

Urological Oncology

Prostate-Specific Antigen Nadir and Time to Prostate-Specific Antigen Nadir Following Maximal Androgen Blockade Independently Predict Prognosis in Patients with Metastatic Prostate Cancer

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Purpose: To evaluate the influence of prostate-specific antigen (PSA) kinetics following maximal androgen blockade (MAB) on disease progression and cancer-specific survival in patients with metastatic, hormone-sensitive prostate cancer.

Materials and Methods: One hundred thirty-one patients with metastatic, hormone-sensitive prostate cancer treated with MAB at our institution were included in this study. Patients' characteristics, PSA at MAB initiation, PSA nadir, time to PSA nadir (TTN), and PSA decline were analyzed by using univariate and multivariate analysis.

Results: At a median follow-up of 30 months, 97 patients (74.0%) showed disease progression and 65 patients (49.6%) died. Fifty-nine patients (45.0%) died from prostate cancer. In the univariate analysis, PSA at MAB initiation, PSA nadir, TTN, and PSA decline were significant predictors of progression-free survival. Also, PSA nadir, TTN, and PSA decline were significant predictors of cancer-specific survival. In the multivariate analysis, higher PSA nadir (≥ 0.2 ng/ml) and shorter TTN (< 8 months) were independent predictors of shorter progression-free and cancer-specific survival. In the combined analysis of PSA nadir and TTN, patients with higher PSA nadir and shorter TTN had the worst progression-free survival (hazard ratio [HR], 14.098; $p < 0.001$) and cancer-specific survival (HR, 14.050; $p < 0.001$) compared with those with lower PSA nadir and longer TTN.

Conclusions: Our results suggest that higher PSA nadir level and shorter TTN following MAB are associated with higher risk of disease progression and poorer survival in patients with metastatic, hormone-sensitive prostate cancer. Furthermore, these two variables have a synergistic effect on the outcome.

Key Words: Prognosis; Prostate-specific antigen; Prostatic neoplasms

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INTRODUCTION

Prostate cancer is the most common cancer of men in the United States and the fifth most common cancer of men in Korea [1]. Recently, with the increase in use of prostate-specific antigen (PSA) as a screening tool, the number of men presenting with metastatic disease has been de-

creasing [2].

Androgen deprivation therapy (ADT) remains the mainstay of treatment for metastatic, hormone-sensitive prostate cancer. Although the majority of patients with metastatic disease initially respond well to ADT, almost all patients will eventually progress to castration-resistant prostate cancer (CRPC). Treatment options for CRPC re-

main limited, and the prognosis of patients with CRPC is dismal [2]. Therefore, an accurate prediction of the response to ADT and individual survival would allow better prognostic evaluation and decision making for the best treatment strategy.

The serum PSA level correlates with tumor volume and increases 6 to 12 months before definitive radiological or clinical proof of disease progression [3-5]. Accordingly, PSA kinetics has been used as a useful prognostic indicator of disease progression or survival in different clinical settings, including radical prostatectomy and radiation therapy [6-9]. However, its prognostic ability for patients with metastatic prostate cancer treated with ADT is still not well understood. The nadir PSA level has been suggested to be the most significant predictor of progression to CRPC in many studies [10-17]. However, there is controversy about the time to PSA nadir (TTN). Whereas earlier reports suggested that shorter TTN correlated with longer remission periods [3,4,18-21] or that TTN did not correlate with progression to CRPC [22], several recent reports suggested that longer TTN correlated with longer remission and survival [2,12,14-17,23-25].

In this study, we retrospectively reviewed our single-center treatment experience of patients with metastatic, hormone-sensitive prostate cancer to evaluate the influence of PSA kinetics following maximal androgen blockade (MAB) on disease progression and cancer-specific survival.

