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ORIGINAL ARTICLE

Impact of nadir PSA level and time to nadir during initial androgen deprivation therapy on prognosis in patients with metastatic castration-resistant prostate cancer

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Abstract

Purpose We determine whether the nadir prostate-specific antigen level (PSA nadir) and time to nadir (TTN) during initial androgen deprivation therapy (ADT) are prognostic factors in metastatic castration-resistant prostate cancer (mCRPC) patients.

Methods We reviewed the Michinoku Japan Urological Cancer Study Group database, including 321 mCRPC patients. Optimal cutoff values for PSA nadir and TTN on survival were calculated with the receiver operating characteristic (ROC) curve. Patients were stratified into unfavorable (higher PSA nadir and/or shorter TTN) and favorable (lower PSA nadir and longer TTN) groups. The inversed probability of treatment weighing (IPTW)-adjusted Cox proportional hazard model was performed to evaluate the impact of the unfavorable group on overall survival (OS) after CRPC diagnosis.

Results Median age and follow-up period were 71 years and 35 months, respectively. ROC curve analysis demonstrated cutoffs of PSA nadir > 0.64 ng/mL and TTN < 7 months. The unfavorable group included 248 patients who had significantly shorter OS after mCRPC. The IPTW-adjusted multivariate model revealed that the unfavorable group had a negative impact on OS in mCRPC patients [hazards ratio (HR) 2.98, $P < 0.001$].

Conclusions Higher PSA nadir and shorter TTN during the initial ADT are poor prognostic factors in patients with mCRPC.

Keywords PSA nadir · Time to nadir · Metastatic castration-resistant prostate cancer · Prognosis

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Introduction

Prostate cancer (PC) is the most commonly diagnosed cancer in men worldwide, and its rate of diagnosis is on the rise [1]. In Japan, approximately 10–20% of patients with newly diagnosed PC have distant metastases [2–6]. PC patients with metastases frequently suffer metastatic castration-resistant prostate cancer (mCRPC) that results in high mortality rates [7–12]. However, to our knowledge, an optimized model that distinguishes poor and favorable prognostic groups in mCRPC patients has not been defined.

Nadir prostate-specific antigen level (PSA nadir) and time to nadir (TTN) have been recognized as prognostic factors in patients with hormone-naïve prostate cancer (HNPC) including metastatic HNPC (mHNPC) [13–17]. However, few studies have investigated the impact of PSA nadir and TTN during initial androgen deprivation therapy (ADT) on prognosis in patients with mCRPC [18]. As the significance of these factors in mCRPC patients has not been well defined, we elucidated the impact of PSA nadir and TTN during initial ADT on prognosis in mCRPC patients with adjustment of potential confounding factors, including treatment for CRPC.

Materials and methods

Study population

This retrospective, multicenter study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Review Board of Hirosaki University School of Medicine (authorization number: 2017–089).

We reviewed patients with mCRPC registered in the Michinoku Japan Urological Cancer Study Group database [5, 19, 20]. This database contained 667 consecutive patients with newly diagnosed mHNPC who were initially treated with ADT between 2008 and 2017 at Hirosaki University Hospital, Akita University Hospital, Tohoku University Hospital, Yamagata University Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Iwate Prefectural Isawa Hospital, Aomori Prefectural Central Hospital, and Sendai City Hospital in Japan. mCRPC patients with valid data, including PSA nadir, TTN, and survival status at last follow-up, were included in the study. The enrollment process is shown in a consort diagram (Fig. 1). mCRPC was defined according to the recommendations of the Prostate Cancer Clinical Trials Working Group 2 [21].

