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Survival benefit of early radium-223 dichloride therapy in castration-resistant prostate cancer patients with osteoblastic bone metastases

Eva TAKACSOVA[1,*], Marek BARTOVIC[1], Jan IVANCIK[2,3], Iveta WACZULIKOVA[2]

[1]*Clinic of Nuclear Medicine, Medical Faculty of Comenius University and St. Elizabeth Cancer Institute, Bratislava, Slovakia;* [2]*Department of Nuclear Physics and Biophysics, Faculty of Mathematics, Physics and Informatics Comenius University, Bratislava, Slovakia;* [3]*Department of Clinical Physics, Faculty of Medicine Slovak Medical University and St. Elizabeth Cancer Institute, Bratislava, Slovakia*

**Correspondence: etakacso@gmail.com*

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The aim of the retrospective cohort study was to evaluate the overall survival of patients with castration-resistant prostate cancer and osteoblastic bone metastases without visceral metastases treated with 223Radium dichloride (223Ra). The cohort included 55 patients aged 48 to 86, with a median age of 71. Overall survival from the first administered cycle (from 7/2015 to 7/2019) was evaluated in 10/2024. The median overall survival was, despite a smaller cohort, 16.27 months (CI: 11.87–20.98 months), comparable to other large real-world studies. Asymptomatic or mildly symptomatic patients with good performance status (ECOG 0-1) at the start of therapy had a significantly higher median survival than more symptomatic patients with ECOG 2 and 3 (22.42 vs. 8.06 and 3.28 months). The number of completed cycles of 223Ra was inversely proportional to the patients' performance status (ECOG) – Kendall's Tau-c = –0.625; p<0.0001. Previous treatment with chemotherapy (41.2 % of patients) was associated with significantly worse survival on multivariable analysis. A decrease of serum PSA by more than 50% (12.7% of patients) was significantly associated with longer survival (31 months; p=0.0043). Severe (Grade 3) anemia, leukopenia, and thrombocytopenia occurred in only 9.1%, 3.6%, and 3.6% of patients. Earlier indication of 223Ra dichloride therapy in asymptomatic or mildly symptomatic patients with good performance status (ECOG 0-1) and without prior chemotherapy improved survival in our cohort. The decrease in serum PSA during treatment was a good prognostic factor associated with longer survival.

Key words: radium-223 dichloride; metastatic castration-resistant prostate cancer; osteoblastic bone metastases

Bone metastases affect approximately 90% of patients with metastatic prostate cancer [1] and significantly impact both the quality of life and overall survival [2]. In Slovakia, since 2015, patients with castration-resistant prostate cancer (CRPC) exhibiting osteoblastic bone metastases confirmed via bone scintigraphy, and without visceral metastases, are eligible for radionuclide therapy using radioactive radium-223 (^{223}Ra dichloride). Radium-223 is the first clinically approved alpha emitter that specifically targets bone metastases in CRPC, reduces pain, and can extend survival [3–5].

Radium-223 is chemically a calcium mimetic that is actively incorporated by osteoblasts and passively into the hydroxyapatite of the bone matrix at sites of increased turnover [6], such as sites of osteoblastic bone metastases. The high energy of ^{223}Ra alpha radiation (alpha particles represent 95.3% of the radiation energy of ^{223}Ra), up to 80 kiloelectronvolts/micrometer, leads to a high frequency of DNA double-strand breaks in surrounding cells, which disrupts the activity of both bone cells and cancer cells [7, 8]. Therefore, ^{223}Ra has, in addition to the analgesic, also a highly localized cytotoxic effect in the target areas which leads to longer survival of patients compared to the control group. The best-known multicenter study, ALSYMPCA, has shown prolongation of the median overall survival by 3.6 months compared to the placebo control group (14.9 months vs. 11.3 months) [4]. The physical half-life of ^{223}Ra is 11.43 days, and a short range of alpha particles (up to 100 micrometers or less than 10 cell diameters) reduces the risk of bone marrow suppression compared to previously used osteotropic beta emitters [7, 9].

The aim of our retrospective analysis was to evaluate the effectiveness of ^{223}Ra dichloride therapy to prolong survival in patients with osteoblastic bone metastases in CRPC.