MATERIALS AND METHODS

A total of 131 patients with newly diagnosed metastatic, hormone-sensitive prostate cancer who started primary ADT with MAB (combination of luteinizing hormone-releasing hormone [LHRH] agonists or bilateral orchiectomy and antiandrogen) at our institution between July 1996 and July 2010 were included in this study. Prostate cancer was diagnosed pathologically in all patients. In 4 patients with a pathologic diagnosis obtained through the biopsy of a metastatic site, the Gleason score could not be identified. LHRH agonist was used in 114 patients (87.0%) and bilateral orchiectomy was done in 17 patients (13.0%) as part of MAB. No patients had received any treatment such as prostatectomy or radiation therapy for the primary lesion.

The patients' characteristics, PSA at MAB initiation, PSA nadir, TTN, and PSA decline were analyzed. The definitions used in this study followed those described by Huang et al. [17,24]. The PSA nadir was defined as the lowest PSA value achieved during ADT. TTN was defined as the duration of time from the initiation of ADT to the date of PSA nadir. PSA decline was calculated from the slope of the linear regression of the PSA values over time from the beginning of ADT to the nadir PSA. Progression was defined as a serial rise in PSA, at least two consecutive rises in PSA (> 1 week apart) greater than the PSA nadir. The date of progression was defined as the date of the first PSA rise.

Patients were dichotomized according to the median value of continuous variables except for the PSA nadir. Dichotomization according to a PSA nadir of 0.2 ng/ml was used because it was previously reported to correlate with prostate cancer-specific survival and disease progression in other studies [15,17,23-27]. To evaluate the interactive effect of PSA nadir and TTN on disease progression and survival, patients were stratified into four groups: 1) PSA nadir < 0.2 ng/ml and TTN \geq 8 months, 2) PSA nadir < 0.2 ng/ml and TTN < 8 months, 3) PSA nadir \geq 0.2 ng/ml and TTN \geq 8 months, and 4) PSA nadir \geq 0.2 ng/ml and TTN < 8 months. Progression-free and cancer-specific survival curves were obtained by the Kaplan-Meier method, and univariate and multivariate analyses were performed by using the log-rank test and the Cox's proportional hazards regression model, respectively. All statistical analyses were performed by using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered to be statistically significant in all of the analyses.

RESULTS

The clinicopathological characteristics of the 131 patients included in the study are summarized in Table 1. At MAB initiation, the median age of the patients was 72 years and their median PSA level was 151 ng/ml. During MAB, the median PSA nadir was 0.5 ng/ml and 53 patients (40.5%)

TABLE 1. Characteristics of the 131 patients who underwent MAB

Characteristic	Value
At MAB initiation	
Age (yr)	72 (42-92)
Clinical stage	
M1	105 (80.2)
\geq N1	88 (67.2)
Biopsy Gleason score	
< 7	5 (3.8)
7	32 (24.4)
\geq 8	90 (68.7)
PSA (ng/ml)	151 (10.38-5,000)
Types of MAB	
LHRH agonists+antiandrogen	114 (87.0)
Bilateral orchiectomy+antiandrogen	17 (13.0)
During MAB	
Nadir PSA (ng/ml)	0.5 (0.003-595.7)
PSA nadir < 0.2 ng/ml	53 (40.5)
PSA nadir \geq 0.2 ng/ml	78 (59.5)
Time to PSA nadir (months)	8 (1-48)
PSA decline after MAB (ng/ml/yr)	242 (2.9-29,878)
Progression/death	
Progression	97 (74.0)
Total death	65 (49.6)
Cancer-specific death	59 (45.0)

Values are presented as median (range) or number (%). MAB, maximal androgen blockade; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

