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Original Article: Clinical Investigation

Administration of radium-223 and the prognosis in Japanese bone metastatic castration-resistant prostate cancer patients: A large database study

Takashi Kawahara,[1,2] Yasuhide Miyoshi,[1] Sahoko Ninomiya,[1] Motoki Sato,[1] Teppei Takeshima,[1] Hisashi Hasumi,[2] Kazuhide Makiyama[2] and Hiroji Uemura[1]

[1]Department of Urology and Renal Transplantation, Yokohama City University Medical Center, Yokohama, Japan
[2]Department of Urology, Yokohama City University, Graduate School of Medicine, Yokohama, Japan

Abbreviations
CRPC = castration-resistant prostate cancer
CSS = cancer-specific survival
DOC = docetaxel
DPC = Diagnosis Procedure Combination
HR = hazard ratio
OS = overall survival
Ra-223 = Radium-223

Correspondence
Takashi Kawahara M.D., Ph.D., Department of Urology and Renal Transplantation, Yokohama City University Medical Center, 4-57, Urafune-cho, Minami-ku, Yokohama, 2320024 Japan.
Email: takashi_tk2001@yahoo.co.jp

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Background: The ALSYMPCA trial revealed radium-223 (Ra-223) to be a life-prolonging agent for bone metastatic castration-resistant prostate cancer (CRPC). However, only 2.8% of enrolled patients in that clinical trial were Asian, and no Japanese patients were enrolled. Several retrospective studies have been published concerning Japanese bone metastatic CRPC patients receiving Ra-223. However, no study has yet reported the correlation between Ra-223 induction and the survival in Japanese bone metastatic CRPC patients. This study investigated the effect of Ra-223 as a life-prolonging agent in a large Japanese healthcare fee database.
Methods: A total of around 410 000 prostate cancer patients were extracted from this database, and 25 934 were diagnosed with CRPC. In these patients, the age, date of the CRPC diagnosis, date of Ra-223 induction, and prognosis were analyzed.
Results: A total of 1628 patients received Ra-223, and 6693 patients were diagnosed with bone metastasis CRPC, with the remaining 17 613 patients diagnosed with CRPC without bone metastasis. The patients who completed six courses of Ra-223 showed a significantly more favorable overall and cancer-specific survival than those who received ≤5 courses ($p < 0.0001$ and $p < 0.0001$, respectively). For time from CRPC diagnosis date to death, the Ra-223 induction group showed a significantly more favorable prognosis with regard to both the overall and cancer-specific survival than the bone metastatic CRPC patients without Ra-223 ($p < 0.0001$ and $p < 0.0001$, respectively).
Conclusions: Bone metastatic CRPC patients who received Ra-223 showed a significantly better prognosis than bone metastatic CPRC patients who did not receive Ra-223.

Key words: bone metastasis, castration-resistant prostate cancer, CRPC, prognosis, radium-223.

INTRODUCTION

Radium-223 (Ra-223) is the first drug targeting alpha radiation for bone metastatic castration-resistant prostate cancer (CRPC).[1] Due to the low incidence of severe adverse effects compared with cytotoxic systemic chemotherapy, elderly and frail bone metastatic patients are able to safely receive Ra-223. However, any PSA decline was only seen in 18.4%.[2] Therefore, while Ra-223 has shown life-prolonging effects and delayed symptomatic skeletal events compared with placebo, patients and clinicians have difficulty recognizing the efficacy of Ra-223.

Only 2.8% of patients in the ALSYMPCA study were Asians, including 5 Singaporean and 21 Hong Kong patients.[1] No Japanese patients were included in either the ALSYMPCA or PEACE III clinical trials.[1] The ERA-223 study included Japanese patients, but no survival benefit using Ra-223 was observed.[3] Thus, no studies have yet confirmed Ra-223 as a life-prolonging agent compared with non-Ra-223 patients in a Japanese patient cohort. Furthermore, there are no ongoing clinical trials confirming the effectiveness of Ra-223 as a life-prolonging agent in a Japanese cohort.

