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ORIGINAL ARTICLE

Clinical outcomes and prognostic factors in patients with newly diagnosed metastatic prostate cancer initially treated with androgen deprivation therapy: a retrospective multicenter study in Japan

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Abstract

Purpose Clinical outcomes of patients with newly diagnosed metastatic hormone-naïve prostate cancer (mHNPC) and initially treated with androgen deprivation therapy (ADT) were evaluated.

Methods The medical records of 605 consecutive mHNPC patients with initial ADT or combined androgen blockade (CAB) at nine study centers between 2008 and 2016 were retrospectively reviewed. Castration-resistant prostate cancer (CRPC)-free and overall survival (OS) were estimated by the Kaplan–Meier method. The association of pretreatment risk factors with CRPC-free survival and OS was evaluated by Cox proportional hazard models and differences in survival were classified by the number of risk factors.

Results Median follow-up was 2.95 years, median CRPC-free survival was 21.9 months and median OS was 5.37 years. Multivariable analysis found that four risk factors, a Gleason score ≥ 9, lymph node metastasis, an extent of disease score ≥ 2, and serum LDH of > 220 IU were independently associated with both CRPC-free survival and OS. Median CRPC-free survival of low-risk patients with no or one factor was 86.5 months, 17.9 months in intermediate-risk patients with two or three factors, and 11.0 months in high-risk patients with four factors. Median OS was 4.72 years in intermediate- and 2.44 years in high-risk patients. It was not reached in low-risk patients.

Conclusion In this series, CRPC-free and OS of a subset of mHNPC patients in Japan who were treated with ADT or CAB had better CRPC-free and overall survivals in Japan. Risk-adapted treatment based on the presence of novel prognostic factors may be beneficial for selected mHNPC patients.

Keywords Androgen deprivation therapy · Castration-resistant prostate cancer-free survival · Hormone-naïve · Hormone-sensitive · Metastatic · Overall survival · Prostate caner

Introduction

Prostate cancer is the second most frequent tumor and the fifth leading cause of cancer mortality in men [1]. Localized prostate cancer is successfully treated by surgery and radiotherapy, but most patients with metastatic disease die of cancer progression [2]. Androgen deprivation therapy (ADT) is a standard treatment of metastatic disease because androgens promote the development and progression of prostate cancer. Newly diagnosed metastatic prostate cancer initially responds to ADT, but becomes resistant and progresses to castration-resistant prostate cancer (CRPC) that ultimately eventually becomes lethal. Recent randomized trials found that combining agents such as docetaxel, abiraterone acetate or local radiation to the prostate improved the outcomes in patients with metastatic hormone-naïve prostate cancer (mHNPC) compared with ADT monotherapy [3–6]. Consequently, the treatment options for newly diagnosed

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mHNPC are changing, but it is important to know who can be expected to have long survival with ADT to minimize overtreatment. Evaluation of clinical experience and outcomes of recently diagnosed mHNPC patients initially treated with ADT would be helpful.

Overall survival (OS) is a benchmark outcome assessment of patients with advanced cancer; previous studies have reported the clinical outcomes and prognostic factors associated with ADT monotherapy in mHNPC [7–10]. However, as subsequent treatment confounds analysis of the impact of initial treatment, it is important to evaluate early surrogate markers in addition to OS. The time to CRPC is known to be correlated with OS [11, 12], but evidence is lacking on the clinical outcomes and baseline characteristics associated with time to CRPC and OS in mHNPC patients, especially in recently diagnosed patients which have a chance to receive life-prolonging agents such as taxanes and androgen receptor-axis targeted (ARAT) agents. This retrospective multicenter study investigated clinical practice patterns and clinical outcomes and prognostic variables associated with CRPC-free survival and OS in patients with recently diagnosed mHNPC who were initially treated with ADT or combined androgen blockade (CAB) in Japan.

Material and methods

Study population

This retrospective multicenter study enrolled a series of 629 consecutive mHNPC patients who were treated with ADT or CAB at nine medical institutions in the Tohoku region of Japan between March 2008 and May 2016. ADT included orchiectomy and luteinizing hormone-releasing hormone (LHRH) agonists and antagonists, and the use of medical or surgical ADT in conjunction with bicalutamide is referred to as CAB. No patients had received upfront docetaxel and/or abiraterone acetate as initial therapy. Sequential treatment was administered after first-line hormonal therapy at the physician's discretion. The study was approved by the ethics committee at each study center. All patients gave opt-out consent for inclusion after being informed of the study and provided information on the institution's website.

