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Brazilian profile of Radium-223 in metastatic prostate cancer: a multicentric, retrospective study

Stephan Souza[1], Felipe Ribeiro[1], Ana Brito[2], Thaís Minekawa[1], Flávia Lopes[3], Sumara Matedi[3], Renata Fockink[4], Dalton Anjos[4], Gustavo Gomes[5], Laura Silva[5], Mariana Camacho[6], Allan Santos[1,6], Whemberton Araújo[7], Ana Teixeira[7], Raul Martins[8], Adelina Sanches[9], Nilton Hanaoka[10], Rafael Tavares[1], Felipe Villela-Pedras[3], Felipe Mourato[2], Caroline Torricelli[1], Thiago Alves[1], Marcelo Tavares[1], Mariana Lima[1,6], André Moraes[11], André Sasse[12], Paulo Almeida[2] and Elba Etchebehere[1,6*]

*Correspondence: elba@unicamp.br

[1] University of Campinas (UNICAMP), Campinas, Brazil
[2] Real Hospital Português, Recife, Brazil
[3] Clínica de Medicina Nuclear Villela Pedras, Rio de Janeiro, Brazil
[4] Hospital Santa Paula, São Paulo, Brazil
[5] Núcleos – Radiologia e Medicina Nuclear, Brasília, Brazil
[6] Medicina Nuclear de Campinas (Grupo MND), Campinas, Brazil
[7] Centro de Diagnósticos por Imagem de Goiânia, Goiás, Brazil
[8] Centro de Tomografia e Medicina Nuclear (CETAC), Curitiba, Brazil
[9] Santa Casa de Misericórdia da Bahia, Salvador, Brazil
[10] DIMEN - Medicina Nuclear, Campinas, Brazil
[11] Centro de Oncologia Clínica (COC), Campinas, Brazil
[12] Grupo SONHE, Campinas, Brazil

Abstract

Background: Radium-223 (^{223}Ra) therapy has been available since 2013 for metastatic castrate-resistant prostate cancer (mCRPC). However, only in 2017 ^{223}Ra was approved by the National Health Surveillance Agency in Brazil. We aimed to perform a multicenter analysis of mCRPC patients treated with ^{223}Ra in referral centers in Brazil and describe their clinical outcomes. For this reason, we retrospectively analyzed mCRPC patients who underwent ^{223}Ra treatment. Clinical and laboratory data were evaluated.

Results: 308 patients submitted to 1402 ^{223}Ra cycles from 9 centers were studied. Previous treatments prior to ^{223}Ra were chemotherapy (59.1%), radiation therapy (54.8%) and hormone therapy (92.2%). ^{223}Ra was used as the fifth or more line of treatment in 58.4% of the patients. The mean number of ^{223}Ra cycles was 4.6; 51% of patients completed all 6 cycles and 52.9% progressed during ^{223}Ra. Concomitant treatment with ^{223}Ra occurred in 69.4% of patients. The median overall survival (OS) for all patients was 13.7 months. The OS was higher for patients completing 6 cycles compared to < 6 cycles (22.6 *vs* 6.4 months, respectively). When stratified according to Brazilian regions, the median OS for the southeast region was higher (range: 14.5–30.2 months) than the other regions.

Conclusions: The OS of ^{223}Ra for patients completing 6 cycles was very high. However, there were major discrepancies when stratified according to different regions in the nation. The data is an important demonstration of the country's educational referral discrepancies related to proper patient management for ^{223}Ra therapy, which has a major impact on maximum OS benefit.

Keywords: Prostate cancer, Radium-223, Overall survival, Progression-free survival, Skeletal-related events

Background

Prostate cancer is one of the most incident and prevalent neoplasms worldwide, ranking second only to lung cancer, excluding non-melanoma skin cancer, in the male population (Ferlay et al. 2024). Upon prostate cancer diagnosis, patients are presented with various primary treatment choices, including radical prostatectomy, primary radiotherapy, or prostate brachytherapy (Mottet et al. 2017). On the follow-up, a subset of patients develops recurrent disease, either local or systemic. Complete or intermittent androgenic blockade is a viable option for systemic recurrence, which often yields an impressive initial clinical response (Kimura et al. 2010; Punnen et al. 2013).

