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Original Article

# Serum testosterone level as possible predictive marker in androgen receptor axis-targeting agents and taxane chemotherapies for castration-resistant prostate cancer

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## Abstract

**Purpose:** Currently, several therapeutic options for castration-resistant prostate cancer (CRPC) are available, for which predictive biomarkers have not been established. Therefore, we aimed to reveal the association between pretreatment serum testosterone level and antitumor outcomes when treated with androgen receptor axis-targeting agents and taxane chemotherapies for CRPC.

**Patients and methods:** The present study included Japanese patients with metastatic prostate cancer whose serum testosterone levels during androgen-deprivation therapy were available. The antitumor outcomes when treated with enzalutamide, abiraterone, docetaxel, and cabazitaxel with clinicopathological parameters including serum testosterone levels during androgen-deprivation therapy, as well as prognoses including progression-free survival and overall survival, were examined.

**Results:** Progression-free survival among men with higher serum testosterone level was superior to that among men with lower serum testosterone level when treated with enzalutamide. On the contrary, progression-free survival and overall survival among men with higher serum testosterone level were significantly inferior to those among men with lower serum testosterone level when treated with docetaxel and cabazitaxel, respectively.

**Conclusions:** The present study indicated distinct prognostic values of serum testosterone level when treated with androgen receptor axis-targeting agent and taxane chemotherapy for CRPC, suggesting that serum testosterone level may be useful predictive biomarker to navigate the appropriate therapy in patients with CRPC. 

*Keywords:* Abiraterone; Cabazitaxel; Docetaxel; Enzalutamide; Testosterone

## 1. Introduction

Androgen-deprivation therapy (ADT) with or without up-front docetaxel or abiraterone is currently the standard treatment for metastatic prostate cancer [1−3]. However, most castration-sensitive prostate cancers (CRPCs) progress in a castration-resistant manner despite consecutive ADT, and become CRPC. For the treatment of CRPC, taxane chemotherapies including docetaxel and cabazitaxel, and radio-isotope radium-223 as well as novel androgen receptor (AR) axis-targeting (ARAT) agents including anti-androgen enzalutamide and CYP17 inhibitor abiraterone have shown various benefits including survival in patients with CRPC in clinical trials [4]. Several therapeutic options for CRPC therapy are available. Therefore, biomarkers for selecting the most appropriate therapy for the patient are urgently required.

Several possible biomarkers have been suggested for prediction of the antitumor response of ARAT agents and taxane chemotherapies. Prostate specific antigen (PSA) response and progression-free survival (PFS) when treated with ARAT agents were favorable if patients responded to

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primary ADT over 12 months [5]. In contrast, no significant difference in PSA response and PFS by responding duration to primary ADT was observed when treated with docetaxel [6]. As well, the presence of visceral metastasis and aggressive phenotype may be possible predictors for navigating the selection of ARAT agent or chemotherapy as suggested in APCCC 2017 [7]. Furthermore, various laboratory tests such as AR V7, and aberrations of the *AR* gene such as amplification and mutation, as well as aberrations in DNA repair genes and tumor-suppressor genes have been suggested as possible predictive biomarkers of therapeutic agents for CRPC [8−10]. However, it remains unclear which agent should be utilized according to the patient's characteristics since there is no established predictive biomarker for selection of a suitable therapy for the patient.

Serum testosterone levels before ADT [11,12] and during ADT [13,14] are well known prognostic factors for primary ADT. In addition, de novo androgen synthesis in prostate cancer tissues promotes the progression to CRPC, resulting in increased androgen level in CRPC [15,16]. In the COU-AA-301 trial, it was reported that pretreatment serum testosterone level was a prognostic marker when treated with abiraterone and placebo in a postchemotherapy setting [17]. However, the significance of pretreatment serum testosterone level on antitumor outcomes when treated with ARAT agents and taxane chemotherapies for CRPC remains limited. Thus, in the present study, we aimed to reveal the association between pretreatment serum testosterone level and antitumor outcomes when treated with ARAT agents and taxane chemotherapies for CRPC.

