

Gleason Pattern 5 May Be a Prognostic Factor in Radium-223 Treatment

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Abstract. Background/Aim: Radium-223 treatment reduces the risk of death in patients with metastatic castration-resistant prostate cancer (CRPC). This study analyzed the prognostic factors in patients treated with radium-223 dichloride. Patients and Methods: Patients who received radium-223 dichloride were retrospectively analyzed. Prostate-specific antigen (PSA) response and alkaline phosphatase (ALP) decline rates were analyzed. Overall survival (OS) was evaluated using Kaplan–Meier curves, and prognostic factors for OS were assessed using Cox proportional hazards analysis. Results: Fifty-six patients were included in the study. The five-year OS rate in patients after diagnosis of CRPC was 62.2% [95% confidence interval (CI)=27.55–112.45], while the five-year OS rate in patients at the initiation of radium-223 treatment was 21.3% (95%CI=17.20–36.79). Six patients (11.1%) had a >50% PSA decline rate, and 10 (17.9%) had a >50% ALP decline rate. Cox proportional hazards analysis showed that PSA levels at the initiation of radium-223 treatment [hazard ratio (HR)=1.00; 95%CI=1.00–1.00; $p=0.0054$] and Gleason Pattern (GP) 5 (HR=5.42; 95%CI=1.08–27.27; $p=0.0400$) were associated with OS. Patients with GP 5 had a significantly poorer

prognosis compared with patients with a GP ≤ 4 . Early administration of radium-223 as a first- or second-line treatment was not associated with OS compared with late administration of radium-223 as a third-line or later treatment. Conclusion: GP 5 and high PSA levels at radium-223 initiation were associated with worse OS. Radium-223 as first- or second-line treatment was not associated with OS. Therefore, a treatment strategy for CRPC based on GP 5 is needed.

In 2012, the U.S. Preventive Services Task Force (USPSTF) recommended prostate-specific antigen (PSA)-based screening for prostate cancer, regardless of age. However, the incidence of metastatic prostate cancer has rapidly increased since 2012 (1). Consequently, the incidence of metastatic castration-resistant prostate cancer (mCRPC) has been increasing. Several therapeutic agents are available for the treatment of mCRPC. However, the prognosis of patients with mCRPC remains poor. First-line treatments for castration-resistant prostate cancer (CRPC) include docetaxel and androgen receptor signaling inhibitors (ARSIs), such as enzalutamide, apalutamide, and abiraterone acetate.

Radium-223 treatment of mCRPC in the ALpharadin in SYMPtomatic Prostate Cancer (ALSYMPCA) trial was shown to reduce the risk of death by 30.5% compared with placebo and significantly improve overall survival (OS) with or without prior docetaxel treatment (2). However, it is unclear for whom or when radium-223 should be administered. In this study, we retrospectively analyzed the efficacy of radium-223 and its prognostic factors in patients with mCRPC.

Patients and Methods

The patients included in this study received radium-223 at the Kindai University Hospital from July 2016 to June 2022. All datasets are shown in Figure 1. Patients with an unclear Gleason Pattern (GP) or neuroendocrine carcinoma were excluded. Overall, 56 patients with mCRPC who received radium-223 were retrospectively analyzed.

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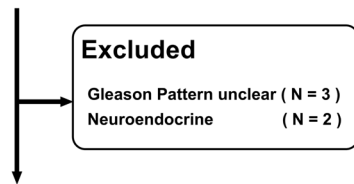
All CRPC received Radium-223 Dataset (N = 61)**Metastatic CRPC received Radium-223 (N = 56)**

Figure 1. Cohort dataset.

The following clinical and pathological data were obtained from medical records: age, PSA level, Eastern Cooperative Oncology Group performance status (ECOG-PS), pathological reports of transrectal ultrasound-guided needle prostate biopsy, follow-up data, and OS. The patients were followed up every three months. The metastatic site was evaluated using computed tomography (CT) and bone scintigraphy. Extent of disease (EOD) score was used to classify bone metastases (3).

This study was approved by the Institutional Ethics Committee of Kindai University (R02-247). The requirement for written informed consent was waived due to the retrospective nature of the study.

Statistical analysis. The results are presented as median values (range). The two groups (GP ≤ 4 and GP 5) were compared using the Mann–Whitney *U*-test and the χ^2 -test. The Kaplan–Meier estimate of the survival curve and log-rank test were used to explore the association between the parameters and patient survival. Multivariate analyses of patient age, PSA levels, GP, ECOG-PS, PSA changes, and alkaline phosphatase (ALP) changes were performed using Cox proportional hazard analyses to predict OS. All statistical analyses were performed using SPSS version 11.02 (SPSS, Chicago, IL, USA) and GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). All *p*-values were two-sided, and statistical significance was set at *p* < 0.05.

