Prognostic factors for non-metastatic castration-resistant prostate cancer treated with androgen receptor signaling inhibitors

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Abstract. The treatment paradigm for non-metastatic castration-resistant prostate cancer (nmCRPC) has changed in recent years. An observational multicenter study was conducted to evaluate the effectiveness of androgen receptor signaling inhibitors (ARSIs) as a first-line treatment for patients with nmCRPC. The present study included native Japanese patients from four hospitals who received ARSIs as a first-line treatment for nmCRPC. The primary endpoint of the study was to evaluate the efficacy and safety of ARSI in patients with nmCRPC. The secondary endpoint was to develop a novel system to stratify the prognoses of these patients. In total, 160 patients were included in the present study. Within a median follow-up period of 23 months, the median overall survival (OS) was not reached, whereas the median progression-free survival was 26 months. Multivariate Cox regression analyses showed that the time to CRPC, prostate-specific antigen (PSA) level at the initiation of nmCRPC treatment and Geriatric Nutritional Risk Index (GNRI) were independent predictors of OS. The patients for whom information about all three independent OS predictors was available were subsequently divided into three groups as follows: Group 1, 57 patients with negative or one positive independent OS predictor; group 2, 38 patients with two positive independent OS predictors; and group 3, 10 patients with three independent OS predictors. The OS differed significantly among the three groups (P<0.0001). In conclusion, ARSIs as a first-line treatment may be associated with favorable outcomes in Japanese patients with nmCRPC. Time to CRPC, PSA level at the initiation of nmCRPC treatment and GNRI are potential predictors of OS in Japanese patients with nmCRPC who received ARSIs as a first-line treatment.

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Introduction

According to recent studies, approximately 30% of patients with prostate cancer (PCa) undergoing surgery and 40% of patients undergoing radiation therapy experience biochemical recurrence (BCR) within 10 years following local therapies (1). Patients with BCR have variable prognoses, with metastasis-free survival ranging from 1 to >15 years (2).

Non-metastatic castration-resistant prostate cancer (nmCRPC) is defined as an increase in prostate-specific antigen (PSA) in the setting of castrate testosterone levels with no detectable metastases on conventional imaging. Currently, the most accepted definition of progression on androgen deprivation therapy (ADT) is based on PSA increase and follows the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) consensus, which is primarily intended to define endpoints for clinical trial design (3).

Recently, three phase 3 trials (ARAMIS, PROSPER, and SPARTAN) of nmCRPC demonstrated statistically significant improvements in the primary endpoints of metastasis-free survival and overall survival (OS) among patients who received androgen receptor signaling inhibitors (ARSI; darolutamide, enzalutamide, or apalutamide) (4-6). Moreover, treatment with abiraterone acetate (1,000 mg) plus prednisone (5 mg) resulted in a significant reduction in ≥50% reduction of PSA, with encouraging results for time to PSA progression, time to radiographic evidence of disease progression, and safety in patients with high-risk nmCRPC (7). Ultimately, the treatment options for patients with nmCRPC have significantly improved over the past 2 years (8).

Considering these findings, it is necessary to understand the prognostic factors of ARSI for the first-line treatment of Japanese patients with nmCRPC. Therefore, in the current study, we retrospectively analyzed the prognostic outcomes on Japanese patients with nmCRPC who received ARSI as a

first-line treatment. Moreover, we developed a novel system to stratify the prognoses of these patients.

Materials and methods

Patients. In the current study, we retrospectively analyzed the clinical data of 160 Japanese patients with nmCRPC who received ARSI as a first-line treatment between January 2014 and December 2022 at four institutions belonging to the Tokai Urologic Oncology Research Seminar group, including the Fujita Health University School of Medicine, Nagoya City University Graduate School of Medical Sciences, Hamamatsu University School of Medicine and Gifu University Graduate School of Medicine. The study design was approved by the ethics committees of the four institutions <approval no: HM23-098 (Fujita Health University School of Medicine), 60-23-0089 (Nagoya City University Graduate School of Medical Sciences), 23-049 (Hamamatsu University School of Medicine), and 023-120 (Gifu University Graduate School of Medicine)>. The requirement for informed consent from all patients included in this study was waived due to the retrospective design.