Assessment

Patient age, Eastern Cooperative Oncology Group Performance Status score (ECOG-PS), Gleason score, metastasis location (visceral, lymph node, or bone), presence of bone pain, bone metastasis extent of disease (EOD) score, types of initial hormonal therapy, serum PSA, hemoglobin (Hb), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH), Chemotherapy in Treating Patients With Metastatic Prostate Cancer (CHAARTED) criteria, and date of CRPC diagnosis or all-cause death were included in the analysis. ECOG-PS and the presence of bone pain were evaluated by inquiry and physical examination. EOD scores were classified as described by Soloway et al. with bone scintigraphy at the time of the initial diagnosis [13]. CHAARTED criteria included the presence of visceral metastases or ≥ 4 bone lesions with one or more outside the vertebral bodies and pelvis as described by Sweeney et al. [3]. The CRPC was defined as disease progression despite a serum total testosterone < 50 ng/dL and (a) PSA progression as defined by the Prostate Cancer Clinical Trials Working Group (PCWG) 2, (b) soft-tissue disease progression as defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, or (c) bone disease progression as defined by PCWG2 [14]. The time to events was calculated starting on the day of ADT initiation.

Statistical analysis

Continuous variables were reported as means ± standard deviation or as medians and interquartile ranges (IQRs). Categorical variables were reported as numbers and percentages. Cumulative CRPC-free survival and OS were estimated by the Kaplan–Meier method; differences were compared with log-rank tests. Univariate analysis was performed to determine the association of age, ECOG-PS, Gleason score, metastasis location (visceral, lymph node, or bone), presence of bone pain, EOD score, type of initial hormonal therapy, serum PSA, Hb, ALP, LDH, and CHAARTED status with survival. Multivariable analysis was performed using a Cox proportional hazards regression model. Hazard ratios (HRs) and 95% confidence intervals (CRs) were calculated. Statistical analysis was performed with SPSS ver. 24.0. P-values < 0.05 were considered statistically significant.

Results

Patient enrollment and inclusion are summarized in Supplementary Fig.1. Of the 629 eligible patients, 24 were excluded because of missing survival data. The remaining 605 were included in the analysis. Table 1 shows the baseline characteristics of the included patients. The median age was 73 (66–78) years, median baseline PSA was 300.95 (70–838.4) ng/mL, 85.9% had Gleason scores of ≥ 8, 90.9% had bone, 51.4% had lymph node, and 11.6% had visceral metastases. Visceral metastases were found in the lung of 59 (9.8%) patients, liver of 13 (2.1%) patients, and other organs of 22 (3.6%) patients. The CHAARTED criteria of low- and high-volume disease were satisfied in 30.4% and 61.5%, respectively. ADT included combined

Table 1 Patient characteristics

Variables	$n=605$
Age, median (range)	73 (66–78)
ECOG-PS, no (%)	
0	333 (57.9)
1	159 (26.3)
2	83 (13.7)
Unknown	30 (5.0)
Baseline PSA level, ng/ml, median (IQR)	300.95 (70–838.4)
Baseline ALP level, ng/ml, median (IQR)	389(256–840.2)
Baseline Hb level, ng/ml, median (IQR)	13.2 (11.9–14.3)
Baseline LDH level, ng/ml, median (IQR)	227 (185–255.8)
Biopsy gleason score, no (%)	
≤3+4	19 (3.1)
4+3	28 (4.6)
8	209 (34.5)
≥9	311 (51.4)
Unknown	38 (6.3)
Site of metastasis*, no (%)*	
Bone	550 (90.9)
Lymph node	311 (51.4)
Visceral	70 (11.6)
CHAARTED risk criteria, no. (%)	
Low	184 (30.4)
High	372 (61.5)
Unknown	49 (8.1)
Presence of bone pain, no. (%)	
Yes	212 (38.3)
No	341 (61.7)
Unknown	52 (8.6)
EOD score, no (%)	
0	55 (9.1)
1	206 (34.0)
2	160 (26.4)
3	130 (21.5)
4	53 (8.8)
Initial treatment, no (%)	
CAB	492(81.6)
LHRH antagonist	97 (16.1)
Unknown	2 (0.3)

androgen blockade in 81.6% of the patients; 16.1% were treated with an LHRH antagonist. The sequential therapy given after development of CRPC was administered in 185 patients (68.5%), docetaxel in 102 (37.8%), abiraterone acetate in 25 (9.3%), enzalutamide in 47 (17.4%), and cabazitaxel 17 (6.3%). Forty-five (16.7%) of received both taxanes (docetaxel with and without cabazitaxel) and ARATs (abiraterone acetate and/or enzalutamide); estramustine phosphate was given to 105 (38.9%) (Supplementary Table 1).