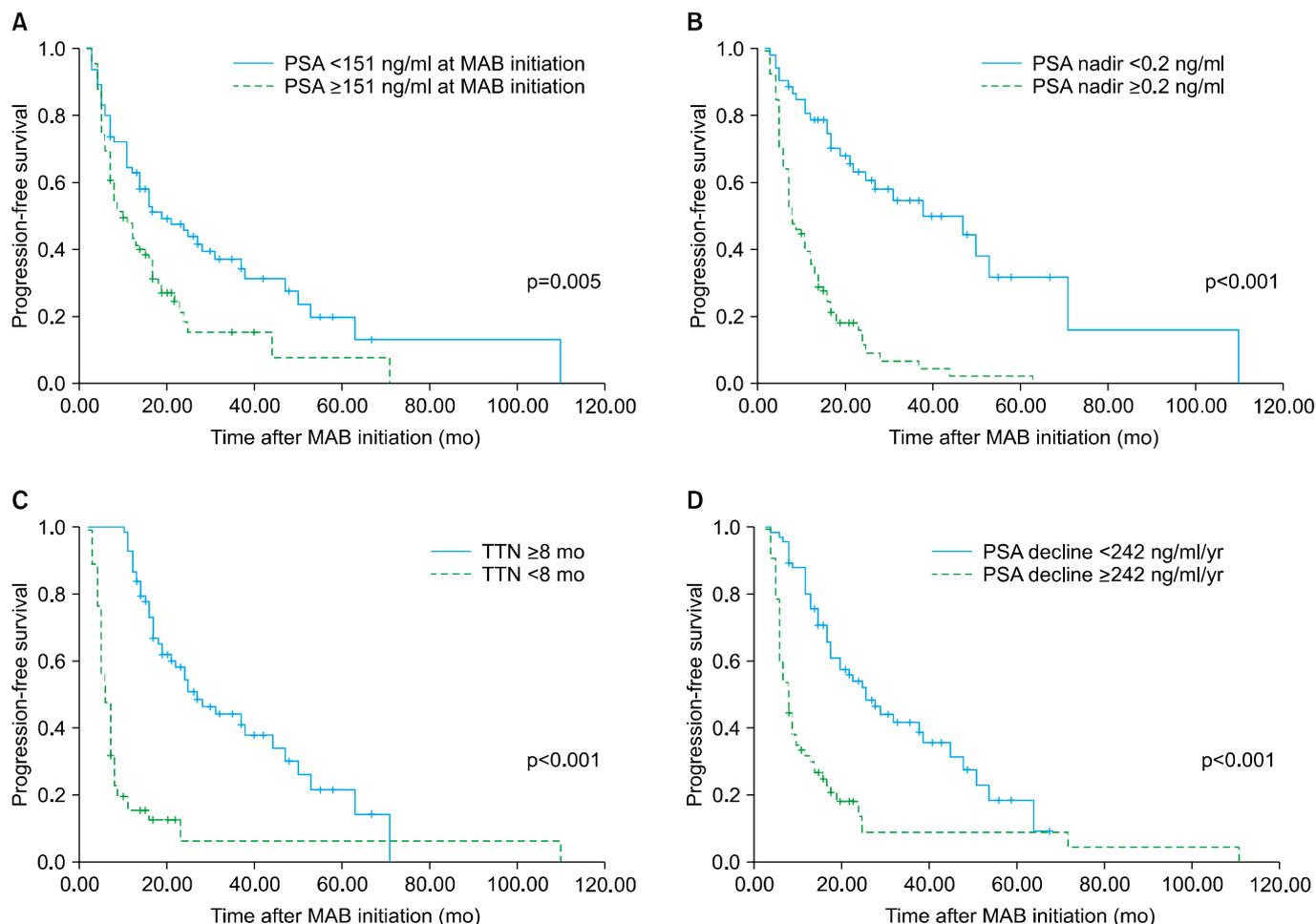


FIG. 1. Kaplan-Meier progression-free survival curves according to prostate-specific antigen (PSA) at maximal androgen blockade (MAB) initiation (A), PSA nadir (B), time to PSA nadir (TTN) (C), and PSA decline (D).

achieved a PSA nadir <0.2 ng/ml. The median TTN was 8 months and the median PSA decline was 242 ng/ml/yr. The median follow-up period was 30 months (range, 7 to 133 months). Of the total 131 patients, 97 patients (74.0%) showed disease progression and 65 patients (49.6%) died during the follow-up. Among them, 59 patients (45.0%) died from prostate cancer.

