The presence of lymph node metastases and time to castration resistance predict the therapeutic effect of enzalutamide for castration-resistant prostate cancer

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Abstract

Background: Enzalutamide is effective against castration-resistant prostate cancer (CRPC). However, it is unclear which patients would benefit more from enzalutamide treatment. Here, we analyzed patients who received enzalutamide as first-line therapy for CRPC and evaluated the factors that predict treatment response and prognosis.

Methods: We retrospectively analyzed 101 patients treated with enzalutamide for CRPC at our institution. As primary endpoints we regarded the prostate-specific antigen (PSA) response rate and PSA progression-free survival (PSA-PFS) from the start of enzalutamide treatment. Laboratory and imaging data were analyzed to predict treatment efficacy.

Results: PSA reductions of ≥50% and ≥90% were observed in 78 (77%) and 47 (47%) patients, respectively, compared with the baseline. During the follow-up period, 67 (66%) patients showed PSA progression, with a median PSA-PFS of 11 months. Moreover, 31 patients (31%) died, with a median OS of 64 months. On multivariate analysis, lymph node metastases at the start of enzalutamide treatment [odds ratio (OR) 0.0575, 95% confidence interval (CI) 0.0105–0.316, p=0.0010] and time to CRPC (OR 0.177, 95% CI 0.0428–0.731, p=0.0167] were associated with ≥90% PSA response. Lymph node metastases (hazard ratio [HR] 3.00, 95% CI 1.48–6.09, p=0.0023) and time to CRPC (HR 1.84, 95% CI 1.02–3.30, p=0.0419) were also predictors of PSA-PFS on a multivariate model.

Conclusion: Time to CRPC and lymph node metastasis were predictors of the PSA response rate and PSA-PFS.

Key words: androgen receptor antagonist, castration-resistant prostate cancer, enzalutamide, lymph node metastasis, progression-free survival, prostate specific antigen

Introduction

Prostate cancer has been the most frequently diagnosed cancer in the United States in 2022 and the second deadliest cancer among men [1]. Of the newly diagnosed prostate cancers, 80% are localized, while the remaining 20% are advanced or metastatic [2]. Metastatic prostate cancers are treated with hormonal therapy, but almost all patients eventually progress to castration-resistant prostate cancer (CRPC) with a poor prognosis after a median of 18–24 months of hormonal therapy [3, 4]. Therefore, the 5-year overall survival rate for advanced and metastatic prostate cancer is very low at 26–30% [5]. The COU-AA-302 and PREVAIL studies demonstrated the usefulness of the androgen receptor-axis-target (ARAT) for chemo-naïve metastatic CRPC [6, 7].

In the COU-AA-302 study cohort, the presence of lymph node metastases and the number of bone metastases at the start of abiraterone acetate treatment were reported to significantly reduce radiographic progression-free survival (rPFS) in patients with metastatic CRPC [8]. Chikamatsu et al. reported that the risk classification by the CHAARTED criteria [9] at the time of CRPC diagnosis could predict prognosis after the start of its treatment [10]. However, Hatakeyama et al. reported that the CHAARTED classification at the initial diagnosis of hormone-sensitive prostate cancer (HSPC) was not associated with prognosis after the progression of CRPC [11]. Thus, there are reports predicting prognosis based on metastatic status after progression to CRPC, rather than at diagnosis. However, there are few reports predicting prognosis or treatment efficacy after the initiation of enzalutamide administration. In this study, using real-world data from Japan, we analyzed the factors influencing the outcome of enzalutamide as a first-line therapy for CRPC, focusing on imaging findings at the time of initial diagnosis and at the start of enzalutamide treatment.

Materials and methods

Study cohort

Docetaxel- and ARAT-naïve patients who received enzalutamide for CRPC at the Osaka University Hospital between 2014 and 2022 were included in the study. Patients were also included if they received docetaxel for HSPC or treated with vintage hormone therapy, steroids, or tegafur/uracil. Patients for whom sufficient clinical data could not be obtained were excluded. Ultimately, 101 patients met the study eligibility criteria (Figure 1).

Endpoints

Since the post-hoc analysis of the PREVAIL trial reported that the prostate-specific antigen (PSA) response rate correlated with OS, rPFS, and quality of life [12], we defined the PSA response rate and PSA progression-free survival (PSA-PFS) from the start of enzalutamide treatment as the co-primary endpoints of the study. The

secondary endpoint was overall survival (OS).

