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ORIGINAL ARTICLE

Prostate Cancer

# Treatment strategy for metastatic prostate cancer with extremely high PSA level: reconsidering the value of vintage therapy

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**The prognostic significance of initial prostate-specific antigen (PSA) level for metastatic prostate cancer remains uncertain. We investigated the differences in prognosis and response to hormonal therapies of metastatic prostate cancer patients according to initial PSA levels. We analyzed 184 patients diagnosed with metastatic prostate cancer and divided them into three PSA level groups as follows: low (<100 ng ml$^{-1}$), intermediate (100–999 ng ml$^{-1}$), and high (≥1000 ng ml$^{-1}$). All patients received androgen deprivation therapy (ADT) immediately. We investigated PSA progression-free survival (PFS) for first-line ADT and overall survival (OS) within each of the three groups. Furthermore, we analyzed response to antiandrogen withdrawal (AW) and alternative antiandrogen (AA) therapies after development of castration-resistant prostate cancer (CRPC). No significant differences in OS were observed among the three groups ($P$ = 0.654). Patients with high PSA levels had significantly short PFS for first-line ADT ($P$ = 0.037). Conversely, patients in the high PSA level group had significantly longer PFS when treated with AW than those in the low PSA level group ($P$ = 0.047). Furthermore, patients with high PSA levels had significantly longer PFS when provided with AA therapy ($P$ = 0.049). PSA responders to AW and AA therapies had significantly longer survival after CRPC development than nonresponders ($P$ = 0.011 and $P$ < 0.001, respectively). Thus, extremely high PSA level predicted favorable response to vintage sequential ADT and AW. The current data suggest a novel aspect of extremely high PSA value as a favorable prognostic marker after development of CRPC.**

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## INTRODUCTION

Prostate-specific antigen (PSA) was discovered by Wang *et al.*[1] in 1979 and its clinical application was first reported by Stamey *et al.*[2] in 1987. Serum PSA level is a tumor marker that is generally used to screen for prostate cancer detection.[3] It is also used in algorithms such as the Partin nomogram or tables, the D'Amico classification, and the Kattan nomogram for risk classification of localized prostate cancer at diagnosis.[4–6] In addition, serum PSA level is essential as a follow-up tool for monitoring prostate cancer after any treatment. In general, a rise in serum PSA level is considered as a marker of prostate cancer progression, which correlates with malignant potential and tumor burden. However, because of tumor heterogeneity, a limitation of serum PSA level as a prognostic marker has recently been reported.[7] Clinicians, therefore, have to evaluate disease state of each patient using complementary findings such as those from imaging studies, other biomarkers, and physical signs and symptoms. Although serum PSA level at diagnosis is considered to be a useful prognostic factor for progression in localized prostate cancer, it is not necessarily of such utility in metastatic prostate cancer. The range of serum PSA level is wider in patients with metastatic prostate cancer than that in patients with localized prostate cancer, and the clinicopathological characteristics of metastatic prostate cancer are generally variable. Development of castration-resistant prostate cancer (CRPC) will occur in a number of metastatic prostate cancer patients after initial androgen deprivation therapy (ADT).[8] However, individual clinicians decide treatment strategies for CRPC by considering patient's clinicopathological characteristics. Here, we focused on PSA levels at diagnosis and divided our patients into three groups as follows: low (<100 ng ml$^{-1}$), intermediate (100–999 ng ml$^{-1}$), and high (≥1000 ng ml$^{-1}$). We then investigated the differences in prognosis and response to treatment of metastatic prostate cancer patients within each of the three groups. Our data may support the establishment of treatment strategy for metastatic prostate cancer according to initial PSA level.

## PATIENTS AND METHODS

### *Study population and clinical variables*

We analyzed 184 patients who were initially diagnosed with metastatic prostate cancer between 2006 and 2014 under the Institutional Review Board approval at Asahi General Hospital (Asahi, Japan;

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#2015091517). All patients gave informed consent on the use of clinical data for research purposes. All patients were diagnosed with adenocarcinoma, without other cancer types determined histopathologically in the biopsy specimens. All the biopsy specimens were obtained through transperineal approach, and 10-core biopsies were performed at the apex, middle, and base of the peripheral zone and in the middle of the transitional zone of the prostate. Clinical tumor, node, metastasis (TNM) classification based on the 2014 National Comprehensive Cancer Network (NCCN) guidelines[9] was determined through computed tomography scan and bone scintigraphy findings. Bone metastasis was classified according to the extent of disease (EOD) score. EOD score is a classification of the number of bone metastasis in five stages which is described as follows: EOD score 0 is no transition, 1 is one to five bone metastases, 2 is six to twenty bone metastases, 3 is more than twenty, but not super scan, and 4 is super scan.[10] The sites of metastases were those of unregional lymph nodes and skeletal and visceral structures (TxNxM1). Only regional lymph node metastases were excluded from this study (TxN1M0). All patients received combined androgen blockade (CAB) therapy immediately after diagnosis. ADT comprised bicalutamide and luteinizing hormone-releasing hormone (LH-RH) agonist, antagonist, or surgical orchiectomy.