Patients and methods

Patients' characteristics. Between July 2015 and July 2019, we initiated treatment with ^{223}Ra dichloride in a cohort of 56 patients. Overall survival from the first administered cycle was evaluated in October 2024. The study cohort comprised 55 patients (one unclassified patient died of a heart attack before receiving the second cycle of ^{223}Ra). The age of the participants ranged from 48 to 86 years, with a median age of 71. All patients had CRPC with osteoblastic bone metastases, featuring three or more lesions; among them, 47 patients (85.5%) had 20 or more lesions confirmed through bone scintigraphy using ^{99m}Technetium-methylene diphosphonate. Patients with visceral metastases were excluded following initial imaging examinations using positron emission tomography/computed tomography (PET/CT) with ^{18}Fluor-fluorocholine [10]. Based on their performance status at the initiation of ^{223}Ra therapy, patients were categorized into three groups according to the Eastern Cooperative Oncology Group (ECOG) scale: 0–1, 2, and 3 [11]. Out of the 55 included patients, 23 (41.8%) received cytotoxic chemotherapy (CHT)-docetaxel or also cabazitaxel, and 26 (47.3%) second-generation antiandrogens (AAs) – abiraterone and/or enzalutamide before the first cycle of ^{223}Ra.

Administration of ^{223}Ra therapy. All patients underwent intravenous ^{223}Ra treatment, administered at an activity level of 55 kilobecquerels (kBq) per kilogram of body weight at intervals of 4 to 6 weeks. Each patient received up to a maximum of 6 cycles of ^{223}Ra, with a minimum of 1 cycle and a median of 6 cycles.

Laboratory tests. Before the first cycle of ^{223}Ra, we excluded patients with leukocytes/neutrophils $<1.5\times10^9$/l, platelets $<100\times10^9$/l, hemoglobin <90 g/l, and we discontinued ^{223}Ra therapy in patients with decrease in leukocytes/neutrophils $<1.0\times10^9$/l, platelets $<50\times10^9$/l to exclude patients with impaired bone marrow reserve [12]. We used Common Terminology Criteria for Adverse Events (CTAEC) [13] to asses hematotoxicity during therapy with ^{223}Ra. We monitored blood counts, serum alkaline phosphatase (ALP) in μkat/l, and prostate-specific antigen (PSA) level in ng/ml one week before each administration of ^{223}Ra.

Statistical analysis. The collected demographic and clinical data were summarized using descriptive statistics. Continuous variables are presented as the mean with standard deviation (SD) for normally distributed variables or as median and interquartile range for data with departures from normality. Categorical variables are presented as counts and relative frequencies. The primary outcome – overall survival (OS) – was defined as the interval between the first administration of the first cycle of ^{223}Ra dichloride and either death or last follow-up. Univariate and bivariate analyses were performed to assess the associations between the explanatory variables and survival status. Between-group differences in continuous variables were tested using the Mann-Whitney U test. The association between each categorical variable and survival status was analyzed using the chi-square test or Fisher's exact test. Survival curves were constructed using the Kaplan-Meier method, and the difference between the survival curves for each level of the selected categorical predictor was evaluated using the log-rank test. Survival differences in the univariate analyses were confirmed using the Cox proportional hazards regression model. After analyzing simple relationships, multivariable modeling was used to determine the unique relationship between patient characteristics and outcome. We run multiple models with manually selected variables significant at the 0.15 level in the simple models. The effect size was expressed as a hazard ratio (HR) and presented along with 95% confidence intervals (95% CI) and the achieved significance level. The level of statistical significance was set at 5% ($p<0.05$). Statistical analyses were performed using StatsDirect 4.0.2 (Stats Direct Ltd., Cheshire, UK) and GraphPad Prism 9.0 (GraphPad Software Inc., San Diego, CA, USA) software.

The study was approved by the local ethics committee (2-2025/EK OÚSA).

Results

The median OS (from the start of ^{223}Ra therapy) in the entire study group was 16.27 months (95% CI: 11.87–20.98 months; Figure 1A). At the time of analysis (October 2024), 2 (3.6%) patients survived with a median survival of 76 months, with maximum survival being 78.2 months.