Clinical variables

Patients' age, Gleason score, PSA nadir during the initial treatment for HSPC, time to CRPC, imaging results at the initial diagnosis and at the start of enzalutamide treatment, PSA levels, hemoglobin (Hb), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and testosterone at the start of enzalutamide administration were obtained from their charts. CRPC was defined as PSA progression despite androgen deprivation therapy (ADT) and serum testosterone level of <50 ng/dL. The imaging evaluation method followed the recommendations of the prostate cancer working group 3 (PCWG3) [13]. The evaluation method for lymph node metastasis was also in accordance with the recommendations of PCWG3, with lymph nodes larger than 15 mm in the short diameter being considered positive, and lymph nodes 10–15 mm in the short diameter being judged clinically. Patients who were positive for lymph node metastasis at the time of diagnosis but whose lymph nodes had shrunk to 5 mm or less at the start of enzalutamide treatment were defined as "no lymph node metastasis at the start of enzalutamide treatment." High-volume tumors were defined as having four or more bone metastases (at least one of which was vertebral or extrapelvic) or one or more visceral metastases, according to the criteria of the CHAATED trial [9]. Other cases were defined as low-volume tumors. PSA-PFS was defined as PSA progression (≥25% and ≥2 ng/mL increase from the nadir point) or time to last follow-up according to PCWG3 recommendations. The PSA response was defined as ≥90% PSA reduction from the baseline according to previous reports [7, 14].

Ethical Considerations

This study was conducted with the approval of the Institutional Review Board of the Osaka University Hospital (ethical review number: 13397-20). All patients provided informed consent for their data to be used for the analysis and included in the publication.

Statistical Analysis

Survival curves were generated using the Kaplan–Meier method and the log-rank test. The association between clinical variables and PSA-PFS and OS was evaluated using the Cox proportional hazards model. The relationship between clinical variables and PSA response was assessed using logistic regression analysis. All of the statistically significant variables in the univariate analysis were included in the multivariate analysis. Statistical significance was set at $p<0.05$. All data were analyzed using JMP Pro version (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

The clinical characteristics of the 101 patients included in the study are shown in Table 1. The median patients' age was 74 years [interquartile range（IQR) 69–81] and the median time to CRPC was 17.5 (IQR 9.0–35.5) months. The median PSA nadir during the initial treatment for HSPC was 0.29 ng/mL (IQR 0.035-1.21). Overall, 42 (42%) patients achieved PSA nadir <0.2ng/mL during the initial treatment for HSPC. The median observation period was 19 (IQR 12–41) months, and the median duration of enzalutamide treatment was 11 (IQR 5–22) months. Just before the introduction of enzalutamide treatment, 21 (21%) patients had metastases in the lymph nodes, 65 (64%) in the bones, 11 (11%) in the internal organs, and 48 (48%) bore high-volume tumors. Overall, 77 (76%) patients had distant metastases at the start of enzalutamide treatment. Of the 21 patients who had lymph node metastases at the start of enzalutamide, 11 cases developed new lymph node metastases. Median Hb, LDH, ALP, PSA, and testosterone at the start of enzalutamide administration were 12.6 (IQR 11.4–13.5), 203 (IQR 175–239), 270 (IQR 209–419), 18.9 (IQR 7.9–61.6), and 0.14 (IQR 0.07–0.22), respectively.

Univariate and multivariate analysis of PSA response rate

A waterfall plot of the maximum PSA response rate is shown in Figure 2A. PSA reductions of ≥50% and ≥90% were observed in 78 (77%) and 47 (47%) patients, respectively, compared to the baseline. The associations between clinical variables and PSA response rates of ≥90% are shown in Table 2. In univariate analysis, PSA nadir ≥0.2 ng/ml during the initial treatment for HSPC [odds ratio (OR) 0.337, 95% confidence interval (CI) 0.143–0.797, p=0.013], shorter time to CRPC (OR 0.197, 95%CI 0.0819–0.475, p=0.0003) and the presence of lymph node metastases at the start of enzalutamide (OR 0.0783, 95% CI 0.017–0.361, p=0.0011) were significantly associated with PSA response. In multivariate analysis, a shorter time to CRPC (OR 0.177, 95% CI; 0.0428–0.731, p=0.0167) and the presence of lymph node metastases at the start of enzalutamide treatment (OR=0.0575, 95%CI; 0.0105-0.316, p=0.0010) were independently and significantly associated with PSA response. In 77 patients with metastatic CRPC (mCRPC), shorter time to CRPC (OR 0.228, 95%CI 0.084–0.617, p=0.0036) and the presence of lymph node metastases at the start of enzalutamide (OR 0.103, 95% CI 0.021–0.501, p=0.0049) were significantly associated with PSA response in univariate analysis.