We collected patient baseline characteristics including age, initial PSA levels, Gleason score (GS), TNM classification, and laboratory results at diagnosis. Laboratory results included levels of hemoglobin (Hb), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), albumin (Alb), and C-reactive protein (CRP). Abbott's architect (Abbott, Tokyo, Japan) was used for serum PSA measurement. High-volume prostate cancer was defined as presence of visceral metastases and/or four or more bone metastases.[11]

### *Outcome measures*

We validated PSA progression at initial ADT and overall survival (OS) among the three groups. We analyzed the association of PSA level at diagnosis with OS in Cox proportional hazard model. Furthermore, we investigated the response to subsequent hormonal therapy (antiandrogen withdrawal [AW] and alternative nonsteroidal antiandrogen [AA] therapies) and survival after development of CRPC. Antiandrogen withdrawal syndrome (AWS) was defined as ≥50% decrease in PSA level within 8 weeks after discontinuation of bicalutamide. All patients were switched from bicalutamide to flutamide for AA in this study. PSA responses were defined as PSA decline of ≥50% for AW and ≥30% for AA therapy in this study. We validated PSA response to AW and AA therapies among the three groups. Decision of AW and AA therapies was performed by judgment of each patient's physician.

### *Definition of PSA progression and CRPC development*

PSA progression was defined as a PSA level of ≥2 ng ml$^{-1}$ above the nadir. For these measurements, the increase had to be at least 25% above the nadir, which was confirmed by a second value measured 3 weeks later. CRPC development was defined as PSA progression or obvious progress on image.

### *Statistical analyses*

Mann–Whitney's U-test, Chi-square test, Kaplan–Meier method (log-rank test), and Cox proportional hazard model were used for statistical analyses. Statistical computations were carried out using JMP 11.0.0 (SAS Institute Inc., Cary, NC, USA). We considered $P < 0.05$ as statistically significant in this study.

## RESULTS

We reviewed data on 184 patients with metastatic prostate cancer. Median observation period was 32 months. Eighty-four (45.7%) patients died during the follow-up periods. Baseline characteristics of the patients are listed in **Supplementary Table 1**. Of the 184 patients, 57 (31.0%), 70 (38.0%), and 57 (31.0%) had low, intermediate, and high PSA values at diagnosis, respectively. In this study, the median age and PSA level were 74 years and 334.94 ng ml$^{-1}$, respectively. Patients with high PSA levels were of significantly older age and had high clinical tumor stages and EOD scores. Furthermore, patients with high PSA levels had significantly high levels of CRP, LDH, and ALP and low levels of Hb and Alb at diagnosis. Patients with high PSA levels had significantly high rates of receiving orchiectomy as ADT. Biopsy GS and node and metastasis classification were not statistically different among the three groups.

**Figure 1a** is a Kaplan–Meier curve showing the OS rates among the three groups. No significant differences in OS were observed among the three groups ($P = 0.654$). The 3-year OS rates were 60.2% (low), 68.1% (intermediate), and 59.2% (high), respectively. In multivariate Cox proportional hazard regression analysis, age (hazard ratio [HR]: 2.18, $P = 0.015$) and LDH level (HR: 2.54, $P = 0.003$) were independent prognostic factors for OS. However, initial PSA level was not associated with OS in this study ($P = 0.201$; **Supplementary Table 2**).

**Figure 1b** shows PSA progression-free survival (PFS) in response to initial ADT. Patients in the high PSA level group had significantly high PSA progression in Kaplan–Meier analysis ($P = 0.037$). Median PSA PFS periods for the three groups were 14.0 (low), 12.4 (intermediate) and 10.3 (high) months, respectively. Nadir PSA values in high PSA group were significantly higher than those in low PSA group ($P < 0.001$; **Supplementary Table 1**). Taken together, patients with high baseline PSA levels at diagnosis had worse outcomes from initial ADT. However, there were no significant differences in OS among the three groups. Therefore, we investigated OS after CRPC development among the three PSA level groups. **Figure 1c** shows OS after CRPC development among the three PSA level groups. The 2-year OS rates after CRPC were 37.2% (low), 44.7% (intermediate), and 54.9% (high), respectively. Patients with high PSA levels had longer survival after developing CRPC, although there were no significant differences among the three groups in Kaplan–Meier analysis ($P = 0.283$). Furthermore, we investigated predictive clinical factors for OS after CRPC development in multivariate Cox proportional hazard regression analysis. Interestingly, initial PSA value was an independent predictor for OS after CRPC development ($P = 0.008$) along with other clinical factors (age, LDH level, nadir PSA value of initial ADT, and PFS periods of initial ADT; **Table 1**).