Results

Patient characteristics are summarized in Table I. Figure 2A and B shows the OS after the diagnosis of CRPC and from the initiation of radium-223 treatment, respectively. The five-year OS rate in patients after diagnosis of CRPC was 62.2% [95% confidence interval (CI)=27.55-112.45], while the five-year OS rate in patients at the initiation of radium-223 treatment was 21.3% (95%CI=17.21-36.79). The median OS in patients after the diagnosis of CRPC was 75.0 months, whereas the median OS rate in patients at the initiation of radium-223 treatment was 29.0 months. Waterfall plots of PSA response and ALP decline rates are shown in Figure 3A and B, respectively. Six patients (11.1%) had a >50% PSA decline rate and 10 (17.9%) had a >50% ALP decline rate.

Next, we analyzed the prognostic factors for OS after initiating radium-223 treatment in patients treated with radium-

Table I. Patient characteristics.

	N=56
Median age [years (range)]	73 (49-83)
Median PSA [ng/ml (range)]	23.23 (0.05-1,001.00)
Median time to CRPC [months(range)]	25 (4-155)
ECOG PS	
0	43 (0.77)
1	13 (0.23)
Lymph node metastasis	
N1	16 (0.29)
EOD score	
≤ 1	26 (0.46)
≥ 2	30 (0.62)
Treatment's line received radium-223	
1 st -2 nd line	14 (25.0)
$\geq 3^{\text{rd}}$ line	42 (75.0)
PSA response rate (%)	255.9 (−88.3-8,433.1)
ALP decline rate (%)	−17.7(−92.5-423.4)
Completion of six cycles of radium-223	37 (62.5)

ECOG-PS: Eastern Cooperative Oncology Group performance status; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen; ALP: alkaline phosphatase.

223. Table II shows the results of univariate and multivariate Cox proportional hazards analyses for OS prediction. In the univariate analysis, the following were significantly associated with OS: PSA levels before radium-223 treatment (HR=1.00; 95%CI=1.00-1.00; *p* < 0.001), GP 5 (HR=7.03; 95%CI=1.60-30.94; *p* = 0.0099), EOD score (HR=3.05; 95%CI=1.20-7.76; *p* = 0.0192), and ALP decline rate (HR=1.01; 95%CI=1.00-1.01; *p* = 0.0278). The early administration of radium-223 as first- or second-line treatment was not associated with OS compared with the late administration of radium-223 as third-line treatment or later (HR=0.54; 95%CI=0.19-1.52; *p* = 0.2412). In the multivariate analysis model 1, GP 5 (HR=5.48; 95%CI=1.10-27.31; *p* = 0.0381), PSA levels before radium-223 treatment (HR=1.00; 95%CI=1.00-1.00; *p* = 0.0050), and ALP change (HR=1.00; 95%CI=1.00-1.01; *p* = 0.0275) were significantly associated with OS.

To predict the efficacy of radium-223, only the variables before the initiation of radium-223 treatment were used. Thus, we performed a multivariate analysis of these variables before radium-223 treatment. Multivariate analysis model 2 showed that GP 5 (HR=5.39; 95%CI=1.09-26.70; *p* = 0.0389) and PSA levels before radium-223 treatment (HR=1.00; 95%CI=1.00-1.00; *p* = 0.0073) were significantly associated with OS.

In both models, GP 5 was a poor prognostic factor for OS in patients treated with radium-223. When comparing the characteristics of two distinct groups of patients, 40 with GP 5 and 16 with GP ≤ 4 , there was no significant difference in age at the time of radium-223 treatment, PSA levels before