## 2. Materials and methods

### 2.1. Patients

Japanese patients who had been treated with ARAT agents including enzalutamide and abiraterone or taxane chemotherapies including docetaxel and cabazitaxel for metastatic CRPC at Kyushu University Hospital (Fukuoka, Japan) between 2008 and 2017 were included. This study was performed in accordance with the principles described in the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research enacted by the Japanese Government, and approved by the institutional review board. All patients were histopathologically diagnosed with adenocarcinoma of the prostate. Clinical staging was determined in accordance with the unified TNM criteria based on the results of a digital rectal examination, transrectal ultrasound, computed tomography, magnetic resonance imaging, and bone scan [18]. Progression was defined according to consecutive PSA increments resulting in 25% increases and 2 ng/ml over the nadir despite consecutive ADT, or progression of soft-tissue lesions or appearance of 2 lesions on a bone scan [19]. Six patients were treated with surgical castration while 73 and 27 patients were treated with medical castration using a GnRH agonist (goserelin acetate or leuprorelin acetate) and a GnRH antagonist (degarelix) continuously during CRPC treatment as backbone ADT, respectively.

### 2.2. Measurement of serum testosterone level

Measurement of serum testosterone level was performed as described previously [14,20]. Patient blood was obtained between 08:00 A.M. and 10:00 A.M. Serum testosterone levels were measured by electrochemiluminescence immunoassay. Pretreatment serum testosterone levels were measured at a timing diagnosed as progressing to CRPC.

### 2.3. Statistical analysis

All statistical analyses were performed using JMP13 software (SAS Institute, Cary, NC). The Wilcoxon test and log-rank test were used to analyze PSA response and survival between groups. Survival curve was determined by the Kaplan−Meier method. Cox proportional hazards model was used to estimate hazard ratios (HRs). All *P* values are 2-sided. Levels of statistical significance were set at $P < 0.05$.

## 3. Results

Patients' background was shown in Table 1. Serum testosterone levels in all cases were confirmed to be below castration level (50 ng/ml). Most cases carried multiple distant metastatic sites to lymph node, bone, and visceral sites. Over half patients were treated as first-line therapy

Table 1
Patients' characteristics

| Variables | |
|---|---|
| Median age, y (IQR) | 73 (68−76) |
| Biopsy Gleason score, *n* (%) | |
| < 8 | 21 (20.6%) |
| ≥ 8 ≥ 8 | 81 (79.4%) |
| NA | 4 |
| Median PSA at pretreatment, ng/ml (IQR) | 26.6 (8.3−124.3) |
| Median pretreatment serum T, ng/ml (IQR) | 0.03 (0.028−0.08) |
| Clinical stage at pretreatment, *n* (%) | |
| N0M0 | 8 (7.5%) |
| N1M0 | 2 (1.9%) |
| M1 | 96 (90.6%) |
| Nonregional lymph node | 14 |
| Bone | 87 |
| Visceral | 6 |
| Therapy line as CRPC treatment, *n* (%) | |
| First | 60 (56.6%) |
| Second | 20 (18.9%) |
| Third | 19 (17.9%) |
| Fourth | 7 (6.6%) |

CRPC = castration-resistant prostate cancer; IQR = interquartile range; NA = not available; T = testosterone.

for CRPC while remaining cases were treated as second-, third-, and fourth-line therapies.

First, the therapeutic outcome of enzalutamide was examined according to pretreatment serum testosterone level, where threshold 0.05 ng/ml was employed similarly to previous study in Japanese [21]. Clinicopathological factors including age, biopsy Gleason score, PSA level at pretreatment and clinical stage were favorable in men with serum testosterone level over 0.05 ng/ml (Supplementary Table 1). As shown in Fig. 1A, the best PSA response after initiation of enzalutamide was comparable between men with serum testosterone level over 0.05 ng/ml (median [interquartile range, IQR]; −71.1% [−93.7% to −45.2%]) and men with serum testosterone level below 0.05 ng/ml (median [IQR]; −50.7% [−94.3% to 16.3%], $P = 0.33$). Notably, all cases with serum testosterone level over 0.05 ng/ml showed some PSA decline. Consistently, PFS among men with serum testosterone level over 0.05 ng/ml was significantly superior to that among men with serum testosterone level below 0.05 ng/ml (Fig. 1B). Also, overall survival (OS) among men with serum testosterone level over 0.05 ng/ml showed the trend of superiority to that among men with serum testosterone level below 0.05 ng/ml although statistical significance was not reached (Fig. 1C). On multivariate analysis incorporating biopsy Gleason score, PSA level at pretreatment and clinical stage in addition to serum testosterone level, serum testosterone level was not a significant risk factor of progression (HR [95% confidence interval]; 0.72 [0.19−2.13], $P = 0.57$, Supplementary Table 2). When another ARAT agent abiraterone was examined, neither PSA response, PFS, nor OS differed between men with serum testosterone level over 0.05 ng/ml and below 0.05 ng/ml (Table 2), where the patient backgrounds were comparable (Supplementary Table 3).

