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Risk Scoring System for Ra-223 Discontinuation and Its Effect on Prognosis: A Retrospective Study

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Abstract. *Background/Aim: Radium-223 therapy prolongs overall survival in castration-resistant prostate cancer (CRPC) patients with bone metastasis. Patients who are unable to complete six courses of radium-223 therapy reportedly have a poor prognosis. This study aimed to develop a risk score using the discontinuation factors of the above therapy modality. Patients and Methods: Seventy patients who received radium-223 therapy for metastatic CRPC at two Japanese Institutions were evaluated. Univariate and multivariate analyses were performed to identify the discontinuation factors and determine the risk scores. Results: The median survival time was 24.3 and 9.5 months in patients who did and did not complete the therapy, respectively. Multivariate analysis revealed haemoglobin and prostate-specific antigen as key factors. A risk score was developed using these factors, and patients were stratified into three groups. The discontinuation rate and survival after radium-223 therapy were significantly different. Conclusion: Our risk score may help evaluate the suitability of radium-223 in CRPC patients.*

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The bone is the most common site of metastasis among patients with metastatic castration-resistant prostate cancer (mCRPC). Approximately 90% of patients are diagnosed with bone metastases during their treatment course (1). Bone metastasis-induced symptomatic skeletal events (SSE), such as bone pain and pathological fractures, reduce the quality of life (2). Radium-223 dichloride (Ra-223) is a radioactive isotope that produces α particles and accumulates in bone metastases. The ALpharadin in SYMPtomatic Prostate CAncer (ALSYMPCA) study reported that a reduction in SSE has been demonstrated to improve the quality of life and overall survival (OS) (3), which met the treatment goals among patients with mCRPC (4). Ra-223 has a broad range of advantages and is widely indicated for mCRPC with bone metastasis. However, the optimal timing for Ra-223 therapy during the treatment sequence of mCRPC remains unclear.

Patients who failed to complete six courses of Ra-223 therapy have been reported to have a poor prognosis (5-9). Some factors such as performance status (PS) at treatment onset, pain, hemoglobin (Hb), alkaline phosphatase (ALP), and prostate-specific antigen (PSA) have been reported as predictors of discontinuation (6-10). We hypothesized that a good timing of Ra-223 therapy is when patients can complete six cycles of Ra-223 therapy. A scoring system to predict discontinuation of Ra-223 therapy using pretreatment data can help suggest the proper timing of administering Ra-223 therapy and treatment sequence for mCRPC.

In this study, we developed a risk scoring system based on the pretreatment factors of Ra-223 therapy discontinuation and examined the prognostic implications of the score at the start and completion of Ra-223 therapy.

