

Appropriate Patient Status for Ra-223 Treatment in the Treatment Sequence for Castration-resistant Prostate Cancer

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Abstract. *Background/Aim:* Radium (Ra)-223 is widely used for treating castration-resistant prostate cancer (CRPC) with bone metastasis based on evidence of increased survival and decreased skeletal-related events. However, the timing of Ra-223 use in the treatment sequence of CRPC remains controversial. Therefore, this study aimed to explore the appropriate patient status for Ra-223 use in the CRPC treatment sequence by examining patients treated with Ra-223 from the time of CRPC diagnosis until death. *Patients and Methods:* The medical records of 67 CRPC patients with bone metastasis who were treated with Ra-223 at two institutes were retrospectively analysed. The impact of 13 factors from the time of CRPC diagnosis until death was analysed using univariate and multivariate Cox hazard ratio models to evaluate the appropriate patient status for Ra-223 treatment. *Results:* The median survival time following CRPC diagnosis for all the patient groups was 3.82 years. Univariate analysis identified a higher-than-normal alkaline phosphatase (ALP) level, bone scan indexes ≥ 2 , and prostate-specific antigen (PSA) doubling time < 3 months before Ra-223 treatment as predominant

adverse prognostic factors. Ra-223 therapy discontinuation was not a significant factor. The survival of CRPC patients with these factors was significantly worse than that of patients without these factors. In the multivariate analysis, a higher-than-normal ALP level at the start of treatment was identified as a poor prognostic factor for mortality. *Conclusion:* The appropriate patient status for Ra-223 use includes low bone metastasis burden and well-controlled PSA levels.

The bone is a common site of metastases for malignant tumours. Approximately 90% of patients with metastatic castration-resistant prostate cancer (CRPC) are diagnosed with bone metastases during their treatment course (1). Bone metastases can cause pain and skeletal-related events (SREs), resulting in the deterioration of the patients' quality of life and shortened survival time (2). A Japanese study has reported that the control of SREs and pain is more important than survival in CRPC patients (3).

The Alpharadin in Symptomatic Prostate Cancer study reported that alpha emitter radium (Ra)-223 injections prolonged survival and reduced the incidence of SREs in CRPC patients with bone metastases (4). Moreover, these injections have few side effects and are widely used in clinical practice as they provide long-term safety (5).

Several studies have analysed survival in patients with metastatic CRPC after Ra-223 treatment. Many factors, such as discontinuation of Ra-223 treatment, performance status (PS), alkaline phosphatase (ALP) levels, lactate dehydrogenase (LDH) levels, neutrophil-lymphocyte ratio (NLR), pain, previous number of drug courses before Ra-223 treatment, haemoglobin (Hb) levels, prostate-specific antigen (PSA) levels, PSA doubling time (PSA-DT), bone scan index (BSI), and chemotherapy use before Ra-223 therapy, reportedly influence survival outcomes after Ra-223 treatment (6, 7).

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However, only a few studies have reported the survival of patients treated with Ra-223 following a CRPC diagnosis. The administration of Ra-223 in the treatment sequence of CRPC remains controversial, and evidence regarding the appropriate status for Ra-223 treatment is insufficient (8, 9). In a previous report, we have highlighted the factors associated with Ra-223 therapy discontinuation (6).

In this study, we aimed to explore the appropriate patient status for Ra-223 administration in the CRPC treatment sequence by examining patients treated with Ra-223 following CRPC diagnosis until death in the same cohort. The findings of this study may contribute towards improving the quality of life in CRPC patients and increase the survival time (10).

Patients and Methods

Study design. This retrospective study was conducted at two institutions in Japan (the Katsura Hospital and Kanazawa University Hospital). The study was approved by the Institutional Review Board of each hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions (the Katsura Hospital: No. 590; the Kanazawa University Hospital: No. 2972-2). All the patients provided informed consent for the use of their medical data.

Patients and treatment. All the CRPC patients diagnosed with metastases on bone scintigraphy imaging who received at least one course of Ra-223 treatment between August 2016 and December 2019 at the Katsura Hospital and between June 2016 and January 2020 at the Kanazawa University Hospital were included in this study. For bone scintigraphy imaging, technetium-99m hydroxy methylene diphosphonate or technetium-99m methylene diphosphonate (99mTc-MDP) was used as the tracer. The last observation was recorded in August 2021 at the Katsura Hospital and in June 2021 at the Kanazawa University Hospital. Ra-223 treatment comprised intravenous injections of 55 kBq/kg of Ra-223 every 4 weeks for up to six cycles.

