World Cancer Research Journal

WCRJ 2024; 11: e2850
DOI: 10.32113/wcrj_202411_2850

PROGNOSTIC VALUE OF PROSTATE-SPECIFIC ANTIGEN IN ADVANCED PROSTATE CANCER TREATED WITH ANDROGEN DEPRIVATION THERAPY AND ABIRATERONE

L. LOU, J. WEI, S. MA, W. CHEN, X.-L. CAO, F.-H. SUN

• • •

Department of Urology, The Affiliated Xuzhou Municipal Hospital of Xuzhou Medical University, Xuzhou, China

Corresponding Author
Fanghao Sun, MD; e-mail: sunfanghao2020@163.com

ABSTRACT – *Objective:* Prostate-specific antigen (PSA) has been a cornerstone in diagnosing and monitoring prostate cancer. With the advent of advanced hormonal therapies, such as the combination of androgen deprivation therapy (ADT) and abiraterone acetate plus prednisone (AAP+ADT), understanding PSA's prognostic value in metastatic castration-sensitive prostate cancer (mCSPC) is crucial for optimizing treatment strategies. This study was designed to explore the prognostic value of prostate-specific antigen in advanced prostate cancer treated with AAP+ADT.

Patients and Methods: This study is a prospective, randomized controlled trial (RCT) comparing the effectiveness of ADT alone vs. AAP+ADT in 236 patients with mCSPC. Participants were randomly assigned to one of the two treatment groups, focusing on evaluating PSA progression-free survival and overall survival. The Kaplan-Meier survival curves and Log-rank tests were used for survival comparisons, and the analysis included both univariate and multivariate Cox regression to identify prognostic factors.

Results: In this RCT study, a total of 236 mCSPC patients were enrolled and 118 patients received AAP+ADT, while the other 118 patients were treated with ADT alone. Our findings revealed that treatment with AAP+ADT emerged as an independent predictor of favorable PSA trajectory (Hazard Ratio [HR]=0.412, 95% Confidence Interval [CI]: 0.288-0.535, $p<0.001$), especially pronounced in patients achieving a 50-90% reduction in PSA levels (HR=0.434, 95% CI: 0.173-0.625, $p<0.001$) and those in the PSA90 reduction category (HR=0.183, 95% CI: 0.103-0.363, $p<0.001$).

Conclusions: The degree of PSA reduction following AAP+ADT therapy was a robust independent prognostic marker for patients with mCSPC.

KEYWORDS: Prostate-Specific Antigen, Metastatic Castration-Sensitive Prostate Cancer, Androgen Deprivation Therapy, Abiraterone Acetate, Prognostic Factors.

INTRODUCTION

Prostate cancer remains a predominant health concern worldwide, with a significant impact on morbidity and mortality among men[1]. In 2023, prostate cancer represented 29% of all new cancer diagnoses in men within the United States, underscoring its prevalence as the foremost cancer affecting this demographic[2]. Despite a notable decline in incidence rates from 2007 to 2014, recent years have witnessed a concerning uptick in diagnoses, particularly of regional and metastatic prostate cancer[3]. This resurgence is influenced by the reduced frequency of prostate-specific antigen (PSA) screening following recommendations issued by the United States Preventive Services Task Force (USPSTF) in 2012[4-12]. Such trends highlight the critical need for revisiting screening protocols and therapeutic strategies to address the evolving landscape of prostate cancer prevalence and mortality.

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License

Notably, prostate cancer outcomes exhibit significant disparities across racial and ethnic groups, with Black individuals experiencing a 70% higher incidence rate and a mortality rate two to four times greater than those of other racial and ethnic groups[2]. Additionally, American Indian/Alaska Native populations face mortality rates surpassing those of white individuals, indicating a pressing need for equitable healthcare interventions and targeted research to mitigate these disparities[3].

The revision of the USPSTF's prostate cancer screening recommendations in 2018, advocating for personalized decision-making among men aged 55 to 69 years, represents a pivotal shift towards more nuanced approaches to early detection[13]. The subsequent increase in PSA testing rates post-2017 draft statement indicates a renewed emphasis on leveraging PSA as a tool for early identification of potentially fatal prostate cancer cases[14]. Concurrently, advancements in imaging and biomarker specificity are poised to diminish the risk of overdetection and overtreatment, thereby maintaining the relatively low prostate cancer mortality rates achieved through early detection and judicious management strategies[3].

In the broader context of global health, prostate cancer ranks as the second leading cause of male cancer-related deaths in developed regions, including Europe and America, trailing only behind lung cancer in terms of mortality[15]. In the realm of advanced prostate cancer treatment, the monitoring of PSA levels has been pivotal in gauging disease progression and response to therapy[3].

Androgen deprivation therapy (ADT) has been the cornerstone of treatment for advanced prostate cancer, and the prognostic value of PSA in this context has been extensively studied[16]. It is well-established that declines in PSA levels during ADT are indicative of a favorable response, correlating with prolonged survival and better overall outcomes[17].

The emergence of metastatic castration-sensitive prostate cancer (mCSPC) at diagnosis, although constituting a small fraction of new cases, poses significant treatment challenges[18]. The standard regimen of ADT for mCSPC often leads to progression to metastatic castration-resistant prostate cancer (mCRPC) within a year, underscoring the imperative for enhanced therapeutic approaches[19]. The therapeutic landscape is evolving, and the combination of ADT with novel agents such as abiraterone acetate plus prednisone (AAP) has become a new standard for treatment, particularly in cases of mCSPC[3].

The advent of abiraterone acetate, in combination with prednisone, has introduced a promising avenue for the management of mCRPC[20,21]. Notably, a randomized controlled trial by Fizazi et al[22] illuminated the superior efficacy of the AAP and ADT combination over the ADT alone in prolonging overall survival and radiographic progression-free survival in mCSPC patients. This combination, known as AAP+ADT, has shown improved efficacy over ADT alone, leading to a paradigm shift in therapeutic approaches[22].