Univariate and Multivariate Analysis of PSA-PFS

The Kaplan–Meier curve for PSA-PFS is shown in Figure 2B. Sixty-seven (66%) patients had PSA progression during the observation period, with a median PSA-PFS of 11 (IQR 8–13) months. The results of the univariate

analysis of the association between clinical variables and PSA-PFS are shown in Table 3. The presence of lymph node metastases at the start of enzalutamide treatment (HR 3.20, 95% CI 1.74–5.86, p=0.0002), shorter time to CRPC (HR 2.05, 95% CI 1.23–3.43, p=0.0058), high-volume tumor at the start of enzalutamide treatment (HR 2.06, 95% CI 1.21–3.49, p=0.0075), lower age (HR 1.65, 95% CI 1.01–2.69, p=0.0439), higher ALP level (HR 1.87, 95% CI 1.06–3.32, p=0.0315), and higher PSA levels (HR 2.68, 95% CI 1.62–4.45, p=0.0001) were significantly associated with shorter PSA-PFS. However, none of the clinical variables at initial diagnosis correlated with a shorter PSA-PFS. In multivariate analysis, the presence of lymph node metastases at the start of enzalutamide treatment (HR 3.00, 95% CI 1.48–6.09, p=0.0023) and time to CRPC (HR 1.84, 95% CI 1.02–3.30, p=0.0419) were significant predictors (Table 3). The presence of lymph node metastases (HR 3.46, 95% CI 1.70–7.07, p=0.0006) and time to CRPC (HR 2.17, 95% CI 1.21–3.91, p=0.0096) were also significant predictors of PSA-PFS in the 77 patients with mCRPC in univariate analysis.

Univariate and Multivariate Analysis of OS

During the observation period, 30 patients continued to receive enzalutamide, and 71 ended enzalutamide treatment. Posterior sequential treatments after the end of enzalutamide treatment are shown in Supplementary Table 1. Among 71 patients who ended enzalutamide treatment, 35 (49%) patients were treated with docetaxel and 14 (20%) with abiraterone acetate. The Kaplan–Meier curve for OS is shown in Figure 2C. Thirty-one (31%) patients died during the observation period, with a median OS of 64 months (IQR 38–84) months. The associations between the clinical variables and OS are shown in Table 4. In univariate analysis, shorter time to CRPC (HR 2.75, 95% CI 1.27–5.93, p=0.0101), the presence of high-volume tumors at the start of enzalutamide treatment (HR 2.89, 95% CI 1.31–6.39, p=0.0087), higher ALP levels (HR 3.08, 95%CI 1.32–7.20, p=0.0095), and higher PSA levels (HR 2.51, 95% CI; 1.18–5.30, p=0.0162) were significantly associated with shorter OS. In multivariate analysis, no factors significantly shortened OS, but a shorter time to CRPC (HR 2.18, 95% CI 0.945–5.04, p=0.0677) tended to lead to a shorter OS. Clinical parameters at diagnosis did not correlate with any of the endpoints.

Discussion

The results of this study showed that the presence of lymph node metastases at the start of enzalutamide treatment and a shorter time to CRPC were significant factors that decreased the PSA response rate and shortened PSA-PFS. There were no significant factors that shortened OS, but a shorter time to CRPC tended to shorten OS.

In particular, lymph node metastases at the start of enzalutamide treatment had the highest HR for PSA-PFS. The presence of lymph node metastases at the start of abiraterone acetate treatment has been reported to significantly reduce rPFS in patients with metastatic CRPC [8], and when combined with the results of this study, the presence of lymph node metastases at the start of ARAT may predict resistance to therapy. In contrast, in a meta-analysis evaluating OS in patients treated with docetaxel for CRPC, classified by metastatic sites, lymph node metastasis did not affect the prognosis [15]. The presence of lymph node metastases may have different implications for docetaxel and ARAT.