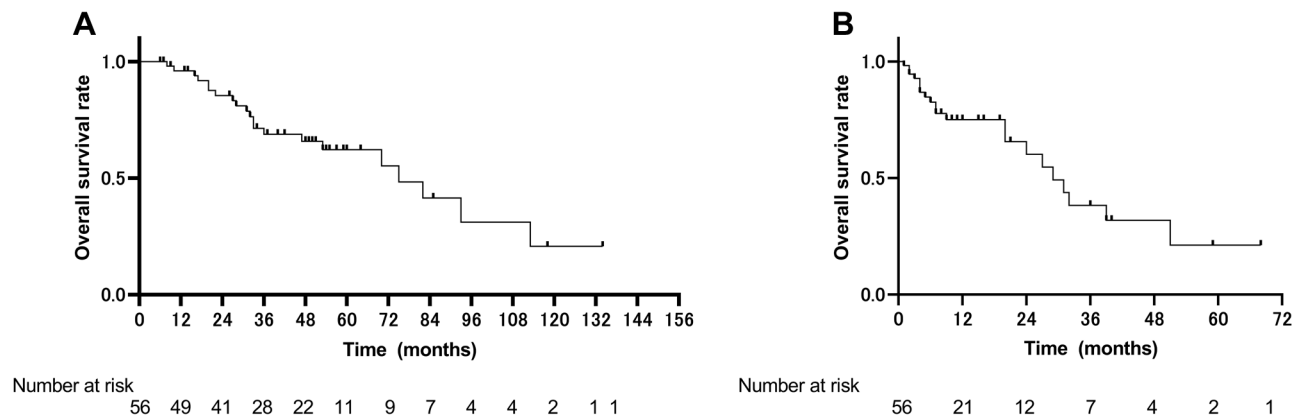


Figure 2. Overall survival after diagnosis of castration-resistant prostate cancer (A) and from the initiation of radium-223 (B).

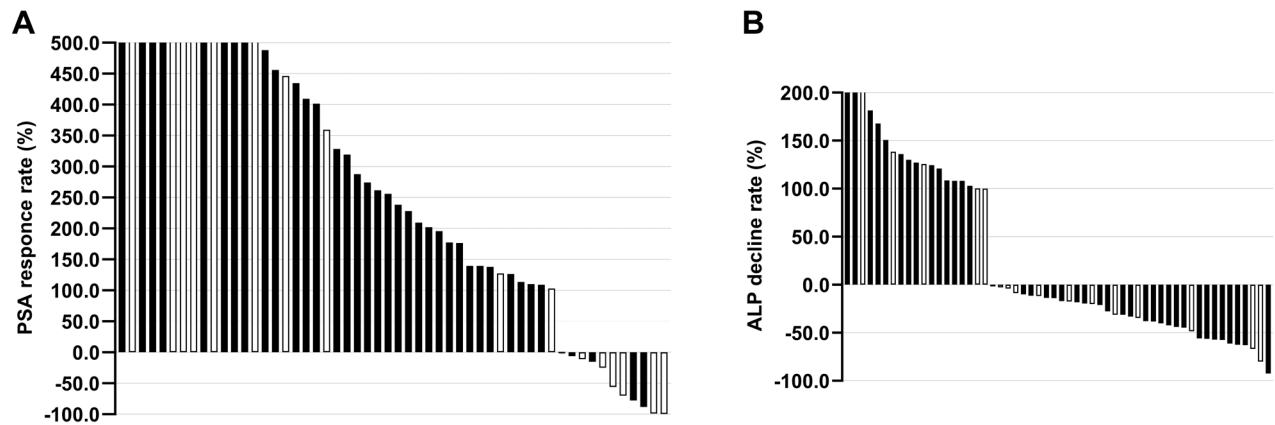


Figure 3. Waterfall plots of PSA response rates (A) and ALP decline rates (B).

Table II. Cox-proportional hazards analysis for overall survival after received radium-223.

Variables	Univariate analysis			Multivariate analysis (model 1)			Multivariate analysis (model 2)		
	HR	95%CI	p-Value	HR	95%CI	p-Value	HR	95%CI	p-Value
Age (years)	0.9998	0.9166, 1.0906	0.9971						
PSA (ng/ml)	1.0029	1.0012, 1.0046	<0.001	1.0026	1.0008, 1.0044	0.0050	1.0024	1.0006, 1.0042	0.0073
Gleason Pattern									
≤4	1.0000			1.0000			1.0000		
5	7.0307	1.5975, 30.9432	0.0099	5.4759	1.0979, 27.3113	0.0381	5.3942	1.0899, 26.6981	0.0389
ECOG PS									
0	1.0000								
1	1.5943	0.6030, 4.2148	0.3471						
EOD score									
≤1	1.0000			1.0000			1.0000		
≥2	3.0508	1.1992, 7.7616	0.0192	1.2611	0.4398, 3.6163	0.6660	1.3208	0.4727, 3.6905	0.5956
PSA response rate (%)	1.0000	0.9998, 1.0003	0.6842						
ALP decline rate (%)	1.0055	1.0006, 1.0104	0.0278	1.0054	1.0006, 1.0102	0.0275			

CI: Confidence interval; CRPC: castration-resistant prostate cancer; ECOG-PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; PSA: prostate-specific antigen; ALP: alkaline phosphatase.