The advent of AAP+ADT therapy poses critical questions regarding the established prognostic frameworks based on PSA levels. The intensified therapeutic effect of AAP+ADT may alter the dynamics of PSA decline, potentially offering a more rapid and profound suppression of PSA levels[3]. This could redefine the thresholds for what constitutes an optimal response to treatment and may also impact the timeline in which these changes become evident[3]. Furthermore, the mechanisms through which AAP acts, primarily by inhibiting androgen synthesis and thus reducing androgen receptor signaling, could modulate the relationship between PSA levels and tumor burden differently than ADT alone[21]. This suggests that the prognostic significance of PSA under the influence of AAP+ADT might differ from that observed with ADT treatment alone.

Given this background, there is a compelling need to investigate whether PSA retains its prognostic significance in patients receiving AAP+ADT and to understand the nuances of its predictive value in this new treatment context. This research will not only inform clinical decision-making but also shed light on the biological underpinnings of PSA production in response to more intensive androgen blockade. Such insights are crucial for optimizing treatment strategies, monitoring disease course, and ultimately improving survival outcomes for patients with advanced prostate cancer. Therefore, this study seeks to delve into the prognostic value of PSA in the era of combination therapy with AAP+ADT, aiming to elucidate its role and refine its application in managing advanced prostate cancer.

PATIENTS AND METHODS

Study Design and Population

This prospective, randomized controlled trial is designed to evaluate the prognostic value of PSA in patients with advanced prostate cancer undergoing treatment with ADT+AAP compared to ADT alone. Participants were randomly assigned to: a) the experimental group receiving the combination therapy of AAP+ADT; or b) the control group receiving ADT monotherapy.

The primary objective was to determine whether PSA levels, measured at baseline and at predefined intervals throughout treatment, served as an effective prognostic indicator of treatment response and overall survival within the context of the combination therapy as opposed to ADT alone. Secondary objectives included assessing time to castration resistance, and progression-free survival of the combined AAP+ADT treatment regimen.

Randomization was stratified based on baseline PSA levels, Gleason score, and the presence of visceral *vs.* non-visceral metastases to ensure a balanced allocation of prognostic factors across both treatment groups. The trial employed a double-blind design, with neither the participants nor the study investigators aware of the assigned treatments, to minimize bias. Regular follow-up visits were scheduled for clinical assessments, imaging studies, and laboratory tests to monitor disease progression and adverse events.

We included 300 patients diagnosed with mCSPC from June 2018 to June 2021 at the Department of Urology, Xuzhou Municipal Hospital (Xuzhou, China). The inclusion criteria were patients with a histopathological or cytological confirmed diagnosis of prostate cancer for the first time, presenting with at least two of the following high-risk factors: a Gleason score > 7, three or more bone metastases, visceral metastasis, or lymph node metastasis. Exclusion criteria encompassed patients with significant cardiac, cerebral, or other vital organ diseases, an expected life expectancy of less than 2 years, incomplete clinical data, or those lost to follow-up or who withdrew from the study. The study was institutionally registered and approved by the Ethics Committee of Xuzhou Municipal Hospital Hospital (Approval No. Ll20180625). The study followed the Declaration of Helsinki and its ethical principles for medical research involving human subjects.

Sample size calculation

To determine the appropriate sample size for our prospective randomized controlled trial evaluating the prognostic value of PSA in patients with advanced prostate cancer, we employed the PASS 15.0 software (Kaysville, UT, USA). We set the significance level (α) at 0.05 to maintain a 95% confidence in detecting a true effect, thus limiting the probability of a Type I error. The study was designed to achieve a power of 90%, thereby reducing the risk of a Type II error and ensuring a high probability of detecting a clinically significant difference between the two treatment arms if it indeed exists. Additionally, we anticipated a loss to follow-up rate of 20%, a realistic estimate given the study duration and the patient population involved. Considering these parameters, the PASS software was utilized to perform a power analysis based on the expected effect size derived from preliminary data and literature reviews. The analysis indicated that a total sample size of 236 would be necessary to achieve the desired power with the specified loss to follow-up rate.

Treatment Protocol

Patients were stratified and randomly assigned to two groups: the AAP+ADT group and the ADT-only group. The treatment cycle for both groups was set at every 28 days. Specifically, patients in the AAP+ADT group received 1000 mg of abiraterone acetate daily plus 5 mg of prednisone in addition to the standard ADT regimen.

Subgroup Analysis Based on PSA Response

For detailed analysis, the AAP+ADT group was further divided based on the PSA response into three subgroups: PSA50 (<50% decrease from baseline PSA level), PSA50~90 (50% to <90% decrease from baseline PSA level), and PSA90 (≥90% decrease from baseline PSA level). This stratification allowed for a nuanced examination of the impact of PSA changes on overall survival (OS) in the AAP+ADT-treated cohort.

Follow-up and Outcome Measures

Follow-up was conducted by two experienced attending physicians, with the maximum follow-up duration being 2 years. PSA progression was defined as a 25% increase in PSA levels from the baseline at any point from the initiation of treatment to during follow-up. Baseline PSA levels were established at hospital admission for routine PSA testing, with subsequent measurements taken every 3 months post-treatment initiation until the end of the first treatment cycle, followed by bi-monthly hospital visits

for PSA screening until follow-up termination or treatment cessation. Overall survival was determined from the start of treatment to death from any cause, with follow-up assessments every 3 months post the first treatment cycle until the occurrence of an outcome event or the end of the follow-up period.

Statistical Analysis

Data analysis was performed using IBM SPSS software version 23.0 (Armonk, NY, USA) and GraphPad Prism version 8.0.1 (La Jolla, CA, USA). Continuous variables with normal distribution were presented as mean ± standard deviation (SD) and compared using two independent samples *t*-tests or one-way analysis of variance (ANOVA) for between-group comparisons. Rate differences between groups were evaluated using the chi-square test. Correlation analysis was conducted using Spearman's rank correlation coefficient. Survival data were statistically described and inferred using the Kaplan-Meier method and Log-rank test. Univariate and multivariate Cox regression models were utilized to identify independent prognostic factors. A p-value of <0.05 was considered statistically significant for all tests.