Next, the therapeutic outcome of docetaxel was examined according to pretreatment serum testosterone level. The patient backgrounds between men with serum testosterone level over 0.05 ng/ml and below 0.05 ng/ml were comparable (Supplementary Table 4). As shown in Fig. 2A, the best PSA response after initiation of docetaxel chemotherapy was inferior among men with serum testosterone level over 0.05 ng/ml (median [IQR]; −20.2% [−68.4% to 40.9%]), compared with that among men with serum testosterone level below 0.05 ng/ml (median [IQR]; −97.4% [−95.0% to 17.1%], $P = 0.097$) although statistical significance was not reached (Table 2). Consistently, PFS among men with serum testosterone level over 0.05 ng/ml was significantly inferior to that among men with serum testosterone level below 0.05 ng/ml (Fig. 2B). Docetaxel chemotherapy for men with serum testosterone level over 0.05 ng/ml showed the trend of inferior OS compared with that for men with serum testosterone level below 0.05 ng/ml, although statistical significance was not reached (Fig. 2C). Even on multivariate analysis incorporating biopsy Gleason score, PSA level at pretreatment and clinical stage in addition to serum testosterone level, serum testosterone level was a significant risk factor of progression (HR [95% confidence interval]; 2.94 [1.18−7.70], $P = 0.020$, Supplementary Table 2).