Ra-223 is widely used in daily clinical practice in Japan for bone metastatic CRPC, with a total of 5852 vials administered annually in 2018.[4] There were several studies to confirm that completion of six-course Ra-223 showed longer survival compared to the one- to five-course group and examined the factors who showed longer prognosis who received Ra-223 in Japanese patients.[5–14] However, almost all studies of Ra-223 from Japan have used patient cohorts receiving Ra-223, with no non-Ra-223 induction patient cohorts included.[2,5,7,10,11]

The present retrospective study investigated the efficacy of Ra-223 as a life-prolonging agent in Japanese bone metastatic CRPC patients with Ra-223 comparing with those without Ra-223 using a Japanese healthcare fee database.

MATERIALS AND METHODS

This study used the database of healthcare fees, which covers around 25.6% of Diagnosis Procedure Combination (DPC) hospitals in Japan. These data were obtained from Medical Data Vision (Tokyo, Japan). A total of around 410 000 prostate cancer patients were extracted from this database, and 25 934 were diagnosed with CRPC. Regarding these patients, the age, date of the CRPC diagnosis, date of Ra-223 induction, combination of docetaxel (DOC) or not, and prognosis were analyzed.

A total of 8321 were diagnosed with bone metastatic CRPC. In these patients, 1628 patients underwent Ra-223, and the rest of 6693 patients did not receive Ra-223. And 17 613 patients were diagnosed with CRPC but were not diagnosed with bone metastasis. The patients who received Ra-223 were divided by the number of courses of Ra-223 induction for analyses. The overall survival (OS) and cancer-specific survival (CSS) were analyzed both from the time of the CRPC diagnosis and from the Ra-223 induction date to examine the impact of Ra-223 as a life-prolonging agent in Japan. We also used the comparison group as bone metastatic CRPC and non-bone metastatic CRPC cohort without Ra-223. Due to the limitation of this database study based on healthcare diagnosis name, non-bone metastatic CRPC cohort included non-metastatic CRPC, and metastatic CRPC except for bone metastasis.

Statistical analyses

The participants' characteristics and scores were analyzed using Mann–Whitney *U* tests. The OS and CSS were written by Kaplan–Meier curve and log-rank test was used as a comparison. These tests were conducted using the Graph Pad Prism software program (Graph Pad Software). p values of <0.05 were considered to indicate statistical significance.

RESULTS

The age distributions of the Ra-223 induction group, bone metastatic CRPC group, and non-bone metastatic CRPC group are shown in Figure 1. The median (mean ± standard deviation) age at the time of the CRPC diagnosis was 85 (85.0 ± 3.5) years old in the Ra-223 induction group, 81 (81.0 ± 1.41) years old in the bone metastatic CRPC group, and 87 (87.0 ± 4.95) years old in the non-bone metastatic CRPC group. In the Ra-223 induction group, 942 of 1628 (57.9%) received six courses of Ra-223, 125 (7.7%) received five courses, 145 (8.9%) received four courses, 150 (9.2%) received three courses, 128 (7.9%) received 2 courses, and 138 (8.5%) received one course. Pre- and post-Ra-223 anti-