Evaluation. Clinical characteristics and blood data, including age, body mass index (BMI), PSA, PSA doubling time (PSADT), Gleason score, treatment, Eastern Cooperative Oncology Group-Performance status (ECOG-PS), Hb, ALP, LDH, neutrophil-to-lymphocyte ratio (NLR), and Geriatric Nutritional Risk Index (GNRI) were assessed. GNRI was proposed by Bouillanne *et al* (9) in 2005, and has been widely used for nutritional assessment in older patients. Calculation of GNRI was as follow: GNRI=14.89 X serum albumin (g/dL) + 41.7 X BMI/22. Patients also underwent radiological examinations, including pelvic magnetic resonance imaging, computed tomography, and radionuclide bone scanning. Clinical staging of PCa was determined according to the 8th edition of the American Joint Committee on Cancer manual (10). Clinically, biochemically, or radiographically progressive disease was defined according to the criteria of the PCWG3.

The primary endpoint of the study was to evaluate the efficacy and safety of ARSI in patients with nmCRPC. The secondary endpoint was to develop a novel system to stratify the prognoses of these patients.

Statistical analysis. All data were analyzed using IBM SPSS Statistics version 23 (SPSS Japan). Each optimum cut-off value was determined from the receiver operating characteristic (ROC) curve using Youden's index. Statistical significance was set at $P<0.05$. OS and progression-free survival (PFS) were estimated using the Kaplan-Meier method, and differences were determined using the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression.

Results

In the present study, we retrospectively analyzed 160 patients who received ARSI as a first-line treatment for nmCRPC between January 2014 and December 2022 at four institutions belonging to the Tokai Urologic Oncology Research Seminar

Table I. Baseline patient characteristics (n=160).

Baseline patient characteristics	Value
Median age, years (IQR)	79 (73-83)
Median BMI, kg/m^2 (IQR)	23.2 (20.5-25.5)
Median initial PSA, ng/ml (IQR)	20.5 (10.2-74.0)
Primary Gleason score, n (%)	
3+3	9 (5.6)
3+4	17 (10.6)
4+3	17 (10.6)
4+4	44 (27.5)
4+5	27 (16.9)
5+4	27 (16.9)
5+5	10 (6.3)
Unknown	9 (5.6)
Initial treatment, n (%)	
ADT	12 (7.5)
CAB	89 (55.6)
RP	25 (15.6)
ADT + RP	6 (3.8)
Extrabeam	6 (3.8)
ADT or CAB + extrabeam	17 (10.6)
BT	1 (0.6)
ADT or CAB + BT + extrabeam	4 (2.5)
Median time to CRPC, months (IQR)	48 (19-86)
Median PSA at nmCRPC, ng/ml (IQR)	3.7 (2.3-7.6)
PSA doubling time, n (%)	
<6 months	83 (51.9)
≥6 months	6 (3.8)
Unknown	71 (44.4)
cN at nmCRPC, n (%)	
0	131 (81.9)
1	26 (16.3)
Unknown	3 (1.9)
nmCRPC first-line treatment, n (%)	
Enzalutamide	90 (56.3)
Abiraterone	28 (17.5)
Apalutamide	22 (13.8)
Darolutamide	20 (12.5)
ECOG PS, n (%)	
0	103 (64.4)
1	33 (20.6)
2	4 (2.5)
3	1 (0.6)
Unknown	19 (11.9)
Median Hb, g/dl (IQR)	12.7 (11.9-13.5)
Median ALP, IU/ml (IQR)	120.5 (86.0-245.5)
Median LDH, IU/l (IQR)	198.5 (175.3-229.0)

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; BT, brachytherapy; CAB, combined androgen blockade; ECOG PS, Eastern Cooperative Oncology Group-Performance status; Hb, hemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy.