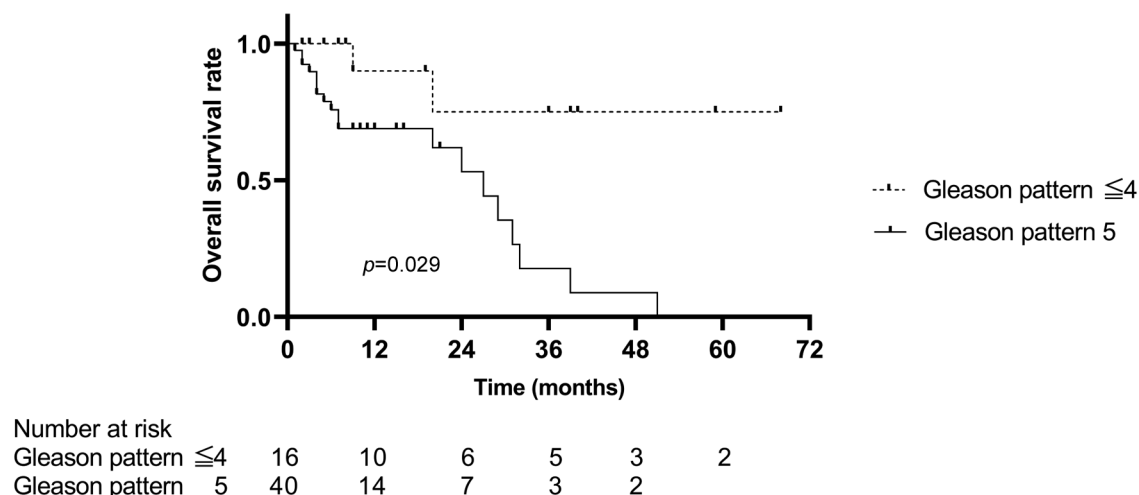


Figure 4. Overall survival with or without Gleason Pattern 5.

radium-223 treatment, or time to CRPC between patients with GP 5 and GP ≤ 4 . There were significant differences in ECOG-PS and EOD scores between the two groups in which patients received radium-223. Figure 4 shows the Kaplan-Meier curves of the OS of GP 5 and GP ≤ 4 . The five-year OS rate in patients with GP 5 was 0% (95%CI=0.00-0.00) and 75.0% (95%CI=17.21-36.79) in patients with GP ≤ 4 . The median OS with GP ≤ 4 was 27.0 months. A significant difference in OS was observed between the GP 5 and GP ≤ 4 groups (log-rank test, $p=0.0029$).

Discussion

In this study, we retrospectively analyzed the prognosis of patients with mCRPC treated with radium-223 and found that GP 5 was a poor prognostic factor in CRPC patients treated with radium-223.

The ALSYMPCA trial, which evaluated the efficacy of radium-223 in patients with advanced prostate cancer and bone metastases, demonstrated an increase in OS regardless of prior docetaxel therapy (2). In 2018, the European Medicines Agency (EMA) issued a statement recommending that radium-223 be restricted to third-line treatments or cases where other treatments are not applicable (4). Furthermore, one report advised against the concurrent use of abiraterone acetate and radium-223, citing concerns related to OS and the risk of fractures (4). Baucknht *et al.* developed a BIO-Ra score to categorize patients into three risk groups and predict outcomes in patients receiving radium-223 treatment (5, 6). The BIO-Ra score consists of neutrophil-to-lymphocyte ratio (NLR: <3.1 vs. ≥ 3.1), ECOG-PS (0-1 vs. 2-3), number of bone metastases (<6 vs. 6-20 vs. ≥ 20), and ALP (<220 vs. ≥ 220). The median OS of the high-risk group was significantly lower than those of the