During a median 2.95 years of follow-up, 208 patients died, 169 died of progressive disease. Ninety-four patients (14.9%) were missing information on their CRPC status, and 270 (52.8%) patients were diagnosed with CRPC during follow-up. The Kaplan–Meier estimates of CRPC-free survival and OS of all patients are shown in Fig. 1. Median CRPC-free survival was 21.9 months and median OS was 5.37 years. 2- and 5-year CRPC-free survival was 48.7% and 30.9%, whereas 2- and 5-year OS was 79.9% and 52.6%, respectively. Via the univariate and multivariable analysis for CRPC-free survival, as shown in Table 2, univariate analysis found that an ECOG-PS of ≥2 ($p=0.002$), a Gleason score ≥9 ($p=0.011$), presence of lymph node metastasis ($p=0.010$), presence of bone pain ($p=0.001$), an EOD score of ≥2 ($p<0.001$), PSA ≥301 ng/ml ($p=0.003$), Hb <12 g/dl ($p=0.001$), ALP ≥350 IU ($p<0.001$), LDH ≥220 IU ($p<0.001$), and CHAARTED high-volume disease ($p<0.001$) were prognostic of CRPC-free survival (Table 2, Fig. 2). Multivariable analysis found that age (HR, 0.98; 95% CI 0.97–0.99; $p=0.041$), Gleason score of ≥9 (HR, 1.55; 95% CI 1.18–2.03; $p=0.002$), lymph node metastasis (HR, 1.53; 95% CI 1.16–2.01; $p=0.003$), an EOD score ≥2 (HR, 2.11; 95% CI 1.50–2.96; $p<0.001$), and an LDH ≥220 IU (HR, 1.50; 95% CI 1.11–2.00; $p=0.006$) independently increased the risk of shorter CRPC-free survival (Table 2).

The results of univariate analysis of OS in these mHNPC patients are shown in Table 3. Increased age ($p=0.002$), an ECOG-PS ≥2($p=0.001$), Gleason score of ≥9 ($p=0.003$), EOD score of ≥2 ($p=0.001$), Hb <12 g/dl ($p<0.001$), an ALP ≥350 IU ($p<0.001$), an LDH of ≥220 IU ($p<0.001$), and CHAARTED high-volume disease ($p<0.001$) were prognostic of OS (Table 3, Fig. 3). Multivariable analysis of OS found that a Gleason score of ≥9 (HR, 1.50; 95% CI 1.09–2.07; $p=0.013$), lymph node metastasis (HR, 1.50; 95% CI 1.08–2.08; $p=0.016$), an EOD score of ≥2 (HR, 2.55; 95% CI 1.69–3.83; $p<0.001$), a PSA ≥301 ng/ml (HR 0.58, 95% CI 0.40–0.83; $p=0.003$), Hb <12 g/dl (HR 0.68, 95% CI 0.46–0.99; $p=0.044$), and an LDH ≥220 IU (HR, 1.69; 95% CI 1.21–2.37; $p=0.002$) were independently prognostic of shortened OS (Table 3). The multivariate model including the CHAARTED criteria (Supplementary Table 2) revealed the CHAARTED high-volume to be an independent prognostic factor for shortened CRPC-free survival and OS (HR 1.68, 95% CI 1.21–2.33; p=0.002; HR 1.74, 95% CI 1.18–2.57; $p=0.005$, respectively).