Data collection. Clinical data were collected from the medical records. The diagnosis date of prostate cancer was defined as the date of prostate biopsy or clinical decision to start treatment. The date of CRPC diagnosis was defined as the earliest day from one of the following:

- 1: The day the PSA level started to increase under classical hormonal therapy (day of the next examination of PSA nadir under classical hormonal therapy).
 - 2: The day the attending physician initiated prostate cancer treatment other than classical hormonal therapy (the day the attending physician diagnosed the patients with CRPC).
 - 3: The day the PSA level was >2 ng/ml among patients who received radiation therapy under adjuvant hormonal therapy.
- The BSI was calculated using BONENAVI® (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) in patients who underwent bone scintigraphy with 99mTc-MDP. The most recent blood test results were used to obtain baseline data before Ra-223 treatment and at the time of CRPC diagnosis. The pre-treatment therapy before Ra-223 treatment included chemotherapy after the CRPC diagnosis and administration of androgen receptor axis-targeted agents. Pre-treatment with any oestrogen-related drug was considered as one

treatment course. The re-administration was considered another one treatment course. The PSA-DT was calculated using PSA levels at the time of Ra-223 treatment and at three and six months before Ra-223 treatment using an online calculator (11).

Statistical analysis. Fisher's exact test was used to determine differences in nominal functions. The Mann-Whitney *U*-test was used to determine differences in continuous variables. In the univariate analysis, we examined the following 13 factors: PS, PSA-DT, Hb, PSA, ALP, pain, LDH, NLR, and BSI before Ra-223 treatment, number of treatment lines before Ra-223 treatment, chemotherapy use before Ra-223, Ra-223 treatment discontinuation, and duration from CRPC diagnosis to Ra-223 treatment. The cut-off value for the continuous variables was considered as the median value. The ALP level was divided as follows: within the normal range (WNR) and over the normal range (ONR) at each institute. The BSI cut-off value was 2, as reported previously (7). We performed multivariate logistic regression analysis including factors that were found to be significant in the univariate analysis. Survival analysis was performed using the Kaplan-Meier method with a log-rank test for differences between the factors that were significant in the univariate analysis. For overall survival, the start date was considered as the date of CRPC diagnosis. Patients who were lost to follow-up were considered terminated at that point. Statistical significance was set at $p < 0.05$. In univariate analysis, the following equation was used to correct for multiplicity (Bonferroni correction):

$$(\text{Total number of patients}) \div 10 \div (\text{All factor's number}) \times 0.05$$

To investigate the effect of bone metastases on bone marrow suppression by Ra-223 injection, we investigated the relationship between ALP and blood components level. Then, we compared the rate of decline in Hb, platelet, neutrophil, and lymphocyte levels before and after Ra-223 treatment. When the Ra-223 treatment was incomplete, the blood component value obtained before the last course of Ra-223 treatment was used to calculate the rate of decline in blood component levels. The rate of decline in the blood component levels by Ra-223 treatment was calculated using the following equation divided by ALP:

$$\{(\text{blood component before Ra223 treatment}) - (\text{blood component at the end of Ra223 treatment})\} \div (\text{blood component before Ra223 treatment}) \times 100$$

We drew the Swimmers' plot using CRPC diagnosis and first and last Ra-223 injections divided by the number of the remaining factors in multivariate analysis.

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (12).

Results

Patient characteristics. A total of 36 consecutive patients each from the Katsura Hospital (between August 2016 and December 2019) and Kanazawa University Hospital (between June 2016 and January 2020) who received at least one course of Ra-223 treatment were included. The CRPC data of five patients from the Kanazawa University Hospital

Table I. Patient characteristics at castration-resistant prostate cancer (CRPC) diagnosis.

