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ORIGINAL ARTICLE

Prostate Disease

Association of time to prostate-specific antigen nadir and logarithm of prostate-specific antigen velocity after progression in metastatic prostate cancer with prior primary androgen deprivation therapy

Jeremy YC Teoh¹, James HL Tsu², Steffi KK Yuen², Peter KF Chiu¹, Samson YS Chan¹, Ka-Wing Wong², Kwan-Lun Ho², Simon SM Hou¹, Chi-Fai Ng¹, Ming-Kwong Yiu²

We investigated the association of time to prostate-specific antigen nadir (TTPN) and logarithm of prostate-specific antigen velocity after progression Log(PSAVAP) in metastatic prostate cancer with prior primary androgen deprivation therapy (ADT). All metastatic prostate cancer patients treated with primary ADT from 2000 to 2009 were reviewed. Patients who developed disease progression were included in the subsequent analyses. Patients were categorized into three groups according to their TTPN: TTPN of <3 months, 3–17 months, and >17 months. We compared the Log(PSAVAP) between the different TTPN groups using Mann–Whitney U-test and Kruskal–Wallis test. Further multiple linear regression analyses on Log(PSAVAP) were performed to adjust for other potential confounding factors. Among 419 patients who were treated with primary ADT, 306 patients developed disease progression with a median follow-up of 28 months. Longer TTPN was associated with lower Log(PSAVAP) ($P = 0.008$) within all subgroup analyses (TTPN of <3 vs 3–17 months, $P = 0.020$; TTPN of 3–17 vs >17 months, $P = 0.009$; and TTPN of <3 vs >17 months, $P = 0.001$). Upon multiple linear regression analyses, baseline PSA (regression coefficient 0.001, $P = 0.045$), PSA nadir (regression coefficient 0.002, $P = 0.040$), and TTPN (regression coefficient -0.030 , $P = 0.001$) were the three factors that were significantly associated with Log(PSAVAP). In conclusion, a longer TTPN was associated with lower Log(PSAVAP) in metastatic prostate cancer patients following primary ADT. TTPN cut-offs at 3 months and 17 months appeared to have prognostic significance in predicting Log(PSAVAP). TTPN may serve as a good prognostic indicator in deciding the treatment strategy in patients with disease progression.

Asian Journal of Andrology (2016) 18, 1–5; doi: 10.4103/1008-682X.164921; published online: 10 November 2015

Keywords: androgen deprivation therapy; prostate cancer; prostate-specific antigen velocity after progression; time to prostate-specific antigen nadir

INTRODUCTION

Androgen deprivation therapy (ADT), either in the form of gonadotropin-releasing hormone (GnRH) agonists or bilateral orchiectomy, is the mainstay of treatment in advanced or metastatic disease. It has been shown that early ADT could reduce prostate cancer-related morbidities including pathological fracture, spinal cord compression, bilateral ureteric obstruction, and extra-skeletal metastases.¹ However, most patients would develop disease progression even after ADT. A reliable prognostic indicator may help to identify prostate cancer with more aggressive behavior and aid subsequent treatment decision.

Prostate-specific antigen (PSA) has long been investigated as an immunohistological marker for prostatic neoplasms.^{2,3} It has been

extended to a number of parameters including PSA velocity, PSA doubling time, PSA nadir, and PSA progression that may serve as prognostic indicators at different circumstances.^{4,5} Previous studies have investigated the associations between time to PSA nadir (TTPN) and different survival outcomes,^{6–12} which however were subjected to immortal time bias. Immortal time bias is defined as bias resulting from cohort studies with follow-up time during which a subject cannot incur the outcome event under study. Taking a patient with a TTPN of more than 12 months as an example, he must have survived 12 months before he can have such TTPN. Hence, this immortal time bias favors a positive correlation between TTPN and survival. To confirm the prognostic significance of TTPN, such immortal time bias should be avoided. In previous studies, PSA velocity has been shown to be a significant

¹Division of Urology, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China; ²Division of Urology, Department of Surgery, Queen Mary Hospital, University of Hong Kong, Hong Kong, China.