The mean progression-free survival in patients with PSA <151 ng/ml at MAB initiation was significantly longer than that in patients with PSA ≥151 ng/ml at MAB initiation (34.4 months vs. 17.9 months, $p=0.005$) (Fig. 1A), but there was no significant difference in cancer-specific survival between the two groups ($p=0.236$) (Fig. 2A). The mean progression-free and cancer-specific survival in patients with PSA nadir <0.2 ng/ml were significantly longer than those in patients with PSA nadir ≥0.2 ng/ml (46.5 months vs. 13.0 months, $p<0.001$; 91.7 months vs. 49.8 months, $p<0.001$) (Figs. 1B, 2B). The mean progression-free and cancer-specific survival in patients with TTN ≥8 months were significantly longer than those in patients with TTN <8 months (35.1 months vs. 13.9 months, $p<0.001$; 88.4 months vs. 42.7 months, $p<0.001$) (Figs. 1C,

2C). The mean progression-free and cancer-specific survival in patients with PSA decline <242 ng/ml/yr were significantly longer than those in patients with PSA decline ≥242 ng/ml/yr (31.8 months vs. 16.3 months, $p<0.001$; 79.2 months vs. 50.0 months, $p<0.001$) (Figs. 1D, 2D).

In the univariate analysis, PSA at MAB initiation, PSA nadir, TTN, and PSA decline were significant predictors of progression-free survival. Also, PSA nadir, TTN, and PSA decline were significant predictors of cancer-specific survival (Table 2). In the multivariate analysis, higher PSA nadir (≥0.2 ng/ml) and shorter TTN (<8 months) were independent predictors of shorter progression-free and cancer-specific survival (Table 3). In the combined analysis of PSA nadir and TTN, patients with higher PSA nadir and shorter TTN had the worst progression-free survival (hazard ratio [HR], 14.098; $p<0.001$) and cancer-specific survival (HR, 14.050; $p<0.001$) compared to those with lower PSA nadir and longer TTN (Table 3, Fig. 3).