Of 135 patients who had PSA progression following initial ADT, 81 (60.0%) received AW, 68 (50.4%) received AA therapy, and 51 (37.8%) received both AW and AA therapies after developing CRPC. In Kaplan–Meier analysis, patients in the high PSA level group had significantly longer PSA PFS when treated with AW than those in the low PSA level group ($P = 0.047$; **Figure 2a**). Initial PSA value was not a significant predictive factor for PSA response to AW, and time to nadir PSA and PFS periods of initial ADT were predictive factors in univariable analysis. There was no significant predictor in multivariate analysis (**Table 2**). PSA ≥1000 (*vs* <100) was a predictive factor for AW response in univariable analysis (HR: 0.52, $P = 0.047$, data not shown). Furthermore, patients with high PSA levels had significantly longer PSA PFS when provided with AA therapy ($P = 0.049$; **Figure 2b**). In multivariable analysis, initial PSA value and nadir PSA of initial ADT were independent predictive factors for AA therapy response (**Table 3**). **Supplementary Table 3** shows PSA response and treatment duration

of AW and AA therapies among the three PSA groups. Patients in the high PSA level group showed marginally better PSA response to AW with 5.3% (low), 14.7% (intermediate), and 25.0% (high) ($P = 0.073$) and had significantly longer AWS periods with 1.9 ± 0.9 months (low), 4.4 ± 7.3 months (intermediate), and 4.7 ± 6.7 months (high) ($P = 0.03$), respectively. Furthermore, patients with high PSA levels had better PSA response to AA therapy with 20.0% (low), 44.8% (intermediate), and 66.7% (high) ($P = 0.007$). Similarly, high PSA levels were significantly associated with longer AA therapy periods with 4.3 ± 4.4 months (low), 5.8 ± 5.1 months (intermediate), and 15.7 ± 22.2 months (high) ($P = 0.013$), respectively. Furthermore, PSA responders to AW and AA therapies had significantly longer survival after CRPC development than nonresponders ($P = 0.011$ and $P < 0.001$, respectively) in this study (**Figure 3**).

## DISCUSSION

In this study, we focused on PSA levels at diagnosis to investigate the differences in prognosis and response to hormonal therapy in patients with metastatic prostate cancer. Our data demonstrated that serum PSA level at diagnosis was not associated with OS in metastatic prostate cancer. Interestingly, patients with high PSA levels had significantly short PSA PFS periods after initial ADT; however, they responded favorably to AW and AA therapies. We concluded that serum PSA level was not associated with OS and suggested a novel aspect of extremely high PSA value as a favorable prognostic marker after development of CRPC.

Correlation between serum PSA levels and prognosis of metastatic prostate cancer has been reported.[12–15] Although serum PSA level is a significant prognostic factor in localized prostate cancer, previous studies have showed that it may not be a significant prognostic factor in advanced prostate cancer. As in our study, age and LDH levels were independent prognostic factors for OS, and serum PSA level was not associated with OS. Some authors have reported that PSA response to initial ADT rather than initial PSA level was associated with survival in metastatic prostate cancer.[16] Metastatic prostate cancer with low PSA level should be considered as the presence of a neuroendocrine tumor combined with adenocarcinoma.[17] Furthermore, adenocarcinoma may

**Table 1: Univariable and multivariable Cox proportional hazard regression models for overall survival after castration-resistant prostate cancer**

| *Variables* | *Univariable* | | | *Multivariable* | | |
|---|---|---|---|---|---|---|
| | *HR* | *95% CI* | *P* | *HR* | *95% CI* | *P* |
| Age (≥74 years)[a] | 1.72 | 1.06–2.78 | 0.016 | 1.93 | 1.16–3.2 | 0.011 |
| Initial PSA (ng ml$^{-1}$) | 0.99 | 0.98–0.99 | 0.044 | 0.99 | 0.98–0.99 | 0.008 |
| GS ≥9 | 1.48 | 0.82–2.68 | 0.194 | NA | NA | NA |
| Hb (>13 g dl$^{-1}$)[b] | 1 | 0.62–1.62 | 0.991 | NA | NA | NA |
| Alb (>4 g dl$^{-1}$)[b] | 0.73 | 0.45–1.18 | 0.191 | NA | NA | NA |
| ALP (>354 U l$^{-1}$)[a] | 1.18 | 0.72–1.92 | 0.519 | NA | NA | NA |
| LDH (>214 U l$^{-1}$)[a] | 2.39 | 1.39–4.09 | <0.001 | 2.23 | 1.27–3.93 | <0.001 |
| CRP (>0.24)[a] | 1.57 | 0.85–2.91 | 0.146 | NA | NA | NA |
| T stage ≥T3b | 1.42 | 0.74–2.70 | 0.291 | NA | NA | NA |
| EOD ≥3 | 1.53 | 0.95–2.45 | 0.078 | NA | NA | NA |
| High-volume prostate cancer | 1.65 | 0.93–2.93 | 0.086 | NA | NA | NA |
| Nadir PSA of initial ADT (<2 ng ml$^{-1}$) | 0.49 | 0.31–0.80 | <0.001 | 0.53 | 0.32–0.88 | 0.002 |
| PFS periods of initial ADT (>12 months) | 0.39 | 0.23–0.65 | <0.001 | 0.47 | 0.27–0.82 | 0.001 |