Correspondence: Dr. MK Yiu (yiumk2@ha.org.hk)

Received: 26 December 2014; Revised: 28 March 2015; Accepted: 27 August 2015

predictor for biochemical recurrence,¹³ cancer-specific mortality, and all-cause mortality¹⁴ for prostate cancer patients after radical prostatectomy. Theoretically, prostate cancer with more aggressive behavior should progress at a higher PSA velocity upon disease progression. In this study, we investigated the association between TTPN and PSA velocity after progression (PSAVAP) in a relatively homogeneous group of metastatic prostate cancer patients who were treated primarily with ADT. Logarithm of PSAVAP (Log(PSAVAP)) was used as the primary outcome to adjust for an expected skewed and wide distribution of PSAVAP.

METHODS

All prostate cancer patients who were treated primarily with ADT, either in the form of GnRH agonists or bilateral orchiectomy, in two university institutes from year 2000 to 2009 were reviewed. Patients who had radiological or histological evidence of bone metastases upon presentation and those who developed disease progression after primary ADT were included in the subsequent analyses. Disease progression was defined as at least two serial rises in PSA (taken at least 1 week apart) from its nadir level. Initiation of any secondary hormonal treatment for rising PSA was also considered as a progression event. Patients who had prior radical prostatectomy or radical radiotherapy were excluded from our study.

Patients' and disease characteristics including age, Gleason score, clinical T-stage, number of sites of bone metastases, any presence of visceral metastases, mode of ADT, treatment modality upon disease progression, baseline PSA, PSA nadir, TTPN, PSAVAP, and Log(PSAVAP) were reviewed. PSA level was checked every 3 months during the follow-up period. PSA nadir was defined as the lowest PSA level achieved after the initiation of ADT. TTPN was defined as the duration needed for the PSA level to reach its nadir after the initiation of ADT. PSAVAP was defined as the increase in PSA level per month after disease progression, which was calculated by dividing the difference between the latest PSA level and the PSA level upon disease progression by the duration between the two junctures.

We categorized the patients into three groups according to their TTPN: TTPN of <3 months, 3–17 months, and >17 months. The stratification of TTPN into these three groups was based on our previous finding that the progression-free survival (PFS) beyond TTPN for patients in these three groups were different.¹⁵ The Log(PSAVAP) of each TTPN group was presented with Box-and-Whisker plots. The association of TTPN and Log(PSAVAP) was first analyzed with Kruskal–Wallis test, followed by subgroup analyses using Mann–Whitney U-test. Further multiple linear regression analyses on Log(PSAVAP) were performed to adjust for other potential confounding factors. The PFS and overall survival (OS) analyses of the three TTPN groups using the Kaplan–Meier method were also presented with the significance being determined by log-rank test. All statistical analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA). A $P < 0.05$ was considered as statistically significant.

RESULTS

During the study period, a total of 419 metastatic prostate cancer patients were treated with primary ADT. Among them, 306 patients developed disease progression and were included in our analyses (Table 1). The mean age was 73.9 ± 8.2 years with a median follow-up of 28 months. The median baseline PSA level was 245.5 ng ml^{-1} . The majority of the patients had a Gleason score of 8 to 10 (70.4%) and clinical T-stage 3 or 4 disease (46.3%) upon presentation. Most of the patients (77.1%) had extensive bone metastases of more than 4-site involvement, and

Table 1: Patients and disease characteristics of the cohort

	Value	Percentage
Mean age (years)	73.9±8.2	
Follow-up (months)		
Median	28.0	
IQR (months)	34.0	
Median baseline PSA (ng ml ⁻¹)	245.5	
IQR (ng ml ⁻¹)	807.8	
Gleason score		
≤6		8.6
7		21.0
8–10		70.4
Clinical T-stage		
1		8.4
2		45.3
3/4		46.3
Number of sites of bone metastases		
1		6.2
2		8.8
3		7.8
>4		77.1
Presence of visceral metastases		7.2
Mode of ADT		
GnRH agonists		15.4
Bilateral orchiectomy		84.6
Treatment upon disease progression		
Flutamide		84.5
Bicalutamide		8.1
Ketoconazole		3.2
Cyproterone acetate		1.1
Etoposide		3.2
Median PSA nadir (ng ml ⁻¹)	2.6	
IQR (ng ml ⁻¹)	14.3	
Median TTPN (months)	4.0	
IQR (months)	7.0	
TTPN group (months)		
<3		29.1
3–17		62.3
>17		8.6
Median PSAVAP	14.9	
IQR	95.6	
Median Log(PSAVAP)	1.2	
IQR	1.8	

