in vivo *35*: 373-384 (2021)
doi:10.21873/invivo.12268

Prognostic Factors in Hormone-sensitive Prostate Cancer Patients Treated With Combined Androgen Blockade: A Consecutive 15-year Study at a Single Japanese Institute

YOSHIYUKI MIYAZAWA, YOSHITAKA SEKINE, SEIJI ARAI, DAISUKE OKA, HIROSHI NAKAYAMA, TAKAHIRO SYUTO, MASASHI NOMURA, HIDEKAZU KOIKE, HIROSHI MATSUI, YASUHIRO SHIBATA and KAZUHIRO SUZUKI

Department of Urology, Gunma University Graduate School of Medicine, Gunma, Japan

Abstract. *Background/Aim: There are several treatment options for metastatic hormone-sensitive prostate cancer (mHSPC) in the world. In recent years, the use of docetaxel, abiraterone, enzalutamide, and apalutamide has been used for mHSPC, but combined androgen blockade (CAB) therapy using first-generation antiandrogens has been widely used in Japan. There is a background. We performed a consecutive study of patients who received combined androgen blockade (CAB) at a single institute to determine the prognostic factors for mHSPC. Patients and Methods: We conducted a consecutive study of 237 mHSPC patients treated with CAB from 2003 to 2017 at the Gunma University Hospital. Prostate-specific antigen progression-free survival (PSA-PFS) and overall survival (OS) were estimated by the Kaplan-Meier method. The associations between pre-treatment risk factors and the PSA response 3 months after starting CAB, PSA-PFS, and OS were evaluated by the Cox proportional hazards model. Results: Among the 237 cases, the median PSA-PFS and OS times were 63.0 and 91.4 months, respectively. The median PSA-PFS and OS times of M1 cases (174 cases, 73.4% of all 237 cases) were 36.1 and 75.9 months, respectively. The Eastern Cooperative Oncology Group performance status (ECOG PS) score, hemoglobin (Hb), lactate dehydrogenase, extent of disease, visceral metastasis (no vs. yes), and PSA response after 3 months were significant predictors of OS according to Cox regression analysis of prognostic factors in M1 patients. The ECOG PS, Hb, visceral metastasis (no vs. yes), and PSA response after 3 months predicted OS high-risk patients in LATITUDE criteria. The OS was 92.1 months in the low-risk group (0-1 risk factors), 48.2 months in the intermediate-risk group (2 risk factors), and 16.9 months in the high-risk group (3-4 risk factors). Conclusion: CAB should be considered as a treatment option for strictly selected patients with mHSPC, even though novel treatments are available.*

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Correspondence to: Yoshiyuki Miyazawa, Department of Urology, Gunma University Graduate School of Medicine 3-9-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81 272208306, Fax: +81 272208307, e-mail: miya.yoshi@gunma-u.ac.jp

Key Words: Prostate cancer, metastatic hormone-sensitive prostate cancer, combined androgen blockade, androgen deprivation therapy, risk classification.

The incidence of prostate cancer has increased in certain Western countries and is increasing in Japan (1). Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer-related death worldwide (2). According to the results of a statistical study published in 2019 by the National Cancer Center of Japan, the 5-year relative survival rate for localized prostate cancer and locally advanced prostate cancer is 100%, and the prognosis is good; however, the 5-year relative survival rate of metastatic prostate cancer is only 61.3% (3). The conventional treatment for metastatic hormone-sensitive prostate cancer (mHSPC) is androgen deprivation therapy (ADT). Whether adding other drugs to conventional ADT can improve the prognosis is an important question. Several studies have been conducted to further improve the prognosis of mHSPC patients. In 2015, the use of six courses of docetaxel therapy, which has proven effective in castration-resistant prostate cancer (CRPC), was shown to improve the prognosis of mHSPC (4). Sweeny *et al.* reported that the combination of standard ADT and six cycles of docetaxel significantly improved overall survival (OS) compared to standard ADT alone in the Chemohormonal Therapy *Versus* Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study. They stratified mHSPC

patients by the metastatic burden ("low-volume" or "high-volume"). In 2017, the efficacy of abiraterone acetate (AA) plus prednisolone for prolonging the mHSPC survival time was reported by Fizzazi *et al*. in the LATITUDE study. They stratified mHSPC patients into high-risk and non-high-risk groups, and demonstrated the added benefit of AA in high-risk patients (5). In 2019, a combination of enzalutamide and apalutamide, which are second-generation antiandrogens, with ADT was shown to improve the prognosis of mHSPC patients in the ARCHES, ENZAMET, and TITAN studies (6-8). According to the Japanese Urological Association guidelines, combined androgen blockade (CAB) using non-steroidal agents, such as bicalutamide, in combination with ADT therapy is recommended as grade B, and has been widely used to treat mHSPC (9). In the present study, we examined the efficacy of CAB therapy, which has been used at our institute, and the prognostic factors for mHSPC in Japanese patients. We also investigated the prognostic factors of the PSA response 3 months after treatment, in addition to known pre-treatment prognostic factors.

Patients and Methods

A consecutive study was conducted with all mHSPC patients who underwent CAB therapy at Gunma University Hospital from January 2003 to December 2017. The total number of mHSPC patients who underwent CAB therapy during the study period was 237. ADT included orchiectomy, luteinizing hormone-releasing hormone (LHRH) agonists and gonadotropin-releasing hormone (GnRH) antagonists. CAB was defined as the administration of anti-androgens such as bicalutamide in addition to surgical or medical castration. No patient received upfront docetaxel and/or AA acetate as the initial therapy. Sequential treatment was administered after first-line hormonal therapy at the physician's discretion. In this study, prostate-specific antigen progression-free survival (PSA-PFS) and OS began at the CAB or ADT start date. As all patients who started treatment with ADT alone transitioned to CAB, the endpoint of the PSA-PFS measurement was the day on which PSA progressed during CAB therapy. Disease progression was assessed following the Prostate Cancer Working Group 2 criteria. A performance status (PS) evaluation was performed following the Eastern Cooperative Oncology Group performance status (ECOG PS) definition. The bony metastasis burden was evaluated using an extent of disease (EOD) score that was classified as described by Soloway *et al*., based on bone scintigraphy at the time of the initial diagnosis (10). We used the CHAARTED criteria [where "high-volume" is defined as the presence of visceral metastases or ≥4 bone lesions, with ≥1 beyond the vertebral bodies and pelvis (4)] and the LATITUDE criteria (where "high-risk" cases are those with at least two high-risk prognostic features [*e.g*., Gleason score (GS) ≥8, presence of ≥3 bone lesions, or the presence of measurable visceral metastasis (5)] as stratification factors, based on the burden of metastasis and pathological grade. We collected data and examined prognostic factors, including age, PS, symptoms at diagnosis, body mass index (BMI), PSA, hemoglobin (Hb), albumin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) levels at diagnosis; primary GS; location and number of metastases; year diagnosed; PSA reduction (%) 3 months after starting treatment compared to baseline; CHAARTED risk criteria; LATITUDE risk criteria; and all treatment parameters. In Japan, the CRPC drug docetaxel first became available in 2008, while enzalutamide and AA became available in 2014. Based on the time when each drug first became available, the diagnosis was examined every 5 years from 2003 to 2007, 2008 to 2012, and 2013 to 2017, and compared to that at the start of treatment. The PSA-PFS and OS rates were examined by the Kaplan-Meier method. Differences were compared using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards regression model. Hazard ratios and 95% confidence intervals were calculated. SPSS software (ver. 25.0; IBM Corp., Armonk, NY, USA) was used for the statistical analysis. A p-value<0.05 was considered significant.