The patients were stratified by the variables that were independently associated with survivals into groups with Gleason scores of ≥9 or <9, EOD scores of ≥2 or <2, an LDH of ≥220 IU or <220, and the presence or absence of lymph node metastasis. Those with no or one risk factor were low-, those with two or three risk factors were intermediate- and those with all four risk factors were high-risk patients. The Kaplan–Meier cumulative CRPC-free survival

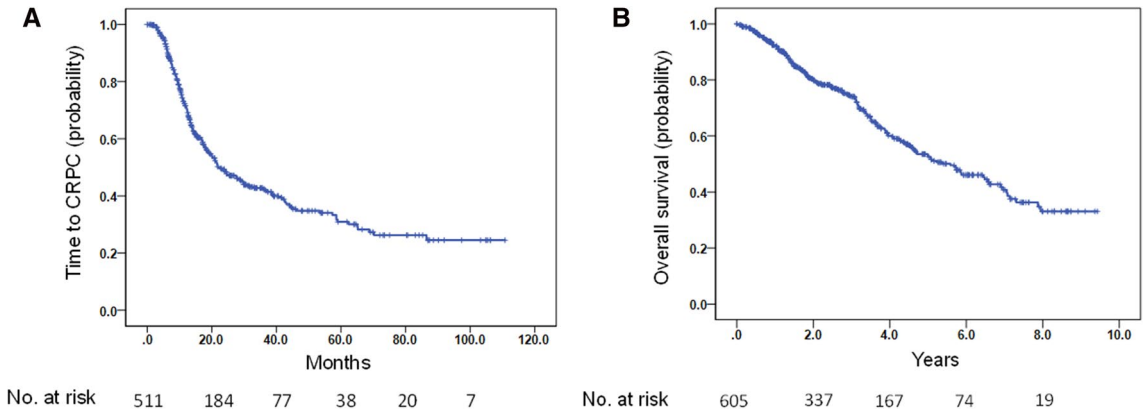

Fig. 1 Kaplan–Meier estimates of cumulative CRPC-free survival (**a**) and OS (**b**) in all patients

and OS are shown in Fig. 4. Median CRPC-free survival was 86.5 months in the low-, 17.9 months in the intermediate-, and 11.0 months in the high-risk patients. Median OSs was 4.72 years in the intermediate-, 2.44 years in the high-, and not reached in low-risk patients. Intermediate-risk patients had significantly shorter median CRPC-free survival and OS intermediate-risk patients (both $p < 0.001$, Fig. 4). High-risk patients had significantly shorter median CRPC-free survival and OS than intermediate-risk patients (both $p < 0.001$, Fig. 4). The patient outcomes indicate that the four baseline characteristics identified by multivariate analysis were prognostic of differences in the survival of mHNPC patients and the patients with low-risk had better prognosis after ADT or CAB.

Discussion

This study retrospectively analyzed clinical practice outcomes in patients with newly diagnosed mHNPC patients initially treated with ADT or CAB at nine study centers in Japan. All patients included in the study can had a chance to receive docetaxel because it was approved in Japan for treatment for CRPC in 2008. In consistent with the previous study evaluating clinical outcomes in patients with mHNPC using a Japanese cohort [8], the survival in patients with mHNPC who received ADT seems to be better than those in the ADT alone groups of the recent clinical trials as a control group [3, 5]. In special, the difference becomes obvious in patients with a longer follow-up which can be speculated that the reasons are not only specific responses to initial hormonal therapy in Asian population but also the exposure and timing of sequential treatment after CRPC. In fact, sequential treatment for CRPC was given to 185 (68.5%) of the study patients and included both taxanes and ARAT in 16.7%, both abiraterone acetate and enzalutamide was 8.9%, and estramustine phosphate in 38.9%.

The prognostic values of the CHAARTED criteria are widely accepted, but the median CRPC-free survival and OS of low-volume patients were 44.3 months and 6.70 years in this study. The results suggested that low-volume disease may have included patients with a poor survival, although there was a significant difference of CRPC-free survival and OS of low- and high-risk patients within the CHAARTED criteria (Supplementary Fig. 2). On the other hand, risk models including metastasis location, performance status, Gleason score, pain intensity, serum PSA, ALP, Hb, and LDH, and bone metastases have been previously proposed for mHNPC patients [7, 10]. In a previous study of mHNPC in Japan, Miyoshi et al. published a prognostic nomogram including five risk factors, age, serum PSA, clinical T stage, EOD score, and Gleason score [9]. A more recent study by Akamatsu et al. stratified patients into three groups using a risk model including a EOD score ≥ 2, the presence of liver metastasis, an LDH of > 250 U/L, and a primary Gleason score of 5 [8]. These studies were limited by including patients who had been treated over a long interval from 1989 to 2016 during which routine clinical practice has changed. In addition, these risk models focused on the prognostic factors for OSs which cannot eliminate the impact of sequential therapies after progression. In this study, novel prognostic markers included some risk factors previously evaluated for their impact on both CRPC-free survival and OS, and which potentially reflect the response to initial treatment for mHNPC directly.