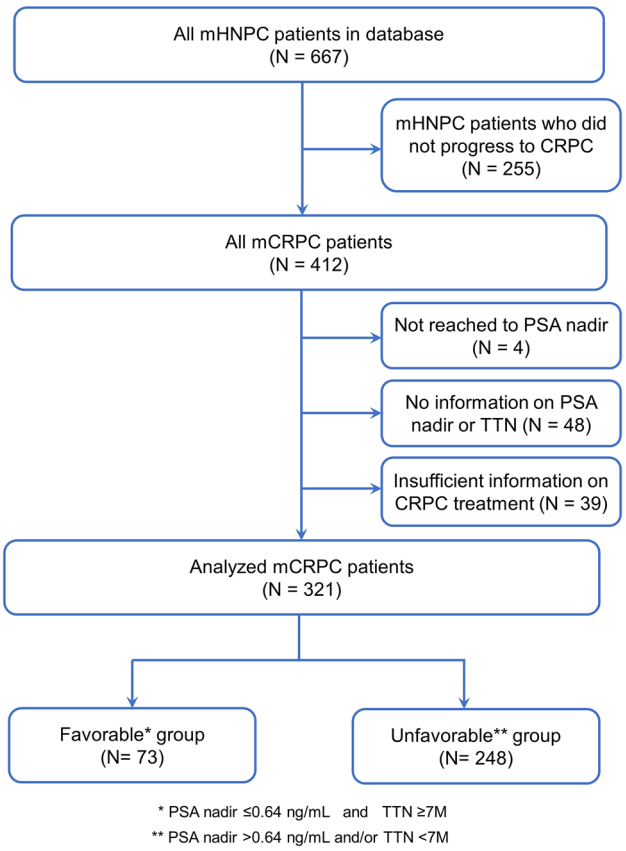

Fig. 1 Consort diagram for the enrollment process of patients with mCRPC. The Michinoku Japan Urological Cancer Study Group database contains 667 patients with mHNPC. After excluding patients who did not eventually progress to CRPC or did not present complete data, 321 patients were selected as objectives of analysis. Of 321, 73 and 248 patients were stratified as the favorable and unfavorable groups, respectively, according to the cutoff values for PSA nadir and TTN determined by the ROC analysis

Analyzed variables

As patient backgrounds, we assessed age, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), Gleason score (GS), visceral metastases, extent of disease (EOD) for bone metastases, CHAARTED high-volume disease [22], LATITUDE high-risk disease [23], presence of bone pain, initial PSA (iPSA), and treatment with chemotherapy (docetaxel [DTX] and/or cabazitaxel [CBZ]), abiraterone acetate (AA) and/or enzalutamide (ENZ), and bone-modifying agents (BMA). PSA nadir was defined as the lowest PSA level since the beginning of the initial ADT. The lowest PSA after CRPC treatment was not defined as the nadir. TTN was defined as the duration (months) from initiation of ADT to the date the PSA nadir was observed [15, 16]. Metastatic status was detected with chest and body

computed tomography and bone scintigraphy before initiating ADT. CHAARTED high volume was defined as the presence of visceral metastases and/or ≥ 4 bone metastases with at least one outside of the vertebral column and pelvis [22]. LATITUDE high risk was defined as patients with at least two of the following three high-risk factors: GS ≥ 8, ≥ 3 bone metastases, and the presence of visceral metastases [23]. However, our database did not contain the exact number of bone metastases. Therefore, we used EOD > 1 (≥ 6 bone metastases) as a substitute for ≥ 3 bone metastases. Overall survival (OS) after CRPC was defined as the interval from the date of initial CRPC diagnosis to the date of death. CRPC-free survival was defined as the interval from the date of initial diagnosis with mHNPC to the date of CRPC diagnosis. Patients were censored when the event was not observed until the end of follow-up.

Risk group stratification

The optimal cutoff values in PSA nadir and TTN were calculated with receiver operating characteristic (ROC) curve analysis. Patients were stratified into unfavorable (PSA nadir > cutoff and/or TTN < cutoff) and favorable (PSA nadir ≤ cutoff and TTN ≥ cutoff) groups. Belonging to the unfavorable group also was assessed as a candidate variable for prognostic factors.

Treatment protocol

All patients with mHNPC were treated initially with ADT (medical or surgical castration with or without antiandrogen receptor antagonists) and/or BMA, such as bisphosphonate or denosumab. After CRPC diagnosis, patients basically received treatments with systemic chemotherapy (DTX and/or CBZ) and/or second-generation ADT (AA and/or ENZ). Patients who chose neither chemotherapy nor second-generation ADT were treated with alternative antiandrogen therapy, antiandrogen withdrawal therapy, estramustine, and/or low-dose oral steroid therapy. No companion diagnostics were used for the determination of treatment options.