Ethics approval and consent to participate. We explained the study to all participants in this study. All participants agreed in writing to participate. This study was approved by the Institutional Review Board at the Gunma University Hospital (No1339). There are no administrative permissions or licenses to access the data to formally note. Present studies were conducted according to International Conference on Harmonization/Good clinical Practice (ICH/GCP) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Patient characteristics. The patient characteristics are shown in Table I. A total of 237 patients were analyzed. The median follow-up was 3.48 years (range=0.5-14.8 years). Of the 237 patients, 63 died from prostate cancer and 31 died from other causes. The median age was 73.2 years. The median PSA before treatment was 97.4 ng/ml. The GS was 8-10 in 206 cases (86.9%). A total of 174 patients (73.4%) had distant metastases. In total, 107 cases (45.1%) were classified as high-volume disease (HVD) according to the CHAARTED criteria, and 116 (48.9%) were classified as high-risk prostate cancer according to the LATITUDE criteria. Only 17 cases (14.8% in all LATITUDE high-risk cases) met all three of the three LATITUDE criteria. Ninety-one cases (78.4% of all LATITUDE high-risk cases) met the criteria of both GS ≥8 and ≥3 bone metastases. LHRH agonists were the most frequently used agents in 165 cases (69.6%). The first-line treatment was CAB therapy in most cases (218 cases, 92.0%). Delayed CAB therapy was performed in all patients who started with ADT alone. Local prostate treatment was performed in 40 cases (16.9%), all with external-beam radiation therapy, and no surgery was performed. The median PSA 3 months after the start of ADT or CAB was 1.6 ng/ml [range=0.001-1,420.1 ng/ml; standard deviation (SD), 125.1 ng/ml]. The median decline in PSA after 3 months compared to the initial level was 97.0% (range=19.3% increase to 99.1% decrease). Table II provides the summary of patient background by treatment generation. The proportions of cases that matched the high-volume CHAARTED criteria and high-risk LATITUDE criteria were

Table I. *Patient characteristics*.

Characteristic	Median±SD	Range	Characteristic	Median±SD	Range
Age (y)	73.2±8.6	48-91	EOD		
Initial PSA (ng/ml)	97.4±1,447.7	3.18-10,455	1	55 (23.2%)	
Testosterone (ng/ml)	4.19±2.42	0.2-11.4	2	63 (26.6%)	
ALP (IU/ml)	265.5±686.4	81-7,270	3	15 (6.3%)	
LDH (IU/ml)	194.5±87.7	89-913	4	7 (3.0%)	
Hb (g/dl)	13.4±2.04	6.8-17.9	CHAARTED high volume	107 (45.1%)	
BMI	22.4±3.26	14.5-32.0	LATITUDE high risk	116 (48.9%)	
Stage	n (%)		In LATITUDE high risk group,		
N1M0	63 (26.6%)		(≥GS 8)+(≥3 bone metastasis)	91 (78.4%)	
N0M1a	2 (0.8%)		(≥GS 8)+(visceral metastasis +)	7 (6.0%)	
N0M1b	57 (24.1%)		(≥3 bone metastasis)+	1 (0.8%)	
N0M1c	9 (3.8%)		(visceral metastasis +)		
N1M1a	21 (8.9%)		Met all three criteria	17 (14.8%)	
N1M1b	63 (26.6%)		Castration procedure		
N1M1c	22 (9.2%)		LHRH agonist	165 (69.6%)	
Gleason score			GnRH antagonist	40 (16.9%)	
6	6 (2.5%)		Surgical castration	32 (13.5%)	
7	22 (9.3%)		Timing of CAB		
8	38 (16.0%)		CAB from the start of treatment	218 (92.0%)	
9	147 (62.0%)		Delayed CAB	19 (8.0%)	
10	21 (8.9%)		Local treatment		
Unknown	3 (1.3%)		None	197 (83.1%)	
ECOG PS			Radiation	40 (16.9%)	
0	196 (82.7%)		Prostatectomy	0 (0.0%)	
1	23 (9.7%)		Symptoms at diagnosis	119 (50.2%)	
2	18 (7.6%)		Total regimens during	3.0±1.62	1-7 (range)
Metastasis site			observation period	(median±SD)	
Non regional lymph node	83 (35.0%)		Docetaxel	25 (10.5%)	
Lung	23 (0%)		Enzalutamide/Abiraterone	25 (10.5%)	
Liver	4 (1.7%)		Cabazitaxel	4 (1.7%)	
Bone	140 (59.1%)		Bone-modifying agents	66 (27.8%)	

SD: Standard deviation, PSA: prostate-specific antigen, ALP: alkaline phosphatase, Hb: hemoglobin, LDH: lactose dehydrogenase, BMI: body mass index, ECOG PS: Eastern Cooperative Oncology Group performance status, EOD: extent of disease, CHAARTED: Chemohormonal Therapy *Versus* Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer, GS: Gleason score, LHRH: luteinizing hormone-releasing hormone, GnRH: gonadotropin-releasing hormone, CAB: combined androgen blockade.

significantly lower in 2013-2017 than in other generations (Mantel-Haenszel tests, both $p<0.01$).