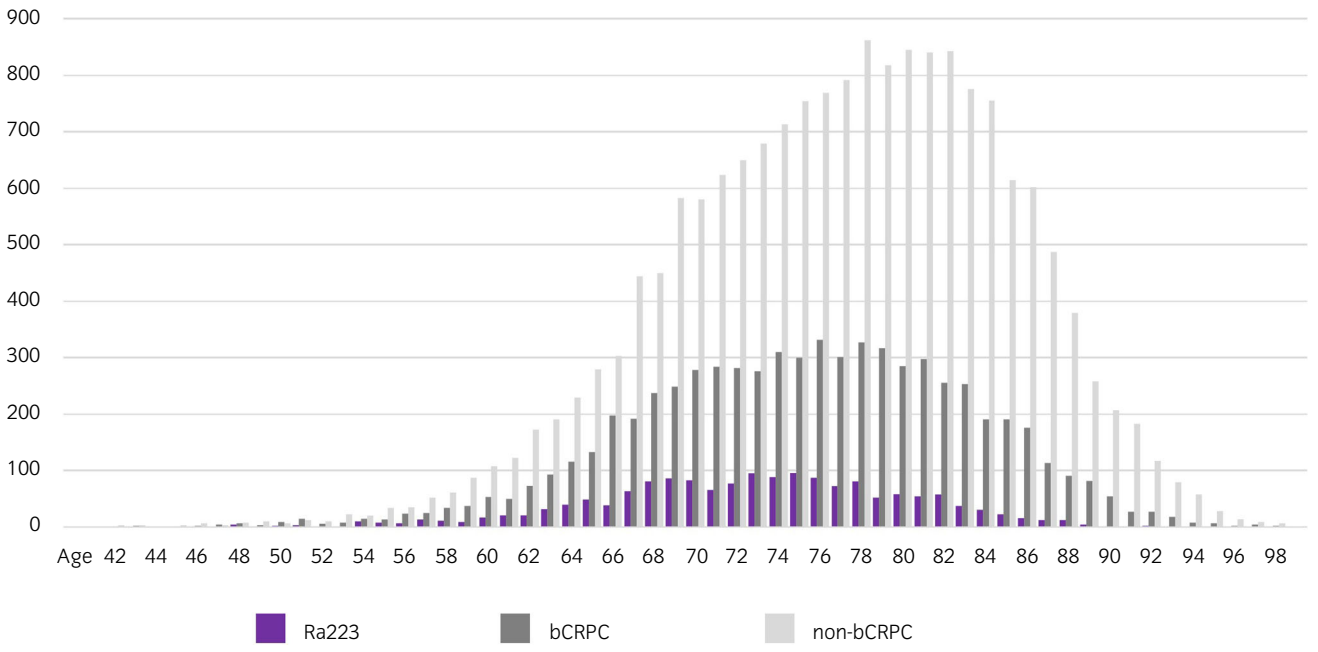


FIGURE 1 Age distribution in Ra-223 induction group, bone metastatic castration-resistant prostate cancer (CRPC) patients, and non-bone metastatic CRPC patients.

cancer agents are shown in Table 1. A total of 1254 of 1628 (77.05) received bone modifying agents. In these patients, 954 received denosumab and 300 received zoledronic acid.

The patients who completed six courses of Ra-223 showed a significantly better OS and CSS from the date of initial Ra-223 induction than those who received ≤5 courses (OS hazard ratio [HR] 0.33, $p < 0.0001$; CSS HR: 0.31, $p < 0.0001$). The Ra-223 induction group also showed a significantly better OS and CSS from the date of the CRPC diagnosis to death than those without Ra-223 (OS HR: 0.43; $p < 0.0001$, CSS HR 0.40, $p < 0.0001$) (Figure 2).

The survival curves for each course of Ra-223 are shown in Figure S1. There were no marked differences in the OS or CSS from the date of the CRPC diagnosis between the Ra-223 with DOC and Ra-223 without DOC groups (OS HR: 1.04, 61.0 months vs. undefined, $p = 0.734$; CSS HR: 1.22, 66.0 months vs. undefined, $p = 0.127$, respectively) (Figure 3).

Regarding the CRPC patients without Ra-223 induction, the bone metastatic CRPC patients showed a poorer OS and CSS than the non-bone-metastatic CRPC patients (OS HR: 1.64, 50 vs. 78 months, $p < 0.0001$; CSS HR: 1.77, 76 months vs. undefined, $p < 0.0001$) (Figure 4). The patients who completed six courses of Ra-223 showed a significantly better OS and CSS than those who did not (OS HR: 0.39, 83 vs. 56 months, $p < 0.0001$; CSS HR: 0.44, 83 vs. 76 months, $p < 0.0001$). The patients who received one to five courses of Ra-223 showed a favorable OS and CSS, but no significant difference was observed in the CSS (OS HR: 0.83, 49 vs. 50 months, $p = 0.024$; CSS HR: 0.97, 58 vs. 76 months, $p = 0.722$).