The median time to CRPC in this study was 20.1 months, which is consistent with the 1.85 year result reported by a previous retrospective study of the clinical outcomes in patients with PC who had developed metastatic disease and had progressed to CRPC [11]. On the other hand, another retrospective study in Japan that patients with metastatic disease at initial diagnosis developed CRPC after a median of 26.6 months, which is longer than that seen in this study [15]. A direct comparison is difficult because of the lack of

Table 2 Univariate and multivariable analysis of prognostic factors for CRPC-free survival

Variables		Univariate				Multivariable			
		95% CI				95% CI			
		HR	Lower	Upper	*p* value	HR	Lower	Upper	*p* value
Age, *y*									
Continuous		0.99	0.97	1.00	0.146	0.98	0.97	0.99	0.041
ECOG-PS									
≥2 vs. 1		1.71	1.21	2.40	0.002	1.30	0.87	1.93	0.199
Biopsy Gleason Score									
≥9 vs. ≤8		1.73	1.14	2.64	0.011	1.55	1.18	2.03	0.002
Site of metastasis									
Lymph node	Yes vs. no	1.39	1.08	1.78	0.010	1.53	1.16	2.01	0.003
Visceral	Yes vs. no	0.66	0.41	1.06	0.083	0.64	0.38	1.08	0.092
Presence of bone pain									
Yes	Yes vs. No	1.53	1.18	1.99	0.001	0.94	0.69	1.29	0.715
EOD score	≥2 vs. ≤1	2.67	2.06	3.44	<0.001	2.11	1.50	2.96	<0.001
Serum marker at baseline									
PSA level, ng/ml	≥301 vs. >301	1.46	1.14	1.87	0.003	0.93	0.68	1.26	0.642
Hb level, g/dl	≥12 vs. <12	0.62	1.22	2.13	0.001	0.75	0.53	1.05	0.091
ALP level, IU	≥350 vs. <350	1.70	1.32	2.18	<0.001	1.04	0.76	1.43	0.787
LDH level, IU	≥220 vs. <220	1.82	1.41	2.36	<0.001	1.50	1.11	2.00	0.008
Initial therapy									
LHRH antagonist	Yes vs. No	1.23	0.86	1.75	0.261	1.01	0.67	1.52	0.969
CAB	Yes vs. No	1.06	0.76	1.49	0.725	1.06	72.00	1.57	0.770
CHAARTED criteria									
High vs. low		2.00	1.50	2.66	<0.001	–	–	–	–

CRPC castration-resistant prostate cancer, *HR* hazard ratio, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group-performance status, *EOD* extent of bone disease, *PSA*, prostate specific antigen, *Hb* hemoglobin, *ALP* alkaline phosphatase, *LDH* lactate dehydrogenase, *LHRH* luteinizing hormone-releasing hormone, *CAB* conbined androgen blockade

detailed participant characteristics in the previous studies, this study evaluated clinical outcomes in a larger patient sample with more recent diagnosis that the previous series. The previous study also showed that there was no difference in OS after the definition of CRPC in the patients with de-novo metastases and with metastasis observed after initial treatment [11], which suggests that prolongation of CRPC-free survival is important for achieving longer OS. Another retrospective analysis found that the time to CRPC was independently prognostic of OS [12]. As real-world data on the time to CRPC in mHNPC patients is lacking, further validation is needed to identify patient baseline characteristics independently associated with the time to CRPC.

One of the strong prognostic factors for both time to CRPC-free survival and OS was EOD score of > 2. The definitions of high disease tumor burden in recent clinical trials such as the CHAARTED [3] (≥4 bone metastasis) and LATITUDE [5] (≥3 bone metastasis) were applied, and the use of bone metastatic status to characterize disease burden has been useful as a prognostic marker in current real-world practice [16, 17]. Tosoian et al. reported that oligometastatic PC, which in known be a biologically distinct PC, was defined by the presence of fewer than five metastatic tumors [18]. The available evidence including that reported here, indicate that fewer than five bone metastases is a reliable threshold of survival in nHNPC. Regarding another prognostic factor, serum LDH was found to be an independently associated with CRPC-free survival and OS. LDH catalyzed the forward and backward conversion of pyruvate to lactate in the tissue microenvironment and it is important in cancer metabolism [19]. LDH is an intracellular enzyme present in many cell types and is released into the blood following tissue injury [20]. The prognostic impact of serum LDH in mHNPC found here is consistent with existing evidence of impact of serum LDH in prostate cancer in addition to mHNPC [21, 22].