Age had no significant independent effect on survival in the univariate ($p=0.3941$) analysis (Table 1; Figure 1B).

There was a significant difference in survival between patients depending on the number of administered cycles of ^{223}Ra ($p<0.0001$; Table 1; Figure 1C).

The number of ^{223}Ra cycles administered and survival decreased significantly with the deterioration of the ECOG status of the patients (Table 2). The correlation between the ECOG category and the number of completed cycles expressed as Kendall's Tau-c coefficient (–0.625; 95% CI: –0.802 to –0.448) was highly significant ($p<0.0001$). The Kaplan-Meier curve showing survival depending on the ECOG status at the beginning of ^{223}Ra therapy is shown in Figure 1D.

Depending on the dynamics of serum PSA and ALP, we evaluated the survival of all 55 patients. Three patients, who received only one cycle of ^{223}Ra due to their death, thus missing data on PSA and ALP dynamics, were included in the category with PSA and ALP progression. If the PSA level continued to rise during treatment, the median survival in 38 (69.1%) of 55 patients was 9.76 months (95% CI: 7.33–12.76, $p=0.0013$). If the PSA level decreased or remained unchanged (in 17 (30.9%) of 55 patients), the median survival improved significantly – 27.81 months (95% CI: 21.27–31.00).

Seven of these 17 patients experienced a PSA decline of more than 50%, and their median survival was the longest – 31.0 months (95% CI: 27.81–35.01; Table 1; Figure 2A).

Table 1. Kaplan-Meier univariate analysis of OS in the study population (N=55).

Characteristics	Categories	N	Median survival	95% CI (months)	p-value
Cycles	1–3	11	2.50	0.82–3.29	<0.0001
	4–5	8	7.33	6.87–8.06	
	6	36	21.27	17.26–25.32	
ECOG	0–1	32	22.42	17.95–27.81	<0.0001
	2	13	8.06	6.51–11.87	
	3	10	3.28	0.82–6.08	
PSA categories	Regressed above 50%	7	31.00	27.81–35.01	0.0013
	Stable or regressed	10	22.42	18.67–25.32	
	Progressed	38	9.76	7.33–12.76	
ALP categories	Stable or regressed	41	19.50	13.81–22.55	0.0129
	Progressed	14	3.29	2.37–12.43	
Biochemical dynamics	Responders	17	27.81	21.27–31.00	0.0012
	Non–responders I	14	3.29	2.37–12.43	
	Non–responders II	24	11.87	7.53–17.26	
Age groups (range in years)	48–60	8	11.87	6.90–17.95	0.3941
	61–70	17	13.81	6.87–29.26	
	71–86	30	18.67	7.96–22.55	
Pretreatment with CHT	yes	23	12.40	6.90–13.09	0.0705
	no	32	20.98	13.81–23.70	
Pretreatment with AA	yes	26	16.27	7.53–20.98	0.0739*
	no	29	17.26	9.76–23.70	

Notes: *in case of crossing survival curves, the log-rank test has low power
Abbreviations: N-number of patients in the category; CI-confidence interval; P-log-rank probability value; ECOG-the Eastern Cooperative Oncology Group performance status; PSA-prostate specific antigen; ALP-serum alkaline phosphatase, responders - PSA and ALP stable or regressed; Non-responders I-PSA and ALP progressed; Non-responders II-PSA progressed but ALP remained stable or regressed