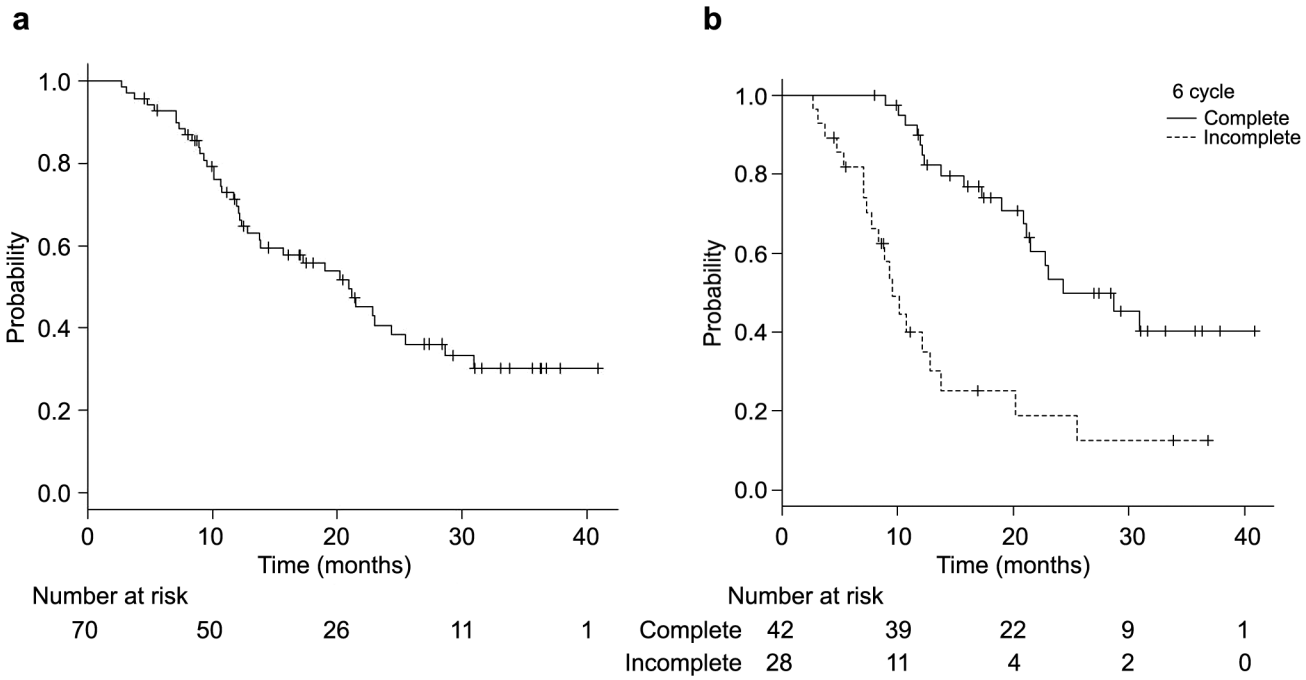


Figure 1. *Kaplan-Meier curves showing overall survival from the first injection of Ra-223 for all patients (a) and for the completed and incomplete groups, respectively (b).*

Patients and Methods

Data collection. This was a retrospective study conducted at two Japanese centers (Katsura Hospital and Kanazawa University Hospital). Patients who received a Ra-223 injection at least once were examined. This study was approved by the institutional review board of each hospital (No. 590 in Katsura Hospital, No. 2972-2 in Kanazawa University Hospital). All patients provided their informed consent for the use of their medical records.

Clinical data were collected from the medical records. Baseline data were collected from the most recent blood test before the start of the therapy. Pretreatment with any chemotherapy, androgen receptor axis targeted agents (ARTA), or estrogen-related drugs after mCRPC was considered one treatment course. Androgen withdrawal syndrome was not counted as one course of therapy. Rechallenge of any of the above therapy was accounted as one course of therapy. PSA-doubling time (PSA-DT) was calculated from the most recent data before three months of treatment and the baseline data using a web-based calculator (accessible at https://www.mdcalc.com/psa-doubling-time-psadt-calculator).

Patients and treatment. All patients with mCRPC diagnosed with bone metastasis were evaluated using bone scintigraphy and were administered at least one course of Ra-223 therapy between August 2016 and August 2019 at Katsura Hospital and between June 2016 and January 2019 at Kanazawa University Hospital. For imaging bone scintigraphy, we used Technetium-99m hydroxymethylene diphosphonate (99mTc-HMDP) and Technetium-99m methylene diphosphonate (99mTc-MDP) as tracers at Katsura Hospital and Kanazawa University Hospital, respectively. Ra-223 therapy involved an intravenous injection of 55 kBq/kg every 4 weeks.

Statistical analysis. Fisher's exact test and univariate analysis were used to assess factors responsible for discontinuation. Thirteen factors were examined: Age, PS, Pain, Hb, PSA, PSA-DT, lactate dehydrogenase (LDH), neutrophil-lymphocyte ratio (NLR) as a nutritional status factor, C-reactive protein (CRP) as an inflammation factor, ALP, total number of therapeutic line before Ra-223, no pretreatment chemotherapy, and ARTA. The cutoff for continuous value was the median or normal value.

We performed multivariate logistic regression analysis using all the factors determined to be responsible for discontinuation. We used these factors to create a risk scoring system. Survival analysis was performed using the Kaplan-Meier method, and log-rank tests were performed for differences between risk groups. The start day of the overall survival (OS) was the first day of Ra-223 injection.

A p-value <0.05 was considered significant. In multivariate analysis, the following equation was used to compensate for multiplicity

(Total number of patients)÷10÷(All factor's number)×0.05.

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) (11).

Results

Patient characteristics and treatment outcome. A total of 70 patients (34 patients in the Katsura Hospital, 36 patients in the Kanazawa University Hospital) were consecutively treated with Ra-223. Baseline patient characteristics are shown in Table I. Forty-two patients (60%) completed six courses of Ra-223 therapy. The most common reason for discontinuation was deterioration of the patients' clinical status (15 patients: 21.4%). The next common reason for discontinuation was fatigue (6 patients, 8.6%). Only two patients (2.9%) discontinued Ra-223 therapy due to bone marrow suppression. The median follow-up time was 14.1 months for all patients, 20.4 months among survivors, and the median OS in all patients was 20.9 months (Figure 1A). The median survival time among patients who discontinued the therapy was 9.5 months, and that for patients who completed the treatment was 24.3 months (Figure 1B) (p-value <0.0001).