DISCUSSION

It is generally accepted that serum PSA parameters, such

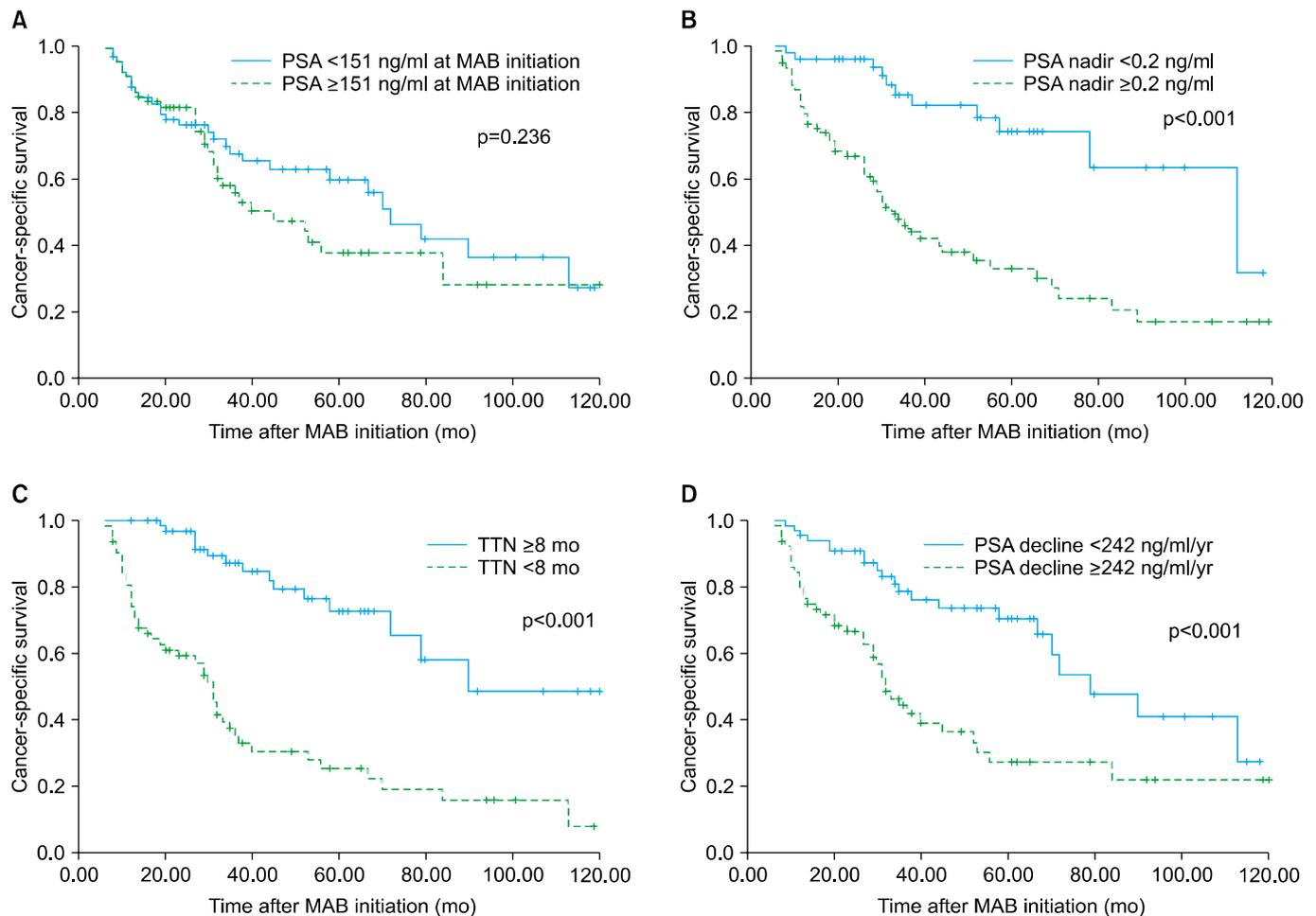


FIG. 2. Kaplan-Meier cancer-specific survival curves according to prostate-specific antigen (PSA) at maximal androgen blockade (MAB) initiation (A), PSA nadir (B), time to PSA nadir (TTN) (C), and PSA decline (D).

TABLE 2. Univariate analysis of potential prognostic factors for progression-free and cancer-specific survival

Variable	p-value	
	Progression-free survival	Cancer-specific survival
Age at MAB initiation (<72 yr vs. ≥72 yr)	0.054	0.347
Biopsy Gleason score (≤7 vs. >7)	0.060	0.064
PSA at MAB initiation (<151 ng/ml vs. ≥151 ng/ml)	0.005	0.236
PSA nadir (<0.2 ng/ml vs. ≥0.2 ng/ml)	<0.001	<0.001
Time to PSA nadir (≥8 mo vs. <8 mo)	<0.001	<0.001
PSA decline (<242 ng/ml/yr vs. ≥242 ng/ml/yr)	<0.001	<0.001

MAB, maximal androgen blockade; PSA, prostate-specific antigen.

as pretreatment PSA level, PSA nadir level after treatment, TTN, and the pattern of PSA decline after treatment, are useful indicators for evaluating the response to ADT in patients with metastatic prostate cancer. However, the prognostic significance of these PSA parameters is still controversial.