RESULTS

The basic characteristics between the AAP+ADT and ADT Groups

In this study, we initially screened 300 patients diagnosed with mCSPC. After the initial screening, 20 patients were excluded due to incomplete clinical data, leaving 280 patients. Further exclusions were made based on medical criteria: 15 patients with significant cardiac, cerebral, or other vital organ diseases and 10 patients with an expected life expectancy of less than 2 years, resulting in 255 patients remaining. Subsequent evaluations focused on histopathological or cytological confirmation of prostate cancer and the presence of at least two high-risk factors (Gleason score > 7, three or more bone metastases, visceral metastasis, or lymph node metastasis). This step excluded 5 patients whose diagnosis was not confirmed and 20 patients who did not meet the high-risk criteria, leaving 230 patients eligible. Finally, 12 patients were lost to follow-up or withdrew from the study, leading to a total of 218 patients being included in the trial. The detailed inclusion and exclusion process is depicted in **Table 1**.

The mean age of participants was similar across both groups, with the AAP+ADT group averaging 76.32 years (SD = 7.93) and the ADT group 76.26 years (SD = 7.89), yielding no significant difference (t = 0.058, p = 0.954). Body Mass Index (BMI) scores were also comparable between the groups (AAP+ADT: 20.41±1.25 *vs.* ADT: 20.39±1.23, t = 0.124, p = 0.902, **Table 2**).

Diagnostic timelines, including the time from initial prostate cancer (PCa) diagnosis to mCSPC diagnosis, showed no significant differences between the two groups (**Table 2**). The mean time from PCa diagnosis to mCSPC diagnosis was 52.46 months (SD = 7.36) for the AAP+ADT group and 51.95 months (SD = 7.32) for the ADT group (t = 0.534, p = 0.594, **Table 2**).

Laboratory values, including hemoglobin (Hb), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) levels, as well as PSA levels, did not significantly differ between the groups, indicating similar baseline disease characteristics. For instance, PSA levels were 25.48 ng/mL (SD = 6.63) in the AAP+ADT group and 25.46 ng/mL (SD = 6.62) in the ADT group (t = 0.023, p = 0.982, **Table 2**). Prostate volume and the extent of nerve sparing during surgical interventions were also assessed, with no significant differences observed. For example, bilateral nerve-sparing was reported in 8.47% of cases in both groups.

Table 1. Patient inclusion and exclusion flow chart.

Stage	Criteria	Excluded (n)	Remaining (n)
Initial Screening	Incomplete clinical data	20	280
Medical Criteria Exclusion	Significant cardiac/cerebral/ organ diseases, < 2 years LE	25	255
Confirmation and Risk Factor Check	Not confirmed, insufficient risk factors	25	230
Consent and Follow-up	Lost to follow-up, withdrew	12	218

Table 2. Comparison of Baseline Characteristics Between Different Treatment Groups ($\bar{x}\pm s$).

Indicator	AAP+ADT Group (n=118)	ADT Group (n=118)	t/X^2 value	*p*-value
Age (years)	76.32±7.93	76.26±7.89	0.058	0.954
BMI Index	20.41±1.25	20.39±1.23	0.124	0.902
PCa Diagnosis Time (months)	52.46±7.36	51.95±7.32	0.534	0.594
mCSPC Diagnosis Time (months)	46.45±8.26	46.26±8.24	0.177	0.860
Hb (g/L)	130.25±9.19	129.85±9.16	0.335	0.738
ALP (mmol/L)	142.42±20.15	142.38±20.13	0.015	0.988
LDH (IU/L)	197.34±31.52	197.29±31.44	0.012	0.990
PSA (ng/mL)	25.48±6.63	25.46±6.62	0.023	0.982
Prostate volume (cm^3)	32.34±6.27	32.30±6.24	0.049	0.961
Nerve spearing [cases (%)]			0	1.000
None	63 (53.39)	62 (52.54)		
Unilateral	45 (38.14)	46 (38.98)		
Bilateral	10 (8.47)	10 (8.47)		
Biopsy Gleason Score [cases (%)]			0	1.000
≤7 points	63 (53.39)	64 (54.24)		
>7 points	55 (46.61)	54 (45.76)		
Pathological Gleason Score [cases (%)]			0	1.000
≤7 points	51 (43.22)	50 (42.37)		
>7 points	67 (56.78)	68 (57.63)		

Abbreviations - BMI: Body Mass Index; mCSPC: Metastatic Castration-Sensitive Prostate Cancer; PCa: Prostate Cancer; Hb: Hemoglobin; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; PSA: Prostate-Specific Antigen.

Biopsy and pathological Gleason scores, which are critical in assessing prostate cancer aggressiveness, were similarly distributed across the two groups, indicating comparable disease severity at baseline. The proportion of patients with a biopsy Gleason score of >7 points was 46.61% in the AAP+ADT group and 45.76% in the ADT group ($\chi^2 = 0$, $p = 1.000$, **Table 2**).

Overall, the baseline characteristics and pathological findings of our study cohort did not significantly differ between the two treatment arms, indicating well-matched groups for the evaluation of treatment efficacy and the prognostic value of PSA in the context of mCSPC treated with ADT alone or in combination with AAP.

PSA progression-free rate between the AAP+ADT and ADT Groups

In our investigation into the efficacy of combined ADT with AAP (AAP+ADT) *vs.* ADT alone in the treatment of mCSPC, a pivotal outcome measure was PSA progression-free survival (PFS). This metric, indicative of the duration patients remained free from PSA progression, serves as a critical indicator of treatment response and disease management efficacy. The analysis revealed a marked distinction in PSA PFS between the two treatment groups. Patients in the AAP+ADT group experienced a median PSA PFS of 19.3 months, substantially extending the period of disease control compared to the ADT group, which reported a median PSA PFS of only 6.8 months. This significant extension underscores the enhanced efficacy of the combined treatment approach in delaying disease progression as measured by PSA levels.

Kaplan-Meier (KM) survival curves, employed to visually represent the difference in PSA PFS between the groups, further corroborated these findings. The KM curves distinctly diverged, illustrating a pronounced improvement in PSA PFS for patients receiving the combination therapy of ADT and AAP compared to those on ADT alone (**Figure 1**, $p < 0.001$).