Statistical analysis

Data were analyzed statistically using SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA), GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical, normally distributed, and nonnormally distributed variables were expressed as percentages, means with standard deviations (SDs), and medians [interquartile ranges (IQRs)], respectively. CRPC-free survival and OS between the groups were investigated by the Kaplan–Meier method and compared with the log-rank test. Cutoff values for PSA nadir and TTN were defined as the closest point to the upper left corner of the ROC graph. Multivariate Cox hazard proportion analyses were performed to evaluate the impact of candidate predictive factors on OS. Additionally, the Inverse probability of treatment weighted (IPTW)-adjusted Cox regression analysis was used to evaluate the impact of the unfavorable group on OS. The IPTW model reweighted affected and unaffected groups to mimic a propensity score-matched population [24]. Hazard ratios (HRs) with 95% confidence interval (95% CI) in the multivariate and IPTW analyses were calculated after controlling for potential confounders. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Of the total 667 mHNPC patients, 412 had mCRPC, including 321 with valid information who were analyzed in this study. Median age and follow-up period were 71 (IQR, 64–77) years and 35 (IQR, 18–57) months, respectively. The patient proportions with GS ≥ 8, visceral metastases, and EOD > 1 (≥ 6 bone metastases) were 94, 13, and 63%, respectively. As a result, CHAARTED high-volume and LATITUDE high-risk disease based on the aforementioned criteria occurred in 68% and 60% of the patients, respectively. Medians for iPSA at initialization of ADT, PSA nadir, and TTN were 360 (88–1243) and 0.9 (0.2–6.8) ng/mL, and 6.3 (3.7–10.7) months, respectively. After mCRPC diagnosis, 213 (66%) patients underwent treatment with chemotherapy and/or second-generation ADT. Specifically, 143 (45%) patients received treatment with DTX and 135 (42%) with AA (70 patients, 22%) and/or ENZ (100 patients, 31%; Table 1).

Patients' stratification based on the cutoff values for PSA nadir and TTN

To define optimal cutoff values of PSA nadir and TTN for patient survival, ROC curve analyses were performed. ROC analysis of PSA nadir and TTN for OS after CRPC diagnosis showed an area under the curve (AUC) of 0.645 ($P < 0.001$) and 0.626 ($P < 0.001$), respectively, indicating cutoff values of 0.64 ng/mL (Fig. 2a) and 7 months (Fig. 2b), respectively. Based on these findings, we classified patients into favorable (PSA nadir ≤ 0.64 ng/mL and TTN ≥ 7 months, $n = 73$) and unfavorable (PSA nadir > 0.64 ng/mL and/or TTN < 7 months, $n = 248$) groups. There were significant

Table 1 Background of patients with mCRPC ($n = 321$)

	Mean (± SD)/median (IQR)/number (%)			*P* value (favorable vs. unfavorable)
	All	Favorable group[b]	Unfavorable group[a]	
Total *N*	321	73 (23%)	248 (77%)	
Age (years)	71 (64–77)	70 (63–74)	72 (64–78)	0.036
BMI (kg/m^2)	23 (21–25)	24 (22–25)	22 (20–25)	0.022
ECOG PS > 1	43 (13%)	7 (10%)	36 (15%)	0.277
Gleason score ≥ 8	301 (94%)	66 (90%)	235 (95%)	0.177
Visceral metastases	42 (13%)	8 (11%)	34 (14%)	0.54
EOD > 1	203 (63%)	37 (51%)	166 (67%)	0.011
CHAARTED high-volume disease	219 (68%)	40 (55%)	179 (72%)	0.005
LATITUDE high-risk disease	193 (60%)	34 (47%)	159 (64%)	0.007
Presence of bone pain	125 (42%)	25 (38%)	100 (43%)	0.349
iPSA (ng/mL)	360 (88–1243)	376 (108–1435)	357 (77–1195)	0.629
iPSA ≥ 360 ng/mL	160 (50%)	37 (51%)	123 (49%)	0.87
PSA nadir (ng/mL)	0.9 (0.2–6.8)	0.1 (0–0.3)	2.3 (0.6–10.4)	< 0.001
PSA nadir > 0.64 ng/mL	183 (57%)	0 (0%)	183 (74%)	< 0.001
TTN (months)	6.3 (3.7–10.7)	12.8 (9.5–21.9)	5.1 (3.4–7.4)	< 0.001
TTN < 7 M	181 (56%)	0 (%)	181 (73%)	< 0.001
Treatment with DTX	143 (45%)	25 (34%)	117 (47%)	0.051
Treatment with CBZ	24 (7.6%)	7 (9.7%)	17 (7.0%)	0.435
Treatment with AA and/or ENZ	135 (42%)	39 (53%)	96 (39%)	0.025
Cancer death	132 (41%)	14 (19%)	118 (48%)	< 0.001
Deceased	146 (45%)	17 (23%)	129 (52%)	< 0.001
Follow-up period (months)	35 (18–57)	65 (46–86)	26 (15–43)	< 0.001