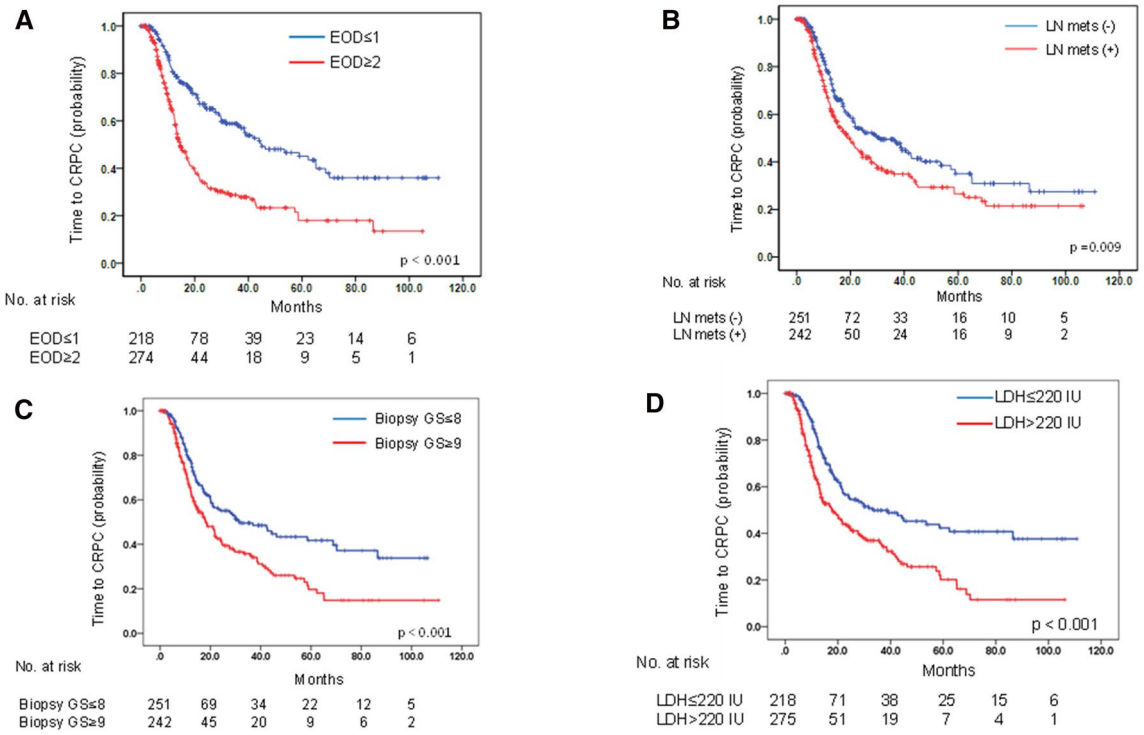

Fig. 2 Kaplan–Meier estimates of cumulative CRPC-free survival including EOD score (**a**), presence of lymph node metastasis (**b**), Gleason score (**c**) and serum LDH level (**d**). *P*-values were computed using log-rank tests

Table 3 Univariate and multivariable analysis of prognostic factors for overall survival