low- and moderate-risk groups. Han-Chung Yang *et al.* reported a comparison between the Radium-223 treatment groups of less than 4 cycles and those receiving 5-6 cycles. They reported that both the median PSA progression-free survival and OS were prolonged in the group receiving ≥ 5 cycles compared to the group receiving less than ≤ 4 cycles (7). Matsumoto *et al.* reported that the presence or absence of anemia (Hb <12) and bone pain before treatment were prognostic factors associated with OS (8). Additionally, a distinction in OS was noted between radium-223 treatments comprising ≤ 2 cycles and those with ≥ 3 cycles, indicating that higher treatment completion rates associated with extended OS. Okabe *et al.* reported that the pre-DOC group exhibited significantly better outcomes compared to the post-DOC group in terms of the radium-223 treatment completion rate of 6 cycles, progression-free survival (PFS), and cause-specific survival (CSS) (9). The findings suggest the potential benefit of treating patients before disease progression, or in other words, administering treatment at an earlier stage. However, in the present study, there was no difference in survival between patients who received radium-223 earlier *versus* later. When examining the patients' backgrounds between the two groups, it was noted that those who received radium-223 as the first- and/or second-line treatment had a shorter time to CRPC and poorer ECOG-PS than those who received it as third-line therapy or beyond (data not shown). In other words, the treatment could have been administered to patients with advanced disease. Nakashima *et al.* reported that serum ALP and BAP levels decreased in response to treatment, and regarding OS, the group with a BSI value of <2 showed a significant improvement compared to those with a BSI value of ≥ 2 (10). In the present study, we investigated the association between EOD score and OS, but no significant difference was observed. EOD score is defined on a 4-point scale (1-4), which

may be problematic because it equally categorizes large and small metastatic lesions.

In most clinical studies, a Gleason score (GS) ≥ 8 was categorized as high-risk (11-13). The higher the GS, the more likely it is that the prostate cancer will progress rapidly. A GP 5 is pathologically different from GP 4 (14). GP 5 is characterized by a complete loss of glandular lumina, whereas GP 4 is characterized by fused glands or cribriform patterns (15). As the microscopic characteristics of GP 4 and 5 differ, the aggressiveness and responsiveness to therapeutic agents for GS 9, including GP 5, may differ from those for GS 8. GS is a prognostic factor for mCRPC (16). Previous studies suggested that the presence of GP 5 tumors in biopsy and surgical specimens is a prognostic factor after local and systemic treatments (13, 17). Although little is known about the molecular alterations in these poorly differentiated tumors, Velho *et al.* characterized GP 5 prostate cancers using whole prostatectomy specimens (15). They reported a 4-fold increased risk of metastasis, and *TP53* mutations, PTEN loss, and ERG expression were associated with biochemical failure and the risk of metastasis (15). Immunohistochemical analysis showed that in 22% of GP 5 patients with mutations in the homologous recombination pathway, 12% had mismatch repair deficiency, and 50% had PTEN loss. In the present study, radium-223 treatment for mCRPC, including GP 5, resulted in a poor prognosis. However, radium-223 treatment for mCRPC containing GP 5 may have a better prognosis than for mCRPC patients with GP 5 who did not receive radium-223, as the present study did not compare the radium-223-treated and radium-223-untreated groups. Patients with mCRPC GP 5 may benefit from treatment with PARP inhibitors, immuno-oncological drugs, and AKT inhibitors.

Study limitations. The study was based on a limited dataset and conducted exclusively with Japanese participants at a single facility. Therefore, regional factors must be considered when interpreting these results. Furthermore, this was a retrospective study. A prospective randomized trial is preferable for a more comprehensive understanding of treatment sequences.

Conclusion

Patients with mCRPC with GP 5 and high PSA levels before radium-223 treatment had a poor prognosis compared with patients with GP ≤ 4 and low PSA levels. In contrast, first- and second-line radium-223 treatments were not associated with OS. Further studies are necessary to determine the optimal timing of radium-223.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: Mitsuhsa Nishimoto and Kazutoshi Fujita; Methodology: Mitsuhsa Nishimoto and Kazutoshi Fujita; Software and Validation: Mitsuhsa Nishimoto and Kazutoshi Fujita; Formal Analysis: Mitsuhsa Nishimoto, Kazutoshi Fujita and Saizo Fujimoto; Investigation: Mitsuhsa Nishimoto, Kazutoshi Fujita, Aritoshi Ri, Saizo Fujimoto, Yasuo Oguma, Shingo Toyoda, Mamoru Hashimoto, Takashi Kikuchi, Shogo Adomi, Yoshitaka Saito, Yasunori Mori, Takafumi Minami, Masahiro Nozawa, Kazuhiro Yoshimura, Makoto Hosono and Hirotsugu Uemura; Resources: Mitsuhsa Nishimoto, Kazutoshi Fujita; Data Curation: Mitsuhsa Nishimoto, Kazutoshi Fujita; Writing – Original Draft Preparation: Mitsuhsa Nishimoto; Writing – Review & Editing: Kazutoshi Fujita; Visualization: Mitsuhsa Nishimoto and Kazutoshi Fujita; Supervision: Makoto Hosono and Hirotsugu Uemura; Project Administration: Makoto Hosono and Hirotsugu Uemura.

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