In patients with metastatic HSPC (mHSPC) treated with ADT, it has been reported that patients with only lymph node metastases had significantly longer OS and time to CRPC compared to patients with bone plus/minus lymph node metastases [16]. On the other hand, several recent reports have shown that the presence of lymph node metastases shortens the time to CRPC and OS in mHSPC patients [17-19]. The impact of the presence of lymph node metastases on the efficacy and prognosis of ADT is controversial. To date, it also remains unclear whether the presence of lymph node metastases is associated with the efficacy of ARAT in patients with mHSPC.

Chikamatsu et al. reported that a high-volume tumor at diagnosis of CRPC is a prognostic factor predicting PFS and OS after the initiation of treatment with ARAT or docetaxel [10], while Hatakeyama et al. reported that risk classification by the CHAARTED criteria at the initial presentation of HSPC was not associated with OS after progression to CRPC [11]. In our study, the presence of high-volume tumors at the start of enzalutamide treatment was also a significant factor for the shortened PSA-PFS in univariate analysis. In contrast, the presence of lymph node metastases or high-volume tumors at diagnosis did not correlate with PSA response, PSA-PFS, or OS. Thus, imaging findings after progression to CRPC are more accurate predictors of response to ARAT than the findings at initial diagnosis.

A shorter time to CRPC was associated with a significantly shorter PSA-PFS and lower PSA response. A shorter time to CRPC also tended to shorten OS, although not significantly, and was associated with all endpoints. Time to CRPC has long been described as an important prognostic factor for OS in patients with CRPC [20, 21]. Loriot et al. also reported that a time to CRPC of less than 12 months correlated with PFS and PSA response rates for ARAT [22]. A polymorphism in the androgen metabolism pathway, which has been reported to correlate significantly with the time to CRPC [23, 24], may confer resistance to ARAT. Time to CRPC did not correlate with prognosis in patients who received docetaxel in a subgroup analysis of the TAX327 trial [25], although some reports indicated that it was correlated with OS and PFS [26, 27]. Recently, Shigeta et al. reported

that in patients with less than 16 months to CRPC, the longer time to docetaxel initiation was significantly associated with shorter cancer-specific survival and recommended earlier docetaxel administration for patients with shorter ADT efficacy [27].

Five laboratory parameters were analyzed in this study: Hb, LDH, ALP, PSA, and testosterone levels. Higher LDH and ALP levels were reported to be poor prognostic factors in patients with CRPC receiving abiraterone acetate in the COU-AA-301 cohort [28], and lower Hb levels were reported to shorten OS and PFS in CRPC patients receiving enzalutamide [29]. Hb and ALP levels were also reported to be poor prognostic factors for CRPC patients who received docetaxel in the TAX327 trial [30]. Templeton et al. also reported Hb, LDH, and ALP levels as poor prognostic factors for CRPC patients who received docetaxel [31]. Thus, Hb, LDH, and ALP are accepted as poor prognostic factors for CRPC. Although a high testosterone level was reported as a prognostic factor for patients with CRPC who received ARAT [32, 33], it was not a prognostic factor in the present study.

The limitations of this study are that it was a retrospective study and was conducted at a single institution with a small number of patients. Lymph node metastases at the start of enzalutamide treatment correlated with PSA response and PSA-PFS, but not with OS. This suggests that patients with lymph node metastases may not respond to enzalutamide treatment but may respond to subsequent therapies such as docetaxel.

This study demonstrated that the time to CRPC and the presence of lymph node metastases at the start of enzalutamide treatment correlated with the enzalutamide treatment response. Therefore, it will be of great help in determining treatment strategies for patients with chemo- and ARAT-naïve CRPC.

Conclusion

A shorter time to CRPC and the presence of lymph node metastases at the start of enzalutamide were predictors of response to enzalutamide treatment in terms of both ≥90% PSA reduction and PSA-PFS.