Characteristic			Evaluable number of patients
Total N		67	
Age at CRPC diagnosis (years)	Range (median)	50-85 (71)	67
ISUP; Grade group	2	1	67
	3	2	
	4	21	
	5	39	
	NE	4	
iPSA (ng/ml)	Range (median)	5.899-8,949 (219.02)	65
Diagnosis to CRPC (days)	Range (median)	120-3,728 (435)	67
Hb at CRPC (g/dl)	Range (median)	10-15.1 (12.7)	47
PSA at CRPC (ng/ml)	Range (median)	0.035-643.67 (4.37)	61
ALP at CRPC	ONR	15	50
	WNR	35	
BSI at CRPC	Range (median)	0-13.67 (1.01)	30
	≥2	11	

ISUP: International Society of Urological Pathology; iPSA: initial prostate-specific antigen; Hb: hemoglobin; NE: not evaluated; PSA: prostate-specific antigen; ALP: alkaline phosphatase; BSI: bone scan index; ONR: over the normal range; WNR: within the normal range.

Table II. Patient characteristics before Ra-223 treatment.

Characteristic			Evaluable number of patients
Total N		67	
Age at Ra-223 treatment (years)	Range (median)	53-86 (73)	67
Performance status	0-1	56	67
	≥2	11	
PSA-DT	<3 months	23	67
	≥3 months	44	
Hb (g/dl)	Range (median)	8.9-14.7 (12.4)	67
PSA (ng/ml)	Range (median)	0.02-1,086 (25.9)	67
ALP	ONR	20	67
	WNR	47	
Pain	Yes	39	67
	No	28	
LDH (U/L:JSCC)	range (median)	89-387 (211.5)	64
NLR	range (median)	1.05-20.6 (3.41)	49
BSI	range (median)	0-11.02 (3.57)	35
	≥2	23	
Total number of therapeutic lines before Ra-223	Range (median)	0-9 (2)	67
	0-2	44	
	≥3	23	
Chemotherapy use before Ra-223 therapy	+	23	67
	-	44	
Ra-223 treatment	Complete	43	67
	Incomplete	24	
CRPC to Ra-223 therapy (days)	range (median)	3-4,243 (499)	67

PSA-DT: Prostate-specific antigen doubling time; H:b hemoglobin; PSA: prostate-specific antigen; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; JSC:C Japan Society of Clinical Chemistry; NLR: neutrophil-lymphocyte ratio BSI bone scan index; CRPC: castration-resistant prostate cancer.

were not available; thus, they were excluded from this study. Finally, 67 patients were included in the analysis. The patient characteristics at CRPC diagnosis and before Ra-223 treatment are shown in Table I and Table II, respectively.

Details on some factors could not be retrieved from the medical records. The reason for treatment discontinuation in 24 patients was disease progression (n=13), fatigue (n=5), myelosuppression (n=2), and others (n=4).

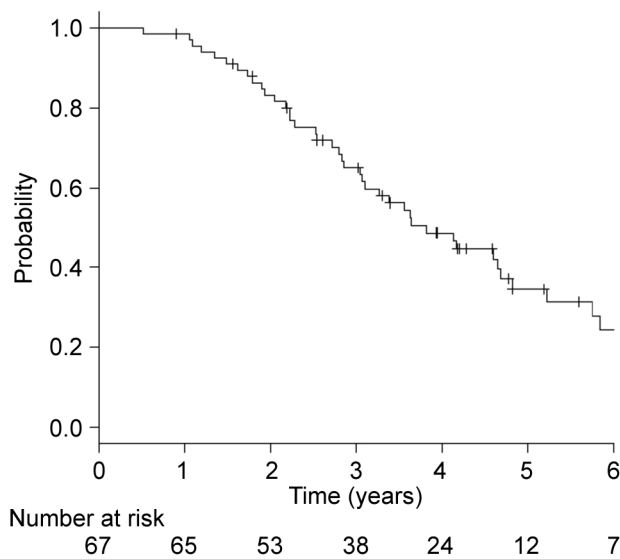


Figure 1. Kaplan–Meier curve showing overall survival from the date of castration-resistant prostate cancer diagnosis for all patients.