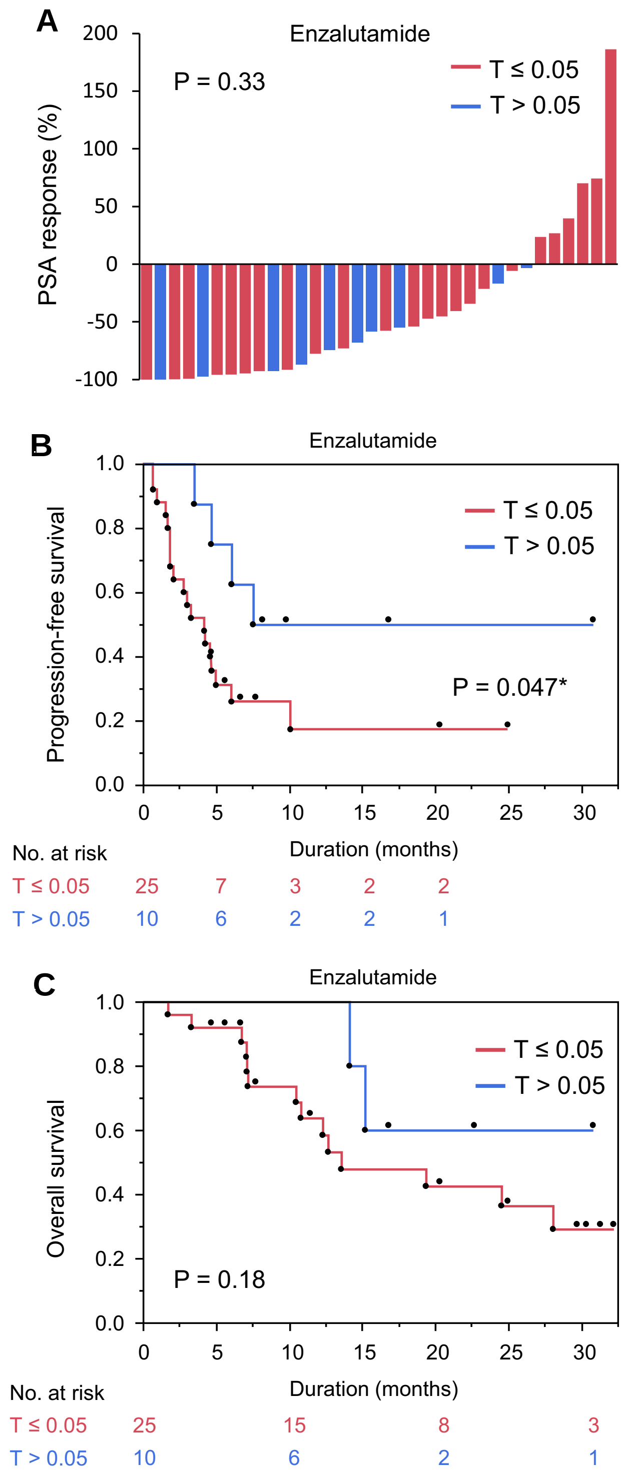


Fig. 1. Antitumor outcome of enzalutamide according to pretreatment serum testosterone level. Waterfall plots showing greatest decline in prostate specific antigen values from baseline (A), progression-free survival (B), and overall survival (C) in 35 patients with castration-resistant prostate cancer who received enzalutamide treatment according to pretreatment serum testosterone level.

Finally, the therapeutic outcome of cabazitaxel was examined according to pretreatment serum testosterone level. The patient backgrounds differed, where biopsy

Table 2
Antitumor outcome according to agents for CRPC

| | PSA response | | PFS | | | OS | | |
|---|---|---|---|---|---|---|---|---|
| Agents | Median (IQR) | *P* value | Median (IQR) | HR (95% CI) | *P* value | Median (IQR) | HR (95% CI) | *P* value |
| Enzalutamide | | | | | | | | |
| $T \leq 0.05$ ($n = 25$) | −50.7% (−94.3% to 16.3%) | | 4.2 (1.9−10.1) | ref | | 13.6 (7.2−NR) | Ref | |
| $T > 0.05$ ($n = 10$) | −71.1% (−93.7% to −45.2%) | 0.33 | NR (5.4−NR) | 0.35 | 0.037* | NR (15.2−NR) | 0.37 | 0.15 |
| Abiraterone | | | | | | | | |
| $T \leq 0.05$ ($n = 17$) | 10.6% (−51.8% to 72.5%) | | 2.3 (1.4−9.6) | ref | | 14.2 (8.0−32.7) | Ref | |
| T > 0.05 (n = 4) | 34.9% (−70.6% to 88.3%) | 0.79 | 1.4 (0.7−2.3) | 2.50 | 0.15 | NR (6.8−NR) | 0.87 | 0.86 |
| Docetaxel | | | | | | | | |
| $T \leq 0.05$ ($n = 23$) | −76.5% (−95.0% to 17.1%) | | 8.8 (2.1−12.4) | ref | | 22.1 (10.8−59.1) | Ref | |
| $T > 0.05$ ($n = 15$) | −20.2% (−68.4% to 40.9%) | 0.097 | 2.3 (0.9−5.1) | 3.49 | 0.0028* | 20.8 (8.6−28.7) | 1.68 | 0.21 |
| Cabazitaxel | | | | | | | | |
| $T \leq 0.05$ ($n = 9$) | −49.5% (−78.8% to −0.5%) | | 5.9 (4.2−8.9) | ref | | 12.3 (8.4−14.9) | Ref | |
| $T > 0.05$ ($n = 3$) | 49.1% (2.5% to 77.3%) | 0.079 | 1.4 (1.4−5.8) | 3.32 | 0.14 | 5.8 (2.3−5.8) | 11.94 | 0.043* |

* Statistically significant; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; NR = not rearched; T = testosterone.