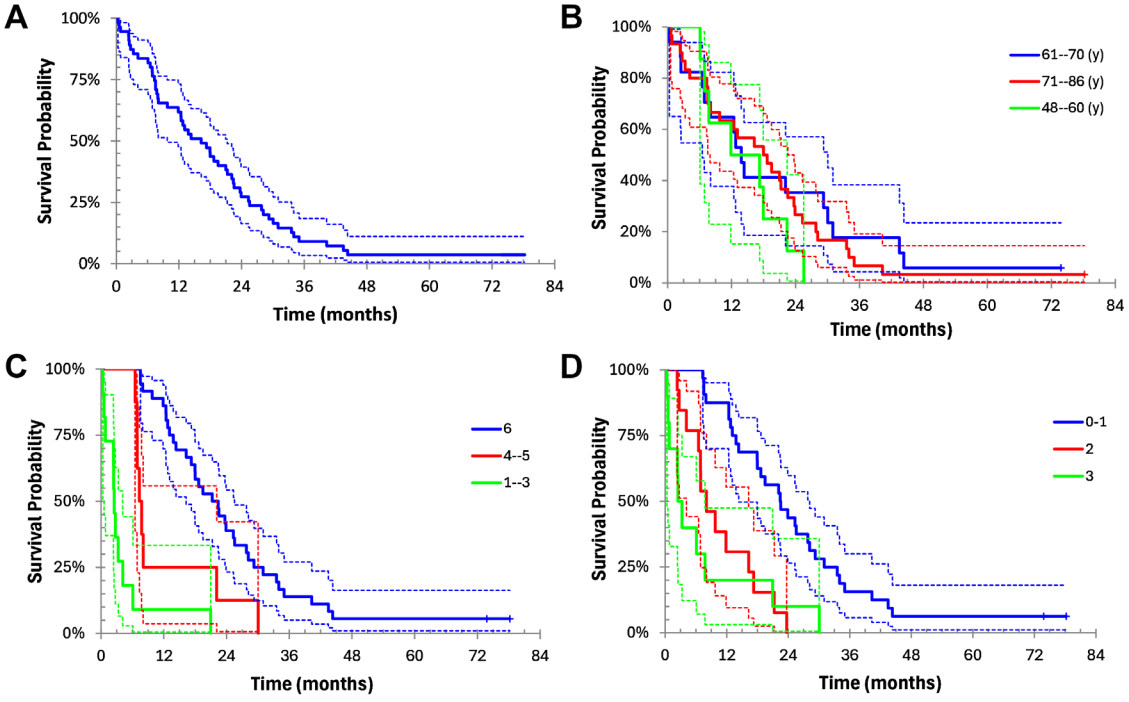

Figure 1. A) Kaplan-Meier curve showing OS from the first injection of ^{223}Ra in the entire group of patients. The lower and upper bounds of the 95% CI are displayed as dashed lines. B) Kaplan-Meier curve with 95% CI as dashed lines showing survival depending on age during ^{223}Ra therapy; p=0.3941. C) Kaplan-Meier curve with 95% CI as dashed lines showing survival depending on the number of administered cycles of ^{223}Ra (p<0.0001). D) Kaplan-Meier curve with 95% CI as dashed lines showing survival depending on ECOG status at the start of ^{223}Ra therapy; two-sided p<0.0001.

Furthermore, we found statistically significant differences in survival depending on the dynamics of ALP (p=0.0129; Table 1; Figure 2B).

Based on the dynamics of serum PSA and ALP, we divided the patients into three groups: group of responders (PSA and ALP stable or regression); non-responders I (PSA and ALP progression); non-responders II (PSA progression and ALP stable or regression). We investigated their dynamics in terms of median survival and occurrence of hematotoxicity (Table 3).

The most common adverse event during ^{223}Ra treatment was hematotoxicity, occurring in 28 (50.9%) of 55 patients (Table 3), with the most severe toxicity Grade 3 – in only 6 of 55 (10.9%) patients. Of these 6 patients, 5 patients underwent cytotoxic chemotherapy prior to ^{223}Ra therapy (9.1% of the cohort), and only 1 patient did not receive prior chemotherapy (1.8% of the cohort).

Grade 2 and 3 thrombocytopenia, leukopenia, anemia occurred in 2 (3.6%) and 2 (3.6%); 7 (12.7%) and 2 (3.6%); 10 (18.2%) and 5 (9.1%) patients, respectively. Two of the 5 patients with severe anemia during treatment were already anemic (Grade 1) at the start of ^{223}Ra treatment.

Gastrointestinal side effects (nausea, diarrhea) were reported in 5 of 55 patients (9.1%).

Due to missing data in several patients from the cohort, we did not investigate the occurrence of a bone event after discontinuation of ^{223}Ra dichloride treatment.