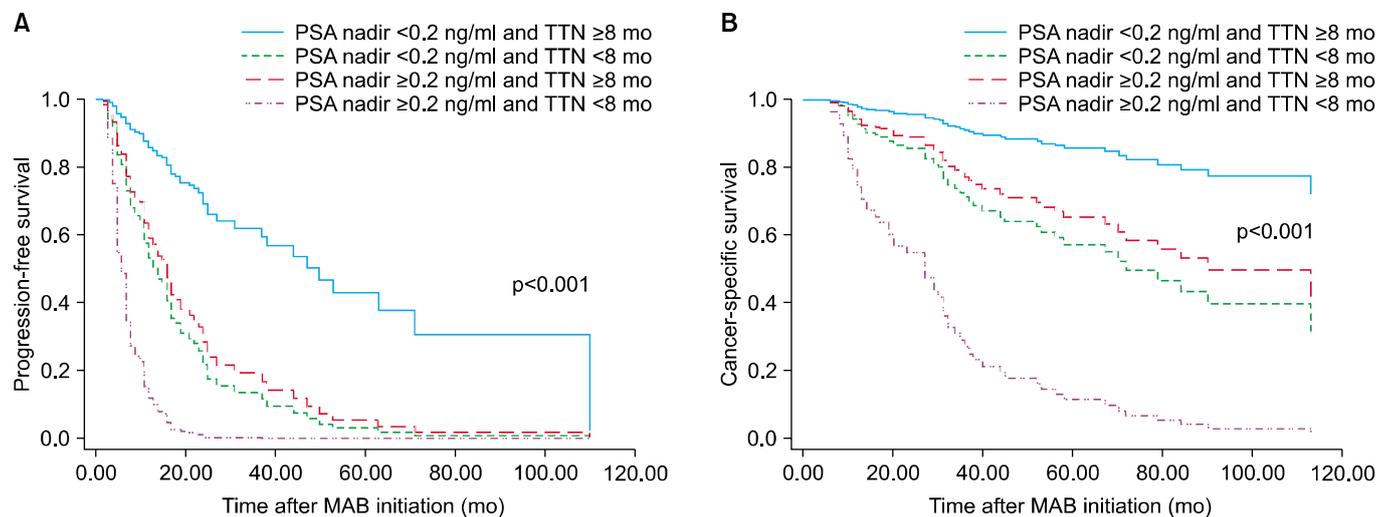
Whereas the pretreatment PSA level has been suggested to predict the response to ADT in some reports [4,13,15,28], it did not predict the interval to progression to CRPC in other studies [11,16,29]. In our study, the pretreatment PSA level was a significant predictor of progression-free survival in the univariate analysis, but it lost statistical significance in the multivariate analysis.

Nadir PSA level after ADT has been suggested to be the most significant predictor of progression to CRPC [10-17] and survival [23-25] in many studies. Our study also demonstrated that lower PSA nadir after MAB is an independent predictor of longer progression-free and cancer-specific survival. However, there is no consensus on the optimal threshold of PSA nadir after ADT for predicting disease progression and survival. Kwak et al. [13] reported that a lower limit for the nadir PSA level of 1.1 ng/ml gives

TABLE 3. Multivariate analysis of potential adverse prognostic factors for progression-free and cancer-specific survival