TABLE 1 Pre- and Post-Ra-223 combination treatment

	All	Pre-Ra-223	Post-Ra-223
Enzalutamide	1087 (66.8%)	793 (48.7%)	294 (18.1%)
Abiraterone	907 (55.7%)	624 (38.3%)	283 (17.4%)
Apalutamide	68 (4.2%)	21 (1.3%)	47 (2.9%)
Darolutamide	8 (0.5%)	3 (0.2%)	5 (0.3%)
Docetaxel	604 (37.1%)	335 (55.5%)	269 (44.5%)
Cabazitaxel	425 (26.1%)	176 (10.8%)	249 (15.3%)
Orapalib	3 (0.2%)	0 (0.0%)	3 (0.2%)

DISCUSSION

The ALYSYMPCA study analyzed the survival impact of Ra-223 in bone metastatic CRPC patients.[3] In that study, Asians accounted for only 2.8% of the total number of patients; however, it is important to recognize differences in health insurance systems and economic disparities, including with regard to new drugs and radiotherapy among countries. And some Asian countries could use prostate specific membrane antigen treatment, which Japanese insurance system had not covered currently, firstly instead of Ra-223. It is particularly important to evaluate the survival benefits of a given treatment in a country like Japan, where all citizens are

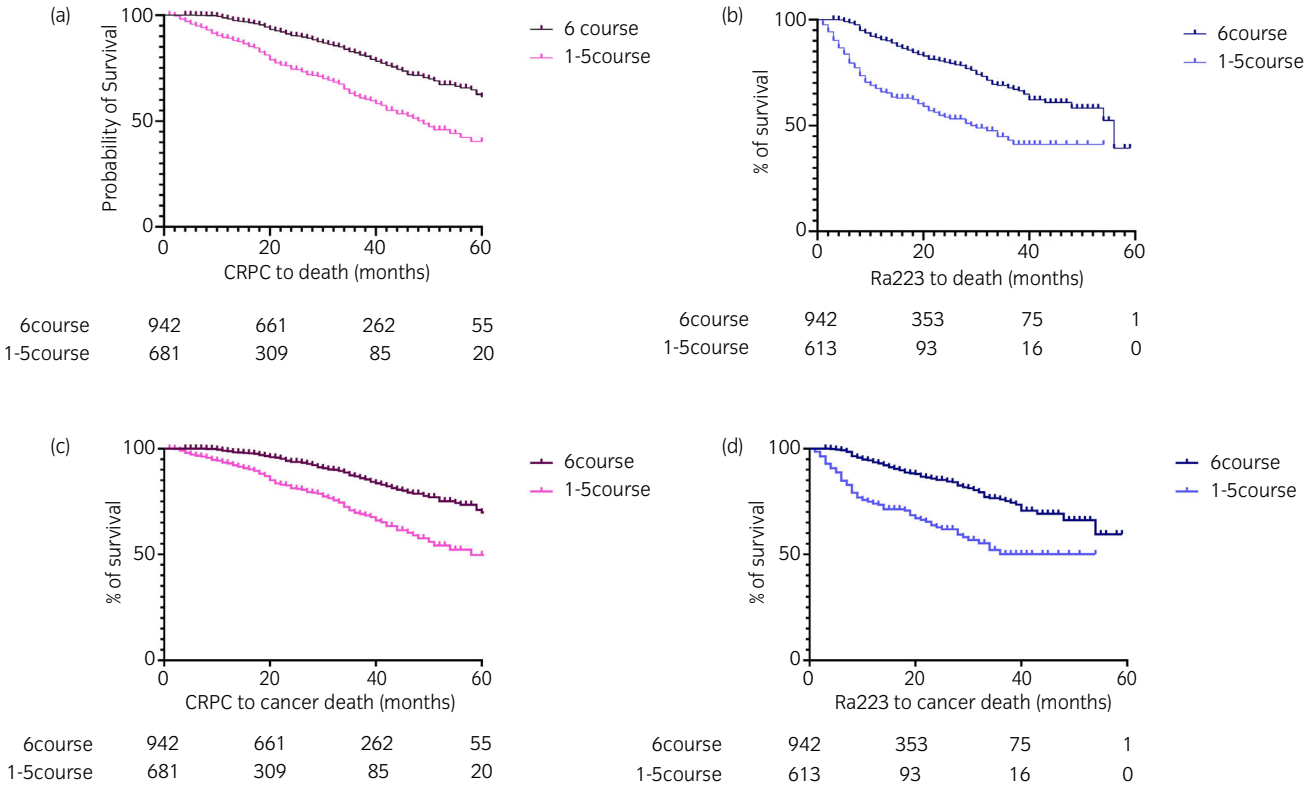
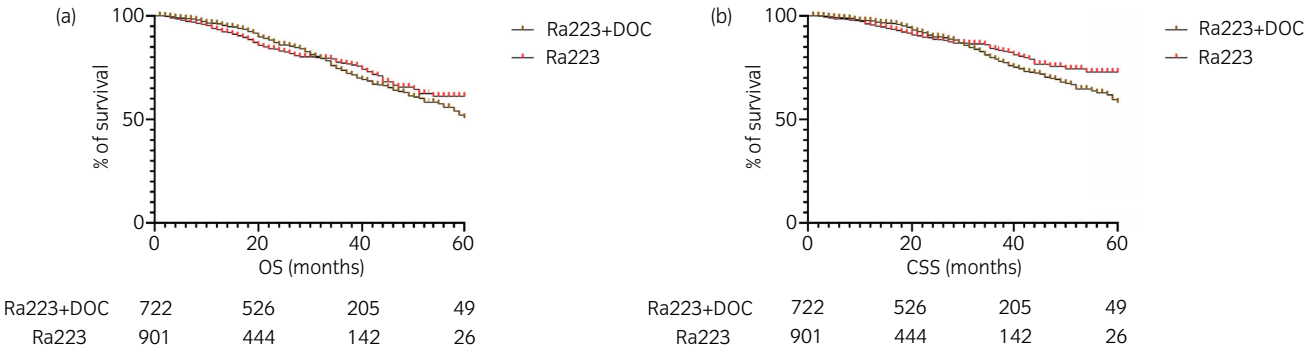