IQR: interquartile range; ADT: androgen deprivation therapy; GnRH: gonadotropin-releasing hormone; PSA: prostate-specific antigen; TTPN: time to prostate-specific antigen nadir; PSAVAP: prostate-specific antigen velocity after progression

7.2% had concomitant visceral metastases. Concerning the mode of ADT, 84.6% had bilateral orchiectomy while the rest (15.4%) had GnRH agonists. Upon disease progression, flutamide was given to 84.5%, bicalutamide to 8.1%, ketoconazole to 3.2%, cyproterone acetate to 1.1%, and etoposide to 3.2% of the patients. The median PSA nadir was 2.6 ng ml^{-1} , and the median TTPN was 4 months. The median PSAVAP was $14.9 \text{ ng ml}^{-1} \text{ month}^{-1}$, and the median Log(PSAVAP) was 1.2.

Concerning the TTPN grouping, 29.1% of the patients had TTPN of <3 months, 62.3% had TTPN of 3–17 months, and 8.6% had TTPN of >17 months. The median Log(PSAVAP) was 1.4 for TTPN of <3 months, 1.1 for TTPN of 3–17 months, and -0.2 for TTPN of >17 months (Figure 1); the differences in Log(PSAVAP) were significant upon Kruskal–Wallis test ($P = 0.008$). Longer TTPN

was significantly associated with lower Log(PSAVAP) within all subgroup analyses (TTPN of <3 vs 3–17 months, $P = 0.020$; TTPN of 3–17 vs >17 months, $P = 0.009$; and TTPN of <3 vs >17 months, $P = 0.001$) (Table 2).

Upon multiple linear regression analyses (Table 3), after adjusting for other potential confounding factors, baseline PSA, PSA nadir, and TTPN were the three factors that were significantly associated with Log(PSAVAP). A higher baseline PSA (regression coefficient 0.001, $P = 0.045$) and a higher PSA nadir (regression coefficient 0.002, $P = 0.040$) were associated with higher Log(PSAVAP), and a longer TTPN was associated with lower Log(PSAVAP) (regression coefficient -0.030 , $P = 0.001$). Upon Kaplan–Meier analyses, longer TTPN was associated with better PFS ($P < 0.001$) (Figure 2) and better OS ($P < 0.001$) (Figure 3).

DISCUSSION

PSA has been widely used for diagnosis and management of prostate cancer.^{16,17} It has been extended to a number of parameters including PSA velocity, PSA doubling time, PSA nadir, TTPN, and PSA progression that may have prognostic significance at different circumstances.^{4,5} In advanced prostate cancer, a reliable and accurate prognostic indicator may help to identify prostate cancer with more aggressive behavior and may aid the decision in starting add-on or second-line treatment at an earlier juncture. In this study, we investigated the prognostic significance of TTPN by analyzing its association with PSAVAP, in patients with metastatic prostate cancers following primary ADT.

A number of studies have investigated the prognostic significance of TTPN.⁵ Some studies showed that a longer TTPN was associated with reduced risk of prostate cancer-specific mortality,¹⁰ better PFS,⁹ and better OS.^{6,10,18} On the contrary, a longer TTPN was shown to be associated with increased risk of prostate cancer-specific mortality^{7,8} in the other studies. It is worthy of note that the association of TTPN and survival outcome is subjected to immortal time bias, which may potentially affect the accuracy of the results. For example, a patient with TTPN of more than 12 months must have survived 12 months

before he can have such TTPN. Hence, this immortal time bias favors a positive correlation between TTPN and survival outcome and imposes a major limitation in previous studies investigating the association of

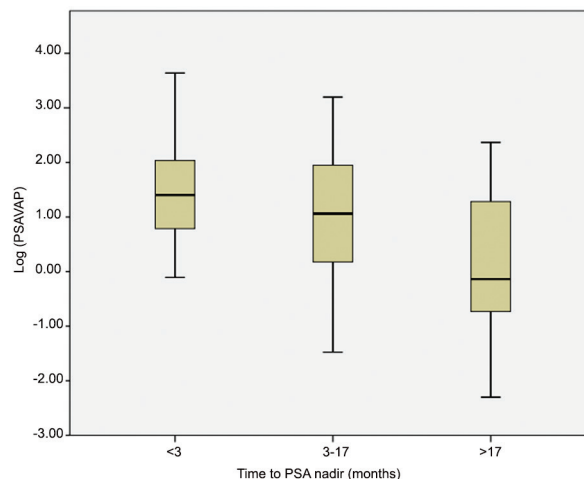


Figure 1: Log(PSAVAP) in the different TTPN groups.