PSA-PFS and OS in the patient groups. Of the 237 total cases, the median PSA-PFS and OS times were 63.0 and 91.4 months, respectively (Figure 1A and B). The median PSA-PFS and OS times were 36.1 and 75.9 months, respectively, in the M1 cases (174 cases, 73.4%) (Figure 1C and D). The OS time was 124.8 months for M1a, 62.6 months for M1b, and 53.2 months for M1c. The OS time in the M1c group was significantly shorter than that in the other two groups. All of the M1 cases (n=174) were stratified by the CHAARTED criteria, and the PSA-PFS and OS were compared using the Kaplan-Meier method. The HVD group had a PSA-PFS time of 17.5 months, whereas in the low volume disease (LVD) group it was 125.8 months (log-rank test, $p<0.0001$). The HVD group had an OS time of 49.4 months, whereas in the LVD group it was 175.3 months (log-rank test, $p<0.0001$) (Figure 2A and B). Similarly, we compared the PSA-PFS and OS after stratification based on the LATITUDE criteria. The PSA-PFS and OS times were 21.2 and 58.6 months in the high-risk group, and 102.7 and 129.3 months in the non-high-risk group (log-rank test, $p<0.05$) (Figure 2C and D). We summarize the PSA-PFS and OS data after 1, 3, 5, 7, and 10 years by patient group in Table III.

Prognosis according to the time of treatment generation. Figure 3A and B summarize the PSA-PFS and OS times by treatment generation. The PSA-PFS times for patients during 2003-2007, 2008-2012, and 2013-2017 were 37.6 months, 38.2 months, and not yet reached (NYR), respectively. PSA-PFS was significantly better in the cases of the 2013-2017 group than in the other groups. The OS times for patients

Table II. *Patient characteristics by treatment*.

Characteristic	Total N=237	2003-2007 n=62	2008-2012 n=95	2013-2017 n=80	*p*-Value
Stage	n (%)	n (%)	n (%)	n (%)	
N1M0	63 (26.6%)	9 (14.5%)	24 (25.3%)	30 (37.5%)	0.606*
N0M1a	2 (0.8%)	1 (1.6%)	1 (1.1%)	0	
N0M1b	57 (24.1%)	23 (37.1%)	19 (20.0%)	15 (18.8%)	
N0M1c	9 (3.8%)	5 (8.1%)	2 (2.1%)	2 (2.5%)	
N1M1a	21 (8.9%)	2 (3.2%)	10 (10.5%)	9 (11.3%)	
N1M1b	63 (26.6%)	19 (30.6%)	27 (28.4%)	17 (21.3%)	
N1M1c	22 (9.2%)	3 (4.8%)	12 (12.6%)	7 (8.8%)	
Gleason score					
6	6 (2.5%)	0	1 (1.1%)	5 (6.3%)	0.514*
7	22 (9.3%)	12 (19.4%)	6 (6.3%)	4 (5.0%)	
8	38 (16.0%)	9 (14.5%)	15 (15.8%)	14 (17.5%)	
9	147 (62.0%)	33 (53.2%)	63 (66.3%)	51 (63.8%)	
10	21 (8.9%)	7 (11.3%)	9 (9.5%)	5 (6.3%)	
Unknown	3 (1.3%)	1 (1.6%)	1 (1.1%)	1 (1.3%)	
ECOG PS					
0	196 (82.7%)	59 (95.2%)	68 (71.6%)	69 (89.2%)	0.062*
1	23 (9.7%)	1 (1.6%)	16 (16.8%)	6 (7.5%)	
2	18 (7.6%)	2 (3.2%)	11 (11.6%)	5 (6.3%)	
Metastasis site					
Non regional lymph node	83 (35.0%)	22 (35.5%)	41 (43.3%)	20 (25.0%)	0.260*
Lung	23 (0%)	8 (12.9%)	10 (10.5%)	5 (6.3%)	
Liver	4 (1.7%)	0	3 (3.2%)	1 (1.3%)	
Bone	140 (59.1%)	46 (74.2%)	55 (47.9%)	39 (48.8%)	
EOD					
1	55 (23.2%)	20 (32.3%)	16 (16.8%)	39 (48.8%)	0.004*
2	63 (26.6%)	16 (25.8%)	28 (29.5%)	19 (23.8%)	
3	15 (6.3%)	6 (9.7%)	8 (8.4%)	19 (23.8%)	
4	7 (3.0%)	4 (6.5%)	3 (3.2%)	1 (1.3%)	
CHAARTED high volume	107 (45.1%)	36 (58.1%)	49 (51.6%)	22 (27.5%)	<0.001*
LATITUDE high risk	116 (48.9%)	38 (32.8%)	55 (47.4%)	23 (19.8%)	<0.001*
In LATITUDE high risk group, (≥GS 8)+(≥3 bone metastasis)	91 (78.4%)	30 (78.9%)	43 (78.2%)	18 (78.3%)	0.256*
(≥GS 8)+(visceral metastasis +)	7 (6.0%)	3 (7.9%)	3 (5.4%)	1 (4.3%)	
(≥3 bone metastasis)+(visceral metastasis +)	1 (0.8%)	1 (2.7%)	0	0	
Meets all three criteria	17 (14.8%)	4 (10.5%)	9 (16.4%)	4 (17.3%)	
Castration procedure					
LHRH agonist	165 (69.6%)	62 (100%)	67 (70.5%)	36 (45.0%)	0.001*
GnRH antagonist	40 (16.9%)	0	1 (1.1%)	39 (48.8%)	
Surgical castration	32 (13.5%)	0	27 (28.4%)	5 (6.3%)	
Timing of CAB					
CAB from the start of treatment	218 (92.0%)	54 (87.1%)	88 (92.6%)	76 (95.0%)	0.589*
Delayed CAB	19 (8.0%)	8 (12.9%)	7 (7.4%)	4 (5.0%)	
Local treatment					
None	197 (83.1%)	57 (91.9%)	84 (88.4%)	56 (70.0%)	0.002*
Radiation	40 (16.9%)	5 (8.1%)	11 (11.6%)	24 (30.0%)	
Prostatectomy	0	0	0	0	
Total regimens in observation period after CAB (median±SD)	3.0±1.62	3.4±1.62	3.2±1.62	2.4±1.12	
Docetaxel	25 (10.5%)	6 (9.7%)	16 (16.8%)	3 (3.8%)	0.128*
Enzalutamide/Abiraterone	25 (10.5%)	2 (3.2%)	16 (16.8%)	7 (8.8%)	
Cabazitaxel	4 (1.7%)	1 (1.6%)	3 (3.2%)	0	
Bone-modifying agents	66 (27.8%)	7 (11.3%)	35 (36.8%)	24 (30.0%)	

SD: Standard deviation, PSA: prostate-specific antigen, ALP: alkaline phosphatase, Hb: hemoglobin, LDH: lactose dehydrogenase, BMI: body mass index, ECOG PS: Eastern Cooperative Oncology Group performance status, EOD: extent of disease, CHAARTED: Chemohormonal Therapy *Versus* Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer, GS: Gleason score, LHRH: luteinizing hormone-releasing hormone, GnRH: gonadotropin-releasing hormone, CAB: combined androgen blockade. *Kruskal-Wallis test.