Before the first administration of ^{223}Ra, 23 of 55 (41.8%) patients underwent cytotoxic chemotherapy, with a median survival of 12.40 months (95% CI: 6.90–13.09). Without prior chemotherapy, 32 (58.2%) patients had a median survival of 20.98 months (95% CI: 13.81–23.70; p=0.0705; Table 1; Figure 2C). Even if this difference did not meet the predetermined level of significance on the univariate analysis, the overlap of the two 95% CIs is negligible, so we consider this difference as clinically significant.

Prior treatment with cytotoxic chemotherapy did not correlate with performance status, allowing us to test the effect of treatment on a multivariable analysis, taking into account the effects of other relevant predictor variables (PSA

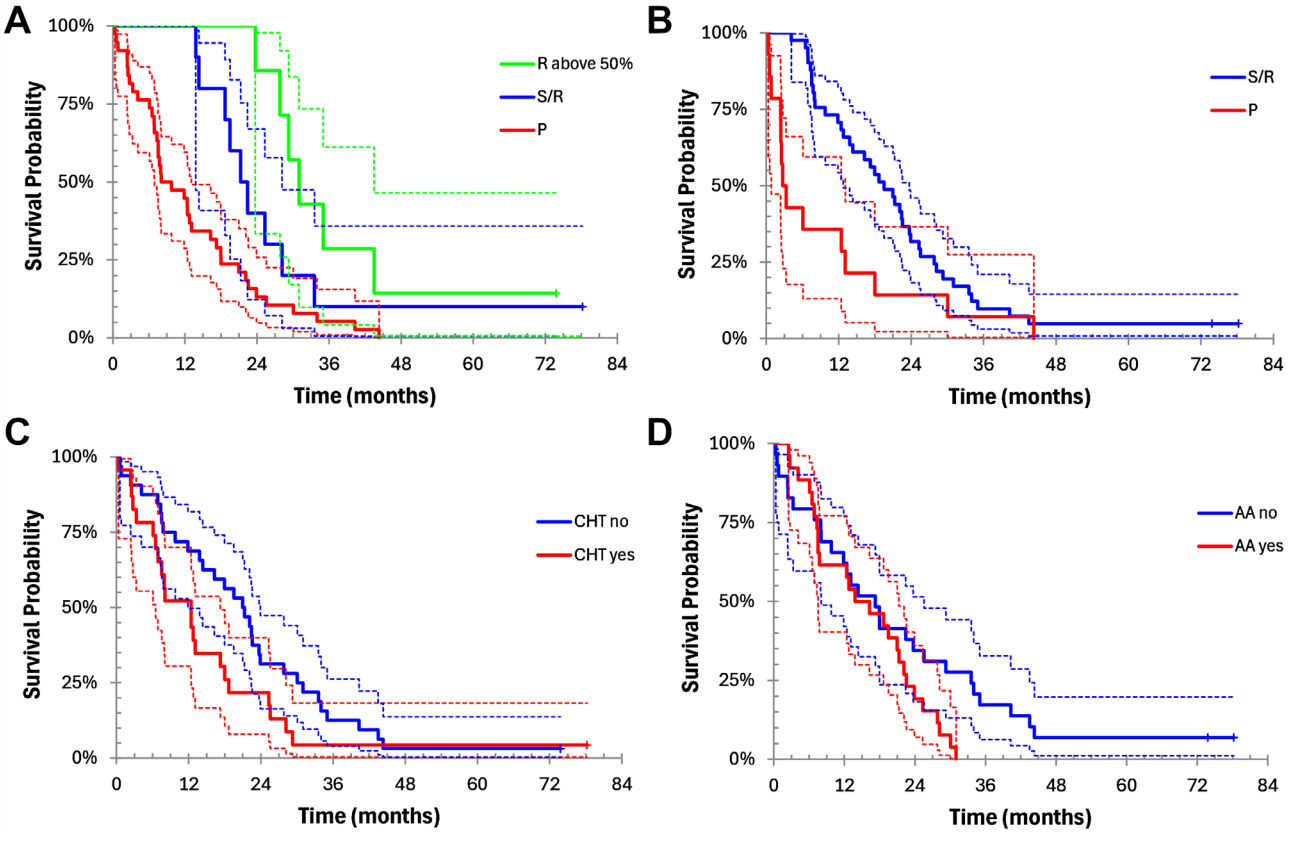

Figure 2. A) Kaplan-Meier curve with 95% CI as dashed lines showing survival depending on PSA dynamics during ^{223}Ra therapy; p=0.0013. Abbreviations: P-progressed; S/R-stable or regressed; R above 50%-regressed above 50%. B) Kaplan-Meier curve with 95% CI as dashed lines showing survival depending on ALP dynamics during ^{223}Ra therapy; two-sided p=0.0129. Abbreviations: P-progressed; S/R-stable or regressed. C) Kaplan-Meier curve with 95% CI as dashed lines showing survival depending on prior chemotherapy treatment (CHT) before ^{223}Ra therapy; p=0.0705. D) Kaplan-Meier curve with 95% CI as dashed lines showing survival depending on pretreatment with second-generation antiandrogens (AA) before ^{223}Ra therapy. The result of the log-rank test (p=0.0739) is not interpreted because the observed survival curves cross, implying nonproportional hazards.

levels and ECOG status) on the relationship between OS and ^{223}Ra therapy. We found that prior chemotherapy was independently associated with worse survival (p=0.0101), therefore, we kept this variable in the model to adjust the effect of ^{223}Ra therapy for differences in OS associated with CHT.

The final multivariable prediction model for the independent dose contribution of ^{223}Ra therapy, adjusted for PSA, ECOG status, and previously administered chemotherapy, was statistically highly significant (p<0.001; Table 4).

In patients pretreated with second generation AAs and in patients without AAs therapy was a statistically nonsignificant difference (p=0.0739; Table 1; Figure 2D) in both, univariate and multivariable analysis (p=0.8065; HR=1.08, 95% CI: 0.57–2.05), therefore, the variable was not included in the final prediction model.

Discussion