mCRPC, metastatic castration-resistant prostate cancer; SD, standard deviation; IQR, interquartile range; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; iPSA, initial PSA; EOD, extent of disease; TTN, time to nadir; DTX, docetaxel; CBZ, cabazitaxel; AA, abiraterone acetate; ENZ, enzalutamide

[a]Unfavorable group: PSA nadir > 0.64 ng/mL and/or TTN < 7 months

[b]Favorable group: PSA nadir ≤ 0.64 ng/mL and TTN ≥ 7 months

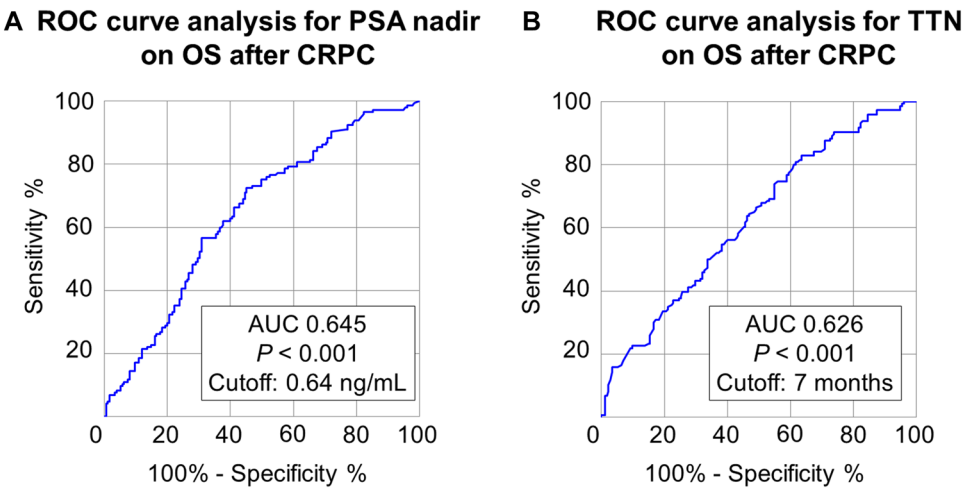

Fig. 2 ROC analysis for PSA nadir and TTN on OS after CRPC diagnosis. The ROC analysis of PSA nadir for OS after CRPC diagnosis in 321 mCRPC patients showed the area under the curve (AUC) of 0.645 ($P < 0.001$), suggesting a cutoff value of 0.64 ng/mL (**a**). The analysis of TTN for OS after CRPC diagnosis in 321 mCRPC patients showed an AUC of 0.626 ($P < 0.001$), suggesting the cutoff value of 7 months (**b**)

differences in age, BMI, CHAARTED high-volume and LATITUDE high-risk disease, PSA nadir, TTN, and AA and/or ENZ use between the groups (Table 1).

Kaplan–Meier analysis between the unfavorable and favorable groups

In the Kaplan–Meier survival curve analysis, significant differences were observed in OS after CRPC diagnosis ($P < 0.001$; Fig. 3a) and CRPC-free survival ($P < 0.001$; Fig. 3b) between the favorable and unfavorable groups.

Analysis for prognostic factors in mCRPC patients

In univariate analyses with the Cox hazard model, iPSA ≥ 360 ng/mL (HR, 0.70; 95% CI 0.50–0.97; $P = 0.031$), unfavorable group (HR, 3.61; 95% CI 2.17–6.01; $P < 0.001$), treatment with AA and/or ENZ (HR, 0.53; 95%