Variable	Progression-free survival		Cancer-specific survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1				
Age at MAB initiation (< 72 yr vs. ≥ 72 yr)	1.062 (0.689-1.636)	0.787	1.170 (0.676-2.026)	0.575
Biopsy Gleason score (≤ 7 vs. > 7)	1.515 (0.898-2.556)	0.120	1.741 (0.913-3.318)	0.092
PSA at MAB initiation (< 151 ng/ml vs. ≥ 151 ng/ml)	1.212 (0.667-2.204)	0.528	0.445 (0.196-1.009)	0.052
PSA nadir (< 0.2 ng/ml vs. ≥ 0.2 ng/ml)	3.022 (1.781-5.128)	< 0.001	3.394 (1.680-6.857)	< 0.001
TTN (≥ 8 mo vs. < 8 mo)	4.334 (2.504-7.501)	< 0.001	3.864 (1.979-7.543)	< 0.001
PSA decline (< 242 ng/ml/yr vs. ≥ 242 ng/ml/yr)	1.066 (0.544-2.090)	0.851	2.396 (0.973-5.899)	0.057
Model 2^a				
< 0.2 ng/ml / ≥ 8 mo	1 (Reference)	-	1 (Reference)	-
< 0.2 ng/ml / < 8 mo	4.180 (1.803-9.693)	< 0.001	3.603 (1.038-12.505)	0.043
≥ 0.2 ng/ml / ≥ 8 mo	3.440 (1.816-6.518)	< 0.001	2.746 (0.853-8.841)	0.09
≥ 0.2 ng/ml / < 8 mo	14.098 (7.399-26.864)	< 0.001	14.050 (4.974-39.692)	< 0.001

HR, hazard ratio; CI, confidence interval; MAB, maximal androgen blockade; PSA, prostate-specific antigen; TTN, time to PSA nadir.
^a:Combined analysis of PSA nadir/TTN.

**FIG. 3.** Kaplan-Meier progression-free (A) and cancer-specific (B) survival curves according to prostate-specific antigen (PSA) nadir and time to PSA nadir (TTN). MAB, maximal androgen blockade.

optimal sensitivity and specificity for predicting the progression to CRPC. Park et al. [22], Morote et al. [14], and Miller et al. [11] suggested that nadir PSA levels of 0.5, 2, and 4 ng/ml were the optimal thresholds for predicting the progression to CRPC, respectively. Hussain et al. [26] reported that a PSA of < 4 ng/ml after 7 months of ADT was a strong predictor of survival. However, in many other studies, the nadir PSA level of 0.2 ng/ml was suggested to be the optimal threshold for predicting the progression to CRPC [15,17] and survival [23-25,27]. Morote et al. [15] reported that the nadir PSA level of 0.2 ng/ml was the optimal threshold for predicting the progression to CRPC and that the failure to achieve a nadir PSA level of 0.2 ng/ml was associated with a 20 times likelihood of progression to CRPC within 24 months. Stewart et al. [27] suggested that a PSA nadir of > 0.2 ng/ml after 8 months of ADT was significantly associated with prostate cancer-specific mortality in pa-

tients with biochemical recurrence after radical prostatectomy or radiation therapy. Therefore, the nadir PSA level of 0.2 ng/ml was chosen as the threshold in our study and the results showed that higher PSA nadir (≥ 0.2 ng/ml) after MAB was an independent predictor of shorter progression-free and cancer-specific survival.

The prognostic significance of TTN after ADT on disease progression and survival is also controversial. Earlier reports suggested that shorter TTN correlated with longer remission periods [3,4,18-21]. Stamey et al. [18] reported that patients whose PSA decreased rapidly to an undetectable level after ADT had prolonged survival and showed that the PSA level at 6 months after ADT was capable of distinguishing patients with a favorable response from those with a limited response to ADT. Cooper et al. [4] also reported that the PSA nadir reached within 6 months after ADT was a predictor of survival in a uni-

variate analysis. Arai et al. [3] showed that patients whose PSA decreased rapidly to an undetectable level within 1 month after ADT had the best prognosis and that patients whose PSA level remained elevated for more than 3 months had a risk of disease progression within 2 years. Petros and Andriole [20] and Furuya et al. [21] also demonstrated that normalization of PSA at 3 months after ADT was associated with a more favorable prognosis. However, Park et al. [22] reported that TTN after MAB did not correlate with progression to CRPC.