Radium-223 dichloride therapy is now an integral component of standard care for patients with bone metastases in CRPC and is incorporated into all prostate cancer treatment guidelines [14–17]. Therapy is recommended for symptomatic patients (ECOG 0-2) with predominant bone metastatic disease and no visceral metastases [4, 18]. We incline to the view of the researchers who emphasize the importance of earlier use of ^{223}Ra, even in asymptomatic patients, to enhance OS [19–23]. In our study cohort, patients who were asymptomatic or mildly symptomatic with a good performance status (ECOG 0-1) at the onset of therapy exhibited the highest median survival and significantly longer survival compared to patients with ECOG scores of 2 and 3 (23.8 vs. 8.1 and 3.3 months, respectively). All patients with ECOG 3 had advanced stage disease, were distinctly algic, and received ^{223}Ra in the prospect of an analgesic effect.

Presumably, earlier ^{223}Ra therapy also increases the chance of completing all 6 cycles. In our cohort, the number of ^{223}Ra cycles was inversely proportional to the level of performance status (ECOG) of the patients (Kendall's Tau-c = –0.63; p<0.0001).

The rate of severe hematotoxicity in our cohort was low – Grade 3 thrombocytopenia, anemia, leukopenia occurred in only 3.6%, 9.1%, and 3.6% of patients, respectively. Compared to the literature, in the ALSYMPCA study [4], a similarly low rate of severe (Grade 3–4) thrombocytopenia, anemia, and neutropenia was reported in 6%, 13%, and 3% of patients, respectively. The low rate of hematotoxicity after ^{223}Ra therapy allows a combination with other life-prolonging therapies. Subsequent radionuclide therapy with ^{177}Lutetium-prostate-specific membrane antigen (^{177}Lu-PSMA) in patients with PSMA-positive (also visceral) metastases [24, 25] is considered safe despite previous ^{223}Ra treatment [26, 27]. While ^{223}Ra treatment only affects osteoblastic bone metastases, treatment with ^{177}Lu-PSMA (PSMA radioligands with high binding strength to PSMA transmembrane glycoprotein on the surface of tumor cells) is also effective in nodal and visceral PSMA-positive metastases [28]. Therefore, it can also be effective in patients with more advanced disease.

In contrast to ^{177}Lu-PSMA, ^{223}Ra administration does not necessitate prior chemotherapy or the use of androgen receptor pathway inhibitors, allowing for its early utilization to maximize therapeutic benefits. Recent studies have demonstrated that patients who are docetaxel-naive exhibit

Table 2. Median survival time depending on the ECOG performance status and on the number of administered cycles of ^{223}Ra.