Factors of discontinuation. The univariate analysis for discontinuation is shown in Table II. Because some data are missing, the number of patients differs by a factor. The univariate analysis, Hb, PSA, CRP, and the total number of therapeutic lines before Ra-223 were significant. Multivariate analysis was performed for these factors (Table III). A cutoff p-value of 0.027 was used to compensate for the multiplicity. Hb and PSA were left as discontinuation factors.

Risk score for discontinuation. The risk scoring system was created based on Hb <12.3 g/dl and PSA ≥25.9 ng/ml, which were assigned 1 point each, and the sum of the two parameters was used to determine the risk score; 2 points: high-risk, 1 point: intermediate-risk, and 0 points: low-risk. The discontinuation rate was 82.4% (14/17) in the high-risk group, 34.3% (11/32) in the intermediate-risk group, and 5.6% (1/18) in the low-risk group (p<0.0001, Fisher's exact test.) Data points were missing for three patients.

Risk score at each cycle. We evaluated Hb and PSA at each cycle of Ra-223 therapy. Of the 28 patients who discontinued Ra-223 treatment, 3/8/9/5/3 patients discontinued the treatment after 1/2/3/4/5 courses, respectively. Hb/PSA values were measured in 25 before discontinuation. Risk classification based on pre-discontinuation data showed that 6 patients were in the intermediate-risk group and 19 patients were in the high-risk group. The low-risk group did not have any cases.

In patients who completed six courses of Ra-223 therapy, risk scores were assessed using Hb and PSA after the last Ra-223 injection. All patients who were in the low-risk category before treatment remained at low-risk after treatment (data were not examined in 2 patients). Among patients who had intermediate-risk before therapy, one patient changed to low-risk and 10 patients each from high- and intermediate-risk groups after the therapy. The patients at high-risk before therapy were 1 patient each low- and intermediate- and high-risk after the therapy.

Table I. *Baseline patient characteristics*.

Total N		70
Age	Median (range)	73 (53-86)
iPSA (ng/ml)	Median (range)	187.9 (5.899-8,949)
ISUP Grade Group	2	1
	3	4
	4	20
	5	40
	NA	5
Initial T stage	T2	6
	T3	38
	T4	16
	NA	10
Initial N Stage	0	27
	1	34
	NA	9
Initial M Stage	0	10
	1	58
	NA	2
PS	≤1	59
	≥2	11
Pain	–	40
	+	30
Hb (g/dl)	Median (range)	12.3 (8.9-14.7)
PSA (ng/ml)	Median (range)	25.9 (0.02-1086)
LDH (IU/l)	Median (range)	207 (89-387)
NLR	Median (range)	3.77 (1.05-20.57)
CRP	Under normal range	28
	Over normal range	35
ALP	Under normal range	49
	Over normal range	21
Total number of therapeutic lines before Ra-223	Median (range)	2 (0-9)
	≤2	43
	≥3	27
	NA	1
Pretreatment chemotherapy	–	44
	+	26
Pretreatment ARTA	–	13
	+	57

ALP, Alkaline phosphatase; ARTA, androgen receptor axis targeted agents; CRP, C-reactive protein; Hb, haemoglobin; ISUP, International Society of Urological Pathology; LDH, lactate dehydrogenase; LNR, neutrophil-lymphocyte ratio; NA, not assessed; PS, performance status; PSA, prostate-specific antigen.

The relationship between risk score and survival outcome. The median OS from the first Ra-223 injection for each group was 30.9, 21.5, and 8.9 months in the low-, intermediate-, and high-risk groups, respectively (Figure 2) (p-value=0.0009, log-rank test). The risk score from the data after the Ra-223 therapy could predict the prognosis after the last Ra-223 injection between high-risk, and low- and -intermediate-risk (Figure 3) (p-value=0.0177, log-rank test).

Table II. *Univariate analysis for Ra-223 therapy discontinuation.*

		HR	95% CI	*p*-Value
Age	≤75	ref		
	≥76	0.4	0.16-1.04	0.06142
Performance status	≤1	ref		
	≥2	2.02	0.55-7.4	0.29
Pain	–	ref		
	+	1.09	0.41-2.91	0.86
Hb (g/dl)	≥12.3	ref		
	<12.3	8.46	2.73-26.2	**0.00021**
PSA (ng/ml)	≥25.9	ref		
	<25.9	0.26	0.092-0.729	**0.015**
PSA-doubling time	≥3 months	ref		
	<3 months	2.02	0.746-5.49	0.167
LDH (IU/l)	≥207	ref		
	<207	0.93	0.35-2.47	0.882
NLR	≥3.77	ref		
	<3.77	0.69	0.21-2.29	0.545
CRP	Under normal range	ref		
	Over normal range	3.33	1.16-9.61	**0.0258**
ALP	Under normal range	ref		
	Over normal range	2.07	0.74-5.85	0.17
Total number of therapeutic lines before Ra-223	≤2	ref		
	≥3	5.76	2.02-16.5	**0.0011**
Pretreatment chemotherapy	–	ref		
	+	2.5	0.92-6.80	0.072
Pretreatment androgen receptor treatment	–	ref		
	+	4.61	0.93-22.7	0.06

The bold *p*-values are statistically significant. ALP, Alkaline phosphatase; CRP, C-reactive protein; Hb, haemoglobin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PSA, prostate-specific antigen.