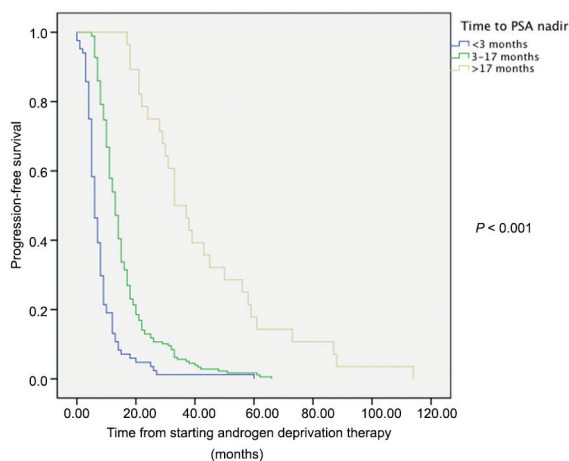


Figure 2: Progression-free survival of the different TTPN groups.

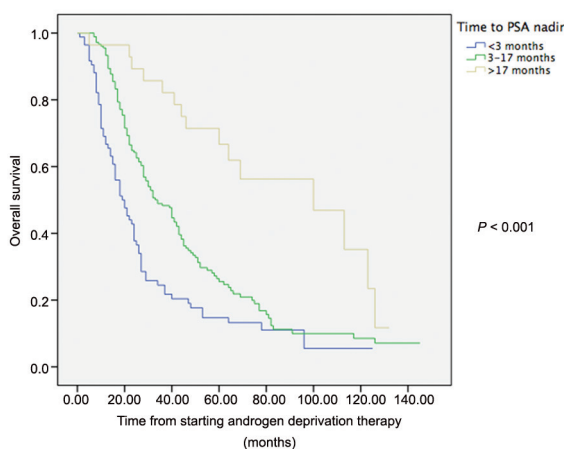


Figure 3: Overall survival of the different TTPN groups.

Table 2: Associations of TTPN and Log(PSAVAP)

	TTPN (months)			P
	<3	3–17	>17	
Median Log(PSAVAP) ^a	1.4	1.1	-0.2	0.008
Median Log(PSAVAP) ^b	1.4	1.1	-	0.020
	-	1.1	-0.2	0.009
	1.4	-	-0.2	0.001

^aP value determined by Kruskal–Wallis test; ^bP values determined by Mann–Whitney U-test. TTPN: time to prostate-specific antigen nadir; PSAVAP: prostate-specific antigen velocity after progression

Table 3: Multiple linear regression analyses on clinicopathological factors predicting Log(PSAVAP)

	Regression coefficient	95% CI		P
		Lower limit	Upper limit	
Age	-0.011	-0.036	0.011	0.302
Baseline PSA	0.001	0.001	0.002	0.045
Gleason score	0.098	-0.121	0.277	0.439
Clinical T-stage	0.104	-0.131	0.385	0.361
PSA nadir	0.002	0.001	0.003	0.040
TTPN	-0.030	-0.051	-0.013	0.001

CI: confidence interval; PSA: prostate-specific antigen; TTPN: time to prostate-specific antigen nadir

TTPN and survival outcomes. Alternative statistical method or analysis is necessary to ascertain the prognostic significance of TTPN.

We previously reported the use of survival beyond TTPN as an alternative outcome measurement in a similar cohort including patients without disease progression.¹⁵ Using survival beyond TTPN as the primary outcome, the effect of immortal time bias from TTPN on survival can be reduced. A longer TTPN was shown to have better PFS beyond TTPN and better OS beyond TTPN. Interestingly, it appeared that the relationship of TTPN and survival beyond TTPN consisted of three phases; <3 months, 3–17 months, and >17 months for PFS beyond TTPN, and <6 months, 6–20 months, and >20 months for OS beyond TTPN. The survival beyond TTPN increased with TTPN during the first phase, remained relatively static during the second phase, and then increased exponentially with TTPN during the third phase. The correlations between TTPN and both PFS ($R^2 = 0.944$) and OS ($R^2 = 0.861$) were excellent, showing that TTPN is a reliable prognostic indicator for both PFS and OS beyond TTPN.