[a]Median; [b]Normal or abnormal value. ADT: androgen deprivation therapy; Alb: albumin; ALP: alkaline phosphatase; CI: confidence interval; CRP: C-reactive protein; EOD: extent of disease; GS: Gleason score; Hb: hemoglobin; HR: hazard ratio; LDH: lactate dehydrogenase; PFS: progression-free survival; PSA: prostate-specific antigen; NA: not analyzed

**Table 2: Univariable and multivariable Cox proportional hazard regression models for prostate-specific antigen progression-free survival for antiandrogen withdrawal**

| *Variables* | *Univariable* | | | *Multivariable* | | |
|---|---|---|---|---|---|---|
| | *HR* | *95% CI* | *P* | *HR* | *95% CI* | *P* |
| Age (≥74 years)[a] | 1.36 | 0.85–2.18 | 0.192 | NA | NA | NA |
| Initial PSA (ng ml$^{-1}$) | 0.99 | 0.99–1.00 | 0.451 | NA | NA | NA |
| GS ≥9 | 1.42 | 0.82–2.64 | 0.220 | NA | NA | NA |
| Hb (>13 g dl$^{-1}$)[b] | 1.08 | 0.67–1.73 | 0.754 | NA | NA | NA |
| Alb (>4 g dl$^{-1}$)[b] | 0.91 | 0.56–1.45 | 0.683 | NA | NA | NA |
| ALP (>354 U l$^{-1}$)[a] | 1.11 | 0.69–1.77 | 0.671 | NA | NA | NA |
| LDH (>214 U l$^{-1}$)[a] | 1 | 0.63–1.59 | 0.992 | NA | NA | NA |
| CRP (>0.24)[a] | 1.05 | 0.60–1.87 | 0.961 | NA | NA | NA |
| T stage ≥T3b | 0.85 | 0.49–1.57 | 0.594 | NA | NA | NA |
| EOD ≥3 | 1.24 | 0.76–1.98 | 0.391 | NA | NA | NA |
| High-volume prostate cancer | 1 | 0.62–1.64 | 0.997 | NA | NA | NA |
| Nadir PSA of initial ADT (<2 ng ml$^{-1}$) | 1.09 | 0.67–1.84 | 0.741 | NA | NA | NA |
| Time to nadir PSA of initial ADT (≥6 months) | 0.56 | 0.34–0.92 | 0.022 | 0.73 | 0.27–1.97 | 0.543 |
| PFS periods of initial ADT (≥12 months) | 0.49 | 0.29–0.81 | 0.005 | 0.67 | 0.25–1.71 | 0.412 |

[a]Median; [b]Normal or abnormal value. ADT: androgen deprivation therapy; Alb: albumin; ALP: alkaline phosphatase; AW: antiandrogen withdrawal; CI: confidence interval; CRP: C-reactive protein; EOD: extent of disease; GS: Gleason score; Hb: hemoglobin; HR: hazard ratio; LDH: lactate dehydrogenase; PFS: progression-free survival; PSA: prostate-specific antigen; NA: not analyzed

**Table 3: Univariable and multivariable Cox proportional hazard regression models for prostate-specific antigen progression-free survival for alternative antiandrogen therapy**