On the contrary, several recent reports have suggested that a longer TTN is correlated with longer remission and survival [2,12,14-17,23-25]. Morote et al. [15] suggested that patients with a longer TTN (> 12 months) after ADT had an 18 times higher likelihood of being free of progression to CRPC within 24 months than did those with shorter TTN (\leq 12 months). Huang et al. [17] also reported that patients with a shorter TTN (< 10 months) after ADT had a significantly shorter time to disease progression. Choueiri et al. [23], Huang et al. [24], and Sasaki et al. [25] suggested that longer TTN (\geq 6 months, \geq 10 months, > 9 months, respectively) after ADT correlated with longer survival duration. Moreover, Huang et al. [17,24] reported that the patients with higher PSA nadir (\geq 0.2 ng/ml) and shorter TTN (< 10 months) had a significantly higher risk of disease progression, cancer-specific mortality, and all-cause mortality than did those with lower PSA nadir (< 0.2 ng/ml) and longer TTN (\geq 10 months) (HR, 3.11, 6.30, 4.79, respectively, all $p < 0.001$). Sasaki et al. [25] also suggested that the combination of lower PSA nadir (< 0.2 ng/ml) and longer TTN (> 9 months) after ADT was the most important early predictor of longer survival. The results of our study also support these recent findings. Shorter TTN (< 8 months) after ADT was an independent predictor of shorter progression-free and cancer-specific survival in the multivariate analysis. Moreover, in the combined analysis of PSA nadir and TTN, patients with a higher PSA nadir (\geq 0.2 ng/ml) and shorter TTN (< 8 months) had the worst progression-free and cancer-specific survival compared with those with lower PSA nadir (< 0.2 ng/ml) and longer TTN (\geq 8 months) (HR, 14.098, 14.050, respectively, all $p < 0.001$). The mechanisms responsible for the association of shorter TTN with worse prognosis are not clear. The rapid decrease in the PSA level may be related to a transcriptional effect of ADT on PSA production rather than prostate cancer cell death [23,25]. The rapid decrease in the PSA level after ADT may be due to ablation of androgen receptor function, and the quick suppression of androgen/androgen receptor during ADT may have a negative effect on disease progression, because androgen receptor can act as a tumor suppressor for prostate cancer [17]. Another possibility is that a rapid removal of hormone-sensitive prostate cancer cells may induce an adequate environment for the growth of hormone-resistant prostate cancer cells [25]. But, further studies will be needed to verify these hypotheses.

Whereas biopsy Gleason score was not a predictor of pro-

gression to CRPC [13] or overall survival [25] in patients treated with ADT in some reports, it was an independent predictor of progression to CRPC [12,14,16,17,22,28] or survival [23,24,26] in many other studies. In our study, biopsy Gleason score showed only marginal significance as a predictor of progression-free and cancer-specific survival in a univariate analysis ($p=0.060$, $p=0.064$, respectively). Whereas other studies included patients without metastasis [16,17,22,24,28] or applied ADT as a primary treatment in only 56 to 56.9% of patients [16,17,24], all of our patients had metastasis at diagnosis and received ADT as the primary treatment. Moreover, among the studies with the same homogeneity of patients' characteristics as ours, the proportion of patients with Gleason score > 7 in our study (68.7%) was much higher than that in other studies (46.9 to 58.9%) [14,23,26]. This might explain the lack of significance of Gleason score as a prognostic factor in our study.

This study had several limitations. First, this study was conducted in a single center. Second, it was retrospective in nature and the size of the study population was small. Third, some important factors, such as performance status and lactate dehydrogenase were not included in this study, because these data were not available in all patients. Nevertheless, we believe that the results of our study support the already reported role of PSA nadir and TTN following ADT as independent predictors of disease progression and survival in patients with metastatic prostate cancer.

CONCLUSIONS

Our results demonstrated that higher PSA nadir level and shorter TTN following MAB are associated with higher risk of disease progression and poorer survival in patients with metastatic, hormone-sensitive prostate cancer. Furthermore, these two variables have a synergistic effect on the outcome. These results may be helpful in predicting the prognosis after MAB and in guiding decision making concerning the best treatment strategy in patients with metastatic, hormone-sensitive prostate cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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