Despite this initial response, chemical castration resistance is frequently the natural history of the disease (Cornford et al. 2017). When this occurs, within approximately 2 years, patients typically develop metastatic and castration-resistant prostate cancer (mCRPC) (Smith et al. 2005). These patients predominantly develop bone metastatic disease characterized by osteoblastic lesions (Hess et al. 2006). In Brazil, the exact prevalence of de novo M1 subpopulation is not documented, and in Latin America, the incidence of de novo metastatic prostate cancer is higher compared to other regions of the world due to the absence of organized screening programs (Reis et al. 2020). There are other therapeutic options that have demonstrated a significant increase in survival, including Radium-223 chloride (^{223}Ra), lutetium-177 PSMA (^{177}Lu-PSMA), chemotherapy (docetaxel, cabazitaxel), hormonal treatments (abiraterone, enzalutamide), immunotherapy (sipuleucel-T) and, more recently, PARP inhibitors.

Radium-223 is a high energy (27.4 MeV) alpha particle emitter. Its short-range emitted alpha particles deposit its energy in fewer than 10 neighboring cells, which reduces the occurrence of adverse events. Its high Linear Energy Transfer (LET) enables it to effectively target neoplastic cells within bone tissues by inducing irreversible damage to the double helix of metastatic cell DNA, resulting in a cytotoxic effect. Due to its chemical similarities with calcium, it undergoes biodistribution to areas with increased bone remodeling, particularly in osteoblastic metastases, after intravenous administration (Nilsson 2016).

Although it has been available around the world since 2013, after the results of the Apharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, which showed significantly increased survival in mCRPC patients treated with ^{223}Ra (n = 614) when compared to placebo (n = 307) (14.9 versus 11.3 months; HR = 0.70; 95% CI 0.58–0.83, $p < 0.001$) (Parker et al. 2013), only in 2017 ^{223}Ra treatment was approved by the National Health Surveillance Agency (ANVISA) in Brazil. However, even after Radium-223 treatment was government-approved to be covered by insurance companies in 2017, many insurance companies delayed coverage approval of ^{223}Ra treatment of Brazilian patients in some parts of the country, which contributed to uneven care distribution nationwide. Health insurance coverage in Brazil is inconsistent and lacks uniformity. In some regions, procedures are authorized relatively quickly, while in others, patients face prolonged approval times, which directly impacts treatment initiation, leading to disparities in care and clinical outcomes across the country.

Radium-223 therapy increases overall survival (OS) and promotes benefits such as pain relief and reduced risk of fractures. Several studies have shown that ^{223}Ra is effective for treating patients with mCRPC, reducing mortality by 30%, leading to an increase in average survival and improvement of quality of life, with effect on tumor biomarkers such as prostate-specific antigen (PSA) and alkaline phosphatase (ALP)(Parker et al. 2013). Time to skeletal events is also enlarged, with reduced hospitalization time (Brito and Etchebehere 2020).

Other radiopharmaceuticals previously used for the treatment of bone metastases, mostly β-emitters, such as ethylene-diamine-tetramethylene-phosphonic acid (EDTMP) labeled with Samarium-153, which has been used in Brazil since 1995, do not lead to overall survival gain in mCRPC patients (Porter et al. 1993; Zacho et al. 2017).

The ideal moment to offer ^{223}Ra is still questionable, but it is already known that patients with multiple therapies and a greater volume of bone disease tend to show less response. The theoretical indication for treatment with ^{223}Ra is in patients with mCRPC and exclusive bone metastases with low tumor volume, but the exact clinical scenario of the use of this treatment is still little known in Brazil.

The purpose of our investigation was to perform a multicenter analysis of mCRPC patients treated with ^{223}Ra in referral centers in Brazil to determine their clinical outcomes overall, and according to the different regions in the country.

Methods

Study design

This observational, retrospective, and multicenter study was undertaken in accordance with *Good Clinical Practice Guidelines.* The study was approved by the Institutional Ethics Review Board (CAAE: 28788220.0.1001.5404).

We reviewed the records of patients with metastatic castrate resistant prostate cancer (mCRPC) treated with ^{223}Ra between January 2017 and December 2019 from 9 centers in the country.

Inclusion criteria consisted of male patients over 18 years old, with biopsy confirmed prostate cancer and submitted to ^{223}Ra therapy.

Exclusion criteria consisted of patients with incomplete charts that precludes the analysis. There were no limits regarding the number of prior hormonal agents or chemotherapy received in order to include patients.

Radium-223 treatment

Regimens of intravenous infusions of 50 kBq/kg (1.4 μCi/kg) of $Ra^{223}Cl_2$ doses were administered every 4 to 6 weeks. All patients completed between 1 and 6 cycles of ^{223}Ra.

Additionally, the off-label use of ^{223}Ra was considered. This included patients with visceral metastases detected in their baseline imaging before starting ^{223}Ra treatment; patients in whom chemotherapy and/or secondary hormonal therapy were administered concomitantly with ^{223}Ra therapy; and patients with baseline hemoglobin levels below 10 g/dl prior to the initiation of ^{223}Ra therapy.