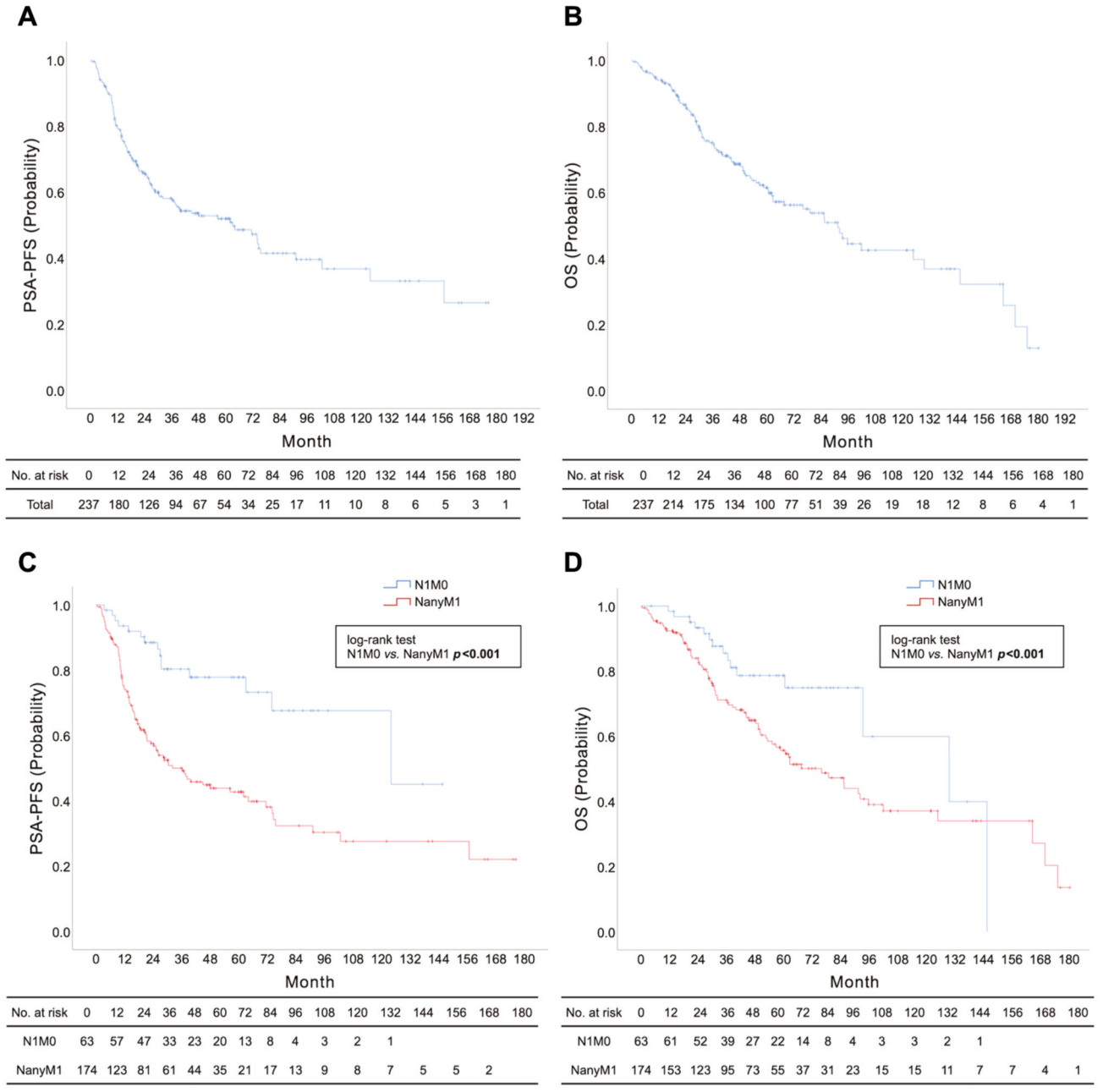


Figure 1. Kaplan-Meier estimates of cumulative PSA-PFS (A) and OS (B) in all patients (n=237). Kaplan-Meier estimates of cumulative PSA-PFS (C) and OS (D) compared by stage (N1M0 *vs*. NanyM1). *p*-Values were computed using log-rank tests.

during 2003-2007, 2008-2012, and 2013-2017 were 85.3 months, 78.9 months, and NYR, respectively. The OS time of the patients in the 2013-2017 group was significantly better than that of those in the other groups.

Prognostic factors in M1 patients. A multivariate Cox regression analysis of prognostic factors in M1 patients (n=174), including the PSA response at 3 months, was performed. The ECOG PS (0 *vs*. ≥1), Hb (≥13.4 *vs*. <13.4 g/dl), LDH (<195 *vs*. ≥195 IU/ml), EOD (0-1 *vs*. ≥2), visceral metastasis (no *vs*. yes), and PSA response at 3 months (≥97.0% *vs*. <97.0%) predicted OS significantly (all $p<0.05$) (Table IV). The OS was stratified and analyzed using the identified predictors. The OS of low-risk (0-1 risk factors), intermediate-risk (2-3 risk factors), and high-risk (4-6 risk factors) were NYR, 75.9 months, and 20.9

