadir ≥0.2 ng/ml and a time to PSA nadir <10 months were associated with worse progression-free survival (Table II).

In the multivariate analyses, PSA nadir and time to PSA nadir remained significant predictors of disease progression after adjusting for age, clinical stage and biopsy Gleason Score and PSA level (Table III, Model 1). 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 disease progression-free survival. The group with the higher PSA nadir level and shorter time to PSA nadir had the worst progression-free survival: the hazard ratios (HR) were 3.11 compared to those with lower PSA nadir and longer time to PSA nadir, suggesting potential a synergistic effect of these two variables on disease progression (Table III, Model 2).

DISCUSSION

The present study showed that both higher PSA nadir (≥0.2 ng/ml) and shorter time to PSA nadir (<10 months, dichotomized by the median value), were significantly associated with shorter survival for disease progression after ADT. There was a clear and independent association between time to PSA nadir and disease progression even after adjusting for other covariates. Furthermore, combined analysis revealed a potential synergistic effect of PSA nadir and time to PSA nadir on disease progression. Patient with higher

TABLE I. Characteristics of the Cohort (n = 650)

Characteristic	No.	%
Age at diagnosis, years		
Mean ± SD	72.2 ± 8.8	
Median	73	
PSA at ADT initiation		
Mean ± SD	268.8 ± 801.9	
Median	34.6	
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	56.0
ADT for post-RP PSA recurrence[a]	74	11.4
ADT for post-RT PSA failure[b]	21	3.2
Neoadjuvant/adjuvant ADT with RT	133	20.3
Others	58	9.0
Type of ADT		
LHRH analog 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
>1.0–10.0	124	19.1
>10.0	63	9.7
Median	0.19	
IQR	0.01–1.36	
Time to PSA nadir, months		
Mean ± SD	13.6 ± 13.0	
Median	10	
IQR	5–17	

PSA, prostatic-specific antigen; ADT, androgen-deprivation therapy; RP, radical prostatectomy; RT, radiotherapy; LHRH, luteinizing hormone-releasing hormone; IQR, interquartile range.
[a]PSA recurrence defined as two consecutive PSA measurements greater than 0.2 ng/ml at an interval of more than 3 months.
[b]1996 ASTRO definition for PSA failure post-RT: three consecutive increases in PSA is a reasonable definition of biochemical failure after radiation therapy.

PSA nadir and shorter time to PSA nadir had the worst disease progression, whereas those with lower PSA nadir and longer time to PSA nadir had the best ones. To 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 disease progression in PCa patients receiving ADT.

In 2007, the American Society of Clinical Oncology published clinical practice guidelines on initial hormone management of androgen-sensitive, metastatic PCa [27]. Today ADT remains the mainstay of treatment for men with metastatic hormone sensitive PCa. 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 others on disease progression and survival in patient with hormone sensitive prostate cancer has not been well studied [28–32]. An accurate prediction for patients at higher risk for disease progression after ADT is of paramount important