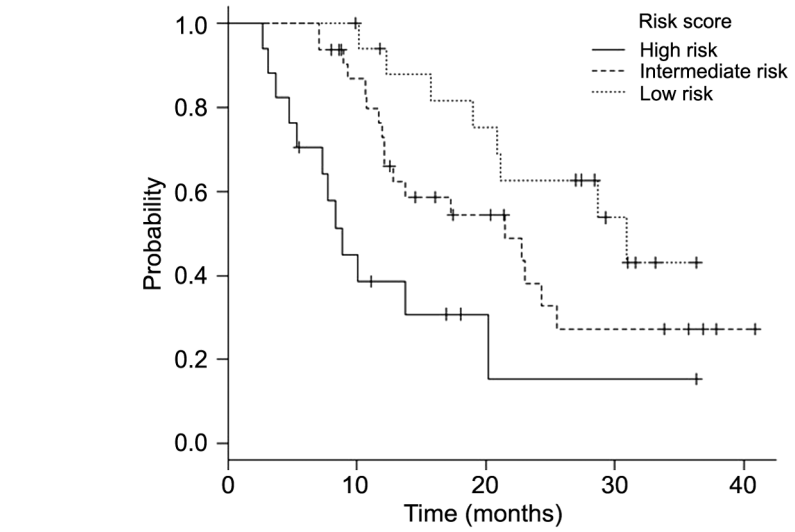
Table III. *Multivariate analysis for Ra-223 therapy discontinuation.*

		Multivariate analysis		
		HR	95% CI	*p*-Value
Hb (g/dl)	≥12.3	ref		
	<12.3	7.12	1.71-29.6	**0.007**
PSA (ng/ml)	≥ 25.9	ref		
	<25.9	0.17	0.041-0.67	**0.013**
CRP	Under normal range	ref		
	Over normal range	1.82	0.481-6.86	0.38
Total number of therapeutic lines before Ra-223	≤2	ref		
	≥3	3.21	0.893-11.5	0.074

The bold *p*-values are statistically significant. Hb, Haemoglobin; PSA, prostate-specific antigen; CRP, C-reactive protein.

Discussion

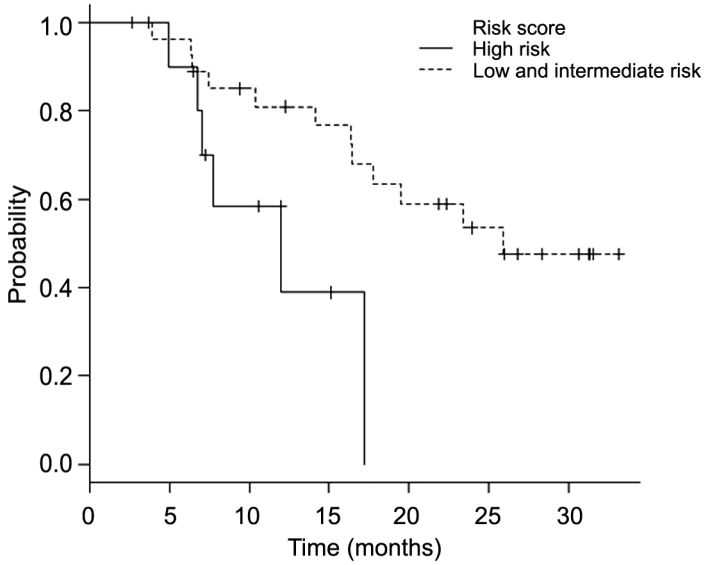
In this study, we developed a discontinuation risk scoring system by using data before Ra-223 treatment. This risk score predicts discontinuation rate, Ra-223 treatment outcome after the first course and last course. Among patients in whom Ra-223 therapy could not be completed, the risk score indicated high- or intermediate-risk before the last injection. This risk score may help identify patients with reasonable indications for Ra-223 therapy, suggest good



Number at risk

High risk	17	7	2	1	0
Intermediate risk	32	25	12	5	1
Low risk	18	17	12	5	0

Figure 2. *Kaplan-Meier curves showing overall survival from the first injection of Ra-223 for each risk group.*



Number at risk

High risk	11	9	5	2	0	0	0
Low and intermediate risk	28	26	21	18	13	9	5

Figure 3. *Kaplan-Meier curves showing overall survival from last Ra-223 injection for high-risk and low-intermediate-risk groups among 6 cycle completed patients.*

timing of Ra-223 within mCRPC treatment sequence, and find appropriate timing to stop Ra-223 therapy and switch to another treatment.