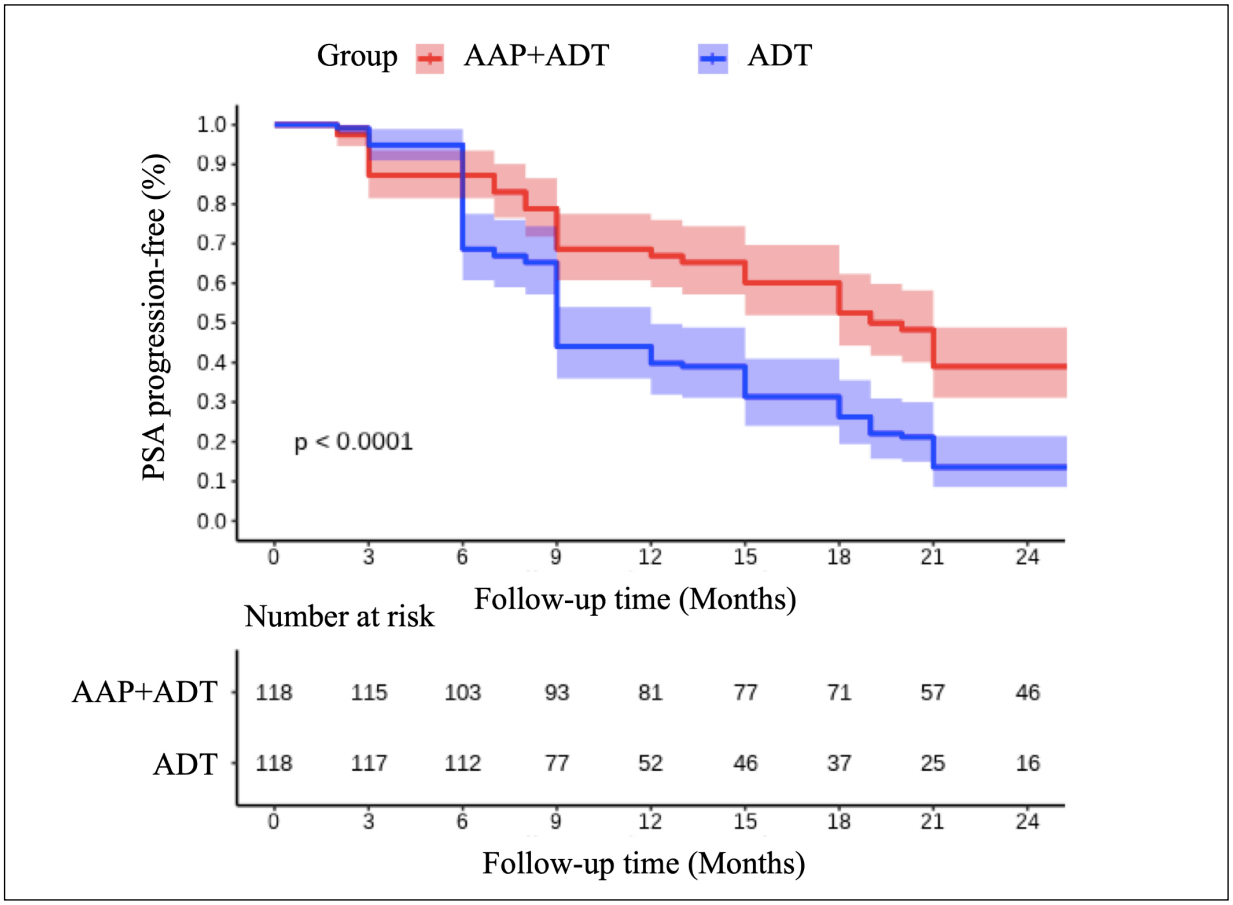

Figure 1. The PSA progression-free rate of AAP+ADT and ADT groups. (Abbreviations - ADT: Androgen Deprivation Therapy; AAP+ADT: ADT in conjunction with Abiraterone Acetate plus Prednisone).

Baseline characteristics of different PSA decline subgroups in the AAP+ADT Groups

Patients were stratified into three groups based on the percentage reduction in PSA levels from baseline: PSA 50 Group (less than 50% reduction, n=9), PSA 50-90 Group (50% to less than 90% reduction, n=14), and PSA 90 Group (90% or greater reduction, n=95). The analysis focused on various clinical and pathological indicators to assess their correlation with PSA response levels (**Table 3**).

The age of participants differed significantly across the groups (F=4.431, *p*=0.014, **Table 3**), with the PSA 50 Group presenting the highest mean age (78.34 years, SD=7.26) compared to the PSA 50-90 Group (76.78 years, SD=8.25) and the PSA 90 Group (75.88 years, SD=8.12, **Table 3**). This suggests a potential association between older age and lower PSA response.

Body Mass Index (BMI) scores across the groups did not show a statistically significant difference (F=2.136, *p*=0.120, **Table 3**), indicating that BMI might not play a significant role in PSA response to treatment in this cohort.

Diagnostic timelines, including the time from initial prostate cancer diagnosis to mCSPC diagnosis, showed no significant differences across the groups (**Table 3**), suggesting that the timing of cancer progression does not significantly impact the degree of PSA response to treatment.

Laboratory values, including hemoglobin (Hb), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) levels, as well as PSA levels and prostate volume, did not significantly differ across the groups in a way that correlated with PSA response levels.

A notable finding was observed in the distribution of biopsy and pathological Gleason scores. A significant association was found between the PSA response groups and the Gleason score distribution (Biopsy Gleason Score: χ^2=31.449, *p*<0.001; Pathological Gleason Score: χ^2=21.383, *p*<0.001, **Table 3**). The PSA 90 Group had a notably higher proportion of patients with a Gleason score of ≤7 points (66.32% for biopsy and 53.68% for pathological, **Table 3**) compared to the PSA 50 and PSA 50-90 Groups, where the majority of patients had a Gleason score of >7 points. This suggests a strong correlation between higher PSA response and lower Gleason scores, indicating a less aggressive disease profile in patients who achieved a greater reduction in PSA levels.