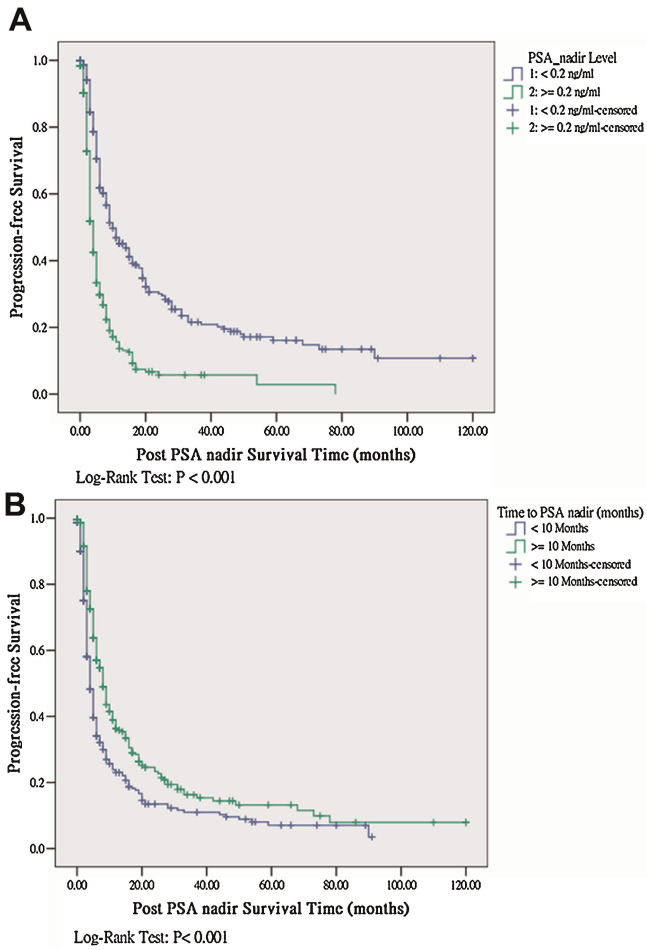

Fig. 1. Kaplan–Meier analyses of time to progression stratified by PSA nadir level of <0.2 ng/ml versus ≥ 0.2 ng/ml (**A**) or time to PSA nadir <10 months versus ≥ 10 months (**B**), respectively, log-rank test: $P < 0.001$.

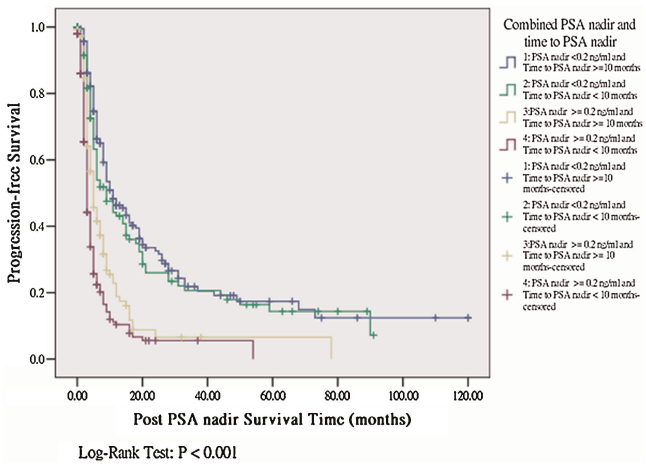

Fig. 2. Kaplan–Meier analyses of time to progression after androgen deprivation therapy, stratified by PSA nadir level and time to PSA nadir groups: group 1: PSA nadir <0.2 ng/ml and time to PSA nadir ≥ 10 months, group 2: PSA nadir <0.2 ng/ml and time to PSA nadir <10 months, group 3: PSA nadir ≥ 0.2 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: $P < 0.001$).

because: so far, no effective therapy for CRPC can improved survival much, second, PSA level increase 6–12 months before definitive radiological or clinical proof of disease progression [33,34]. This period is important in planning treatment because during this period the tumor burden is minimal and the patients is otherwise healthy can tolerate alternative treatments.

In accordance with previous reports [15,16], we also demonstrated that a lower PSA nadir (<0.2 ng/ml) was independently associated with longer progression-free periods in our dataset. Moreover, the PSA nadir showed a dose-dependent fashion in our Kaplan–Meier analysis. Together, these findings confirm the importance of PSA nadir as a biomarker for disease progression in PCa receiving ADT.

Few studies have investigated the association between time and PSA nadir on disease progression and survival. In a small series of 179 metastatic hormone-sensitive prostate cancer patients, Choueiri et al. [18] found that a faster time to reach a PSA nadir after initiation of ADT was associated with shorter survival duration, notably, time to PSA nadir was associated independently with survival even after adjusting for other variables. However, they did not investigate the influence of time to PSA nadir on disease progression. In our study, we found that time to PSA nadir was associated independently with time to progression, thus, our finding strongly confirmed that the time to PSA nadir was an independent predictor for clinical outcome of PCa after ADT. So far, the exact mechanism responsible for this clinical observation remains unknown. PSA nadir level and time to PSA nadir may represents for ''capacity'' and ''adapting ability,'' respectively, for prostate cancer to become androgen independent (or castration resistant). In fact, the rapid fall in PSA after ADT may be due to ablation of androgen receptor (AR) function which causes the cell cycle arrest rather than cell death of prostate cancer cells [35]. In addition, instead of its classic proliferation role of androgen receptor, the AR can also act as a tumor suppressor for the prostate cancer [36]. Thus, the quick suppression of androgen/AR during ADT may have a negative impact on disease progression. Our findings also partly reflect the complicated role of androgen/AR signals in the progression of PCa [37,38], though further in vivo and in vitro experiments are needed to confirm this hypothesis. Other possibilities such as a significant heterogeneity in metastatic prostate cancer may cause the striking viability in

TABLE II. Univariate Analyses of Clinicopathological Factors Predicting Disease Progression After Androgen DeprivationTherapy