Clinical, laboratory and imaging evaluation prior to Radium-223

Clinical evaluation consisted of determining the patient's ECOG (Eastern Cooperative Oncology Group) performance status and pain scores according to World Health Organization (WHO) criteria and evaluating current and previous treatments and combined treatments.

Side effects were classified by grades (0–5) according to Common Terminology Criteria for Adverse Events (CTCAE). Pain was assessed by the Simple Verbal Scale from WHO Pain Scale (Haefeli and Elfering 2006) and ECOG for Performance Status was also recorded.

The patient's hematologic status and the dynamics of the disease were evaluated by the serum levels of hemoglobin (Hb), absolute neutrophil counts (ANC), platelets (PLT), ALP, PSA and lactate dehydrogenase (LDH) levels. Imaging studies were performed prior to ^{223}Ra.

These studies consisted of one or more of the following: whole-body skeletal Fluoride-18 (^{18}F) positron emission tomography/ computed tomography (PET/CT) scan; whole-body metabolic ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT scan; whole-body Gallium-68-prostate-specific membrane antigen (^{68}Ga-PSMA) PET/CT scan; whole-body conventional bone scintigraphy; CT scans and/or magnetic resonance imaging (MRI) scans.

Outcome measures

The primary endpoint was overall survival, established from the initial ^{223}Ra dose until the date of death or last follow-up.

Secondary outcome measures were progression-free survival (PFS), number of ^{223}Ra cycles, adverse events during treatment, disease profile (Gleason, staging, nodal, visceral or bone metastasis), previous treatments, pain scale, performance status (ECOG), and demographic information.

Statistical analysis

To describe the profile of the sample according to the variables under study, frequency tables were provided for the categorical variables with absolute frequency (n) and percentage (%) values, and, for the quantitative variables, descriptive measures were obtained (mean, standard deviation, minimum, median and maximum), for baseline measurements and follow-up. Measurements for each ^{223}Ra referral center were also obtained. The Dunn test was applied for pairwise multiple comparisons following a Kruskal–Wallis test, which assessed whether there were significant differences between more than two independent groups. Baseline time was defined as the date of the first ^{223}Ra cycle.

The relationship between the number of ^{223}Ra cycles and factors was evaluated using the Mann–Whitney test for numerical variables and the Chi-square or Fisher's exact test for categorical variables.

We studied the following measures: OS, PFS and time to skeletal-related events (TTSRE). OS, PFS and TTSRE survival curves were produced using the Kaplan–Meier method and the comparison using the log-rank test.

OS was defined as the time between baseline time and time of death. PFS was defined as time between baseline and until any evidence of progressive disease including bone progression, nodal progression, visceral progression, or deterioration of ECOG (by 2 points). Disease progression was assessed using conventional imaging modalities, depending on the clinical protocol and availability at each center, which included bone scan and CT. In more developed centers, patients were also submitted to MRI, FDG PET/CT and PSMA PET/CT. The specific imaging modality used was determined by clinical practices at the respective referral centers.

Kaplan–Meier survival curves stratified by ^{223}Ra treatment type were compared using the log-rank test. Univariable and multivariable Cox regression analyses were conducted using a stepwise selection criterion to identify factors associated with OS.

The TTSRE was calculated from the date of the first ^{223}Ra cycle until the occurrence of any of the following SREs: intractable bone pain/ rapid lesion progression, pathologic bone fracture, spinal cord compression and surgical intervention or radiotherapy to the site of bone metastasis. Although SREs are progression of the disease, due to their specific morbidity and mortality, these events were calculated separately.

Data was analyzed using The SAS System for Windows (Statistical Analysis System), version 9.4. SAS Institute Inc, 2002–2012, Cary, NC, USA and R version 3.4.2. Copyright$^{(C)}$ 2017 (The R Foundation for Statistical Computing). The significance level adopted for the study was 5% (Bland and Altman 1986, 1999; Krouwer and Monti 1995).

Results

Clinical, laboratory and imaging evaluation prior to Radium-223

A total of 308 patients submitted to 1402 ^{223}Ra cycles from 9 centers were studied. The mean patient age was 74 years (43–100 years). Most patients had Hb levels above 10 g/dL, ANC above 1500/mm^3 and PLT counts above 7500/mm^3. Baseline patient clinical characteristics prior to ^{223}Ra treatment are described in Table 1.