Gleason score was lower, but PSA level at pretreatment was higher among men with serum testosterone level over 0.05 ng/ml, compared with men with serum testosterone level below 0.05 ng/ml (Supplementary Table 5). Similar to docetaxel chemotherapy, best PSA response and PFS after initiation of cabazitaxel chemotherapy were inferior among men with serum testosterone level over 0.05 ng/ml, compared with those among men with serum testosterone level below 0.05 ng/ml, although statistical significance was not reached (Table 2). OS among men with serum testosterone level over 0.05 ng/ml was significantly inferior to that among men with serum testosterone level below 0.05 ng/ml ($P = 0.043$, Table 2). However, multivariate analysis could not be performed due to small number of cases treated with cabazitaxel.

## 4. Discussion

PSA response, PSA-PFS, and cause-specific survival were better in men with higher serum testosterone level when treated with traditional antiandrogen such as bicalutamide and flutamide [21]. Consistently, higher serum testosterone level has been reported to be correlated with better PSA response when treated with various AR-targeting therapies such as diethylstilbestrol, ketoconazole, abiraterone, bicalutamide, cyproterone acetate, and enzalutamide [22]. In line with these retrospective studies, higher serum testosterone level before abiraterone with prednisone and prednisone alone showed better OS in the postchemotherapy setting of COU-AA-301 study [17]. Unreported patient backgrounds such as age may influence OS, because young age is known to correlate with higher testosterone level during ADT [23]. However, small cohort analysis failed to show any significant impact of serum androgen levels including testosterone on PSA response rate and PFS when treated with abiraterone [24]. Thus, although it was suggested that higher serum testosterone level may be prognostic factor of better outcome when treated with AR-targeting therapies, the significance of serum testosterone in AR-targeting therapies treatment remains controversial.

In the phase 3 TAX-327 trial in which patients were treated with docetaxel or placebo with prednisone, OS including docetaxel arm and placebo with prednisone arm did not differ between higher and lower serum testosterone levels [25]. Because higher serum testosterone level was correlated with better OS when treated with prednisone alone in COU-AA-301 trial [17], OS among men with higher serum testosterone level is supposed to inversely be worse when treated with docetaxel. In line with this notion, the present study showed that pretreatment serum testosterone level of docetaxel and cabazitaxel chemotherapies were associated with PFS and OS, respectively. Failure to show significant association with OS in docetaxel chemotherapy may be derived from interactions with subsequent therapies after docetaxel, or younger age in men with higher serum testosterone level. Thus, for the first time, this study shows the worse prognoses among men with higher pretreatment serum testosterone level in taxane chemotherapies including docetaxel and cabazitaxel.

Serum testosterone level at progression to CRPC was suggested to be not only a prognostic factor, but also a