Variables		Univariate				Multivariable			
		95% CI				95% CI			
		HR	Lower	Upper	*p* value	HR	Lower	Upper	*p* value
Age, *y*	Continuous	1.03	1.01	1.05	0.002	1.02	0.99	1.04	0.090
ECOG-PS	≥2 vs. 1	1.78	1.25	2.53	0.001	1.06	0.67	1.67	0.814
Biopsy Gleason Score	≥9 vs. ≤8	1.90	1.24	2.91	0.003	1.50	1.09	2.07	0.013
Site of metastasis									
Lymph node	Yes vs. no	1.30	0.99	1.71	0.061	1.50	1.08	2.08	0.016
Visceral	Yes vs. no	1.13	0.74	1.74	0.557	0.82	0.48	1.42	0.485
Presence of bone pain									
Yes	Yes vs. No	1.25	0.34	1.68	0.133	0.85	0.59	1.23	0.398
EOD score ≥2 vs. ≤1		2.26	1.68	3.05	<0.001	2.55	1.69	3.83	<0.001
Serum marker at baseline									
PSA level, ng/ml	≥301 vs. <301	1.11	0.85	1.46	0.456	0.58	0.40	0.83	0.003
Hb level, g/dl	≥12 vs. <12	0.47	1.35	2.37	<0.001	0.68	0.46	0.99	0.044
ALP level, IU	≥350 vs. <350	1.66	1.25	2.20	<0.001	1.03	0.71	1.48	0.893
LDH level, IU	≥220 vs. <220	1.93	1.45	2.56	<0.001	1.69	1.21	2.37	0.002
Initial therapy									
LHRH antagonist	Yes vs. no	1.27	0.80	2.00	0.309	1.29	0.76	2.18	0.346
CAB	Yes vs. no	1.05	0.72	1.54	0.803	1.13	0.72	1.77	0.599
CHAARTED criteria	High vs. low	1.97	1.40	2.78	<0.001	–	–	–	–

CRPC castration-resistant prostate cancer, *HR* hazard ratio, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group-performance status, *EOD* extent of bone disease, *PSA*, prostate specific antigen, *Hb* hemoglobin, *ALP* alkaline phosphatase, *LDH* lactate dehydrogenase, *LHRH* luteinizing hormone-releasing hormone, *CAB* conbined androgen blockade

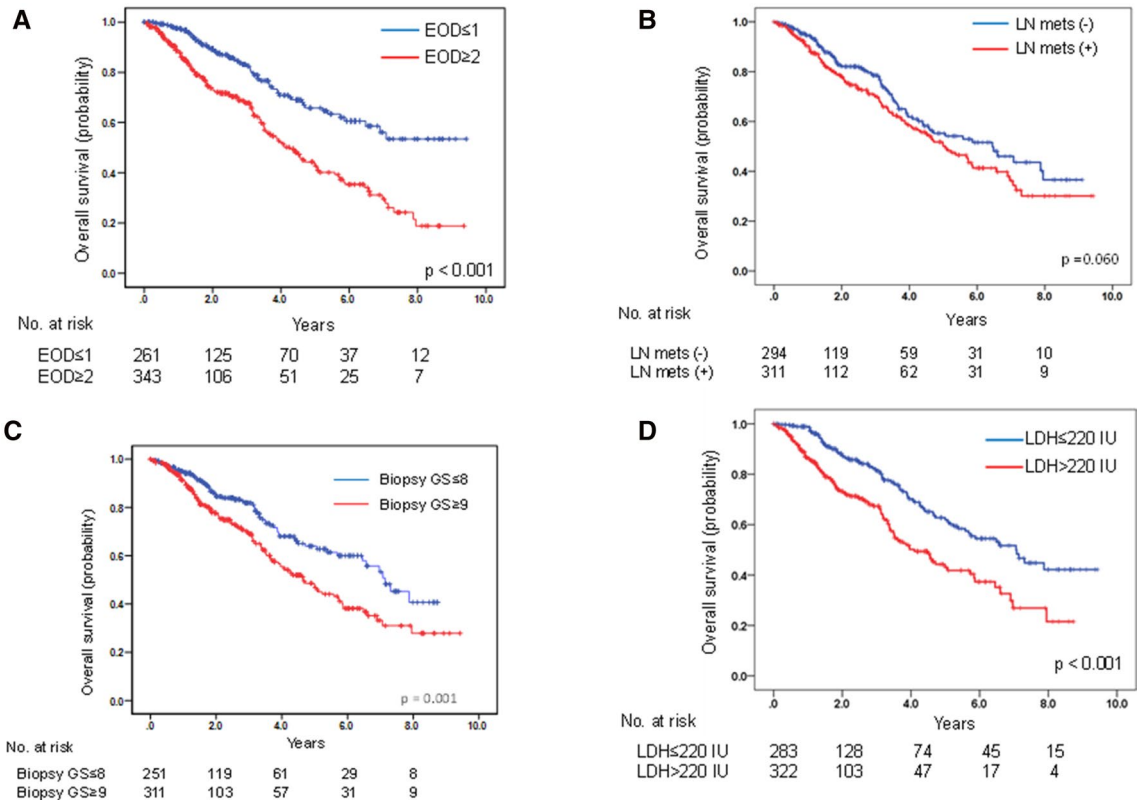

Fig. 3 Kaplan–Meier estimates of cumulative OS including EOD score (**a**), presence of lymph node metastasis (**b**), Gleason score (**c**) and serum LDH (**d**). *P*-values were computed using log-rank tests