ECOG	N	Median survival time	95% CI (months)	No of cycles of ^{223}Ra median (min-max)
0-1	32	22.42	17.95–27.81	6 (5–6)
2	13	8.06	6.51–11.87	5 (3–6)
3	10	3.28	0.82–6.08	2 (1–6)

Notes: increased ECOG status at the beginning of treatment was negatively correlated with the number of administered cycles of ^{223}Ra (Kendall tau-b = –0.74), which translated into significantly worse overall survival (p<0.0001)
Abbreviations: ECOG-the Eastern Cooperative Oncology Group; N-number of patients; CI-confidence interval

Table 3. Hematologic toxicity in ^{223}Ra-treated patients grouped by biochemical response to treatment.

Biochemical dynamics	N	Number of patients with hematotoxicity		
		Grade 1	Grade 2	Grade 3
Responders	17	4	3	1
Non-responders I	14	20	0	3
Non-responders II	24	6	7	2

Abbreviations: Responders-PSA and ALP stable or regressed; Non-responders I-PSA and ALP progressed; Non-responders II-PSA progressed but ALP stable or regressed; N-number of patients

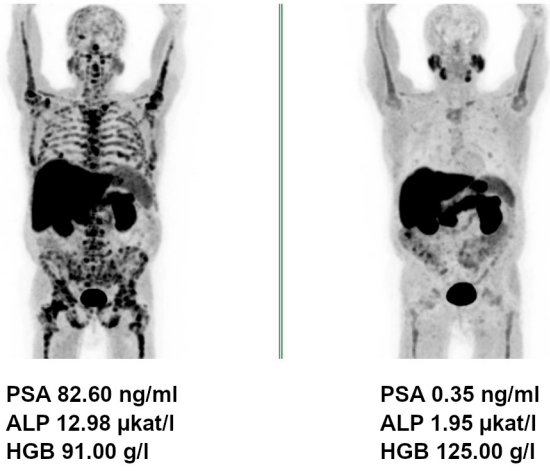

Figure 3. PET with 18F-fluorocholine (maximum intensity projection) and dynamics of PSA (prostate-specific antigen), ALP (alkaline phosphatase), and HGB (hemoglobin) before (left) and after 6 cycles of ^{223}Ra dichloride therapy (right) in a 70-year-old patient with a significant regression of bone lesions.

Table 4. Multivariable Cox regression analysis of overall survival based on treatment and clinicopathological factors.

Variable	Coefficient	Std. error	Z	p-value	HR	95% CI
log PSA	0.515	0.2057	2.504	0.0123	1.67	1.12–2.51
ECOG 0-1	–0.968	0.4679	–2.068	0.0387	0.38	0.15–0.95
ECOG 2-3	reference category				1	
CHT yes	0.796	0.3094	2.573	0.0101	2.22	1.21–4.07
CHT no	reference category				1	
#cycles 6	–1.055	0.4755	–2.218	0.0265	0.35	0.14–0.88
#cycles 1-5	reference category				1	

Notes: continuous variable PSA was log-transformed because of skewness, categorical variables ECOG and CHT were expressed as binary variables. The variable No. of fractions was dichotomized into the full number of fractions (6) or otherwise (1-5); p-values were calculated based on Wald test; global statistical significance of the selected model: $p < 0.0001$; Chi^2 (null model-final solution) = 36.94; Hazard ratios represent change in hazard per unit increase in the covariate (log PSA), or the probability of an event in the higher category relative to the reference category
Abbreviations: Z-the Wald statistic value; P-probability; CI-confidence interval; #-the number of cycles

significantly lower overall mortality rates and higher completion rates of treatment compared to those who have previously undergone docetaxel therapy [29–31].

Pretreatment with second-generation AAs did not have a significant impact on survival in our cohort. However, patients who received chemotherapy prior to ^{223}Ra treatment exhibited significantly poorer survival outcomes on multivariable analysis.