In the present study, we attempted to avoid the immortal time bias by investigating the association of TTPN with Log(PSAVAP), which possibly represents the clinical behavior of prostate cancer as an alternative to other survival outcome measurements. We hypothesized that the patients with longer TTPN progress at a lower PSA velocity upon disease progression. Log(PSAVAP) was used as the primary outcome to adjust for an expected skewed and wide distribution of PSAVAP.

We categorized our cohort into three groups according to their TTPN (TTPN of <3 months, 3–17 months and >17 months) based on our previous analyses on PFS beyond TTPN.¹⁵ A longer TTPN was associated with lower Log(PSAVAP) ($P = 0.008$) upon Kruskal–Wallis test. This association was demonstrated consistently within all subgroup analyses. Upon multiple linear regression analyses, baseline PSA (regression coefficient 0.001, $P = 0.045$), PSA nadir (regression coefficient 0.002, $P = 0.040$), and TTPN (regression coefficient -0.030 , $P = 0.001$) were the three factors that were significantly associated with Log(PSAVAP). Based on their regression coefficients and P values, TTPN appeared to be the most important prognostic factor in predicting Log(PSAVAP). In summary, our study demonstrated that patients with longer TTPN progressed at a lower Log(PSAVAP). By analyzing the association of TTPN with Log(PSAVAP), we believe that our results have confirmed the prognostic significance of TTPN. Interestingly, our understanding on the three-phase relationship between TTPN and PFS beyond TTPN was demonstrated consistently using Log(PSAVAP) as the primary outcome. TTPN cut-offs at 3 months and 17 months appeared to have prognostic significance in predicting Log(PSAVAP). We believe TTPN is a reliable and accurate prognostic indicator that may help to identify prostate cancer with more aggressive behavior. Practically, the use of TTPN as a prognostic indicator can be applied as soon as PSA nadir is reached. Therefore, one might consider earlier systemic treatment for patients with shorter TTPN while watchful waiting might be considered for patients with longer TTPN.

To our knowledge, this is the first study investigating the association of TTPN and Log(PSAVAP). Since survival was not included as the primary outcome measurement, the potential immortal time bias was avoided. Our cohort only consisted of patients with metastatic prostate cancer receiving ADT as the primary treatment. This represents a relatively homogeneous group of patients, and the results would be more reliable. As the primary outcome of our study is Log(PSAVAP), only patients who developed disease progression were included for subsequent analyses. We believe that those patients who did not develop

disease progression were skewed towards longer TTPN.¹⁵ While patients with longer TTPN were associated with lower Log(PSAVAP) as shown in this current study, exclusion of those nonprogressive patients might possibly underpower our study, which however still showed significant results despite such exclusion. Despite the relatively complicated logarithmic calculations of Log(PSAVAP), practically clinicians only have to calculate the TTPN to determine the prognosis of the patient. We believe that TTPN is a simple parameter that could be applied easily for clinical purposes.

However, there are several limitations in our study. First, it is a retrospective study that may affect the accuracy of the results. There is no standard follow-up or imaging protocol, hence any clinical progression or progression in terms of metastases could not be evaluated. Second, the serum testosterone was not routinely checked or monitored in our cohort. While more than 80% of the patients received bilateral orchiectomy as their primary ADT approach, for those patients who were given GnRH agonists, the castrate level could not be ascertained, and the results may be affected. Nevertheless, by analyzing the association between TTPN and Log(PSAVAP), we believe that our results do provide additional evidence that a longer TTPN was associated with better prognosis. Patients with shorter TTPN may potentially have more aggressive disease, and second-line treatment may be considered early on.

AUTHOR CONTRIBUTIONS

JYT and MKY carried out the study. JYT, JHT, SKY, PKC, and MKY participated in the study design. JYT, SKY, SYC, and KWW collected the data. JYT, JHT, KLH, SSH, and CFN coordinated the study. JYT performed statistical analyses. JYT and MKY drafted the manuscript. JHT, SSH, CFN, and MKY supervised the study.

COMPETING INTERESTS

All authors declared no competing interest.

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