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Conflict of interest

KH and NN have the following potential conflict of interest to report: Receipt of grants/research supports: Astellas Global

Author contributions

TO and KH contributed to the study conception and design. Material preparation and data collection and analysis were performed by TO, KH, YO, AY, TU, GY, ET, YI, YY, TK, AK, KF, and NN. Data analysis was performed by TO. The first draft of the manuscript was written by TO, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Table 1. Patients' characteristics

Variable	**Total (n=101)**
Median age, years (IQR)	74 (69–81)
Median serum PSA level at diagnosis, ng/mL (IQR)	47.4 (12.6–162.6)
Clinical T stage at diagnosis, n (%)	
<T3a	33(33%)
≥T3a	58 (57%)
Not available	10 (10%)
Lymph node metastasis at diagnosis, n (%)	
Presence	26 (26%)
Absence	71 (70%)
Not available	4 (4%)
Bone metastasis at diagnosis, n (%)	
Presence	39 (39%)
Absence	58 (57%)
Not available	4 (4%)
Visceral metastasis at diagnosis, n (%)	
Presence	7 (7%)
Absence	90 (89%)
Not available	4 (4%)
Tumor volume at diagnosis, n (%)	
High volume	28 (28%)
Low volume	68 (67%)
Not available	5 (5%)
Gleason sum at diagnosis, n (%)	
<8	21 (21%)
≥8	71 (70%)
Not available	9 (9%)
Treatment for HSPC, n (%)	

CAB	68 (67%)
ADT	27 (27%)
ADT + docetaxel*	5 (5%)
CAB + docetaxel*	1 (1%)
PSA nadir during the initial treatment for HSPC, ng/mL (IQR)	0.29 (0.035-1.21)
Median time to CRPC, months (IQR)	17.5 (9–35.5)
Median time since the start of enzalutamide administration, months (IQR)	19 (12–41)
Median duration of enzalutamide administration, months (IQR)	11 (5–22)
Lymph node metastasis at the start of enzalutamide administration, n (%)	
Presence	21 (21%)
Absence	75 (74%)
Not available	5 (5%)
Bone metastasis at the start of enzalutamide administration, n (%)	
Presence	65 (64%)
Absence	31 (31%)
Not available	5 (5%)
Visceral metastasis at the start of enzalutamide administration, n (%)	
Presence	11 (11%)
Absence	85 (84%)
Not available	5 (5%)
Distant metastasis at the start of enzalutamide administration, n (%)	
Presence	77 (76%)
Absence	18 (18%)
Not available	6 (6%)
Tumor volume at diagnosis at the start of enzalutamide administration, n (%)	
High volume	48 (48%)
Low volume	48 (48%)
Not available	5 (5%)
Laboratory parameters at the start of enzalutamide administration, median (IQR)	

Hb (g/dl)	12.6 (11.4–13.5)
LDH (U/I)	203 (175–239)
ALP (U/I)	270 (209–419)
PSA (ng/ml)	18.9 (7.9–61.6)
testosterone (ng/ml)	0.14 (0.07–0.22)

* Treatment with docetaxel for HSPC was 6 or fewer cycles.

IQR, interquartile range; PSA, prostate-specific antigen; HSPC, hormone-sensitive prostate cancer; CAB, combined androgen blockade; ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase

Table 2. Univariable and multivariable analyses on the PSA response rate (90%)

		Univariable		Multivariable	
Variable	vs. Referent	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	<75 vs. ≥75 years	0.826 (0.378–1.81)	0.633		
Gleason sum	≥8 vs. <8	0.746 (0.281–1.98)	0.556		
Lymph node metastasis at diagnosis	Present vs. absent	0.844 (0.341–2.09)	0.715		
Bone metastasis at diagnosis	Present vs. absent	0.625 (0.273-1.43)	0.264		
High-volume tumor at diagnosis	Present vs. absent	0.556 (0.224–1.38)	0.204		
PSA at diagnosis	>50 vs. ≤50 ng/mL	0.619 (0.278–1.38)	0.24		
PSA nadir for the initial treatment for HSPC	≥0.2 vs.<0.2 ng/mL	0.337 (0.143–0.797)	0.013	0.809 (0.200-3.27)	0.766
Time to CRPC	<18 vs. ≥18 months	0.197 (0.0819–0.475)	0.0003	0.177 (0.0428–0.731)	0.0167
Lymph node metastasis at start of enzalutamide treatment	Present vs. absent	0.0783 (0.017–0.361)	0.0011	0.0575 (0.0105–0.316)	0.0010
Bone metastasis at start of enzalutamide treatment	Present vs. absent	0.914 (0.388–2.15)	0.838		
High-volume tumor at start of enzalutamide treatment	Present vs. absent	0.657 (0.293–1.47)	0.307		
Hb at start of enzalutamide treatment	<12 vs. ≥12 g/dL	0.460 (0.196–1.08)	0.0748		