| *Variables* | *Univariable* | | | *Multivariable* | | |
|---|---|---|---|---|---|---|
| | *HR* | *95% CI* | *P* | *HR* | *95% CI* | *P* |
| Age (≥74 years)[a] | 1.03 | 0.62–1.73 | 0.911 | NA | NA | NA |
| Initial PSA (ng ml$^{-1}$) | 0.99 | 0.98–0.99 | 0.008 | 0.99 | 0.98–0.99 | 0.044 |
| GS ≥9 | 0.85 | 0.48–1.55 | 0.863 | NA | NA | NA |
| Hb (>13 g dl$^{-1}$)[b] | 0.61 | 0.35–1.04 | 0.074 | NA | NA | NA |
| Alb (>4 g dl$^{-1}$)[b] | 0.9 | 0.53–1.52 | 0.692 | NA | NA | NA |
| ALP (>354 U l$^{-1}$)[a] | 0.86 | 0.51–1.48 | 0.594 | NA | NA | NA |
| LDH (>214 U l$^{-1}$)[a] | 1.24 | 0.74–2.11 | 0.411 | NA | NA | NA |
| CRP (>0.24)[a] | 1.03 | 0.57–1.89 | 0.920 | NA | NA | NA |
| T stage ≥T3b | 1.08 | 0.58–2.19 | 0.823 | NA | NA | NA |
| EOD≥3 | 1.52 | 0.91–2.52 | 0.111 | NA | NA | NA |
| High-volume prostate cancer | 1.41 | 0.81–2.58 | 0.232 | NA | NA | NA |
| Nadir PSA of initial ADT (<2 ng ml$^{-1}$) | 0.44 | 0.26–0.76 | 0.003 | 0.41 | 0.19–0.84 | 0.016 |
| Time to nadir PSA of initial ADT (≥6 months) | 0.42 | 0.24–0.72 | 0.001 | 0.35 | 0.12–1.03 | 0.057 |
| PFS periods of initial ADT (≥12 months) | 0.48 | 0.28–0.80 | 0.005 | 0.83 | 0.31–2.24 | 0.713 |

[a]Median; [b]Normal or abnormal value. ADT: androgen deprivation therapy; Alb: albumin; ALP: alkaline phosphatase; CI: confidence interval; CRP: C-reactive protein; EOD: extent of disease; GS: Gleason score; Hb: hemoglobin; HR: hazard ratio; LDH: lactate dehydrogenase; PFS: progression-free survival; PSA: prostate-specific antigen; NA: not analyzed

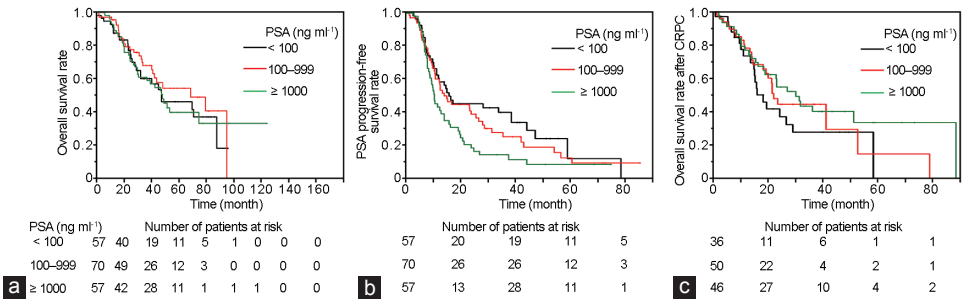


**Figure 1:** Survival curves of the three PSA groups. (**a**) Overall survival rate among the three groups. No significant difference was observed among the three groups ($P = 0.654$). (**b**) PSA progression-free survival rate in response to initial antiandrogen deprivation therapy among the three groups. Patients in the high PSA level group had significantly high PSA progression ($P = 0.037$). (**c**) Overall survival rate after CRPC among the three groups. No significant difference was observed among the three groups ($P = 0.283$). CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen.

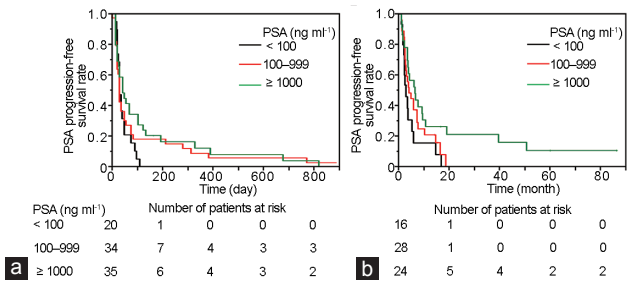


**Figure 2:** PSA progression-free survival curves of the three PSA groups. (**a**) PSA progression-free survival rate in response to antiandrogen withdrawal among the three groups. Patients in the high PSA level group had significantly longer PSA progression-free survival than those in the low PSA level group ($P = 0.047$). (**b**) PSA progression-free survival rate in response to alternative antiandrogen therapy among the three groups. Patients with high PSA levels had significantly longer PSA progression-free survival ($P = 0.049$). PSA: prostate-specific antigen.