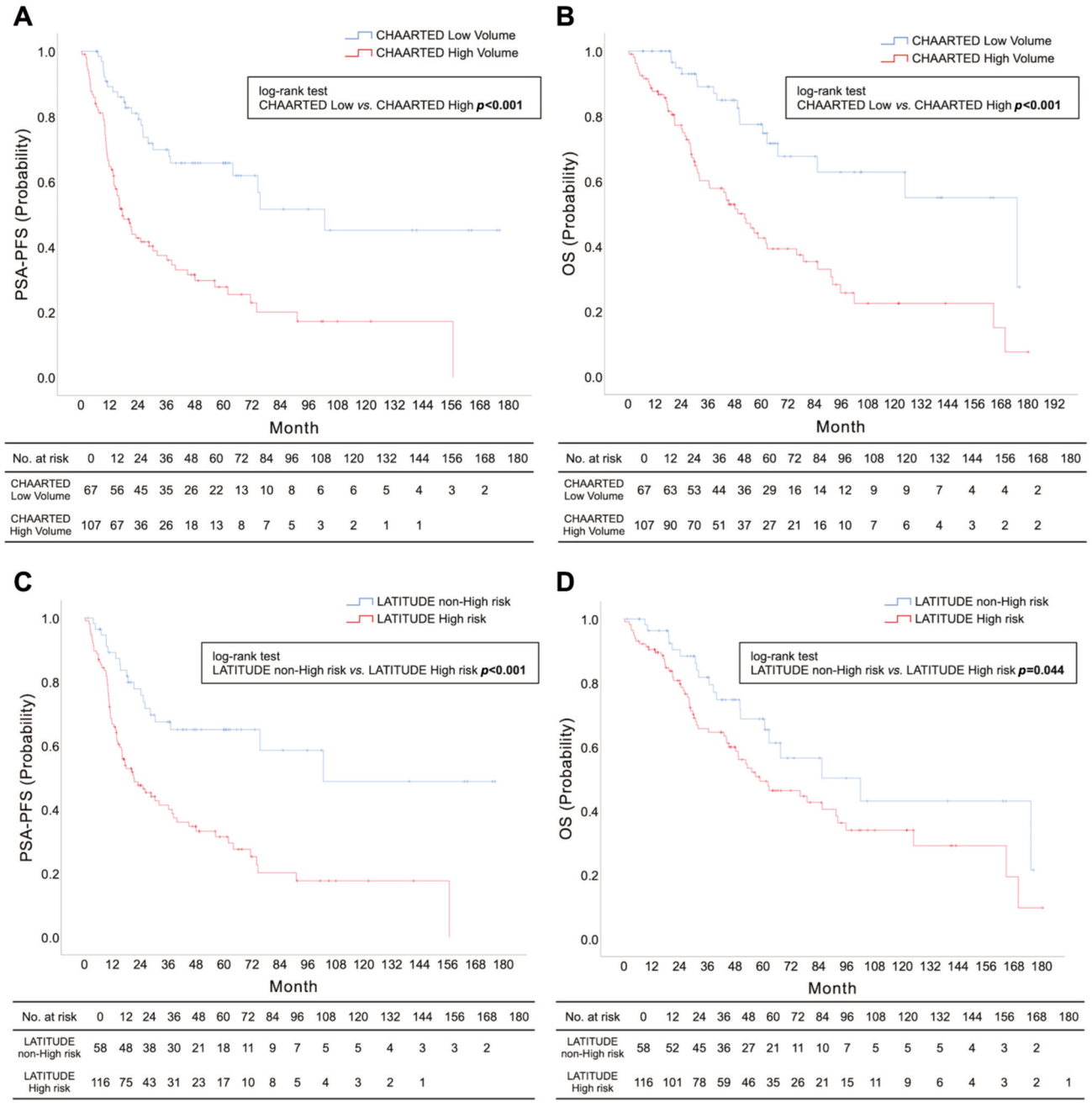


Figure 2. *Kaplan-Meier estimates of cumulative PSA-PFS (A) and OS (B) compared by CHAARTED criteria and PSA-PFS (C) and OS (D) compared by LATITUDE criteria. p-Values were computed using log-rank tests.*

months, respectively, showing a significant difference (all $p<0.05$) (Figure 4).

Prognostic factors in LATITUDE high-risk patients. A multivariate Cox regression analysis of prognostic factors in LATITUDE high-risk patients (n=116), including the PSA response at 3 months, was performed to further stratify the LATITUDE high-risk cases. The ECOG PS (0 *vs.* ≥1), Hb (≥13.4 *vs.* <13.4 g/dl), visceral metastasis (no *vs.* yes), and PSA response at 3 months (≥97.0% *vs.* <97.0%) were significant predictors of OS (all $p<0.05$) (Table V). The multivariate analysis showed that risk could be stratified based on the number of risk factors present. The OS of low-risk (0-1 risk factors), intermediate-risk (2 risk factors), and

Table III. *Summary of PSA-PFS and OS rates*.

	PSA-PFS					OS				
	1 year	3 years	5 years	7 years	10 years	1 year	3 years	5 years	7 years	10 years
Total (N=237)	79.3%	58.1%	51.9%	41.5%	36.8%	94.0%	75.1%	61.5%	53.8%	42.6%
N1M0 (n=63)	93.6%	80.4%	77.8%	67.6%	67.6%	98.4%	85.5%	78.7%	74.9%	59.9%
All M1 (n=174)	74.1%	50.0%	42.7%	32.4%	27.6%	92.4%	71.1%	55.7%	47.3%	37.1%
In all M1 patients (n=174)										
M1a (n=23)	81.8%	72.2%	55.6%	37.1%	–	100.0%	84.4%	77.9%	64.9%	32.5%
M1b (n=120)	74.3%	54.0%	41.0%	34.4%	31.0%	92.3%	72.1%	53.0%	46.1%	35.8%
M1c (n=31)	67.7%	60.6%	40.8%	15.3%	–	87.1%	58.4%	44.8%	38.4%	25.6%
CHAARTED low volume (n=67)	89.2%	69.9%	65.7%	51.2%	45.1%	100.0%	89.0%	77.5%	67.6%	62.8%
CHAARTED high volume (n=107)	64.7%	37.4%	27.7%	20.0%	17.2%	87.6%	60.2%	42.5%	35.3%	22.4%
LATITUDE non-high risk (n=58)	89.2%	67.5%	65.0%	58.5%	38.8%	96.4%	81.8%	68.8%	56.6%	43.1%
LATITUDE high risk (n=116)	66.8%	41.4%	31.5%	20.2%	17.7%	90.5%	65.7%	49.3%	42.7%	34.0%

PSA-PFS: Prostate specific antigen-progression-free survival, OS: overall survival, CHAARTED: Chemohormonal Therapy *Versus* Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer.

high-risk (3-4 risk factors) were 92.1, 48.2 and 16.9 months, respectively, showing a significant difference (all $p<0.05$) (Figure 5). The 5-year OS rate was 69.4% in the low-risk group, 36.9% in the intermediate-risk group, and NYR in the high-risk group.

Discussion

The prognosis of metastatic castration-sensitive prostate cancer is known to vary widely, and many researchers have reported the effects of castration treatment (11-13). Glass *et al*. reported four risk factors: localization of bone disease (appendicular *vs*. axial skeleton), PS (0 *vs*. ≥1), PSA (<65 *vs*. ≥65 ng/ml), and GS (<8 *vs*. ≥8) (14). Gravis *et al*. reported that ALP in particular, as well as pain intensity, Hb, LDH, and bone metastasis, were independent risk factors for castration-sensitive metastatic prostate carcinoma (15). Akamatsu *et al*. stratified patients into three groups using a risk model that included EOD score ≥2, presence of liver metastasis, LDH >250 U/l, and primary GS of 5. Notably, they validated the prognostic model in a validation cohort (16). Narita *et al*. found that four risk factors, *i.e*., GS ≥9, lymph node metastasis, EOD score ≥2, and serum LDH >220 IU/l (17). Stage-specific embryonic antigen-4 (SSEA-4) expression is associated with malignant aggressiveness and is useful as a marker for identifying cancer stem cells. Yuno, *et al*. examined the expression of SSEA-4 and the effect of hormone therapy on prostate cancer. They found that anti-tumor effects of hormonal therapy were inversely correlated with SSEA-4 expression level. It may be possible to predict the prognosis of mHSPC using SSEA-4 (18). We identified six risk factors in this study: ECOG PS (0 *vs*. ≥1), Hb (≥13.4 *vs*. <13.4 g/dL), LDH (<195 *vs* ≥195 IU/l), EOD (0-1 *vs*. ≥2), visceral metastasis (no *vs*. yes), and PSA response at 3 months (≥97.0% *vs*. <97.0%). Although the risk factors that we identified were similar to those reported previously, the PSA response 3 months after treatment was an important additional prognostic factor. It is well known that a reduction in the PSA level after treatment is a good predictor of the response to androgen receptor-based treatment. Matsubara *et al*. reported that patients with a lower PSA after AA and prednisone treatment had a lower risk of death, based on the post-hoc analysis performed in the LATITUDE trial (19). We think the PSA decline rate 3 months after the start of treatment will be a good index for predicting future treatment effects.