LDH at start of enzalutamide treatment	>ULN vs. ≤ULN	0.430 (0.162–1.14)	0.0888
ALP at start of enzalutamide treatment	>ULN vs. ≤ULN	0.606 (0.240–1.53)	0.29
PSA at start of enzalutamide treatment	>20 vs. ≤20 ng/mL	0.679 (0.308–1.50)	0.336
Testosterone at start of enzalutamide treatment	<0.15 vs. ≥0.15 ng/mL	0.675 (0.279–1.63)	0.383

PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval; HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal; ALP, alkaline phosphatase

Table 3. Univariable and multivariate analyses for PSA-PFS

		Univariable		Multivariable	
Variable	vs. Referent	HR (95% CI)	p-value	OR (95% CI)	p-value
Age	<75 vs. ≥75 Years	1.65 (1.01–2.69)	0.0439	1.33 (0.766–2.32)	0.309
Gleason sum	≥8 vs. <8	1.31 (0.675–2.53)	0.426		
Lymph node metastasis at diagnosis	Present vs. absent	1.27 (0.742–2.18)	0.381		
Bone metastasis at diagnosis	Present vs. absent	1.45 (0.872–2.40)	0.153		
High-volume tumor at diagnosis	Present vs. absent	1.64 (0.954–2.81)	0.0735		
PSA at diagnosis	>50 vs. ≤50 ng/ml	0.95 (0.584–1.54)	0.835		
PSA nadir for the initial treatment for HSPC	≥0.2 vs.<0.2 ng/mL	1.36 (0.754-2.44)	0.310		
Time to CRPC	<18 vs. ≥18 months	2.05 (1.23–3.43)	0.0058	1.84 (1.02–3.30)	0.0419
Lymph node metastasis at start of enzalutamide treatment	Present vs. absent	3.20 (1.74–5.86)	0.0002	3.00 (1.48–6.09)	0.0023
Bone metastasis at start of enzalutamide treatment	Present vs. absent	1.36 (0.789–2.34)	0.269		
High-volume tumor at start of enzalutamide treatment	Present vs. absent	2.06 (1.21–3.49)	0.0075	1.54 (0.798–2.99)	0.197
Hb at start of enzalutamide treatment	<12 vs. ≥12 g/dl	1.44 (0.858–2.43)	0.167		
LDH at start of enzalutamide treatment	>ULN vs. ≤ULN	1.42 (0.819–2.46)	0.213		

ALP at start of enzalutamide treatment	>ULN vs. ≤ULN	1.87 (1.06–3.32)	0.0315	1.30 (0.646–2.63)	0.459
PSA at start of enzalutamide treatment	>20 vs. ≤20 ng/ml	2.68 (1.62–4.45)	0.0001	1.54 (0.747–3.19)	0.241
Testosterone at start of enzalutamide treatment	<0.15 vs. ≥0.15 ng/ml	0.910 (0.532–1.56)	0.733		

PSA, prostate-specific antigen; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal

Table 4. Univariable and multivariable analyses for OS

Variable	vs. Referent	Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	<75 vs. ≥75 years	1.02 (0.502–2.06)	0.961		
Gleason sum	≥8 vs. <8	0.731 (0.309–1.73)	0.477		
Lymph node metastasis at diagnosis	Present vs. absent	0.699 (0.300–1.63)	0.406		
Bone metastasis at diagnosis	Present vs. absent	1.71 (0.837–3.47)	0.141		
High-volume tumor at diagnosis	Present vs. absent	2.11 (0.953–4.66)	0.0656		
PSA at diagnosis	>50 vs. ≤50 ng/mL	0.726 (0.345–1.53)	0.398		
PSA nadir for the initial treatment for HSPC	≥0.2 vs.<0.2 ng/mL	1.71 (0.827-3.55)	0.147		
Time to CRPC	<18 vs. ≥18 months	2.75 (1.27–5.93)	0.0101	2.18 (0.945–5.04)	0.0677
Lymph node metastasis at start of enzalutamide	Present vs. absent	1.70 (0.728–3.99)	0.220		
Bone metastasis at start of enzalutamide	Present vs. absent	1.09 (0.508–2.34)	0.824		
High-volume tumor at start of enzalutamide	Present vs. absent	2.89 (1.31–6.39)	0.0087	1.04 (0.389–2.77)	0.941
Hb at start of enzalutamide	<12 vs. ≥12 g/dL	1.39 (0.632–3.06)	0.413		