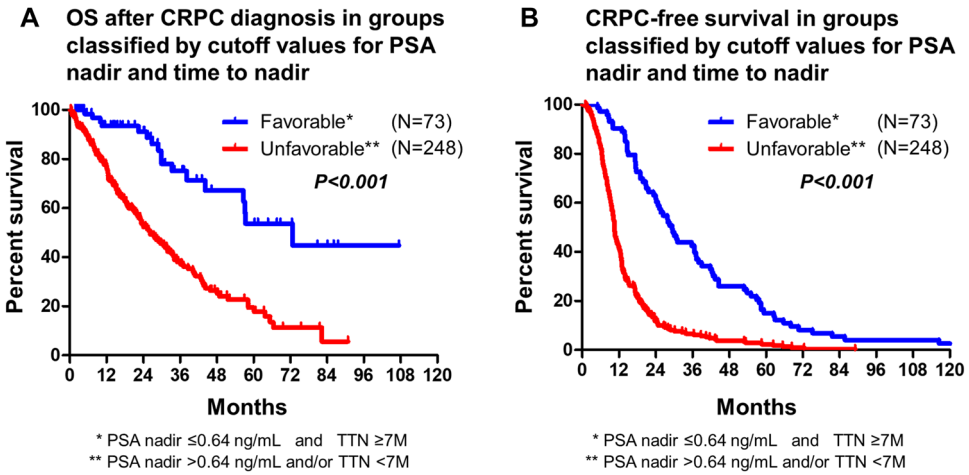

Fig. 3 Kaplan–Meier curve for groups classified by cutoff values for PSA nadir (> 0.64 ng/mL) and time to nadir (< 7 M). The OS after CRPC diagnosis (**a**) and CRPC-free survival (**b**) in patients with PSA nadir > 0.64 ng/mL and/or TTN < 7 M (unfavorable group) were compared to those with PSA nadir ≤ 0.64 ng/mL and TTN ≥ 7 M (favorable group). The Kaplan–Meier survival curve comparing 73 (favorable) and 248 (unfavorable) groups showed significant differences in OS after CRPC ($P < 0.001$) (**a**) and CRPC-free survival ($P < 0.001$) (**b**)

Table 2 Uni- and multivariate analysis with Cox hazard proportional model for OS after CRPC diagnosis in patients with mCRPC ($n = 321$)

Variables	Univariate			Multivariate	
	Risk factor	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	< 70	0.77 (0.56–1.08)	0.128	0.75 (0.53–1.04)	0.091
BMI	≥ 25	1.11 (0.72–1.69)	0.639		
ECOG PS	> 1	0.74 (0.45–1.24)	0.252	0.86 (0.69–1.08)	0.201
GS	≥ 8	1.12 (0.55–2.28)	0.758		
Visceral metastases	Pos.	1.25 (0.78–2.01)	0.347		
EOD	> 1	1.27 (0.89–1.81)	0.186		
LATITUDE	High-risk	1.29 (0.92–1.83)	0.145	1.34 (0.92–1.95)	0.126
CHAARTED	High-vol.	1.23 (0.85–1.78)	0.264		
Presence of bone pain	Pos.	0.98 (0.69–1.39)	0.916		
iPSA	≥ 360 ng/mL	0.70 (0.50–0.97)	0.031	0.68 (0.48–0.96)	0.030
Unfavorable group[a]	Pos.	3.61 (2.17–6.01)	< 0.001	3.34 (1.99–5.61)	< 0.001
Treatment with DTX	Pos.	1.11 (0.80–1.54)	0.539		
Treatment with AA and/or ENZ	Pos.	0.53 (0.37–0.75)	< 0.001	0.49 (0.35–0.70)	< 0.001
Treatment with BMA	Pos.	0.61 (0.42–0.87)	0.007		

mCRPC metastatic castration-resistant prostate cancer, *HR* hazard ratio, *BMI* body mass index, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EOD* extent of disease, *iPSA* initial PSA, *DTX* docetaxel, *CBZ* cabazitaxel, *AA* abiraterone acetate, *ENZ* enzalutamide, *BMA* bone-modifying agents

[a]Unfavorable group: PSA nadir > 0.64 ng/mL and/or TTN < 7 months

Table 3 IPTW-adjusted multivariate Cox hazard proportional analysis in unfavorable group for OS after CRPC diagnosis in patients with mCRPC

	Factor	*P* value	HR	95% CI
Overall survival	Unfavorable group[a]	<0.001	2.98	1.77–5.02

Adjusted variables: Age, ECOG PS, iPSA, LATITUDE high-risk, treatment with DTX, and treatment AA/Enz