The prognostic criteria of the CHAARTED and LATITUDE studies proved useful in our study. In the final LATITUDE analysis, the median OS time was significantly longer in the AA plus prednisone group than in the placebo group (19). Suzuki *et al*. reported that the median OS was NYR in their AA plus prednisone and placebo groups; however, the 5-year OS rate was 69.2% for the AA plus prednisone group and 53.7% for the placebo group in the Japanese subgroup according to the final LATITUDE subgroup analysis (20). According to the results of our analysis of the LATITUDE high-risk group, the median OS time in the low-risk group was 92.1 months, which was better than that in the LATITUDE trial. The 5-year OS rate was 69.4%, which was almost equivalent to that in the Japanese subgroup. AA is much more costly than docetaxel (21, 22); by selecting patients among the LATITUDE high-risk cases with a better prognosis, we propose to introduce CAB therapy as an option for patients experiencing high treatment costs.

In this study, the analysis by treatment generation showed that PSA-PFS and OS rates tended to be better for later generations. In fact, the main reason was likely that diagnoses tended to be made under a relatively low tumor burden in recent years. Expansion of the PSA screening program may also be a factor (23).

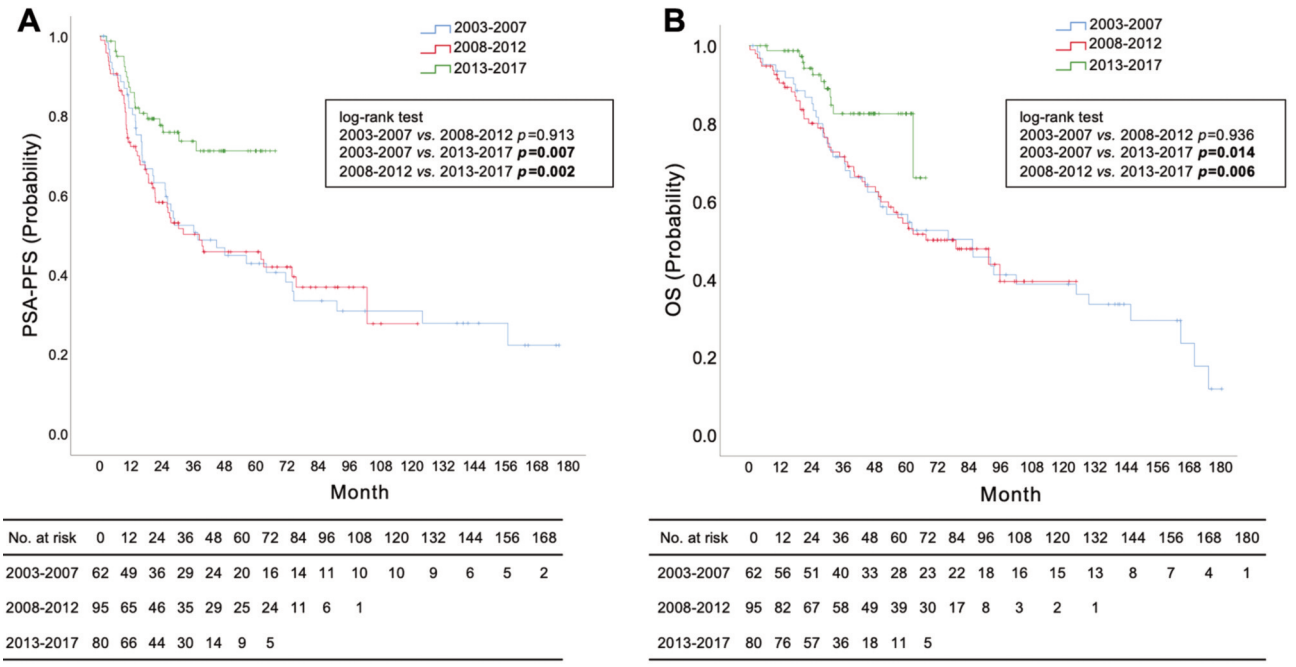
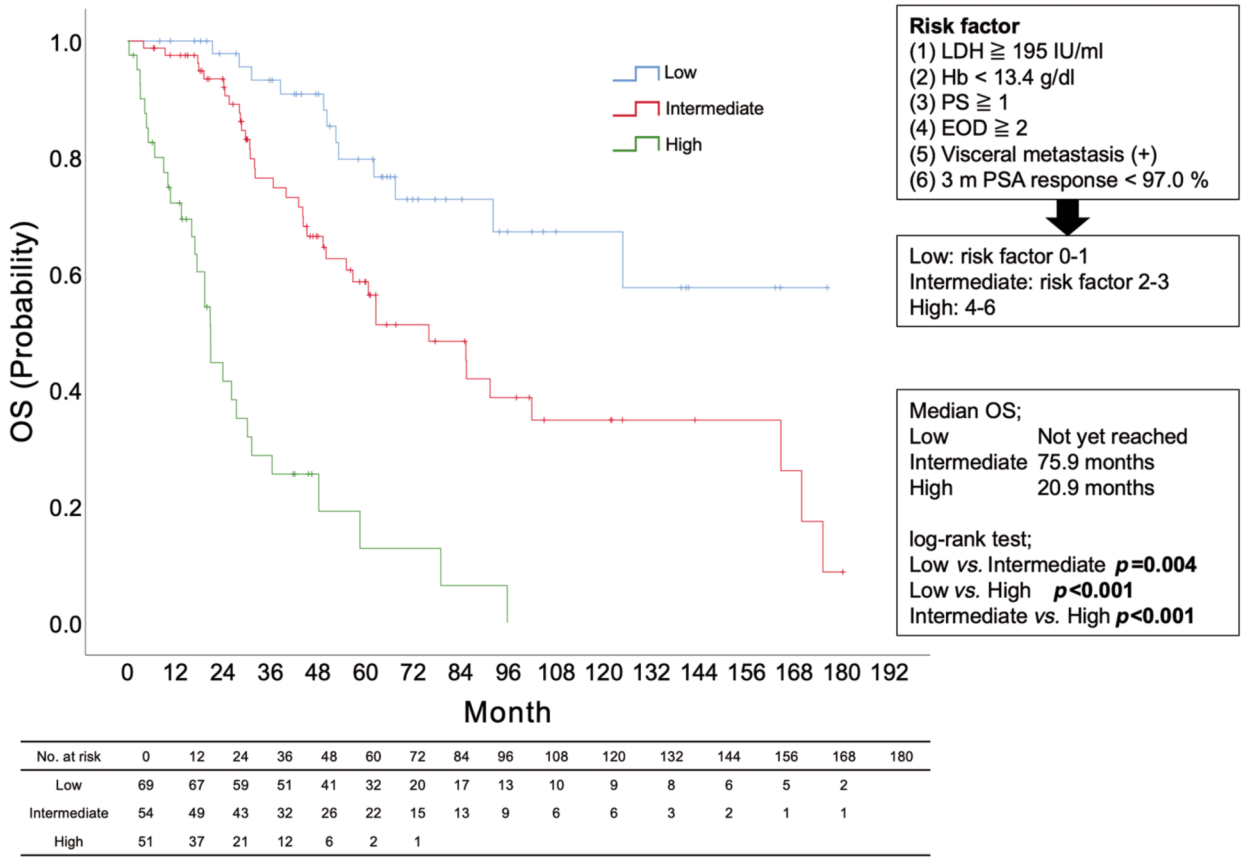