Patients underwent one or more of the following imaging exams performed for staging before ^{223}Ra treatment: bone scintigraphy (n = 232 patients), PSMA PET/CT (n = 63 patients), FDG PET/CT (n = 14 patients), MRI or CT (n = 9 patients) and Fluoride PET/CT (n = 1 patient).

Table 1 Patient characteristics and laboratory data

Variables	N	All patients (N = 308)		
		Median	Min–Max	Mean (SD)
Age	308	74.6	43.2–100	73.6 (10.1)
N° of cycles	308	5	1–6	4.6 (1.7)
Hb (g/dL)	282	11.9	7.7–15.6	11.8 (1.7)
WBC (/mm^3)	236	5959	1800–35,700	6467 (3410)
ANC (/mm^3)	210	3565	700–14,940	3959 (2004)
PLT (/mm^3)	286	229,000	14,700–602,000	233,487 (84,914)
PSA (ng/ml)	257	49.5	0.01–4279	207 (491)
ALP (IU/L)	234	114.5	6–1421	210 (251)
LDH (IU/L)	122	341	137–2164	447 (370)

N, number of patients; SD, standard deviation; Hb, hemoglobin; WBC, white blood cells; ANC, absolute neutrophil count; PLT, platelets; PSA, prostate-specific antigen; IU, International Units; ALP, alkaline phosphatase; LDH, lactate dehydrogenase

The majority of the patients (60%) had a good performance status (ECOG 0–1), while 40% were symptomatic (ECOG 2–4). All patients were submitted to at least one other treatment before ^{223}Ra, which consisted mainly of secondary hormonal therapy (92.2%), more than one chemotherapy regimen (59.1%), and radiation therapy (54.8%). There was a significant difference among the number of patients who underwent chemotherapy prior to ^{223}Ra compared to the number of patients who did not undergo chemotherapy ($p = 0.0136$) as well as the number of patients who underwent radiation therapy ($p < 0.0001$), secondary hormonal therapy ($p < 0.001$), and blood transfusion ($p = 0.0003$) compared to the number of patients that were not submitted to these treatment modalities. ^{223}Ra was employed as ≥ 4th line of therapy in 84.8% of the patients. In patients with visceral metastases or because of the possibility of progression during treatment, 69.4% of patients received ^{223}Ra concomitant with other treatments, such as chemotherapy, secondary hormone therapy, radiation therapy or blood transfusion (Table 2).

Safety/tolerability of Radium-223

Radium-223 treatment was well tolerated by most of the patients as most (60%) maintained a good performance status (ECOG 0–2) during treatment, without Grade 3 or Grade 4 toxicity requiring discontinuation of treatment. There was a decline in performance status from ECOG 2 to ECOG 4 after the 4th cycle of ^{223}Ra (Fig. 1).

All 6 ^{223}Ra cycles were completed in 156 patients (51%) while 5 cycles were completed in 29 patients (9.5%), 4 cycles were completed in 38 patients (12.4%), three cycles in 37 patients (12.1%), two cycles in 28 patients (9.1%); and only one cycle was completed by 20 patients (6.5%). The main reasons for treatment discontinuation or change were

Table 2 Baseline patient clinical and treatment characteristics prior to and during Radium-223

	Classifications	N = 308 (%)
ECOG status[a]	0	43 (18.1)
	1	100 (42.0)
	2	52 (22.3)
	3	39 (16.4)
	4	3 (1.2)
WHO Pain scale[a]	0	55 (21.7)
	1	91 (36.0)
	2	44 (17.4)
	3	62 (24.5)
	4	1 (0.40)
Prior anti-cancer therapies	Chemotherapy	136 (59.1)
	Radiation therapy	126 (54.8)
	Secondary Hormone therapy	283 (92.2)
	3rd	33 (15.2)
Radium-223 Line of therapy[a]	4th	61 (26.4)
	≥ 5th	135 (58.4)
Blood transfusion prior to Radium-223[a]		15 (6.5)
Radium-223 concomitant with other treatments		102 (69.4)

N, number; %, percentage; ECOG, Eastern Cooperative Oncology Group; Unk, unknown; WHO, World Health Organization;[a]missing data include ECOG status (n = 71), WHO Pain scale (n = 55), Radium-223 Line of therapy (n = 77), and Blood transfusion prior to Radium-223 (n = 71)