IPTW inverse probability of treatment weighting

[a]Unfavorable group: PSA nadir > 0.64 ng/mL and/or TTN < 7 M

CI 0.37–0.75; $P < 0.001$), and treatment with BMA (HR, 0.61; 95% CI 0.42–0.87; $P < 0.007$) were factors associated with OS in mCRPC patients (Table 2). Multivariate analysis revealed that the unfavorable group (HR, 3.34; 95% CI 1.99–5.61; $P < 0.001$), iPSA ≥ 360 ng/mL (HR, 0.68; 95% CI 0.48–0.96; $P = 0.03$), and treatment with AA and/or ENZ (HR, 0.49; 95% CI 0.35–0.70; $P < 0.001$) were significant prognostic factors (Table 2). Furthermore, the IPTW-adjusted Cox hazard model indicated that the unfavorable group had a significant negative impact on OS (HR, 2.98; 95% CI 1.77–5.02; $P < 0.001$) after adjustment for age, ECOG PS, LATITUDE high risk, iPSA ≥ 360 ng/mL, treatment with DTX, and treatment with AA and/or ENZ (Table 3).

Discussion

We examined the potential of PSA nadir and TTN during the initial ADT as prognostic factors in patients with mCRPC. First, we established cutoff values of PSA nadir (> 0.64 ng/mL) and TTN (< 7 M) that were significantly correlated with OS after CRPC and CRPC-free survival in 321 mCRPC patients. Next, we defined the patients with PSA nadir > 0.64 ng/mL and/or TTN < 7 M as higher risk for poor prognosis and included them in the unfavorable group. In the Cox hazard model analyses, belonging to the unfavorable group was suggested as the strongest independent factor for shorter OS after CRPC. Furthermore, the IPTW-adjusted Cox regression model confirmed that the unfavorable group significantly impacted shorter OS after CRPC.

To our knowledge, this is the second and largest scale study that investigated the impact of PSA nadir and TTN during the initial ADT on mCRPC prognosis [18]. In addition, while there has been a study investigating the impact of PSA nadir and TTN in Japanese mHNPC patients [14], the present study was specialized in mCRPC patients in a Japanese cohort. Also, this was the first study on nadir PSA and TTN that analyzed mCRPC patients with various treatment backgrounds for CRPC, including chemotherapy, AA, and ENZ. As a result, PSA nadir and TTN remained predictive factors after adjusting for confounders, including choice of CRPC treatment.

The clinical implication of TTN remains controversial. Several studies on mHNPC indicated shorter TTN as an unfavorable factor for prognosis [14–17], whereas a study on localized PC reported shorter TTN as a favorable factor for cancer-specific survival [25]. The clinical implication of TTN may need to be separately assessed in CRPC and non-CRPC patients because the outcomes of short TTN is possibly dependent on how much patients consequently progress to CRPC. Based on our results, we developed a model for heterogeneity of PSA kinetics in mHNPC patients (Fig. 4). In this model, shorter TTN represents an incomplete response to the initial ADT in a certain proportion of mHNPC patients (Fig. 4a, b). Our model suggested the clinical implication of shorter TTN may be associated with an incomplete response to initial ADT in mCRPC patients, while the shorter TTN in non-CRPC patients frequently implies a favorable response.

In this study, we calculated cutoff values for PSA nadir and TTN with the ROC analysis and proposed PSA nadir > 0.64 ng/mL and TTN < 7 months as the distinctive cutoffs. Although the evidences on PSA nadir and TTN in