FIGURE 2 Overall survival in (a) castration-resistant prostate cancer (CRPC) to death and (b) Ra-223 start date to death and cancer-specific death in (c) CRPC to cancer death and (d) Ra-223 start date to cancer death.



Ra223+DOC	722	526	205	49
Ra223	901	444	142	26

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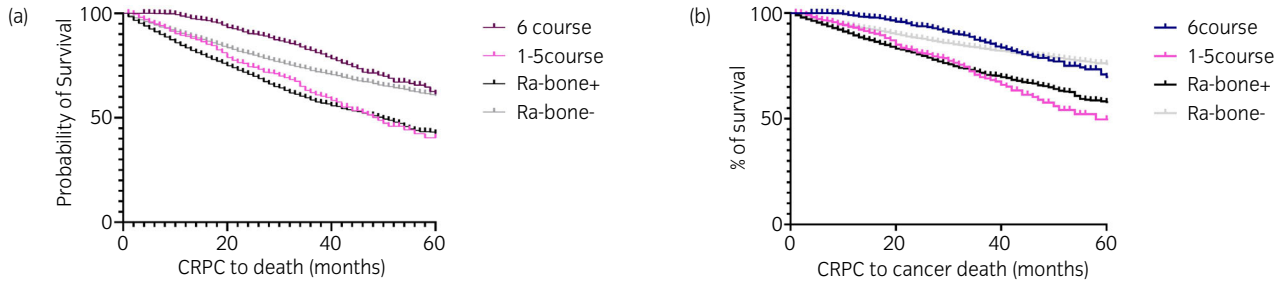
Ra223	901	444	142	26