Table 3. Comparison of baseline characteristics of different PSA decline subgroups in the AAP+ADT Groups ($\bar{x}\pm s$).

Indicator	PSA 50 Group (n=9)	PSA 50-90 Group (n=14)	PSA 90 Group (n=95)	F/X^2 value	*p*-value
Age (years)	78.34±7.26	76.78±8.25	75.88±8.12	4.431	0.014
BMI Index	20.51±1.38	20.07±1.43	20.43±1.28	2.136	0.120
PCa Diagnosis Time (months)	52.82±6.42	50.78±8.24	53.26±9.03	0.530	0.590
mCSPC Diagnosis Time (months)	44.23±8.42	47.23±9.34	46.43±8.25	0.519	0.590
Hb (g/L)	129.35±7.25	128.64±8.53	130.35±9.42	2.828	0.063
ALP (mmol/L)	152.44±20.42	135.46±20.63	142.45±18.53	1.827	0.166
LDH (IU/L)	207.35±34.25	190.23±30.45	195.63±32.04	0.191	0.826
PSA (ng/mL)	24.35±4.45	27.36±4.53	26.36±7.24	0.902	0.409
Prostate volume (cm^3)	30.45±6.52	33.35±6.42	32.53±6.63	1.316	0.272
Nerve spearing [cases (%)]				0.901	0.924
None	5 (55.56)	7 (50.00)	51 (53.68)		
Unilateral	3 (33.33)	5 (35.71)	37 (38.95)		
Bilateral	1 (11.11)	2 (14.29)	7 (7.37)		
Biopsy Gleason Score [cases (%)]				31.449	<0.001
≤7 points	0 (0.00)	0 (0.00)	63 (66.32)		
>7 points	8 (88.89)	13 (92.86)	34 (35.79)		
Pathological Gleason Score [cases (%)]				21.383	<0.001
≤7 points	0 (0.00)	0 (0.00)	51 (53.68)		
>7 points	9 (100.00)	13 (92.86)	45 (47.37)		

Abbreviations - BMI: Body Mass Index; mCSPC: Metastatic Castration-Sensitive Prostate Cancer; PCa: Prostate Cancer; Hb: Hemoglobin; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; PSA: Prostate-Specific Antigen.

The extent of nerve sparing during surgical interventions, assessed as none, unilateral, or bilateral, showed no significant differences across the groups (χ^2=0.901, *p*=0.924, **Table 3**), suggesting that surgical technique did not influence PSA response.

Survival differences among subgroups with different PSA reductions within the AAP+ADT Group

This study also delved into the cumulative survival rates stratified by the degree of PSA reduction achieved post-treatment. Patients were categorized into three groups based on their PSA response: PSA50, PSA50-90, and PSA90. A noteworthy finding from our analysis was the distinct variation in overall survival (OS) across these groups, with the PSA90 group demonstrating the highest cumulative survival rate (**Figure 2**), which indicates not only a strong correlation between the extent of PSA reduction and survival but also suggests that achieving a substantial decrease in PSA levels (90% or greater) following treatment is associated with a significantly improved prognosis.

Conversely, the PSA50 group, characterized by the least reduction in PSA levels, exhibited the lowest cumulative survival rate among the cohorts (**Figure 2**). This finding underscores the prognostic importance of achieving a marked reduction in PSA levels as an indicator of treatment efficacy and a predictor of longer-term survival. The PSA50-90 group occupied an intermediate position in terms of cumulative survival, further reinforcing the dose-response relationship between PSA reduction and patient survival.

Multivariate analysis for the survival

In our comprehensive evaluation of prognostic factors influencing outcomes in advanced prostate cancer, both univariate and multivariate Cox regression analyses were meticulously conducted (**Table 4**).