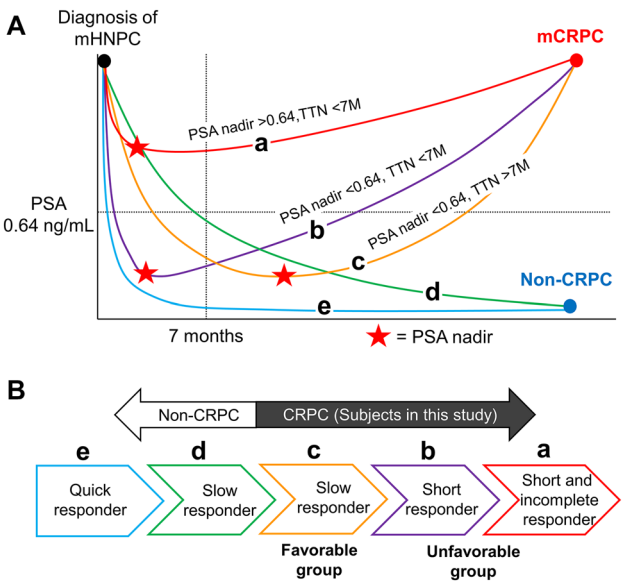

Fig. 4 Model for heterogeneity of PSA kinetics in patients with mHNPC. The graph illustrates a model for heterogenous PSA kinetics in patients with mHNPC including mCRPC (a–c) and non-CRPC (d, e). Among the mCRPC patients, those who quickly respond to the initial ADT but immediately undergo PSA elevation are categorized as short responders (**b**) or short and incomplete responders (**a**) (unfavorable group; a, b). Meanwhile, those slowly and profoundly respond to the initial ADT and develop to CRPC after 7 months are categorized as slow responders (favorable group; c) (**A**). This study included CRPC patients (a–c). The heterogeneity may suggest the necessity to investigate the implication of TTN separately in CRPC and non-CPRC patients

CRPC are insufficient [18], our cutoff of TTN < 7 month was assumed affordable according to several former studies using 7 months as a milestone to evaluate the treatment effect with ADT [26, 27]. A recent study on 790 mHNPC patients suggested that achieving PSA ≤ 0.2 ng/mL at 7 months was a prognostic factor for longer OS in either patient groups with ADT alone and ADT + DTX treatment [26]. Meanwhile, our cutoff of PSA nadir > 0.64 ng/mL is higher than the PSA nadir ≥ 0.2 ng/mL, which was used in former studies in mHNPC patients [14, 15, 17, 26–28]. To interpret this difference, we additionally analyzed our original database ($n = 667$) for median PSA nadir in mHNPC patients who did and did not eventually suffer mCRPC. Of 667 patients, 469 with valid PSA nadir data were analyzed. The median PSA nadir in mCRPC patients ($n = 321$) was 0.90 (0.18—6.88) ng/mL, which was significantly higher than the 0.02 (0.008–0.33) ng/mL in mHNPC who did not progress to mCRPC ($n = 148$, $P < 0.001$). This result may imply that the cutoff for PSA nadir should be different between mCRPC and mHNPC patients. As few studies evaluated prognosis in CRPC by using risk stratification based on PSA nadir and TTN, further studies are necessary to examine the risk stratification and treatment outcomes in CRPC patients. Our risk stratification based on PSA nadir and TTN may provide useful information for decision making in CRPC treatment.

In this study, we also examined patient characteristics associated with tumor burden, such as LATITUDE and CHAARTED criteria, as candidate prognostic factors. Given that CHAARTED (upfront docetaxel plus ADT) [21] and LATITUDE (AA plus prednisone) [23] trials were designed for mHNPC patients, these criteria consisted of factors related to high tumor burden. We evaluated the impact of CHAARTED high volume or LATITUDE high risk; however, not tumor burden risk classifications, but the response to initial ADT demonstrated significant association with poor OS after CRPC. These results suggested that high tumor burden could not predict prognosis after CRPC, and the classification based on the response to initial ADT was a potential predictor for prognosis after CRPC. To confirm the high predictivity of our novel classification, further validation in other populations is warranted.

Interestingly, high iPSA beyond the median value of 360 ng/mL was identified as a favorable prognostic factor for OS after CRPC on multivariate analyses (HR, 0.68; 95% CI 0.48–0.96; $P = 0.03$). The reason for the association between high iPSA and favorable prognosis in our study is indefinite. While high iPSA is recognized as an unfavorable prognostic factor in mHNPC [16], recent studies have proposed that high iPSA does not always imply poor prognosis in CRPC. A recent study including mHNPC with extremely high iPSA revealed that high iPSA was a favorable prognostic factor in mCRPC [29]. Another study utilizing genomic data revealed that low-PSA, high-grade PC patients had a higher risk for cancer death, poor response to ADT, and neuroendocrine genomic features [30]. Their and our results allow a hypothesis that mHNPC with higher PSA may have a higher rate of hormone-sensitive clones, whereas mHNPC with low PSA may have a higher rate of nonhormone-sensitive clones, which may result in treatment-resistant CRPC. As an additional analysis, we stratified the 321 patients into four groups by the number of factors (0–3) among iPSA < 360 ng/mL, PSA nadir > 0.64 ng/mL, and TTN < 7 months. The Kaplan–Meier analysis revealed significant differences in OS after CPRC among those with 0, 1, 2, and 3 factors (Fig. 5). This stratification is potentially beneficial to distinguishing mCRPC patients with favorable and unfavorable prognoses, which requires further validation.