FIGURE 3 (a) Overall and (b) cancer-specific survival with or without docetaxel (DOC) chemotherapy in patients with Ra-223. CSS, cancer-specific survival; OS, overall survival



6 course	942	661	262	55
1-5 course	681	309	85	20
Ra-bone+	6423	2495	699	132
Ra-bone-	16562	6422	2033	455

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FIGURE 4 (a) Overall and (b) cancer-specific survival between Ra-223 induction group and bone metastatic/non-bone metastatic castration-resistant prostate cancer (CRPC). The number of patients pre- and post-Ra-223 docetaxel were 335 (55.5%) in pre-Ra-223 docetaxel and 269 (44.5%) in post-Ra-223 docetaxel.

covered by insurance and can receive adequate post-treatment care.

Other large-scale Phase III trials with the OS as an endpoint include the ERA-223 and PEACE III trials.[3] However, ERA-223 was stopped in the middle of the trial, and the PEACE III trial was mainly conducted in Europe, so Japanese patients were not included. Furthermore, after the ERA-223 trial was stopped, the European Medicines Agency advices Ra-223 only to be used in patients with symptomatic bone mCRPC, without (history of) visceral metastases, having progressive disease after at least two prior lines of systemic treatment (enzalutamide, abiraterone, DOC, or cabazitaxel). In contrast, in Japan, all CRPC patients with bone metastases can be treated with Ra-223. To complete six courses of Ra-223 and thereby obtain an OS benefit, not a few bone metastatic CRPC patients in Japan receive Ra-223 without waiting for two or more new AR inhibitors or DOC.[7,10] While there have been many reports on patients treated with Ra-223 in Japan, none have described the improvement in the OS with Ra-223 compared with a cohort not treated with Ra-223 (Table 2).[5–12] Therefore, in the present study, we investigated whether or not Ra-223 improves the OS in Japanese patients using a large-scale healthcare fee database.

In this study using historical controls, the OS and CSS were found to be improved in the Ra-223-treated group compared with the bone metastatic CRPC patients without Ra-223 treatment, with a particularly significant survival benefit seen in patients who completed six courses of Ra-223. While we suspect that there are some biases involved, no previous studies have included 1623 patients treated with Ra-223 and 6693 patients with bone metastases CRPC in Japan. Previous reports in Japanese subjects involved just patients receiving Ra-223, so the lack of a control group prevented an assessment of the survival benefit. This is because most previous analyses were based on the survival starting from the day of Ra-223 administration, so the starting point for the control group could not be established, and it was not possible to determine whether or not the control group had been indicated for Ra-223. In the present study, the comparison with the control group was based on the date of the CRPC diagnosis, not the date of Ra-223 administration, and a survival difference in the Ra-223 group was still observed. In addition, while we were unable to evaluate individual indications, we included the largest number of CRPC patients in a Japanese population to date, so we suspect that a certain level of evaluation was possible.

In this study, we compared the prognosis of bone metastatic CRPC patients with or without Ra-223 treatment and found that Ra-223 treatment improved the OS and CSS. Our study also compared the OS of CRPC patients with and without bone metastases and found that patients with bone

TABLE 2 Previous retrospective study for the patients underwent Ra-223

Year	Author	Cohort	% of six-cycle completion	Prognosis (Ra-223 administration to death)
Japanese cohort				
2018	Matsubara et al.	Ra: 49pts	28 (57.1%)	N/A
2019	Nakashima et al.	Ra: 26pts	13 (50.0%)	N/A
2020	Miyoshi et al.	Ra: 79pts	—	26.5 months (with ARAT) vs 23.0 (without ARAT)
2020	Hashimoto et al.	Ra: 127pts	81 (63.8%)	17.7 months (all cohort)
2021	Miyoshi et al.	Ra: 122pts	83 (68.0%)	32.5 months (six courses) versus 8.8 months (one to five courses)
2021	Utsumi et al.	Ra: 40pts	30 (75.0%)	48.4 months (six courses) versus 5.9 months (one to five courses)
2021	Uemura et al.	Ra: 296pts	204 (69.0%)	N/A
2021	Yamamoto et al.	Ra: 42pts	29 (69.0%)	16.6 months
2022	Current study	Ra: 1628pts, bmCRPC: 6693pts	942 (57.9%)	56.0 months (six courses) versus 30.0 months (one to five courses)
Non-Japanese cohort				
2019	Dizdarevic et al.	Ra: 564pts	322 (57.1%)	N/A
2020	Badrising et al.	Ra: 300pts	139 (46.3%)	15.2 months (all cohort)