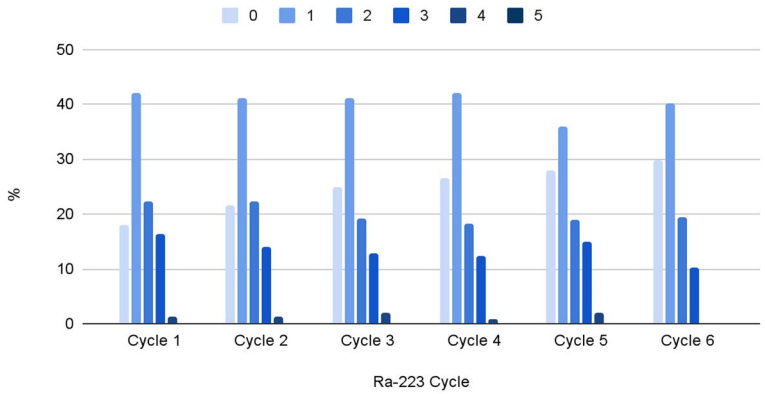

Fig. 1 ECOG status according to Radium-223 cycles

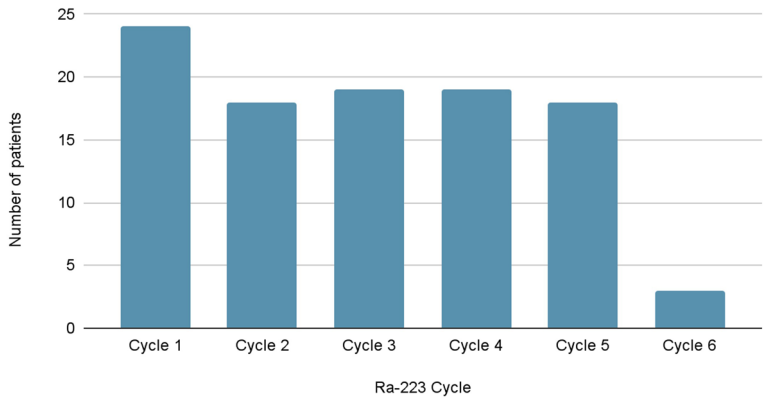

Fig. 2 Number of patients that stopped or had a change in treatment planning during Radium-223 cycles

progression (n = 95), hematologic toxicity (n = 44), ECOG status decline (n = 13), SRE (n = 37) or pain (n = 153), and death.

During treatment with ^{223}Ra, 52.9% of the patients (147/278) progressed, 17.6% of the patients (49/284) had skeletal events, and 38.6% of the patients died (119/308). There was a significant difference between the number of patients who progressed during treatment and the number of patients who did not progress during treatment ($p = 0.0011$); this significant difference was also noted in patients who did not have SREs compared to patients who had SREs ($p = 0.0008$) and in patients that were alive compared to patients that died after or during treatment ($p = 0.0005$).

Discontinuation of ^{223}Ra treatment occurred mainly after the first cycle (16.3%), primarily caused by declining ECOG status and performance status. Although 9 patients experienced severe bone pain in different cycle phases of the treatment, two patients ultimately discontinued ^{223}Ra treatment before the third cycle due to intractable bone pain. Figure 2 illustrates the absolute number of patients who discontinued ^{223}Ra treatment according to the cycle.

After ^{223}Ra, treatment was changed in 91 patients (29.6%) while 99 patients (32.1%) continued with the prior treatment regimen established before ^{223}Ra. On the other hand, all antineoplastic treatment was discontinued in 118 patients (38.3%); some of these