Our OS results with Ra-223 therapy were better than those reported in the ALSYMPCA study. The treatment discontinuation rate was similar to that in another study (7, 12). The reason for OS elongation may be that we used Ra-223 therapy in a group of patients who were still undergoing some other treatments, unlike in the ALSYMPCA study. Patients discontinued treatment due to disease progression rather than myelosuppression, similar to that reported in a previous report (12, 13). As previously reported (5-7, 9, 14, 15), patients who failed to complete Ra-223 therapy had a poor prognosis. Previous studies have reported various factors such as PS, PSA, ALP, LDH, Hb, PSA-DT, and bone scan index as prognostic factors of Ra-223 therapy (7, 14, 16-20). In the present study, we hypothesized that patients who could not complete six cycles of Ra-223 treatment were poorly indicated for Ra-223 treatment, and developing a risk score may help identify the optimal timing of Ra-223 therapy. We developed the risk score based on two simple data points: Hb and PSA.

Ra-223 treatment facilitates OS elongation and improved quality of life; however, the timing of Ra-223 therapy in the treatment sequence of mCRPC is still fiercely debated. In our analysis, we identified some factors behind Ra-223 therapy discontinuation. The number of pretreatment courses and CRP were not included in the risk score but remained as factors of discontinuation in the univariate analysis. Some supposition can be made regarding these factors before the Ra-223 treatment impacts the completion rate. A mild treatment course before Ra-223 therapy suggested that the disease was well-controlled. A high CRP titer suggested an active systemic inflammatory response and may indicate disease progression (21). The effect of the remaining Hb and PSA on the risk score is also suggestive and maybe more important. The high Hb value may reflect better systemic conditions, better bone health (22), and low bone metastases. Given the report by Dondossola et al., cancer cells farther from the site of accumulation in bone scintigraphy may indicate a weaker effect of Ra-223 therapy (23), and a large amount of bone metastasis is suggestive of treatment resistance. A high PSA level implies a significantly high tumor burden. When PSA is high, the Ra-223 treatment may not be good timing as it cannot reduce PSA itself to a lesser extent (24).

From our analysis, it is imperative that better timing of Ra-223 therapy is an earlier sequence in the treatment of mCRPC, and patients with low tumor burden and well-controlled disease status are suitable for Ra-223 therapy.

Additionally, the risk score may help estimate the outcome of Ra-223 treatment, survival after Ra-223 treatment, and treatment ceasing. This score may help deliver individualized treatment courses of Ra-223 therapy. For example, patients with good risk scores after six courses of Ra-223 therapy may be good candidates for Ra-223 rechallenge (25), and patients with worsened scores may receive a recommendation to discontinue Ra-223 therapy and start other therapy. Our study has several limitations. First, this was a retrospective study with a small sample size. Second, we believe that our imaging data were not sufficient to generate a generalizable finding. Third, the precise tumour burden, such as bone scan index, were not known (26). Fourth, the Hb/PSA cut-off values were derived from a small amount of data and should be validated in a larger population. Fifth, owing to the lack of statistical power, an abortive factor was possibly missed because of beta error. Sixth, previous treatment affected Hb and PSA. Multivariate analysis did not include the number of prior treatments before Ra-223 therapy, which was dominant in the univariate analysis, which may suggest this. Finally, our study did not compare the group that received Ra-223 against the group that did not. Although the risk score may help us infer the optimal timing for Ra-223 therapy, further studies are required to determine the kind of treatment given to those not suitable for Ra-223 therapy.

Despite these limitations, we believe that our data might reflect real-world clinical conditions in Japan. This finding seems essential to consider when personalizing the mCRPC treatment sequence for patients with bone metastases. Our analysis suggests that Ra-223 therapy can yield better outcomes when a patient has a low tumor burden and well-controlled disease status.

In conclusion, we developed a practical and straightforward risk score to estimate Ra-223 indication and its outcome. Further investigations in a larger study population are required to confirm our findings.

Conflicts of Interest

The Authors have no conflicts of interest in 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 the 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 agree to be accountable for all aspects of the work 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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