Survival outcome and univariate and multivariate analysis findings. At the last follow-up, three patients were lost to follow-up, 40 patients died, and 24 patients were still alive. With a median follow-up of 3.27 years, the median survival time (MST) from CRPC diagnosis for all the patients was 3.82 years (Figure 1). Univariate analysis was performed considering the period from CRPC diagnosis until death or lost to follow-up as an event. Regarding multiplicity, a p -value of <0.026 was considered significant in univariate analysis. The univariate analysis results are shown in Table III. The ALP level, PSA-DT, and BSI before Ra-223 treatment were identified as significant factors. Upon survival analysis, significant survival differences were observed (Figure 2). The MST was 2.54 and 4.81 years for patients whose ALP levels before Ra-223 treatment were ONR and WNR, respectively ($p<0.0001$, log-rank test). The MST was 2.85 and 4.65 years for patients with PSA-DT <3 months and ≥ 3 months, respectively ($p=0.0081$, log-rank test). The MST was 3.82 and 6.01 years for patients with BSI ≥ 2 and <2 before Ra-223 treatment, respectively ($p=0.019$, log-rank test).

Multiple regression analyses were performed for these factors. The ALP was the only significant factor before Ra-223 treatment (Table IV).

Association between ALP and blood components. We compared the rate of decline in Hb, platelet, neutrophil, and lymphocyte levels before and after Ra-223 treatment. Only the Hb rate was significantly different between patients with ALP levels ONR and those with ALP levels WNR ($p=0.0051$, Mann–Whitney U -test).

Swimmers' plot using CRPC diagnosis and first and last Ra-223 injections divided by ALP levels. Figure 3 shows a simple Swimmer's plot obtained from the first Ra-223 injection date (Figure 3A) and from the CRPC diagnosis date (Figure 3B) classified according to the ALP level. The ALP levels ONR and WNR did not affect the 6-course completion rate of Ra-223 therapy ($p=0.41$, Fisher's exact test). Survival after the last Ra-223 injection was significantly different between patients with ALP levels ONR and those with ALP levels WNR (MST: 10.5 vs. 17.7 months; $p=0.025$, log-rank test); however, the difference was not significant in patients who completed six courses of Ra-223 treatment (MST: 17.2 vs. 21.5 months; $p=0.21$, log-rank test). All the patients with ALP levels WNR who survived >30 months after the Ra-223 treatment were still alive. There were no significant differences in the time from CRPC diagnosis to Ra-223 treatment between patients with ALP levels ONR and those with ALP levels WNR ($p=0.12$, Mann–Whitney U -test).

Discussion

In this study, we analysed the survival of CRPC patients who were treated with Ra-223, and the univariate analysis revealed that PSA-DT, BSI, and ALP levels before Ra-223 treatment affected survival following CRPC diagnosis. The completion rate of Ra-223 treatment, which was reported previously as a predominant survival factor (9), did not affect the survival of patients diagnosed with CRPC in this study. In our study, the MST was comparable to the MST of 33–40 months reported in previous studies (9, 13, 14).

The fact that PSA-DT remained significant in the univariate analysis suggested that Ra-223 treatment should be used when PSA is well-controlled. It is difficult to control the PSA level with Ra-223 treatment alone (15); thus, combination therapies should be explored. The ERA-223 study reported negative results for the combination of abiraterone acetate and Ra-223 (13), which could mainly be due to the increased SRE incidence following the use of this combination. However, SREs were noted primarily at non-metastatic sites, possibly because radiotherapy did not necessarily have a positive effect on the bone environment (16–18). Administration of bone-modifying agents may resolve these issues. Several clinical trials with some agents and Ra-223 have been reported (19–21).

The ALP level before Ra-223 administration remained a significant contributing factor in the multivariate analysis and the primary predictive factor of survival. The ALP level may reflect the extent of bone metastases and the general state of the bone environment (18). The BSI may be used to identify appropriate cases and suitable timing for Ra-223 administration. (7).

The ALP level was associated with the rate of decline in Hb levels before and after Ra-223 treatment. The Hb level

Table III. Univariate analysis for the duration from castration-resistant prostate cancer (CRPC) diagnosis to death.