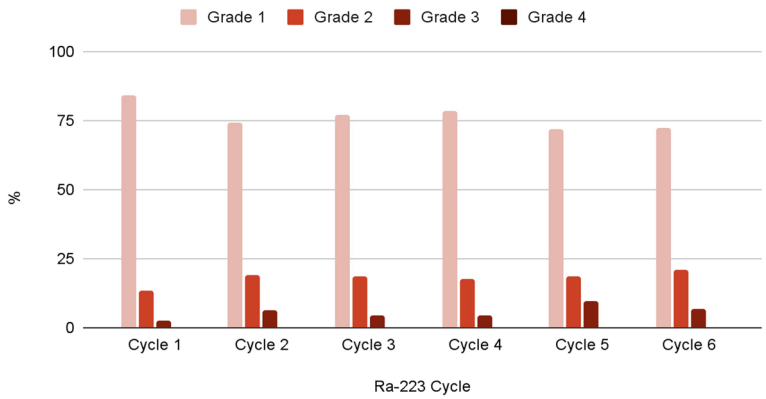

Fig. 3 Hematological adverse events status according to Radium-223 cycles

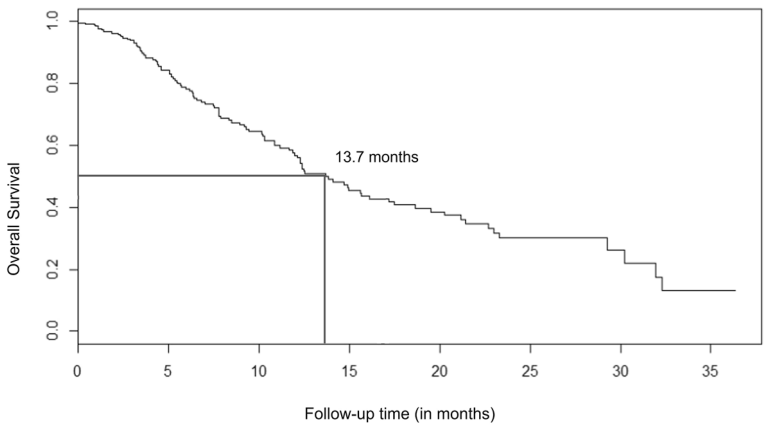

Fig. 4 Kaplan-Meyer curve for overall survival after Radium-223 therapy of the 308 patients submitted to 1402 cycles

patients were initially referred for ^{223}Ra as a palliative treatment and others refused additional treatment.

Adverse events

Blood transfusion was performed prior to ^{223}Ra therapy in 6% of the patients. No hematologic toxicity during treatment and low-grade (G1 and G2) hematological toxicity occurred in the majority (86.9%) of patients. In contrast, 12.3% of patients (n = 34/275) presented grade 3 hematologic adverse events including Hb < 8 g/dL after the first ^{223}Ra cycle and one patient presented grade 4 hematological toxicity (Fig. 3).

Overall survival, progression-free survival, and skeletal-related event

The median OS for all 308 patients was 13.7 months (Fig. 4). There was a significant difference ($p < 0.0001$) in the median OS for patients that completed 6 cycles compared to < 6 cycles (22.6 *vs* 6.4 months, respectively) (Fig. 5).

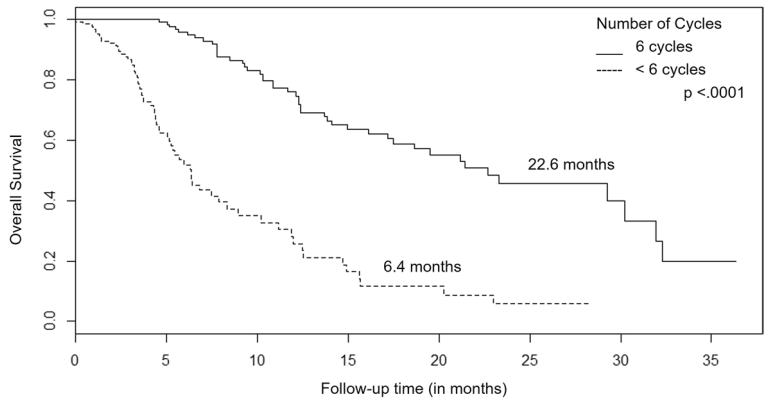

Fig. 5 Kaplan–Meier curves for overall survival for patients according to the number of Radium-223 cycles

Table 3 Characteristics of the participating centers in relation to the number of Radium-223 cycles and overall survival

Site	Region	Patients N (%)	Cycles N (%)	Median OS (months)	6 cycles *versus* < 6 cycles (months)	*p* value
A	NE	16 (5.2)	63 (4.5)	4.3	N/A	N/A
B	NE	22 (7.1)	99 (7.1)	6.6	N/A	N/A
C	C	28 (9.1)	137 (9.7)	10.3	11.7 *vs* 3.5	**0.0020**
D	C	45 (14.6)	176 (12.6)	16.1	16.1 *vs* 4.6	**0.0040**
E	SE	28 (9.1)	134 (9.6)	23.3	23.3 *vs* 12.0	0.0922
F	SE	14 (4.5)	74 (5.3)	14.5	14.8 *vs* 14.1	0.3173
G	SE	82 (26.6)	364 (26)	14.8	22.7 *vs* 5.6	**< 0.0001**
H	SE	47 (15.3)	231 (16.4)	30.2	30.2 *vs* 6.8	**0.0002**
I	S	26 (8.5)	124 (8.8)	6.4	N/A	N/A
Total		308 (100)	1402 (100)	13.7	22.6 *vs* 6.4	**< 0.0001**

Bold values emphasize regional disparities in OS among patients receiving Radium-223 in different Brazilian regions, particularly the longer median OS observed in the southeast region compared to the others

N, number; %, percentage; OS, overall survival; N/A, not applicable (no patient completed 6 cycles); NE, northeast; C, central; SE, southeast; S, south