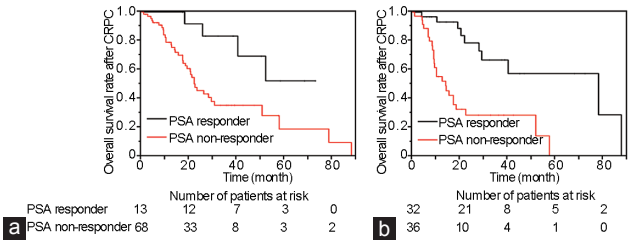


**Figure 3:** Overall survival curves of PSA responders and nonresponders. (**a**) Overall survival rate after CRPC in patients with PSA responders and nonresponders to AW. PSA responders to AW therapy had significantly longer survival than nonresponders ($P = 0.011$). (**b**) Overall survival rate after CRPC in patients with PSA responders and nonresponders to AA therapy. PSA responders to AA therapies had significantly longer survival than nonresponders ($P < 0.001$). AA: alternative antiandrogen; AW: antiandrogen withdrawal; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen.

present with neuroendocrine differentiation during hormonal therapy, which is generally considered to have unfavorable prognosis. Thus, PSA level at diagnosis could not represent prognosis for metastatic prostate cancer as it has been established for localized prostate cancer.

AWS was first reported by Kelly and Scher in patients with discontinuation of flutamide in 1993.[18,19] PSA decline was also observed after discontinuation of bicalutamide in 1994.[20] The response rate (50% or greater PSA decline) was 15.5% for bicalutamide and 12.8% for flutamide in a previous report.[21] In our study, PSA response to AWS was 16% (for bicalutamide) in all patients, which is equivalent to the previous reports. Our study showed that high PSA level predicts high PSA response to AW therapy with bicalutamide. Furthermore,

favorable PSA response to AWS predicts longer survival in our study, and these results were also demonstrated in previous reports.[21] Thus, AWS may be of significant value to selected CRPC patients. The mechanisms of AWS remain uncertain, but they were considered to be related to mutations in the androgen receptor (AR).[22] The hypothesis is that mutations of ARs in CRPC make bicalutamide to act as an androgen agonist.[23]

Fowler *et al*.[24] first reported PSA decline with flutamide as a second-line ADT after PSA relapse to initial ADT. Thereafter, all PSA responses (>0) to AA therapy were observed to be about 60%, and PSA responders had significantly longer survival in previous reports.[21] In our study, PSA response to AA therapy (≥30% decline) was 47.1%. Even two-thirds of patients in the high PSA level group had PSA response (≥30%) associated with longer PSA PFS for AA therapy. Furthermore, PSA responders to AA therapy had significantly longer survival after CRPC development than nonresponders in our study. Thus, AA therapy may provide survival benefit for selected patients. The molecular mechanism of AA therapy was considered to be due to the different functional mechanisms between bicalutamide and flutamide as nonsteroidal antiandrogen. For instance, bicalutamide has evidently higher protein kinase A pathway-mediated suppressive action on AR activation than flutamide.[25] Meanwhile, flutamide, but not bicalutamide, suppresses adrenal androgen secretion.[26]

We hypothesized that PSA level at diagnosis could represent clinicopathological characteristics and modulate with proper treatment strategies. Since PSA is downstream of androgen/AR signaling, high serum PSA level may represent highly activated androgen/AR signaling. Thus, prostate cancer with extremely high PSA level may represent AR dependency and have high probability of mutations in *AR*, functional modification of AR cofactors. This hypothesis would support the better response to AW and AA therapies in the high PSA level group in our study, and AR signaling remains a significant treatment target in CRPC.[27–30]

When we consider treatment strategies for CRPC patients, our data may assist in decision-making regarding treatment modality. Patients with low PSA levels were unfavorable PSA responders to AW (5.3%) and AA (20.0%) therapies in this study. We should therefore carefully choose AW and AA therapies for patients with low PSA levels. It is preferable that these patients change to another treatment modality such as chemotherapy and do not continue hormonal therapy. On the other hand, patients with high PSA levels had significantly better PSA response rate and longer PSA PFS to AW and AA therapies. Furthermore, PSA responders to AW and AA therapies had significantly longer survival than nonresponders. Favorable response to AW and AA therapies prolongs survival after CRPC development, and patients with high PSA levels could be candidates for additional hormonal treatment after they develop CRPC.

In the current therapeutic strategy for metastatic CRPC, the clinical significance of AW and AA therapies has been declining gradually in major guidelines following the development of novel AR-targeted, radioactive (*e.g.*, Ra-223), and novel chemotherapeutic agents. Only the 2016 NCCN guidelines retain secondary hormonal therapy for metastatic CRPC patients with good performance status. Furthermore, following the Systemic Therapy in Advancing or Metastatic Prostate Cancer: evaluation of Drug Efficacy (STAMPEDE) trial, six cycles of docetaxel at the beginning of ADT were added as the initial treatment option for metastatic prostate cancer.[11] Notwithstanding these treatment options, AW and AA therapies are inexpensive with tolerable adverse events compared to other treatment options (*e.g.*, novel AR-targeted, chemotherapeutic, radioactive agents and radiation therapy). Considering these factors, therefore, AW and AA therapies may be considered before initiation of other therapeutic agents for selected patients, such as elderly patients.