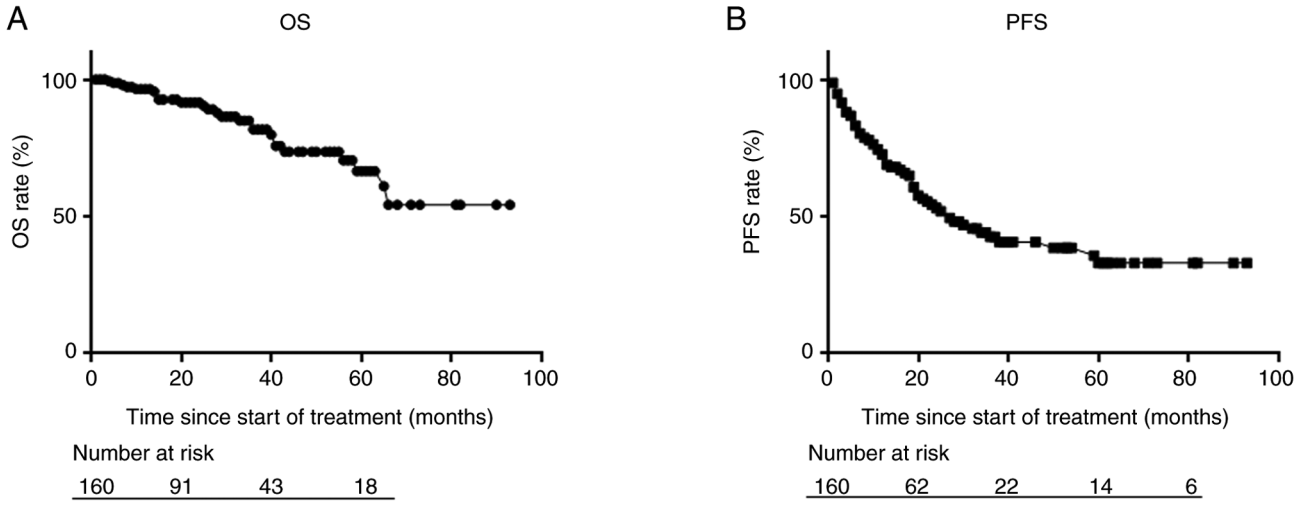

Figure 1. Kaplan-Meier curves of (A) OS and (B) PFS. OS, overall survival; PFS, progression-free survival.

group. The clinical characteristics of the 160 patients are shown in Table I.

Within a median follow-up period of 23 months, the median OS was not reached, whereas the median PFS was 26 months (Fig. 1). The 2-year OS and PFS rates were 91.6 and 53.1%, respectively.

Next, we performed Cox regression analyses for OS to evaluate the prognostic significance of ARSI as a first-line treatment. Univariate analysis demonstrated that the time to CRPC, PSA level at the initiation of nmCRPC treatment, Hb level, and GNRI affected OS (P=0.009, 0.021, 0.016, and 0.003, respectively). Multivariate Cox regression analyses showed that the time to CRPC, PSA level at the initiation of nmCRPC treatment, and GNRI were independent predictors of OS (P=0.045, 0.031, and 0.018, respectively) (Table II).

To properly predict the clinical outcomes of Japanese patients with nmCRPC who received ARSI as a first-line treatment, we attempted to develop a novel system for the prognostic stratification of these patients using three independent OS predictors. From the 160 patients, we selected the 105 for whom information about all three independent OS predictors was available. We stratified the 105 patients into three groups according to these three independent predictors of OS as follows: Group 1, 57 patients with negative or one positive independent OS predictor; Group 2, 38 patients with two positive independent OS predictors; and Group 3, 10 patients with three independent OS predictors. The OS was significantly different among the three groups (P<0.0001, Fig. 2).

Discussion

The treatment landscape for patients with nmCRPC has significantly changed over the past year. First-generation antiandrogen monotherapies (i.e., bicalutamide or flutamide) and switching or withdrawal of antiandrogens provide short-term PSA responses; however, no clinical trial has demonstrated a survival benefit of such approaches (11-13). On the other hand, regarding the treatment of nmCRPC, the recent approval of potent ARSI is specifically linked to the nmCRPC disease state, and these drugs have been shown to result in improved outcomes in patients with nmCRPC (4-7). However, according to a recent meta-analysis, similar results were seen in sensitivity analyses conducted for OS between the PROSPER and SPARTAN trials (14). Collectively, further prognostication should be carried out to provide more precise information regarding the Japanese patients with nmCRPC who received ARSI as a first-line treatment.

In the current study, we retrospectively analyzed the data of 160 Japanese patients with nmCRPC who received ARSI as first-line treatment. Two recent phase 2 trials [PROSPER (6) for enzalutamide with a median 48-months follow-up and SPARTAN (5,15) for apalutamide with a median 52-months follow-up] of nmCRPC treatments reported a median OS of 67.0 and 73.9 months and a median PFS of 'not reached' and 40.5 months, respectively. In the present study, the median OS was 'not reached', whereas the median PFS was 26 months. However, considering that our follow-up period of 23 months was relatively short compared to those of the recent trials described above, prospective studies with longer follow-up periods are warranted to validate our findings regarding OS and PFS.