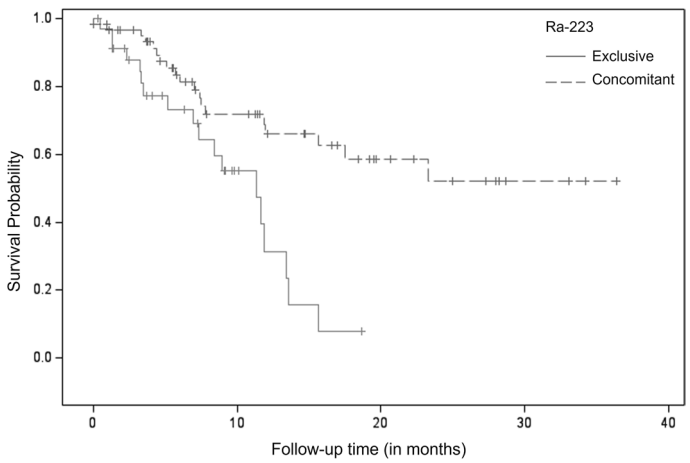

Fig. 6 Kaplan-Meyer curves for overall survival stratified by type of Radium-223 treatment

However, the discrepancies increased when comparing OS and the number of ^{223}Ra cycles stratified according to Brazilian regions. For example, the median OS for patients completing all 6 cycles in the southeast region ranged from 14.5 to 30.2 months and was higher than other parts of the country, especially the south and northeast (Table 3).

OS was significantly longer in patients who received ^{223}Ra concomitant with other treatments, such as in combination with chemotherapy or secondary hormone therapy compared to patients treated exclusively with ^{223}Ra (Fig. 6). The Kaplan–Meier analysis showed that overall survival was consistently higher in the group receiving ^{223}Ra concomitantly with other treatments compared to the group receiving ^{223}Ra exclusively, with a statistically significant difference between the curves (log-rank test, $p = 0.0013$).

The univariable Cox regression model for OS indicated a significantly shorter survival among patients with lower baseline Hb levels, higher baseline PSA, ALP and LDH levels, patients exclusively treated with ^{223}Ra, higher pain scores, and patients with an ECOG performance status of >2. The multivariable Cox regression analysis demonstrated that the predictive independent factors associated with better OS (Table 4) were higher baseline Hb levels and ^{223}Ra concomitant with other treatments. Notably, ^{223}Ra exclusive therapy was associated with a 3.6-fold increased risk of mortality.

Table 4 Univariable and multivariable models of OS in relation to clinical and laboratory parameters

Variables	OS	
	HR (95% CI)	***p* value**
Univariable analysis		
Hb levels prior to ^{223}Ra (g/dL)	0.71 (0.63–0.81)	**< 0.0001**
Leucocytes prior to ^{223}Ra (/mm^3)	0.95 (0.85–1.06)	0.3849
Neutrophil counts prior to ^{223}Ra (/mm^3)	1.05 (0.93–1.18)	0.4208
Platelets prior to ^{223}Ra (K/mm^3)	1.00 (0.99–1.002)	0.9325
Adverse events during ^{223}Ra (yes *vs* no)	1.22 (0.84–1.79)	0.2971
PSA levels prior to ^{223}Ra (ng/mL)	1.07 (1.03–1.11)	**0.0004**
ALP levels prior to ^{223}Ra (IU/L)	1.01 (1.00–1.02)	**< 0.0001**
LDH levels prior to ^{223}Ra (IU/L)	1.00 (1.00–1.003)	**< 0.0001**
^{223}Ra concomitant treatment (yes *vs* no)	2.83 (1.48–5.40)	**0.0017**
WHO Pain scale prior to ^{223}Ra (0 *vs* ….)		
1	1.37 (0.73–2.55)	**0.0001**
2	0.93 (0.44–1.95)	
3 + 4	2.87 (1.58–5.22)	
ECOG score prior to ^{223}Ra (0 *vs* ….)		
1	2.48 (0.86–7.14)	**< 0.0001**
2	4.27 (1.47–12.42)	
3 + 4	10.53 (3.69–30.08)	
Multivariable analysis		
Hb levels prior to ^{223}Ra (g/dL)	0.62 (0.46–0.84)	**0.0022**
^{223}Ra concomitant treatment (yes *vs* no)	3.59 (1.32–9.77)	**0.0122**

Bold values mark significant predictors of OS in both univariable and multivariable Cox regression models, highlighting factors such as lower baseline Hb, higher PSA, ALP, LDH levels, higher pain scores, ECOG performance status >2, and the increased mortality risk associated with Radium-223 monotherapy