		HR	Lower 95% CI	Upper 95% CI	p-Value
Performance status before Ra-223 therapy	0–1	ref			
	≥2	1.08	0.48	2.46	0.85
PSA-DT	<3 months	ref			
	≥3 months	0.45	0.24	0.83	0.001
Hb before Ra-223 therapy	Over median	ref			
	Less than median	1	0.54	1.85	0.99
PSA before Ra-223 therapy	Over median	ref			
	Less than median	0.54	0.29	1.01	0.054
ALP before Ra-223 therapy	ONR	ref			
	WNR	0.255	0.127	0.512	<0.001
Pain before Ra-223 therapy	Yes	ref			
	No	0.9	0.48	1.69	0.73
LDH before Ra-223 therapy	Over median	ref			
	Less than median	0.58	0.31	1.1	0.095
NLR before Ra-223 therapy	Over median	ref			
	Less than median	1.17	0.58	2.35	0.67
BSI before Ra-223 therapy	≥2	ref			
	<2	0.31	0.11	0.86	0.025
Total number of therapeutic lines before Ra-223	0–2	ref			
	≥3	0.79	0.43	1.48	0.47
Chemotherapy use before Ra-223 therapy	Yes	ref			
	No	0.451	0.22	0.93	0.031
Ra-223 therapy	Complete	ref			
	Incomplete	1.76	0.96	3.21	0.067
CRPC to Ra-223 therapy	Over median	ref			
	Less than median	1.99	1.02	3.88	0.044

The bold *p*-values are statistically significant ($p<0.026$). HR: Hazard ratio; CI: confidence interval; PSA-DT: prostate-specific antigen doubling time; Hb: hemoglobin; PSA: prostate-specific antigen; ALP: alkaline phosphatase; ONR: over the normal range; WNR: within the normal range; LDH: lactate dehydrogenase; NLR: neutrophil-lymphocyte ratio; BSI: bone scan index.

Table IV. Multivariate analysis for duration from castration-resistant prostate cancer (CRPC) diagnosis to death.

		HR	Lower 95%CI	Upper 95%CI	p-Value
PSA-DT	<3 months	ref			
	≥3 months	1.1	0.44	2.81	0.82
ALP before Ra-223 treatment	ONR	ref			
	WNR	0.19	0.059	0.61	0.0053
BSI before Ra-223 treatment	≥2	ref			
	<2	0.48	0.15	1.51	0.21

The bold *p*-value indicates statistical significance ($p<0.026$). HR: Hazard ratio; CI: confidence interval; PSA-DT: prostate-specific antigen doubling time; ALP: alkaline phosphatase; ONR: over the normal range; WNR: within the normal range; BSI: bone scan index.

before and after Ra-223 treatment is also a predictive factor of survival after Ra-223 treatment (6); thus, Ra-223 should be preferably used when ALP level is WNR and before the use of chemotherapy, which can induce myelosuppression. In this study, chemotherapy use before Ra-223 was not a significant factor but was borderline negative ($p=0.031$ in univariate analysis). While the chemotherapy re-challenges have demonstrated certain life-prolonging effects (22, 23), Ra-223 can only be administered for six courses. From this

perspective, we recommend that Ra-223 should be used for patients with ALP levels WNR and before chemotherapy administration (24, 25). External beam radiation therapy for bone metastasis may be effective in decreasing the bone tumour burden.

Our study has some limitations. First, due to the retrospective design, the definition of CRPC diagnosis is ambiguous. However, we believe that our definition is convincing from a practical clinical perspective. Second, the