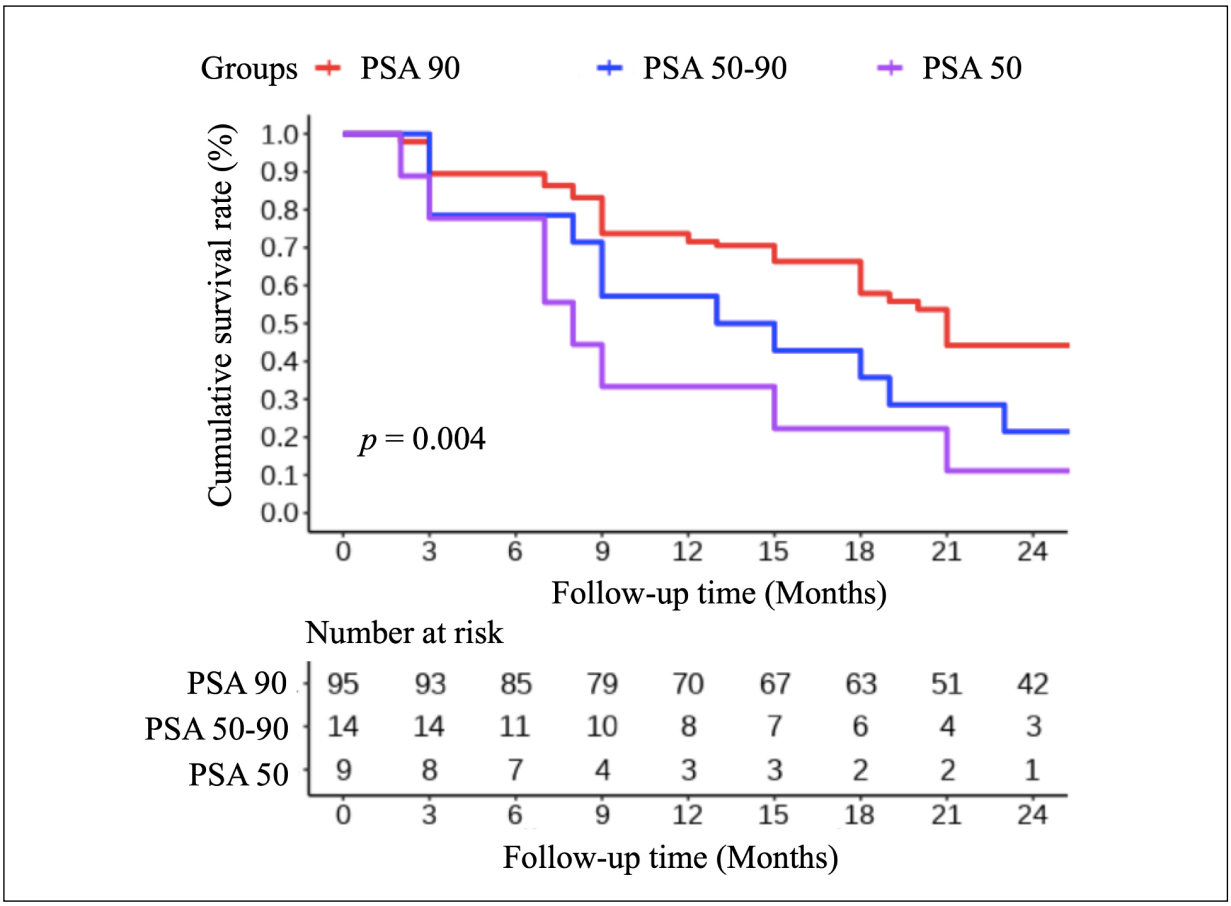

Figure 2. Survival differences among subgroups with different PSA reductions. (Abbreviations - PSA: Prostate-Specific Antigen.

These analyses encompassed a broad spectrum of variables, including baseline age, time from initial PCa diagnosis to mCSPC diagnosis, Gleason score, BMI, and levels of PSA, Hb, ALP, and LDH. The intent was to distill the factors that significantly affect tumor progression and patient prognosis.

A pivotal finding from the multivariate analysis was the emergence of combined ADT with AAP as an independent predictor of tumor progression. Compared to ADT treatment alone, the AAP+ADT regimen markedly reduced the hazard of tumor progression, with a Hazard Ratio (HR) of 0.412 and a 95% Confidence Interval (CI) ranging from 0.288 to 0.535 (p<0.001). Furthermore, the degree of PSA reduction post-treatment emerged as a critical prognostic factor. Patients achieving varying degrees of PSA reduction exhibited significantly different prognoses, with those in the PSA90 group, who achieved the most

Table 4. Multivariate Cox regression analysis results.

Indicator	Hazard Ratio	95% Confidence Interval	*p*-value
PSA progression			
ADT	1		
AAP+ADT	0.412	0.288-0.535	<0.001
Overall survival			
PSA50	1		
PSA50-90	0.434	0.173-0.625	<0.001
PSA90	0.183	0.103-0.363	<0.001

substantial PSA reductions, displaying the most favorable outcomes. Specifically, when using the PSA50 group as the reference, the PSA50-90 group showed an HR of 0.434 (95% CI: 0.173 to 0.625), while the PSA90 group had an even more pronounced reduction in risk, with an HR of 0.183 (95% CI: 0.103 to 0.363), both demonstrating statistical significance (p<0.001).

DISCUSSION

In this comprehensive study, we enrolled a total of 236 patients with mCSPC treated at our hospital, receiving either ADT combined with APP (AAP+ADT) or ADT alone. The baseline characteristics between the two patient groups were carefully matched to ensure comparability. Survival analysis revealed a significant extension in PSA progression-free survival among patients administered with the AAP+ADT regimen compared to those receiving ADT alone, highlighting the superior efficacy of the combination therapy in delaying disease progression.

Further, subgroup analysis within the AAP+ADT cohort underscored a pronounced correlation between the magnitude of PSA reduction and OS. Specifically, patients experiencing substantial PSA declines exhibited significantly longer OS, establishing PSA as an independent prognostic marker for patients undergoing AAP+ADT treatment. This observation aligns with the evolving understanding of PSA dynamics in the management of prostate cancer, particularly in the context of novel hormonal therapies that have shifted the therapeutic landscape.

The significance of ADT, as a foundational treatment modality for metastatic prostate cancer, has been undisputed since Huggins[21] first demonstrated its effectiveness in 1941. Modern approaches encompass both medical and surgical castration, with the former including treatments such as estrogens, antiandrogens, and gonadotropin-releasing hormone agonists or blockers[22], and the latter being an option for patients with limited resources or poor compliance[23]. Despite the initial effectiveness of ADT, the transition to mCRPC represents a pivotal challenge with a notably poorer prognosis[24].

The advent of abiraterone acetate, a potent androgen synthesis inhibitor, has markedly enhanced the therapeutic arsenal against mCSPC. Studies by Fizazi et al[25] and James et al[26] have substantiated the role of AAP+ADT in significantly prolonging median OS and reducing the risk of death and bone metastasis in patients with advanced metastatic prostate cancer, propelling AAP+ADT to the forefront as a first-line treatment recommendation in both international and domestic guidelines, based on the findings presented at the American Society of Clinical Oncology (ASCO) conference.

PSA, a glycoprotein synthesized by prostatic cells, serves as a critical biomarker for diagnosing and prognosticating PCa[27-29] and often used as an important evaluation indicator even in different types of studies[30]. The utility of PSA in predicting outcomes in prostate cancer has been well-documented across various treatment modalities[28]. The study by Hussain et al[29] highlighted the prognostic value of achieving a PSA level below 4 ng/mL post-ADT initiation, and Matsubara et al[30] further corroborated the significant association between PSA reduction and improved OS in patients treated with AAP+ADT, echoing the findings of our research. However, due to the genetic specificity of different races, we need to verify these conclusions in different populations[31], and our study provides important references for the predictive value of PSA in Chinese populations.

The present study boasts several advantages, including its robust prospective, RCT design, which significantly mitigates selection bias and enhances the reliability of the findings by providing a high level of evidence on the prognostic value of PSA in mCSPC treatment. The comprehensive inclusion of baseline demographic and clinical characteristics facilitates a thorough understanding of patient profiles and treatment outcomes. Moreover, the employment of both univariate and multivariate analyses allows for an in-depth exploration of independent prognostic factors, reinforcing the study's contribution to the existing literature on the efficacy of AAP+ADT.