Abbreviations: ARTT, androgen receptor-axis-targeted therapy; bmCRPC, bone metastatic castration-resistant prostate cancer; Ra-223: radium-223.

metastases had a worse prognosis than those without bone metastases.

The median survival from CRPC to death in bone metastatic CRPC was 76 months. This survival time was longer comparing to the previous reports. The median overall survival from the diagnosis of CRPC in Japanese is reported to be 35.2 to 47.8 months by Miyake et al. and 40 to 44 months by Hatakeyama et al.[15,16] Inferring from Figure 4, the median overall survival from CRPC in bone metastatic CRPC without Ra-223 and one to five courses of Ra-223 were around 4 years, which seems to be equivalent to the above-mentioned Japanese data. However, six-course completion of Ra-223 group has longer overall survival of more than 1 year compared to bone metastatic CRPC without Ra-223 and one to five courses of Ra-223 group. Considering that Ra-223 had a survival benefit of 3.6 months in the ALSYMPCA trial, survival benefit of six-course completion of Ra-223 might be overestimated. Although the detailed risk why six-course groups showed big differences to five-course group in terms of CSS and OS, we speculated that not of small number of clinicians prescribed Ra-223 for the patients in lower ADL or for the patients whose cancer control would be difficult for 6 months. While the one- to five-course groups showed a significantly better OS than the bone metastatic CRPC group, no significant difference was observed for the CSS. This suggests that Ra-223 may contribute to at least an improvement in the OS, with the greatest benefit seen in patients who received six courses. In other words, it is important to establish a prescription schedule that allows for six courses of Ra-223.

Several limitations associated with the present study warrant mention. First, these data were obtained from a healthcare fee database of DPC hospitals. And this MDV database does not include all the patients who received Ra-223. Our database covers 25.6% of DPC hospitals, accounting for most hospitals that provide Ra-223 and this database was used in another study for Japanese CRPC patients.[17] Second, this database does not include detailed clinical information including Gleason Score, number of bone metastasis, Hb, lactate dehydrogenase, and so on. And this database did not include why the patients had stopped Ra-223 until five courses. Immortal time bias would be there. Some of the patients in bone metastatic CRPC without Ra-223 group might be dead before Ra-223. Propensity score match would help to decrease this bias. But this database lacked the detailed information to influence prognosis. Although this limitation, this study included the largest number of patients who received Ra-223 and able to investigate the prognosis between CRPC diagnosis to death compared to non-Ra-223 receiving cohort.

In conclusion, this study investigated the survival in the largest Japanese cohort of bone metastatic CRPC patients receiving Ra-223. The Ra-223-treated group showed a significantly better outcome than the bone metastatic CRPC patients without Ra-223 treatment, with the patients who completed six courses of Ra-223 showing a particularly good prognosis.

AUTHOR CONTRIBUTIONS

Takashi Kawahara: Conceptualization; data curation; writing – original draft. **Yasuhide Miyoshi:** Writing – review and editing. **Sahoko Ninomiya:** Writing – review and editing. **Motoki Sato:** Writing – original draft. **Teppei Takeshima:** Writing – review and editing. **Hisashi Hasumi:** Writing – review and editing. **Kazuhide Makiyama:** Writing – review and editing. **Hiroji Uemura:** Writing – review and editing.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The raw data to create tables and figures are available upon request.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

We approved institutional review board of Yokohama City University Medical Center. Approval number is B200900079.

INFORMED CONSENT

N/A due to the anonymous database.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

N/A.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1.