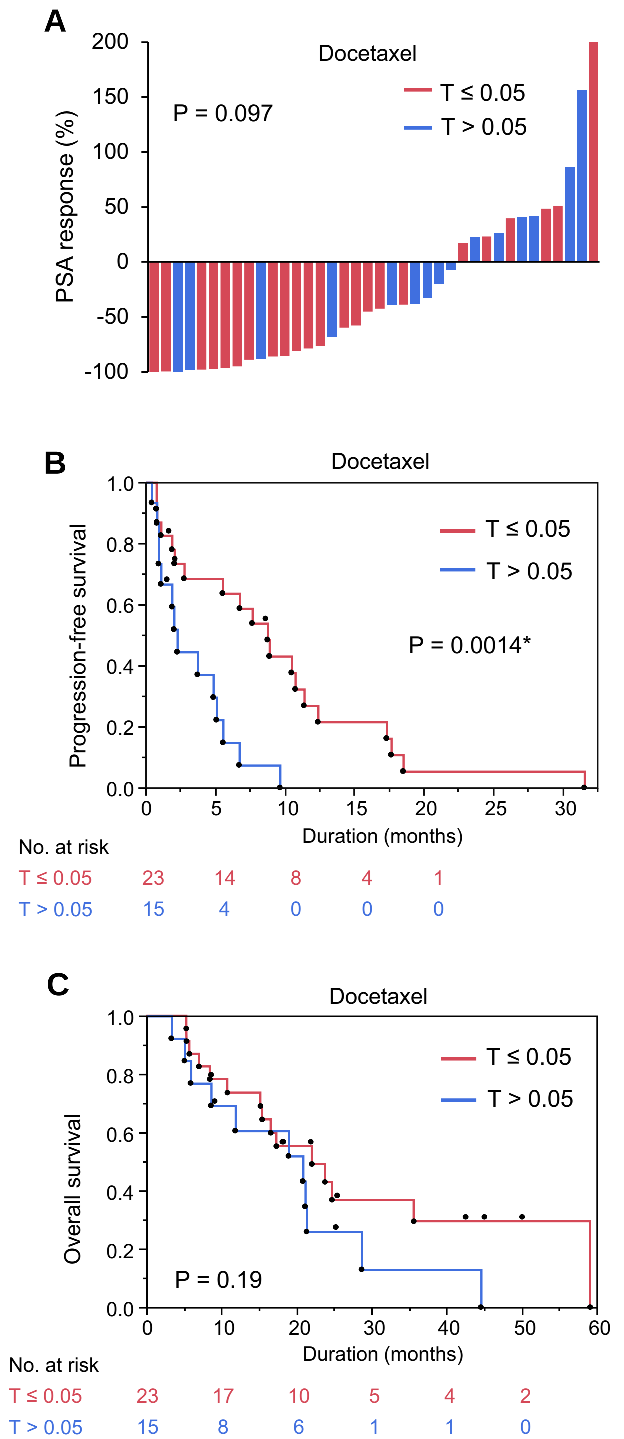


Fig. 2. Antitumor outcome of docetaxel according to pretreatment serum testosterone level. Waterfall plots showing greatest decline in PSA values from baseline (A), progression-free survival (B), and overall survival (C) in 38 patients with castration-resistant prostate cancer who received docetaxel chemotherapy according to pretreatment serum testosterone level.

promising predictive factor of antitumor outcome when treated with ARAT agents and taxane chemotherapies for CRPC. Thus, pretreatment serum testosterone level may be useful when recommending suitable therapy such as ARAT agent or taxane chemotherapy to patients with CRPC, where ARAT agent and taxane chemotherapy would be suitable for men with higher and lower pretreatment serum testosterone level, respectively. Theoretically, persistent AR signaling by the relatively high androgen level in CRPC is predictive of the therapeutic benefit of ARAT agents. Actually, intense AR signaling before enzalutamide treatment was reported to be predictive of better therapeutic response [26]. The reduction of serum testosterone level by abiraterone, but not by prednisone alone was correlated with PSA response [27]. In contrast, AR signaling was shown to confer therapeutic resistance to taxanes in vitro [28]. Moreover, intriguingly, it has recently been reported that testosterone supplement in mice resulted in reduced cabazitaxel concentration in xenograft tumors possibly via reduced intracellular incorporation of cabazitaxel by competitive inhibition of OATP1B3 with testosterone [29]. Thus, poor prognosis in men with impaired suppression of testosterone level may represent therapeutic resistance to taxanes.

The present study has several limitations. The study design is retrospective, and the number in each cohort was relatively small. In addition, the timing of serum testosterone measurement was varied, and mass spectrometry suitable to measure low levels of testosterone was not utilized. In addition, only testosterone level was investigated, where other androgen levels may be more suitable as biomarkers because previous report has shown prognostic significance of free testosterone level in treatment for CRPC, where higher free testosterone level was associated with worse survival in CRPC [30]. Furthermore, this study did not examine tissue androgen levels during ADT. Measuring tissue androgen level may be more promising, because previous studies have reported a discrepancy between serum and tissue androgen levels before ADT [31]. Further exploratory and validation studies on the significance of androgen level in treatments for CRPC are required.

In conclusion, the present study indicated distinct prognostic values of serum testosterone level when treated with ARAT agents and taxane chemotherapies for CRPC. These findings suggest that serum testosterone level may be a useful predictive biomarker when choosing appropriate therapy for patients with CRPC, recommending that patients with higher testosterone should be treated with ARAT agent while patients with low testosterone should be treated with taxane chemotherapy for CRPC.

## Conflict of interest

Masaki Shiota and Masatoshi Eto have received honoraria from Astellas, Janssen, AstraZeneca and Sanofi.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urolonc.2018.10.020.

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