LIMITATIONS

The sample size, while adequate, limits the generalizability of the findings to broader populations. The study's setting in a single institution in the Chinese population may introduce a degree of selection bias, potentially affecting the external validity of the results. Besides, many other factors, such as high dietary acid load, can also be used to influence the development of prostate cancer, but this study did not fully account for the impact of other variables on patient outcomes, which needs to be further verified. Furthermore, the follow-up duration may not capture long-term outcomes and late adverse

effects, which are critical for a comprehensive assessment of the treatment's efficacy and safety. At the same time, the study addresses the prognostic value of PSA levels, but it does not extensively explore other emerging biomarkers that could offer additional insights into treatment response and prognosis in mCSPC.

CONCLUSIONS

The present study provides compelling evidence that the combination of ADT with AAP (AAP+ADT) significantly enhances PSA progression-free survival and overall survival in patients with mCSPC compared to ADT alone. Furthermore, our findings affirm the prognostic value of PSA as an independent predictor of treatment outcomes, particularly highlighting the correlation between greater reductions in PSA levels and improved patient prognosis within the AAP+ADT treatment cohort. This study underscores the therapeutic benefit of incorporating AAP into the standard ADT regimen for mCSPC, offering a more effective strategy for managing this challenging condition. The study reinforces the importance of PSA as a reliable biomarker for monitoring treatment response and guiding clinical decisions in the management of mCSPC. However, this conclusion was drawn from a monocentric based on the Chinese population and it should be verified in the further studies with larger and more diverse populations.

Artificial intelligence-assisted technologies:

In the process of writing this academic paper, AI was employed as an auxiliary tool to enhance the clarity and coherence of the manuscript. Specifically, AI-assisted algorithms were used to organize the logical flow of arguments and refine the language for improved readability and precision. While the content and scientific insights remain the sole work of the authors, the use of AI allowed for a more efficient review of structure and style, ensuring that the paper meets high academic communication standards.

Authors Contributions:

Each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript, following the definition of an author as stated by the International Committee of Medical Journal Editors (ICMJE). We confirm that neither the manuscript nor any part of it has been published or is under consideration for publication elsewhere.

Availability of data and material:

Data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interests:

The authors have no conflict of interest to declare.

Consent for publication:

All the authors have provided the consent for publication.

Ethics Committee approval:

The study was approved by the Ethics Committee of Xuzhou Municipal Hospital Hospital (Approval ID: LI20180625) and followed the Declaration of Helsinki.

Financial support:

There is no financial support for this study.

Funding:

This study was supported by the Top Talent Project of the Affiliated Xuzhou Municipal Hospital of Xuzhou Medical University and the Natural Science Foundation of the Affiliated Hospital of Xuzhou Medical University (XYFM2020032).

Informed consent:

A written informed consent was obtained from the patients involved in the study.