LDH at start of enzalutamide	>ULN vs. ≤ULN	2.00 (0.920–4.34)	0.0801		
ALP at start of enzalutamide	>ULN vs. ≤ULN	3.08 (1.32–7.20)	0.0095	2.21 (0.852-5.71)	0.103
PSA at start of enzalutamide	>20 vs. ≤20 ng/mL	2.51 (1.18–5.30)	0.0162	2.09 (0.806-5.40)	0.13
Testosterone at start of enzalutamide	<0.15 vs. ≥0.15 ng/mL	1.22 (0.546–2.74)	0.623		

OS, overall survival; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal

Figure Legends

Figure 1. Study schematic. HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer.

Figure 2A. Waterfall pot showing maximal PSA reduction. PSA, prostate-specific antigen.

Figure 2B. Kaplan–Meier plot showing PSA-PFS. PSA-PFS, prostate-specific antigen-progression-free survival.

Figure 2C. Kaplan–Meier plot showing OS. OS, overall survival.

Figure 1

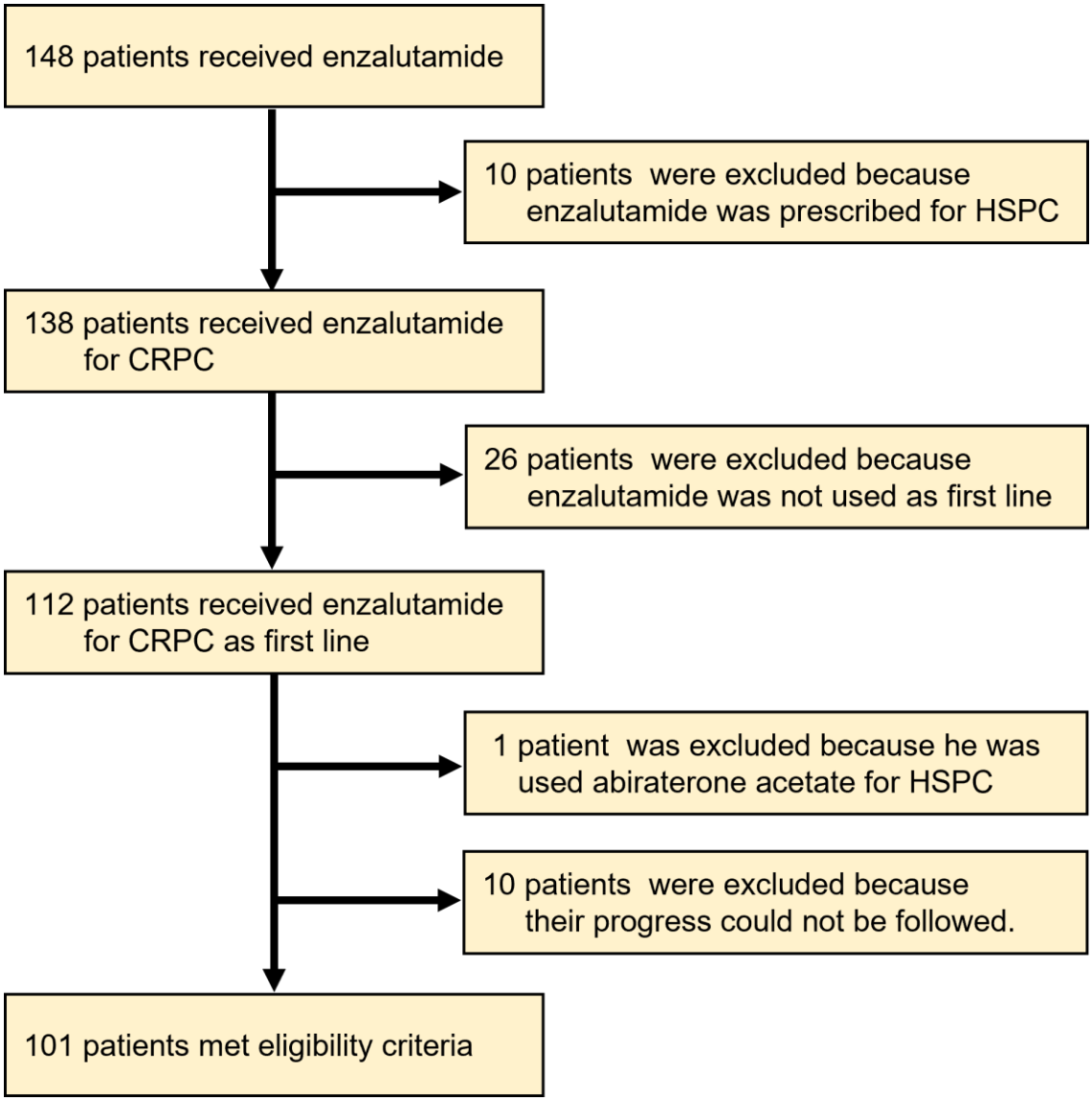
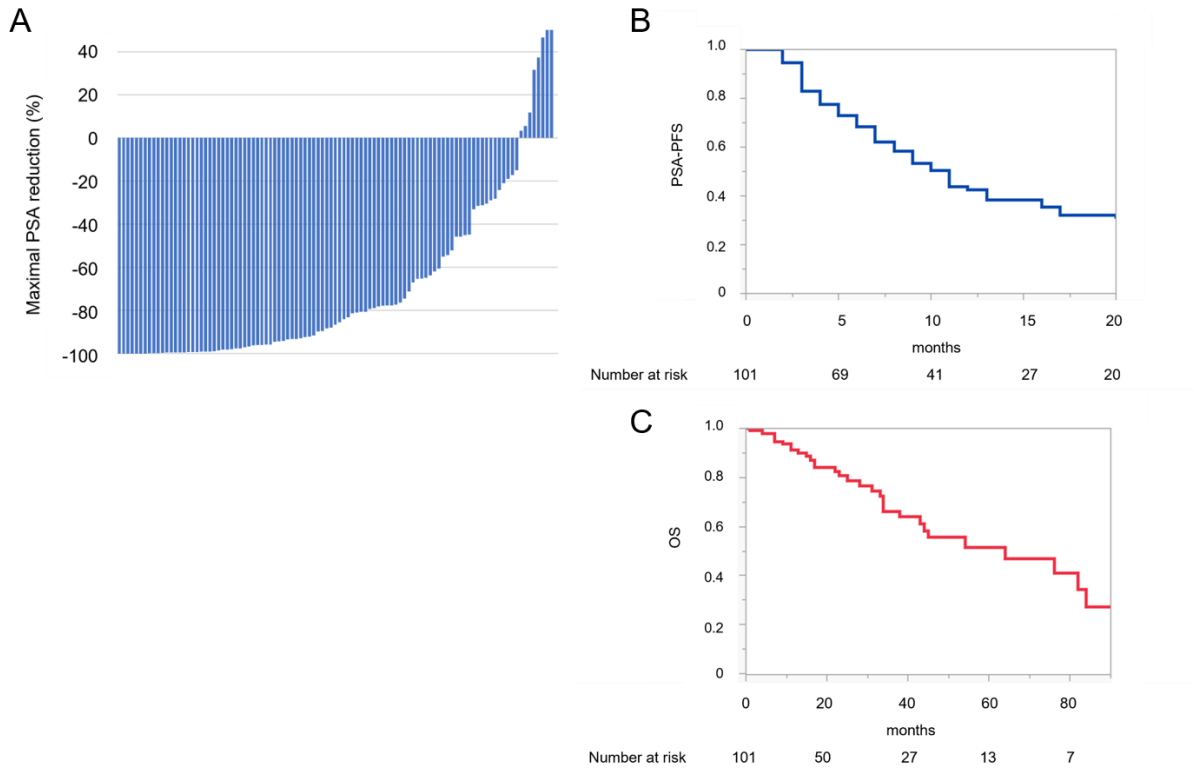

148 patients received enzalutamide
10 patients were excluded because enzalutamide was prescribed for HSPC
138 patients received enzalutamide for CRPC
26 patients were excluded because enzalutamide was not used as first line
112 patients received enzalutamide for CRPC as first line
1 patient was excluded because he was used abiraterone acetate for HSPC
10 patients were excluded because their progress could not be followed.
101 patients met eligibility criteria

Figure 2


A
Maximal PSA reduction (%)
40
20
0
-20
-40
-60
-80
-100
B
PSA-PFS
1.0
0.8
0.6
0.4
0.2
0
0
5
10
15
20
months
Number at risk
101
69
41
27
20
C
OS
1.0
0.8
0.6
0.4
0.2
0
0
20
40
60
80
months
Number at risk
101
50
27
13
7