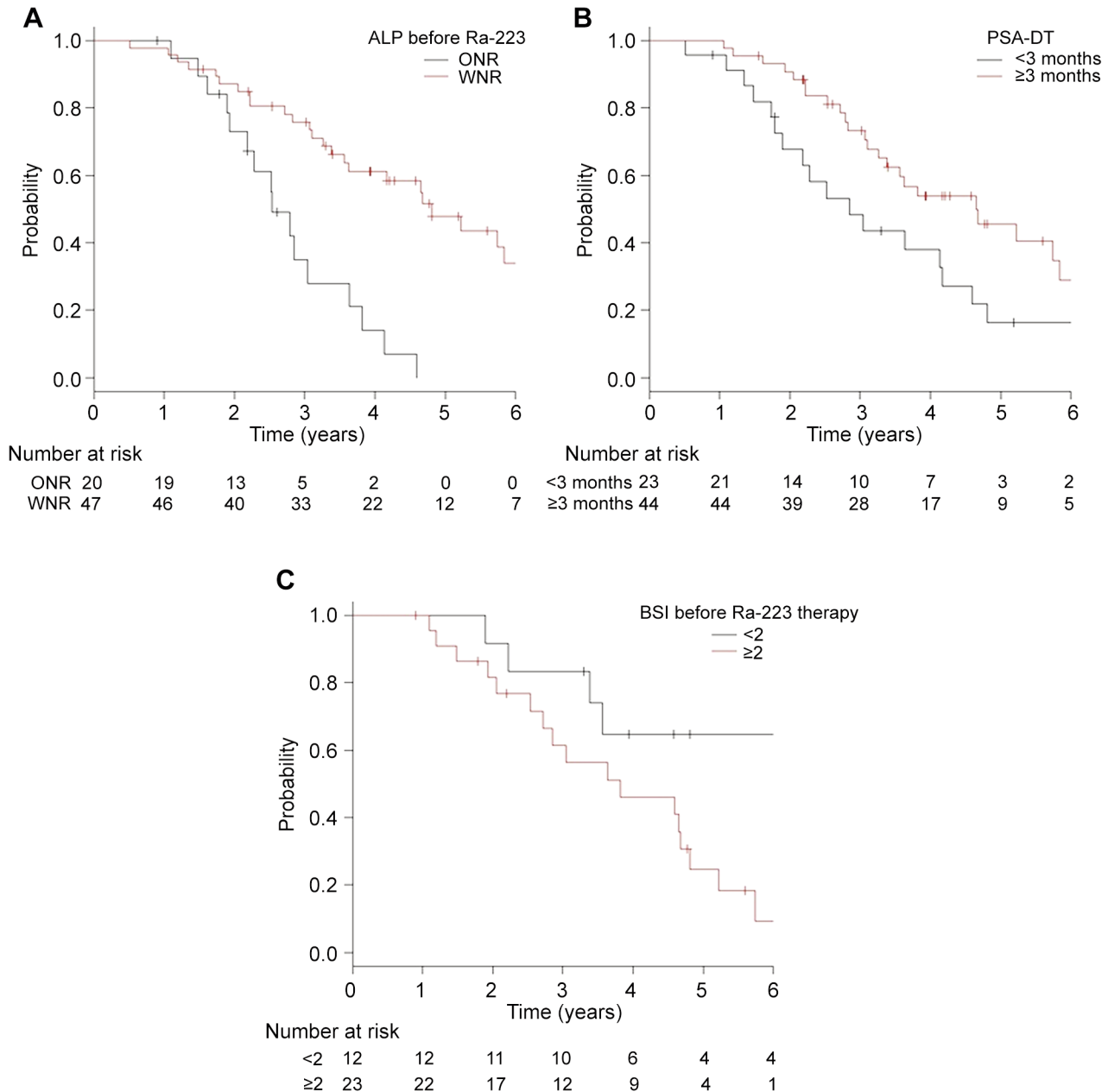


Figure 2. Kaplan–Meier curves showing overall survival from the date of castration-resistant prostate cancer diagnosis according to ALP (A), PSA-DT (B), and BSI (C). ALP: Alkaline phosphatase; ONR: over normal range; WNR: within normal range; PSA-DT: prostate-specific antigen doubling time; BSI: bone scan index.

data were obtained only from 67 patients; therefore, type II errors are likely; further validation with a larger study population is required. Third, our study did not compare the groups that received and did not receive Ra-223 treatment. However, currently in clinical practice, it is unlikely that Ra-223 would not be used because it is reported to have a life-extending effect (4). Finally, because high bone tumour

burden is a well-known poor prognostic factor in metastatic CRPC (26), it may have affected the study outcome.

Despite these limitations, to the best of our knowledge, this is the first study to explore the appropriate patient status for Ra-223 therapy in the CRPC treatment sequence in an Asian population, indicating the substantial clinical value and novelty of our findings.