Although in another analysis [32], authors found that chemotherapy pretreatment did not directly cause shorter survival, it was associated with a higher incidence of severe hematotoxicity (Grade 3) during ^{223}Ra treatment, increasing from 3% to 9%. Our data corroborate this, showing an increase in severe hematotoxicity (Grade 3) from 1 patient without prior chemotherapy to 5 patients among those who received cytotoxic chemotherapy before ^{223}Ra therapy (1.8% vs. 9.1%). However, in some patients with severe hematotoxicity, disease progression with bone marrow infiltration must be considered as a contributing factor to the deterioration of hematological profiles. In our cohort, five of six patients with severe hematotoxicity exhibited biochemical progression (PSA and/or ALP) during ^{223}Ra therapy (Table 3). In a smaller retrospective analysis [33], authors observed in patients treated with ^{177}Lu-PSMA, rather than ^{223}Ra, that non-responders to therapy experienced high-grade hematological adverse events and a significant decline in hematological parameters. Conversely, in an anemic patient from a cohort at the onset of ^{223}Ra therapy who demonstrated regression of serum PSA and ALP during treatment (indicative of successful therapy), blood counts normalized by the conclusion of the treatment course (Figure 3).

Regarding serum biomarkers, we monitored the dynamics of serum PSA and ALP throughout therapy, although PSA is not deemed an optimal marker for assessing the efficacy of ^{223}Ra dichloride, as several patients also present with lymph node involvement or an active primary prostate tumor that are not targeted by ^{223}Ra. Additionally, serum PSA non-responsiveness despite effective treatment may be partially attributed to the fact that ^{223}Ra primarily targets the bone microenvironment rather than prostate cancer cells directly [34]. However, in our cohort, PSA dynamics were as significant a marker as serum ALP dynamics during therapy. A stationary or decreased serum PSA level during ^{223}Ra treatment correlated with longer survival, compared to patients whose PSA levels increased during treatment (p=0.0007). In the ALSYMPCA trial, a PSA decline of more than 30% from baseline was observed in 27% of patients treated with ^{223}Ra [4]. In contrast, in a cohort of 300 real-world patients treated with ^{223}Ra, only 6.3% exhibited a PSA decline of more than 30%, although this decline was associated with improved OS [35].

In our study, a PSA decline or stable level was observed in 17 (30.9%) patients, with over 50% decline in 7 (12.7%) patients, correlating with significantly better survival compared to patients with PSA progression, consistent with findings in a Finnish multicenter retrospective study [36]. We concur with the opinion that an increase in serum PSA levels during ^{223}Ra therapy may indicate the emergence of soft tissue metastases not controlled by ^{223}Ra, suggesting that PSA dynamics may possess predictive and prognostic value in patients with metastatic CRPC treated with ^{223}Ra [34], as our results also demonstrated.

Since PSA may increase as a flare effect in some patients after the initiation of therapy, early changes in PSA levels should not be a reason to discontinue treatment due to perceived progression [34, 37]. Therefore, in patients experiencing biochemical progression, restaging is recommended after the third or fourth cycle of ^{223}Ra treatment to consider alternative, more effective therapies. In patients (already pretreated with AAs and chemotherapy) with progression of PSMA-positive metastases, ^{177}Lu-PSMA treatment is possible as soon as 8 weeks after failure of ^{223}Ra [26]. In addition, in a study where authors evaluated the safety of repeated ^{177}Lu-PSMA-617, they found that in ^{177}Lu-PSMA-617-treated patients, who were pretreated with ^{223}Ra, the median OS was prolonged [38]. This was most evident in the group of patients with 6–20 bone lesions (11 vs. 16 months) and with diffuse bone involvement (7 vs. 11 months).

We support the opinion that ^{223}Ra appears to have comparable efficacy in older and younger patients [39].

The limitation of our work was a retrospective review of a smaller group of patients from one center.

According to our findings, asymptomatic or mildly symptomatic patients with good performance status (ECOG 0-1) at the start of ^{223}Ra dichloride therapy had the longest survival. Since there is no requirement for prior chemotherapy or androgen receptor pathway inhibitors before initiation of ^{223}Ra therapy, it is advisable to use ^{223}Ra earlier to maximize its benefits. Stabilization or reduction of serum PSA and ALP levels during treatment were a good prognostic factors associated with longer survival in our cohort.

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