REFERENCES

1. Kensler KH, Johnson R, Morley F, Albrair M, Dickerman BA, Gulati R, Holt SK, Iyer HS, Kibel AS, Lee JR, Preston MA, Vassy JL, Wolff EM, Nyame YA, Etzioni R, Rebbeck TR. Prostate cancer screening in African American men: a review of the evidence. J Natl Cancer Inst 2024; 116: 34-52.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics 2023. CA Cancer J Clin 2023; 73: 17-48.
3. Schaeffer EM, Srinivas S, Adra N, An Y, Barocas D, Bitting R, Bryce A, Chapin B, Cheng HH, D'Amico AV, Desai N, Dorff T, Eastham JA, Farrington TA, Gao X, Gupta S, Guzzo T, Ippolito JE, Kuettel MR, Lang JM, Lotan T, McKay RR, Morgan T, Netto G, Pow-Sang JM, Reiter R, Roach M, Robin T, Rosenfeld S, Shabsigh A, Spratt D, Teply BA, Tward J, Valicenti R, Wong JK, Shead DA, Snedeker J, Freedman-Cass DA. Prostate Cancer, Version 4.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2023; 21: 1067-1096.
4. Drazer MW, Huo D, Eggener SE. National prostate cancer screening rates after the 2012 US Preventive Services Task Force recommendation discouraging prostate-specific antigen-based screening. J Clin Oncol 2015; 33: 2416-2423.
5. Barocas DA, Mallin K, Graves AJ, Penson DF, Palis B, Winchester DP, Chang SS. Effect of the USPSTF grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the United States. J Urol 2015; 194: 1587-1593.
6. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012; 157: 120-34.
7. Etzioni R, Gulati R. Recent trends in PSA testing and prostate cancer incidence: a look at context. JAMA Oncol 2016; 2: 955-956.
8. Sammon JD, Abdollah F, Choueiri TK, Kantoff PW, Nguyen PL, Menon M, Trinh QD. Prostate-specific antigen screening after 2012 US Preventive Services Task Force recommendations. JAMA 2015; 314: 2077-2079.
9. Houston KA, King J, Li J, Jemal A. Trends in prostate cancer incidence rates and prevalence of prostate specific antigen screening by socioeconomic status and regions in the Unites States, 2004 to 2013. J Urol 2018; 199: 676-682.
10. Fedewa SA, Ward EM, Brawley O, Jemal A. Recent patterns of prostate specific antigen testing for prostate cancer screening in the United States. JAMA Intern Med 2017; 177: 1040-1042.
11. Jemal A, Fedewa SA, Ma J, Siegel R, Lin CC, Brawley O, Ward EM. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. JAMA 2015; 314: 2054-2061.
12. Kearns JT, Holt SK, Wright JL, Lin DW, Lange PH, Gore JL. PSA screening, prostate biopsy, and treatment of prostate cancer in the years surrounding the USPSTF recommendation against prostate cancer screening. Cancer 2018; 124: 2733-2739.
13. U.S. Preventative Services Task Force. Prostate cancer: screening. Accessed July 20, 2023. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening.
14. Leapman MS, Wang R, Park H, Yu JB, Sprenkle PC, Cooperberg MR, Gross CP, Ma X. Changes in prostate-specific antigen testing relative to the revised US Preventive Services Task Force recommendation on prostate cancer screening. JAMA Oncol 2022; 8: 41-47.
15. Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, Lane JA, Noble S, Oliver SE, Evans S, Sterne JAC, Holding P, Ben-Shlomo Y, Brindle P, Williams NJ, Hill EM, Ng SY, Toole J, Tazewell MK, Hughes LJ, Davies CF, Thorn JC, Down E, Davey Smith G, Neal DE, Hamdy FC; CAP Trial Group. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. JAMA 2018; 319: 883-895.
16. Desai K, McManus JM, Sharifi N. Hormonal Therapy for Prostate Cancer. Endocr Rev 2021; 42: 354-373.
17. Boevé LMS, Hulshof MCCM, Vis AN, Zwinderman AH, Twisk JWR, Witjes WPJ, Delaere KPJ, Moorselaar RJAV, Verhagen PCMS, van Andel G. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol 2019; 75: 410-418.
18. Barata PC, Sartor AO. Metastatic castration-sensitive prostate cancer: Abiraterone, docetaxel, or…. Cancer 2019;125: 1777-1788.
19. Conteduca V, Mosca A, Brighi N, de Giorgi U, Rescigno P. New Prognostic Biomarkers in Metastatic Castration-Resistant Prostate Cancer. Cells 2021; 10: 193.
20. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Deprince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S; TITAN Investigators. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2019; 381: 13-24.
21. Huggins C. Endocrine control of prostatic cancer. Science 1943; 97: 541-544.
22. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, Sulur G, Luna Y, Li S, Mundle S, Chi KN. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019; 20: 686-700.
23. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, Chi KN, Sartor O, Agarwal N, Olmos D, Thiery-Vuillemin A, Twardowski P, Mehra N, Goessl C, Kang J, Burgents J, Wu W, Kohlmann A, Adelman CA, Hussain M. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2020; 382: 2091-2102.
24. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, Kramer G, Eymard JC, Bamias A, Carles J, Iacovelli R, Melichar B, Sverrisdóttir Á, Theodore C, Feyerabend S, Helissey C, Ozatilgan A, Geffriaud-Ricouard C, Castellano D; CARD Investigators. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med 2019; 381: 2506-2518.
25. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, De Porre P, Kheoh T, Park YC, Todd MB, Chi KN; LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; 377: 352-360.
26. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, Ritchie AWS, Amos CL, Gilson C, Jones RJ, Matheson D, Millman R, Attard G, Chowdhury S, Cross WR, Gillessen S, Parker CC, Russell JM, Berthold DR, Brawley C, Adab F, Aung S, Birtle AJ, Bowen J, Brock S, Chakraborti P, Ferguson C, Gale J, Gray E, Hingorani M, Hoskin PJ, Lester JF, Malik ZI, McKinna F, McPhail N, Money-Kyrle J, O'Sullivan J, Parikh O, Protheroe A, Robinson A, Srihari NN, Thomas C, Wagstaff J, Wylie J, Zarkar A, Parmar MKB, Sydes MR; STAMPEDE Investigators. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 2017; 377: 338-351.

27. Kohaar I, Petrovics G, Srivastava S. A Rich Array of Prostate Cancer Molecular Biomarkers: Opportunities and Challenges. Int J Mol Sci 2019; 20: 1813.
28. Facchini G, Perri F, Misso G, D'Aniello C, Scarpati GDV, Rossetti S, Pepa CD, Pisconti S, Unteregger G, Cossu A, Caraglia M, Berretta M, Cavaliere C. Optimal Management of Prostate Cancer Based on its Natural Clinical History. Curr Cancer Drug Targets 2018; 18: 457-467.
29. Facchini G, Caffo O, Ortega C, D'Aniello C, Di Napoli M, Cecere SC, Della Pepa C, Crispo A, Maines F, Ruatta F, Iovane G, Pisconti S, Montella M, Berretta M, Pignata S, Cavaliere C. Very Early PSA Response to Abiraterone in mCRPC Patients: A Novel Prognostic Factor Predicting Overall Survival. Front Pharmacol 2016; 7: 123.
30. Meng XB, Li Y, Gao ZH, Wang CJ, Gu YM. Comparison of urinary incontinence following three different prostate apex disconnection techniques in transurethral thulium laser prostatectomy. Eur Rev Med Pharmacol Sci 2024; 28: 2396-2402.
31. Caffo O, Pappagallo G, Brugnara S, Caldara A, di Pasquale MC, Ferro A, Frisinghelli M, Murgia V, Russo LM, Soini B, Valduga F, Veccia A, Galligioni E. Multiple rechallenges for castration-resistant prostate cancer patients responding to first-line docetaxel: assessment of clinical outcomes and predictive factors. Urology 2012; 79: 644-649.
32. Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, Wilding G, Akdas A, Small EJ, Donnelly B, MacVicar G, Raghavan D; Southwest Oncology Group Trial 9346 (INT-0162). Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006; 24: 3984-3990.
33. Matsubara N, Chi KN, Özgüroğlu M, Rodriguez-Antolin A, Feyerabend S, Fein L, Alekseev BY, Sulur G, Protheroe A, Li S, Mundle S, De Porre P, Tran N, Fizazi K. Correlation of Prostate-specific Antigen Kinetics with Overall Survival and Radiological Progression-free Survival in Metastatic Castration-sensitive Prostate Cancer Treated with Abiraterone Acetate plus Prednisone or Placebos Added to Androgen Deprivation Therapy: Post Hoc Analysis of Phase 3 LATITUDE Study. Eur Urol 2020; 77: 494-500.
34. Tan JS, Yan XX, Wu Y, Gao X, Xu XQ, Jiang X, Jia L, Hu S, Hua L, Wang XJ. Rare variants in MTHFR predispose to occurrence and recurrence of pulmonary embolism. Int J Cardiol 2021; 331: 236-242.