The treatment options for CRPC, such as DTX, CBZ, AA, ENZ, or their combinations, also were examined as predictive factors for OS in this study. Among them, treatment with AA/ENZ was identified as a significant factor on multivariate analysis. This result was consistent with those of previous trials of AA/ENZ for CRPC [2, 4, 8]. The next question is the impact of PSA kinetics during initial ADT on the response to the subsequent treatment for mCRPC. The mCRPC patients with favorable PSA kinetics in initial ADT may have favorable response to AA/ENZ due to their favorable treatment outcomes with ADT, and those with unfavorable PSA kinetics in initial ADT may have favorable response to DTX-based chemotherapy. Therefore, our next study will focus on the association between treatment strategy and outcomes in mCRPC patient groups who are stratified by PSA kinetics.

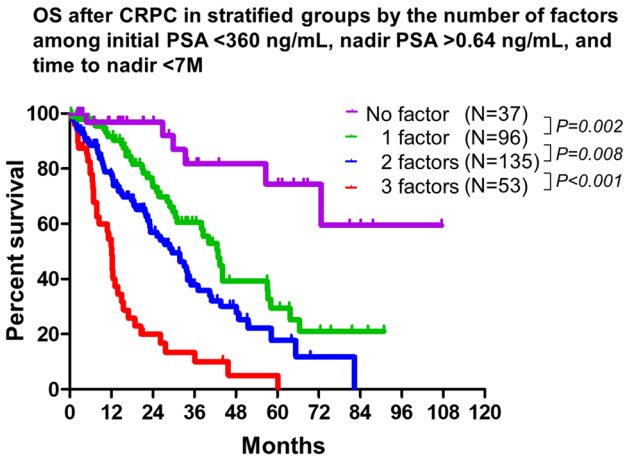

Fig. 5 OS after CRPC in stratified groups by the number of factors among initial PSA < 360 ng/mL, nadir PSA > 0.64 ng/mL, and time to nadir < 7 M. Patients with mCRPC ($N = 321$) were stratified into four groups by the number of factors (0–3) among iPSA < 360 ng/mL, PSA nadir > 0.64 ng/mL, and TTN < 7 M. The Kaplan–Meier analysis revealed significant differences in the OS after CPRC diagnosis among the groups with 0, 1, 2, and 3 factors. The 5-year OS in those with 0, 1, 2, and 3 factors presented 74, 29, 18, and 0.5%, respectively

Several limitations of this study must be acknowledged. First, the retrospective design and limited sample size may cause selection bias and influence confounding factors. In the enrollment process, 91 patients with mCRPC were excluded due to the lack of information on PSA nadir or CRPC treatment, which possibly caused biased patient background. To minimize this problem, we used a multi-institutional and multiregional database and the IPTW model that enables simulation of a pair-matched study. More large-scale study with prospective design is necessary to achieve a definitive conclusion. Second, our database lacked the number of bone metastases. Thus, we used EOD > 1 as a substitution for bone metastases ≥ 4 in CHAARTED criteria and ≥ 3 in LATITUDE criteria. Thirdly, lack of companion diagnostics in this study limited the availability of the data in the current situations requiring precision medicine. While companion diagnostics for PC have not been common for the decade in Japan, further studies including the association between genomic information and treatment outcomes are warranted. Finally, we could not evaluate patient comorbidities, such as cardiovascular disease and diabetic mellitus, which possibly affect mortality. Nevertheless, we acknowledge that this is the largest study to investigate the significance of PSA nadir and TTN during initial ADT for survival in mCRPC patients.

Conclusions

PSA nadir and TTN during initial ADT were significantly associated with OS after CRPC diagnosis in patients with mCRPC. More large-scale and prospective studies are warranted.

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Author contributions IH: manuscript writing, data analysis. SH: manuscript editing, data analysis. SN, MT, TS, SK, SH, MI, TK, SI, JS, HS, KM, and TT: project development, data collection. NT, YA, TH, and CO: project development, critical review and supervision

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