Figure 3. *Kaplan-Meier estimates of cumulative PSA-PFS (A) and OS (B) compared by generations (2003-2007 vs. 2008-2012 vs. 2013-2017). p-Values were computed using log-rank tests.*

Table IV. *Cox regression analysis of all M1 cases (n=174).*

Variable	Univariate analysis			Multivariate analysis		
	p-Value	HR	95% CI	*p*-Value	HR	95% CI
Age (y) (≤73.2 *vs.* >73.2)	0.200					
Symptoms at diagnosis (no *vs.* yes)	0.213					
Initial PSA	0.032	1.683	1.045-2.711	0.872		
ALP (<267 *vs.* ≥267 IU/ml)	0.001	2.225	1.359-3.644	0.269		
LDH (<195 *vs.* ≥195 IU/ml)	<0.001	2.357	1.479-3.756	0.013	1.876	1.143-3.048
Hb (≥13.4 *vs.* <13.4 g/dl)	<0.001	2.589	1.761-4.641	0.008	2.033	1.201-3.442
ECOG PS (0 *vs.* 1-2)	<0.001	3.027	1.850-4.953	0.003	2.223	1.303-3.795
BMI (≥22.4 *vs.* <22.4)	0.004	1.977	1.247-3.134	0.257		
EOD score (0-1 *vs.* 2-4)	<0.001	2.977	1.861-4.738	0.005	2.092	1.246-3.512
EOD score (0-2 *vs.* 3-4)	<0.001	2.836	1.698-4.738	0.354		
GS (6-7 *vs.* ≥8)	0.302					
GS 5 (no *vs.* yes)	0.164					
Visceral metastasis (no *vs.* yes)	0.022	1.904	1.095-3.309	0.013	2.048	1.167-3.595
Local radiation therapy (yes *vs.* no)	0.183					
LATITUDE high risk (no *vs.* yes)	0.047	1.676	1.007-2.790	0.653		
CHAARTED high volume (no *vs.* yes)	<0.001	3.080	1.796-5.280	0.197		
PSA at 3 months (<1.6 *vs.* ≥1.6 ng/ml)	0.001	2.407	1.466-3.952	0.771		
PSA decline at 3 months (≥97.0 *vs.* <97.0%)	0.008	1.835	1.172-2.873	<0.001	2.256	1.427-3.566

PSA: Prostate-specific antigen, ALP: alkaline phosphatase, LDH: lactose dehydrogenase, Hb: hemoglobin, ECOG PS: Eastern Cooperative Oncology Group performance status, BMI: body mass index EOD: extent of disease, GS: Gleason score, CHAARTED: Chemohormonal Therapy *Versus* Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer.



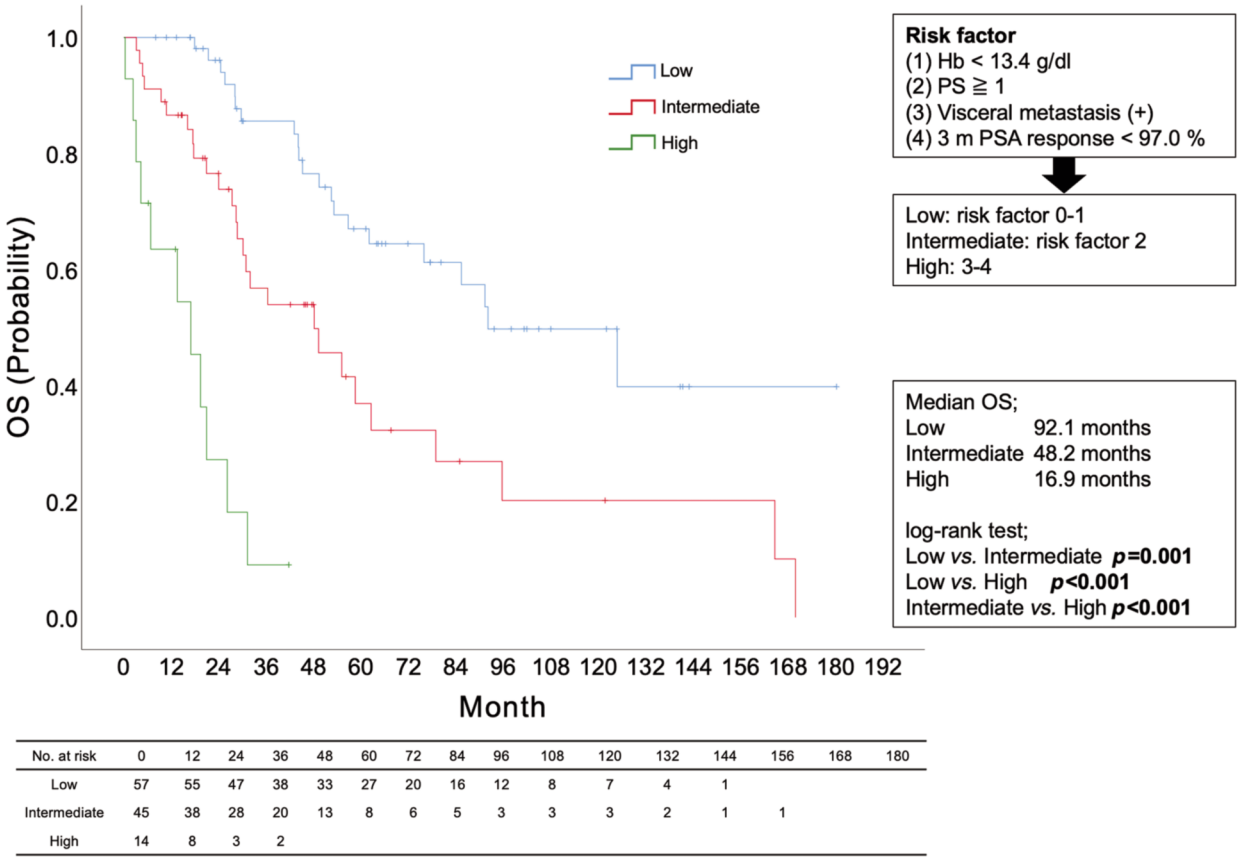
No. at risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180
Low	69	67	59	51	41	32	20	17	13	10	9	8	6	5	2	
Intermediate	54	49	43	32	26	22	15	13	9	6	6	3	2	1	1	
High	51	37	21	12	6	2	1									