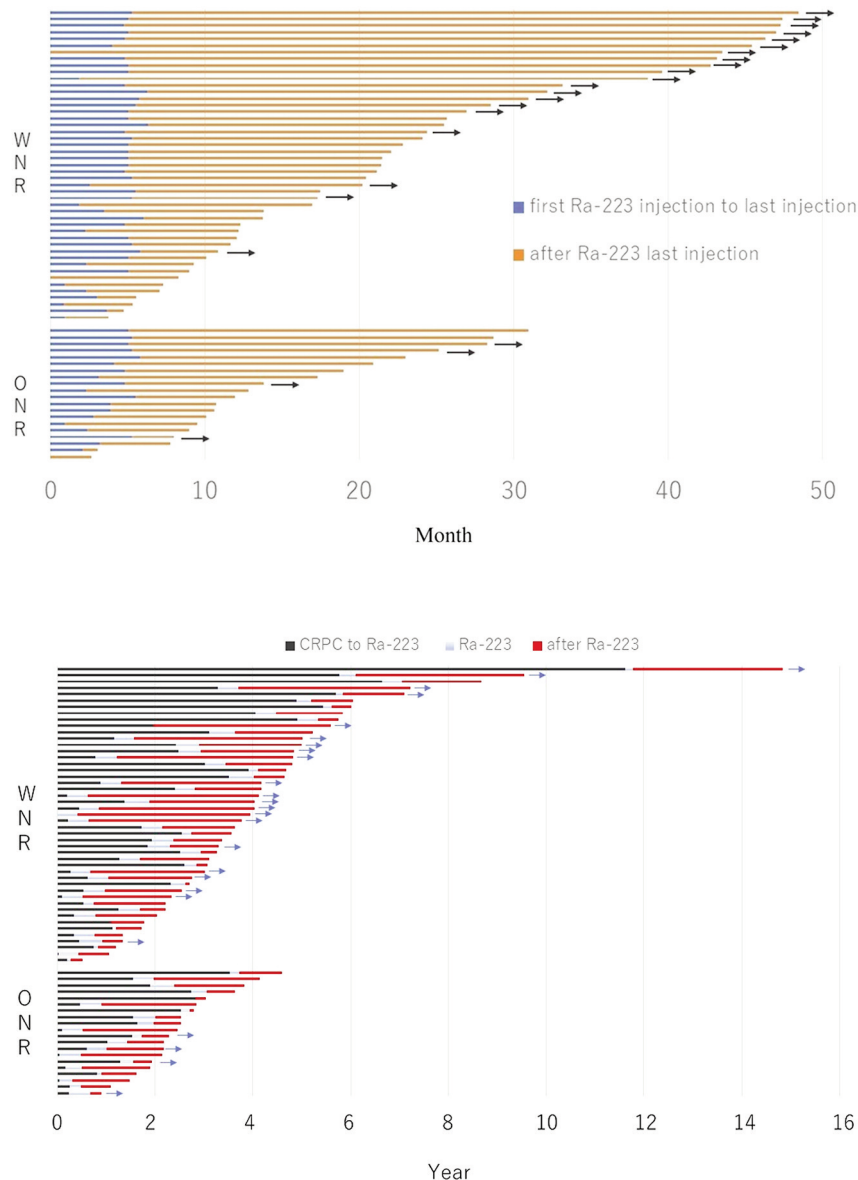


Figure 3. Simple Swimmer's plots showing the duration of Ra-223 treatment and the duration from last injection to the last follow-up for examination of status in Ra-223 treatment (A); and the duration from CRPC diagnosis to Ra-223 treatment, the duration of Ra-223 treatment, and the duration from last injection to the last follow-up for examination of status in Ra-223 treatment (B). CRPC: Castration-resistant prostate cancer; ONR: over normal range; WNR: within normal range.

In the treatment sequence of CRPC, the efficacy of Ra-223 will be maximised in patients with well-controlled PSA levels and limited bone metastases. Further research is needed to verify the study findings.

Conflicts of Interest

The Authors have declared that there are no competing interests in relation to this study.

Authors' Contributions

HI, HY, and YO developed the concept and designed the study. HI, HY, YO, and TS contributed to data collection, analysis, and interpretation. HI and HY performed statistical analysis. HI, HY, and AM drafted the manuscript. TY, KO, TS, and AM supervised the execution of the study and manuscript preparation. All Authors critically reviewed the article. All Authors approved the final version of the article and agreed to be accountable for all aspects of the work and in ensuring that questions related to the accuracy

or integrity of any part of the work are appropriately investigated and resolved.

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