In the present study, we did not obtain sufficient patient information regarding PSADT. PSADT is a strong predictor of metastasis, all-cause mortality, and PCa-specific mortality in patients with nmCRPC. As with patients at earlier disease stages, <3, 3-8.9, 9-14.9 and ≥15 months are reasonable PSADT thresholds for risk stratification in men with nmCRPC (16). Considering this information about PSADT as a strong predictor in patients with nmCRPC, because more than half of the patients in the present cohort showed PSADT in less than 6 months, we considered that PSADT is not needed to assess OS.

Multivariate Cox regression analyses showed that the time to CRPC, PSA level at the initiation of nmCRPC treatment, and GNRI were independent predictors of OS, whereas local treatment, including radiation therapy or prostatectomy, did not affect OS. Considering these results of analyses, PSA level at the initiation of nmCRPC treatment might be prognostic alternatives to PSADT for the Japanese patients with nmCRPC who received ARSI as a first-line treatment. Regarding the

Table II. Univariate and multivariate analyses of the clinical parameters of overall survival.

	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≥70 years vs. <70 years)	0.467 (0.110-1.984)	0.302		
Initial PSA (≥41.7 ng/ml vs. <41.7 ng/ml)	0.337 (0.150-0.754)	0.008	0.786 (0.205-3.011)	0.725
Existence of Gleason pattern 5 (yes vs. no)	2.255 (0.671-7.582)	0.189		
Initial treatment				
ADT or CAB	Ref.			
RP	3.040 (0.707-13.064)	0.135		
Radiation	0.998 (0.166-5.981)	0.998		
Time to CRPC (<38 months vs. ≥38 months)	0.297 (0.119-0.743)	0.009	0.244 (0.062-0.968)	0.045
PSA at nmCRPC (≥2.89 ng/ml vs. <2.89 ng/ml)	0.303 (0.110-0.834)	0.021	0.116 (0.016-0.818)	0.031
cN (positive vs. negative)	0.436 (0.166-1.140)	0.090		
nmCRPC first-line treatment				
Enzalutamide	Ref.			
Abiraterone	0.821 (0.103-6.552)	0.852		
Apalutamide	1.660 (0.199-13.817)	0.639		
Darolutamide	0.000 (0.000-1.251x10233)	0.965		
ECOG PS (≥1 vs. 0)	0.625 (0.241-1.623)	0.335		
Hb (<12.6 g/dl vs. ≥12.6 g/dl)	0.319 (0.125-0.809)	0.016	0.514 (0.153-1.719)	0.280
ALP (≥174 IU/ml vs. <174 IU/ml)	0.720 (0.296-1.754)	0.470		
LDH (≥212 IU/l vs. <212 IU/l)	0.612 (0.259-1.449)	0.265		
NLR (≥2.45 IU/ml vs. <2.45 IU/ml)	2.638 (0.755-9.212)	0.128		
GNRI (<101.6 vs. ≥101.6)	0.214 (0.076-0.601)	0.003	0.225 (0.066-0.774)	0.018

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; CAB, combined androgen blockade; ECOG PS, Eastern Cooperative Oncology Group-Performance status; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy.