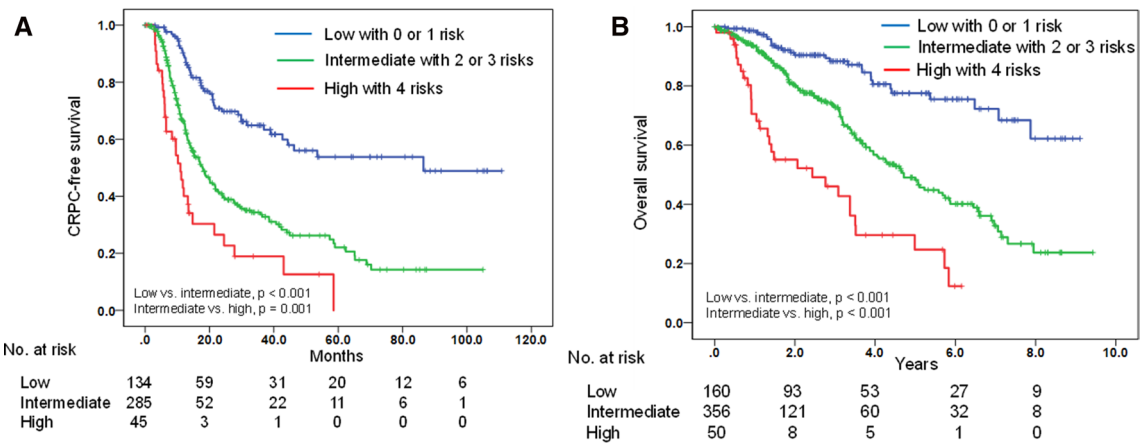

Fig. 4 Kaplan–Meier estimates of cumulative CRPC-free survival (**a**) and OS (**b**) in patients with mHNPC and initially treated with ADT or CAB and stratified by lymph node metastasis, Gleason score ≥ 9, EOD score ≥ 2, and an LDH ≥ 220 IU. Low-risk patients had no or one risk factor, intermediate-risk patients had two or three risk factors, and high-risk patients had all four risk factors. *P*-values were computed using log-rank tests

This study has several limitations. This study is a retrospective multicenter study using the patient treated in a recent year, resulting in a number of potential biases derived from institutional differences, short duration of follow-up and exclusion of the impact of other influential factors without evaluation. Second, we focused on just pretreatment variables in the present study. A numbers of peri-treatment variables such as changes of serum biomarkers [23], time to PSA nadir and PSA nadir levels [24, 25] may have a potential impact of survivals. In addition, sequential therapies

after CRPC may be associated with outcomes in patients with mHNPC. The impacts of docetaxel, ARAT and EMP on OS are described in Supplementary Table 3. However, good long-term survival was observed for several patients after initial hormonal therapy without CRPC. This suggests that the evaluation of the impact of sequential therapies after CRPC on survival in the current study is complex. Further studies are required to elucidate the impact of sequential therapy after CRPC on clinical outcomes among patients with mHNPC in the present-day situation. Finally, we did not investigated more ideal survival analyses such as a conditional and/or a net survival which was proposed in the other setting of prostate cancer and other cancer [26, 27].

In summary, we evaluated the real-world treatment and outcomes in patients with recent-diagnosed mHNPC who were initially treated with ADT or CAB. Patients stratified by four identified prognostic factors identified subgroups with improved CRPC-free survival and OS. The use of ADT with or without bicalutamide may be considered as a therapeutic option for highly selected patients with mHNPC, even in the present era of novel treatment.

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Author contributions Narita: Data collection, statistical analysis, manuscript writing. Hatakeyama, Takahashi, Sakurai, Kawamura, Ishida, Sato, Mitsuzuka: Data collection. Hoshi, Kawaguchi, Ishidoya, Shimoda, Protocol development. Nomura: Data analysis. Tochigi, Tsuchiya, Ohyama, Arai, Habuchi: manuscript editing, supervision. All authors had read and approve of the final manuscript.

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Compliance with ethical standards

Conflict of interest None declared. No competing financial interests exist.

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