Our study had some limitations. These data were reviewed retrospectively and study sample size was relatively small. Larger prospective studies with longer observation periods are needed for further validation of our study.

To our knowledge, this is the first report showing the prognosis of metastatic prostate cancer patients with extremely high PSA levels. The clinicopathological characteristics of prostate cancer patients with extremely high PSA levels remain uncertain. We hope that our study will assist the establishment of treatment strategies for metastatic prostate cancer according to PSA levels at diagnosis.

## CONCLUSIONS

Our study demonstrated that a high serum PSA level was associated with favorable response to AW and AA therapies, in spite of short response to first-line ADT. Thus, serum PSA level was not associated with OS in metastatic prostate cancer. The current data may suggest a novel aspect of PSA value as a favorable prognostic marker of CRPC, which represents remaining potential to respond to androgen-targeted therapy.

## AUTHOR CONTRIBUTIONS

YY participated in the design, acquisition of all data, statistical analysis, and drafted the manuscript. SS contributed to designing the study concept and conducting data acquisition. YA, MS, TS, AK, NS, KA, TI, and HN contributed to the discussion about sequential hormonal therapy. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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**Supplementary Table 1: Baseline characteristics of enrolled patients**

| *Variables* | *Initial PSA level (ng ml$^{-1}$)* | | | *Total* | *P*[#] |
|---|---|---|---|---|---|
| | *<100* | *100–999* | *≥1000* | | |
| Number of patients (%) | 57 (31) | 70 (38) | 57 (31) | 184 | - |
| Age (year) | 73 | 73 | 76 | 74 (50–93)* | 0.042 |
| Median PSA (ng ml$^{-1}$) (quartile) | 42.36 (15.67–74.33) | 334.94 (191.66–611.74) | 3020.68 (1723.89–5258.7) | 334.94 (82.13–1629.1) | |
| Biopsy GS (%) | | | | | |
| ≤7 | 5 (8.7) | 7 (10) | 1 (1.8) | 13 (7.1) | n.s |
| 8 | 11 (19.3) | 16 (22.9) | 13 (22.8) | 40 (21.7) | |
| ≥9 | 40 (70.2) | 45 (64.3) | 42 (73.7) | 127 (69) | |
| Unknown | 1 (1.8) | 2 (2.8) | 1 (1.8) | 4 (2.2) | |
| Number of T stage (%) | | | | | |
| T1c/T2a/T2b/T2c | 3/4/0/2 | 1/0/2/2 | 0/0/0/1 | 4/4/2/5 (8.2) | <0.001 |
| T3a/T3b | 13/17 | 13/18 | 4/20 | 30/55 (46.2) | |
| T4 | 18 | 34 | 32 | 84 (45.6) | |
| Number of N stage (%) | | | | | |
| 1 | 36 (63.2) | 50 (71.4) | 44 (77.2) | 130 (70.7) | n.s. |
| Number of M stage (%) | | | | | |
| 1a/b/c | 5 (8.8)/47 (82.4)/5 (8.8) | 1 (1.4)/65 (92.9)/4 (5.7) | 0 (0)/57 (100)/0 (0) | 6 (3.3)/169 (91.8)/9 (4.9) | n.s. |
| Number of EOD score (%) | | | | | |
| ≥3 | 5 (8.8) | 32 (45.7) | 35 (61.4) | 72 (39.1) | <0.001 |
| Number of high-volume cancer (%) | 21 (36.8) | 47 (67.1) | 50 (89.3) | 118 (64.5) | <0.001 |
| Hb (g dl$^{-1}$) | 13.9 | 12.9 | 12.5 | 12.9 (6.2–16.6)* | 0.008 |
| LDH (U l$^{-1}$) | 201 | 218.5 | 227 | 213 (127–3896)* | 0.042 |
| ALP (U l$^{-1}$) | 283 | 349 | 658 | 354 (99–21417)* | 0.007 |
| Alb (g dl$^{-1}$) | 4.2 | 4.1 | 3.8 | 4.1 (2.2–4.9)* | 0.008 |
| CRP (mg dl$^{-1}$) | 0.1 | 0.24 | 0.8 | 0.2 (0.01–19.1)* | <0.001 |
| Number of initial ADT therapy (%) | | | | | |
| Orchiectomy/LH-RH agonist/ LH-RH antagonist + bicalutamide | 24 (42.1)/33 (57.9)/0 (0) | 57 (81.4)/11 (15.7)/2 (2.9) | 52 (91.2)/4 (7)/1 (1.8) | 133 (72.3)/48 (26.1)/3 (1.6) | <0.001 |
| Number of nadir PSA <2 of initial ADT (%) | 46 (83.6) | 47 (71.2) | 26 (50) | 119 (68.8) | <0.001 |
| Median time to nadir PSA of initial ADT (month) | 5.8 (1.2–55.5) | 7.0 (0–27.1) | 6.5 (1–30.6) | 6.2 (0–55.5)* | n.s. |
| PSA PFS period of initial ADT (months) | 14 | 12.4 | 10.3 | 11.7 (0–85.4)* | 0.031 |