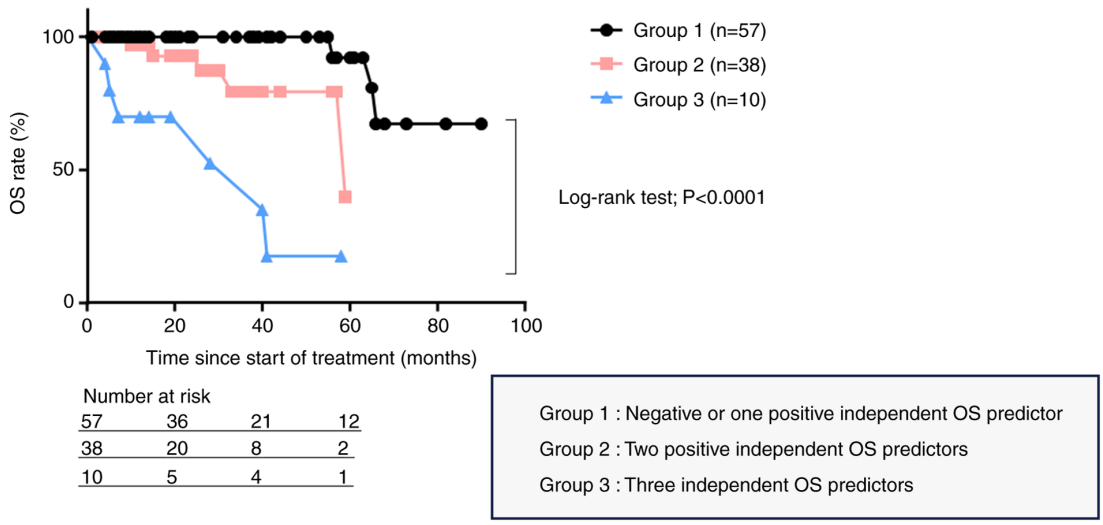

Figure 2. Kaplan-Meier curves for OS according to the number of independent OS predictors. OS, overall survival.

time to CRPC, several recent investigators have advocated it as a significant prognosticator of OS (17-19).

The GNRI is a simple and objective screening tool for clinicians to screen patients' nutritional status based on serum albumin levels, weight, and height. Bouillanne *et al* (9) first introduced the GNRI in 2005 to evaluate the 6-month midterm nutritional outcomes of elderly patients admitted to a rehabilitation unit. They divided the patients into four groups:

a no-risk group (GNRI >98), low-risk group (GNRI 92-98), moderate-risk group (GNRI 82 to <92), and major risk group (GNRI <82), suggesting that the risk of infectious complications or mortality was significantly higher in the major-, moderate-, and low-risk groups than in the no-risk group (9). Considering this GNRI cutoff value, the cutoff value (101.6) obtained from the ROC curve in the present study was reasonable. Regarding PCa, Okamoto *et al* (20) reported that a GNRI <92.0 was an independent prognostic factor for cancer-specific survival and OS in patients with metastatic hormone-naïve PCa. Moreover, in the context of metastatic CRPC (mCRPC), Chang *et al* (21) demonstrated that poor nutritional status with a GNRI <92 was associated with shorter PFS and OS in patients with mCRPC treated with docetaxel.

In the current study, to properly predict the clinical outcomes of Japanese patients with nmCRPC who received ARSI as a first-line treatment, we attempted to develop a novel system for the prognostic stratification of these patients using three independent OS predictors (time to CRPC, PSA at the initiation of nmCRPC treatment, and GNRI). We divided the patients into three groups based on the presence of none, one, two, or three independent OS predictors. We then compared the OS among these three groups and found that the OS was significantly different among them. As described above, the treatment options for patients with nmCRPC have significantly improved over the past 2 years (8); however, there was no significant OS difference among patients with nmCRPC who received ARSI as first-line treatment (14). Considering these findings, we believe that our novel stratification system based on the positive number of independent OS predictors could be a useful tool for the management of Japanese patients with nmCRPC who received ARSI as first-line treatment.

This study had several limitations. First, it was retrospectively conducted with a small sample size; thus, a selection bias may have affected the results. Regarding the selection of ARSI as a first-line treatment for patients with nmCRPC, there was no criteria. Second, the cutoff points used in the current analyses should be assessed in a large-scale study. Third, we could not obtain sufficient patient information regarding PSADT. Prospective studies with larger sample sizes and longer follow-up periods are warranted to confirm our findings.

In conclusion, we identified that ARSI might provide favorable outcomes for Japanese patients with nmCRPC as a first-line treatment. Time to CRPC, PSA level at the initiation of nmCRPC treatment, and GNRI are potential predictors of OS in Japanese patients with nmCRPC who received ARSI as a first-line treatment. Furthermore, our novel stratification system based on the positive numbers of these three independent OS predictors could help guide decision-making for patients who received ARSI as a first-line treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KT, TN, HM, TK, TY and RS conceived and designed the study. KT, TN, KN and HW acquired the data. KT and TN analyzed and interpreted the data and drafted the manuscript. KT, TN, KN and HW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study design was approved by the ethics committees of the four institutions [approval nos. HM23-098 (Ethics Review Committee, Fujita Health University, Toyoake, Japan), 60-23-0089 (Clinical Research Management Center, Nagoya City University Hospital, Nagoya, Japan), 23-049 (Ethics Committee of Hamamatsu University School of Medicine, Hamamatsu, Japan) and 023-120 (Medical Review Board of Gifu University Graduate School of Medicine, Gifu, Japan)], and it was conducted in line with the guidelines of The Declaration of Helsinki. The requirement for informed consent from all patients included in the present study was waived due to the retrospective design.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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