Figure 4. *Kaplan-Meier estimates of cumulative OS according to risk factors in M1 patients (n=174). p-Values were computed using log-rank tests. Low-risk patients had no or 1 risk factor, intermediate-risk patients had 2-3 risk factors, and high-risk patients had 4-6 risk factors.*

Table V. *Cox regression analysis of LATITUDE high-risk cases (n=116).*

Variable	Univariate analysis			Multivariate analysis		
	p-Value	HR	95% CI	*p*-Value	HR	95% CI
Age (years) (≤73.2 *vs.* >73.2)	0.239					
Symptoms at diagnosis (no *vs.* yes)	0.365					
Initial PSA	0.311					
ALP (<267 *vs.* ≥267 IU/ml)	0.009	2.236	1.220-4.098	0.064		
LDH (<195 *vs.* ≥195 IU/ml)	0.006	2.156	1.245-3.733	0.062		
Hb (≥13.4 *vs.* <13.4 g/dl)	<0.001	2.926	1.632-5.246	0.001	2.863	1.582-5.181
ECOG PS (0 *vs.* 1-2)	<0.001	2.756	1.568-4.847	0.001	2.664	1.479-4.801
BMI (≥22.4 *vs.* <22.4)	0.032	1.768	1.050-2.976	0.235		
EOD score (0-1 *vs.* 2-4)	0.004	2.536	1.354-4.749	0.115		
EOD score (0-2 *vs.* 3-4)	0.007	2.222	1.241-3.979	0.416		
GS (6-7 *vs.* ≥8)	0.821					
GS 5 (no *vs.* yes)	0.392					
Visceral metastasis (no *vs.* yes)	0.089					
Local radiation therapy (yes *vs.* no)	0.218					
PSA at 3 months (<1.6 *vs.* ≥1.6 ng/ml)	0.006	2.268	1.271-4.048	0.115		
PSA decline at 3 months (≥97.0 *vs.* <97.0%)	0.034	1.746	1.044-2.922	0.034	1.885	1.050-3.384

PSA: Prostate-specific antigen, ALP: alkaline phosphatase, LDH: lactose dehydrogenase, Hb: hemoglobin, ECOG PS: Eastern Cooperative Oncology Group performance status, BMI: body mass index EOD: extent of disease, GS: Gleason score.



No. at risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180
Low	57	55	47	38	33	27	20	16	12	8	7	4	1			
Intermediate	45	38	28	20	13	8	6	5	3	3	3	2	1	1		
High	14	8	3	2												

Figure 5. *Kaplan-Meier estimates of cumulative OS according to risk factors in M1 LATITUDE high-risk patients (n=116). p-Values were computed using log-rank tests. Low-risk patients had no or 1 risk factor, intermediate-risk patients had 2 risk factors, and high-risk patients had 3-4 risk factors.*

This consecutive study has several limitations and weaknesses. First, it summarized 15 years of treatment from only one institution; thus, the stratification based on the risk factors identified herein will need to be tested in another validation cohort or prospective trial. Second, because of the long data collection period, changes in the drugs available for post-treatment CAB may have affected the prognoses. Third, differences in the methods used for castration by age group may have affected the PSA response 3 months after treatment. In Japan, GnRH antagonists first became commercially available in 2013. Antagonists lower testosterone to the castration level more quickly than agonists (24), which may have affected the PSA response 3 months after starting CAB. One of the strengths and usefulness of this study is that we were able to point out the possibility of finding effective cases even with CAB therapy. In our present study, it was found that low-risk patients have a good prognosis with CAB. If the PSA response is poor 3 months after starting treatment, it is necessary to consider switching treatments. The results of this study will be useful with respect to treatment selection for patients who are experiencing high treatment costs. Also, it may be possible to reduce overtreatment rate by assessing the PSA response after 3 months.

In conclusion, the CHAARTED and LATITUDE criteria showed a prognostic utility for mHSPC patients treated with CAB. We identified six risk factors, including the PSA response 3 months after starting CAB, in M1 HSPC patients. For cases with few risk factors found by present research and good PSA reduction at the early stage of introduction of CAB therapy, it is possible that a long-term prognosis can be expected by continuing. CAB is a treatment option suitable for selected patients with mHSPC, even though novel treatments are available. This study provides useful information for treatment selection in patients who are experiencing high treatment costs.

Conflicts of Interest

Kazuhiro Suzuki has potential financial conflicts of interest as below, Consultancies: Takeda Pharmaceutical, Astellas Pharma, Daiichi-Sankyo, AstraZeneca, Sanofi, Janssen, Bayer, Grants

received: Takeda Pharmaceutical, Astellas Pharma, Daiichi-Sankyo, Ono Pharmaceutical. The other Authors have declared that no conflicts of interest exist.

Authors' Contributions

Yoshiyuki Miyazawa: Conceptualization, data curation, formal analysis, methodology, project administration, writing original draft, and writing review and editing. Yoshitaka Sekine, Seiji Arai, Daisuke Oka, Hiroshi Nakayama and Takahiro Syuto: data curation, formal analysis. Masashi Nomura, Hidekazu Koike, Hiroshi Matsui, Yasuhiro Shibata and Kazuhiro Suzuki: review and editing.

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Received September 28, 2020
Revised October 10, 2020
Accepted October 13, 2020