[#]Difference between PSA <100 and ≥1000 groups; *Median (range). PSA: prostate-specific antigen; EOD: extent of disease; Hb: hemoglobin; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; Alb: albumin; CRP: C-reactive protein; ADT: androgen-deprivation therapy; LH-RH: luteinizing hormone-releasing hormone; PFS: progression-free survival; n.s.: not significant; GS: Gleason score

**Supplementary Table 2: Univariable and multivariable Cox proportional hazard regression models for overall survival**

| *Variables* | *Univariable* | | | *Multivariable* | | |
|---|---|---|---|---|---|---|
| | *HR* | *95% CI* | *P* | *HR* | *95% CI* | *P* |
| Age (≥74 years)[a] | 1.95 | 1.24–3.04 | 0.003 | 2.18 | 1.16–4.1 | 0.015 |
| Initial PSA (ng ml$^{-1}$) | 0.99 | 099–1.00 | 0.201 | NA | NA | NA |
| GS ≥9 | 1.66 | 0.98–2.81 | 0.056 | NA | NA | NA |
| Hb (>13 g dl$^{-1}$)[b] | 0.61 | 0.39–0.94 | 0.025 | 1.08 | 0.49–2.38 | 0.856 |
| Alb (>4 g dl$^{-1}$)[b] | 0.48 | 0.31–0.75 | 0.001 | 0.69 | 0.32–1.52 | 0.363 |
| ALP (>354 U l$^{-1}$)[a] | 1.57 | 1.01–2.44 | 0.044 | 1.36 | 0.65–2.84 | 0.409 |
| LDH (>214 U l$^{-1}$)[a] | 2.64 | 1.66–4.2 | <0.001 | 2.54 | 1.36–4.75 | 0.003 |
| CRP (>0.24)[a] | 2.47 | 1.43–4.25 | 0.001 | 1.39 | 0.69–2.8 | 0.356 |
| T stage ≥T3b | 1.96 | 1.12–3.44 | 0.018 | 1.75 | 0.82–3.74 | 0.146 |
| EOD ≥3 | 1.86 | 1.2–2.88 | 0.005 | 0.77 | 0.36–1.65 | 0.501 |
| High volume | 2.03 | 1.21–3.39 | 0.007 | 1.39 | 0.63–3.08 | 0.412 |

[a]Median; [b]Normal or abnormal value. HR: hazard ratio; CI: confidence interval; PSA: prostate-specific antigen; GS: Gleason score; Hb: hemoglobin; Alb: albumin; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; CRP: C-reactive protein; EOD: extent of disease; NA: not analyzed

**Supplementary Table 3: Prostate-specific antigen response, progression-free survival, and treatment duration of antiandrogen withdrawal and alternative antiandrogen among the three prostate-specific antigen groups**

| *Initial PSA level (ng ml$^{-1}$)* | *AW* | | | | | | *AA* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *≥50% PSA response (%)* | *P* | *PFS: HR (95% CI)* | *P* | *Duration (mean±s.d., month)* | *P* | *≥30% PSA response (%)* | *P* | *PFS: HR (95% CI)* | *P* | *Duration (mean±s.d., month)* | *P* |
| PSA <100 | 5.3 | Reference | Reference | NA | 1.9±0.9 | Reference | 20 | Reference | Reference | NA | 4.3±4.4 | Reference |
| PSA 100–999 | 14.7 | 0.295 | 0.82 (0.46–1.82) | 0.513 | 4.4±7.3 | 0.063 | 44.8 | 0.114 | 0.56 (0.29–1.11) | 0.097 | 5.8±5.1 | 0.331 |
| PSA ≥1000 | 25 | 0.073 | 0.06 (0.29–1.04) | 0.066 | 4.7±6.7 | 0.033 | 66.7 | 0.007 | 0.4 (0.19–0.83) | 0.015 | 15.7±22.2 | 0.013 |

PSA: prostate-specific antigen; AW: antiandrogen withdrawal; AA: alternative antiandrogen; PFS: progression-free survival; CI: confidence interval; s.d.: standard deviation; NA: not analyzed