Variables	Hazard ratio	95% CI	*P*-Value
Age (y/o)	0.99	0.98–1.00	0.192
Clinical stage			
T1/T2	1 (Ref.)	—	—
T3/T4/N1	1.12	0.88–1.43	0.356
M1	1.41	1.13–1.77	0.003
Biopsy Gleason score			
2–6	1 (Ref.)	—	—
7	1.14	0.90–1.45	0.276
8–10	1.38	1.10–1.73	0.006
PSA at ADT initiation (ng/ml)[a]	1.09	1.04–1.14	<0.001
PSA nadir (ng/ml)			
≥0.2 vs. <0.2	2.49	2.05–3.02	<0.001
Time to PSA nadir (months)[b]			
<10 vs. ≥10	1.55	1.29–1.87	<0.001

[a]As continues variable with log transformed.
[b]Divided by median 10 months.

disease progression. The severity of disease characteristics in our cohort were no worse than those reported by other series [18,26] thus, in this study it was improbable that we selected a subset of patients with aggressive PCa that quickly become resistant to ADT.

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 risk for disease progression compared to those with lower PSA nadir and longer time to PSA nadir, suggesting a potential synergistic effect of these two variables on disease progression (Table II, Model 2). However, the detailed mechanism of interaction between these two variables deserves further investigation.

Our study has strength and limitation. The study was conducted using a valid large cohort (n = 650), adequate follow-up period and detailed clinical information allow stable and reliable statistical analyses when stratified by PSA nadir and time to PSA nadir on disease progression for prostate cancer 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 receive ADT in our institutions. Second, heterogeneous clinical backgrounds did exist between our series and other studies. Third, a possible criticism of this study is the use of disease progression end point based on PSA level. We chose this end point because of its biologic and clinical relevance. Usually, the first indication of the failure of ADT and the development of castration-resistant disease is a rising PSA. Thus, the point of PSA progression most closely identifies the timing of the failure of ADT. Moreover, clinically, a rising PSA on ADT typically triggers a change in therapy [31]. However, we recognize that the precise definition of PSA progression after ADT remains controversial [39,40]. Fourth, we conduct post-PSA nadir survival to compromise the lead time bias of the time covariate of time to PSA nadir, this may also raise some statistical concern. Finally, although some other PSA kinetic parameters like PSA decline, PSA response and PSA doubling time already reported, our finding regarding the time to PSA nadir enrich the predictive information in this context.

CONCLUSIONS

Both PSA nadir and time to PSA nadir can independently predict progression of prostate cancer in patients who have received ADT. Potential synergistic effect on disease progression was also found for these two important variables. It might be possible to combine time to PSA nadir with PSA nadir level to identify prostate cancer 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 are needed to confirm our findings.

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TABLE III. Multivariate Cox Proportional Hazards Analyses of Clinicopathological Factors Predicting Disease Progression After Androgen DeprivationTherapy

	Multivariate		
Variables	Hazard ratio	95% CI	*P*-Value
Model 1			
Age (y/o)	0.99	0.98–1.00	0.036
Clinical stage			
T1/T2	1 (Ref.)	—	—
T3/T4/N1	1.18	0.91–1.53	0.218
M1	1.05	0.79–1.40	0.719
Biopsy Gleason score			
2–6	1 (Ref.)	—	—
7	1.12	0.87–1.44	0.371
8–10	1.24	0.97–1.59	0.083
PSA at ADT initiation (ng/ml)[a]	1.03	0.98–1.09	0.267
PSA nadir (ng/ml)			
≥0.2 vs. <0.2	2.38	1.91–2.97	<0.001
Time to PSA nadir (months)[b]			
<10 vs. ≥10	1.31	1.07–1.61	0.009
Model 2 (combined analysis)			
Age (y/o)	0.99	0.98–1.00	0.042
Clinical stage at diagnosis			
T1/T2	1 (Ref.)	—	—
T3/T4/N1	1.20	0.92–1.57	0.170
M1	1.06	0.80–1.41	0.703
Biopsy Gleason score			
2–6	1 (Ref.)	—	—
7	1.10	0.86–1.41	0.454
8–10	1.25	0.97–1.59	0.081
PSA at ADT initiation (ng/ml)[a]	1.03	0.97–1.09	0.320
PSA nadir/time to PSA nadir			
<0.2 ng/ml/≥10 months	1(Ref.)	—	—
<0.2 ng/ml/<10 months	1.09	0.80–1.47	0.592
≥0.2 ng/ml/≥10 months	2.02	1.50–2.71	<0.001
≥0.2 ng/ml/<10 months	3.11	2.39–4.04	<0.001

[a]As continues variable with log transformed.
[b]Divided by median 10 months.

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