OS, Overall Survival; HR, Hazard Ratio; CI, Confidence Interval; ^{223}Ra, Radium-223; Hb, hemoglobin; PSA, prostate-specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group

Table 5 Relationship between variables and number of Radium-223 cycles

Variables	6 cycles		< 6 cycles		*p* value
	N	Mean ± SD/Percentage	N	Mean ± SD/Percentage	
Hb (g/dL)	139	12.2 ± 1.4	143	11.4 ± 1.7	**< 0.0001**
WBC (/mm^3)	117	6162.1 ± 2016.9	119	6497.9 ± 3448.5	0.8234
ANC (/mm^3)	113	3951.6 ± 1749.2	97	3968.0 ± 2276.2	0.7934
PLT (/mm^3)	142	241,585 ± 86,217	144	225,061 ± 80,960	0.0887
PSA (ng/ml)	123	127.1 ± 414.0	133	283.1 ± 546.2	**< 0.0001**
ALP (IU/L)	113	194.3 ± 262.2	121	225.2 ± 240.3	**0.0007**
LDH (IU/L)	60	382.3 ± 193.6	62	510.0 ± 476.7	0.8920
Pain score	137	1.3 ± 1.0	129	1.7 ± 1.1	**0.0044**
ECOG status					
0	27	22.3%	16	13.7%	**0.0009**
1	61	50.4%	39	33.3%	
2	22	18.2%	31	26.5%	
3	10	8.3%	29	24.8%	
4	1	0.8%	2	1.7%	
Progression during Radium-223					
NO	90	64.7%	40	29.0%	**< 0.0001**
Y	49	35.3%	98	71.0%	
Bone event during Radium-223					
NO	130	89.0%	104	75.9%	**0.0035**
Y	16	11.0%	33	24.1%	

Bold values indicate significant associations between baseline clinical variables and the completion of all six Radium-223 cycles. Notably, patients who completed all cycles had significant differences in baseline Hb levels

N, number of patients; SD, Standard Deviation; Hb, hemoglobin; WBC, white blood cell; ANC, absolute neutrophil count; PLT, platelets; PSA, prostate-specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; Y, yes

Table 6 Radium-223 exclusive versus concomitant treatment across centers

Site	Region	Radium-223 exclusive N (%)	Radium-223 concomitant N (%)	Frequency missing
A	NE	N/A	N/A	N/A
B	NE	3 (14%)	18 (86%)	1
C	C	N/A	N/A	N/A
D	C	8 (47%)	9 (53%)	28
E	SE	5 (18%)	23 (82%)	0
F	SE	9 (82%)	2 (18%)	3
G	SE	15 (38%)	25 (63%)	42
H	SE	3 (12%)	22 (88%)	22
I	S	2 (40%)	3 (60%)	21
Total		45	102	161

N, number; %, percentage; N/A, not applicable; NE, northeast; C, central; SE, southeast; S, south

Baseline Hb levels were significantly ($p < 0.0001$) higher among patients who completed all 6 ^{223}Ra cycles compared to patients who did not complete all cycles (12.2 g/dl ± 1.4 *vs* 11.4 g/dl ± 1.7). The same discrepancies were also significant for PSA and ALP levels, pain scores, and performance status (Table 5).

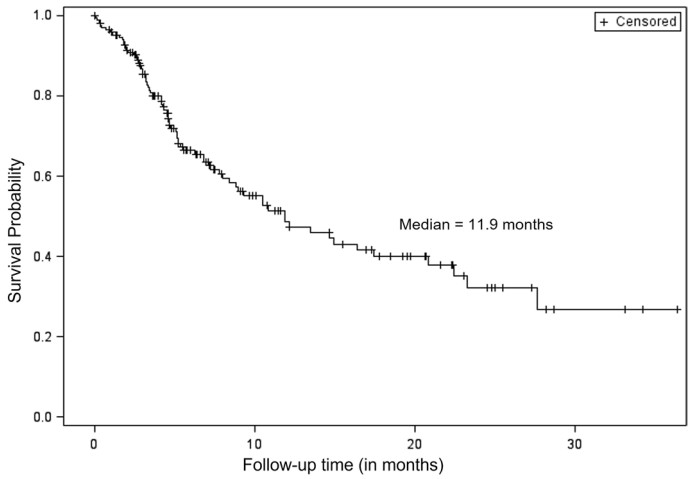

Fig. 7 Kaplan-Meyer curve for progression-free survival after Radium-223 therapy of 172 patients

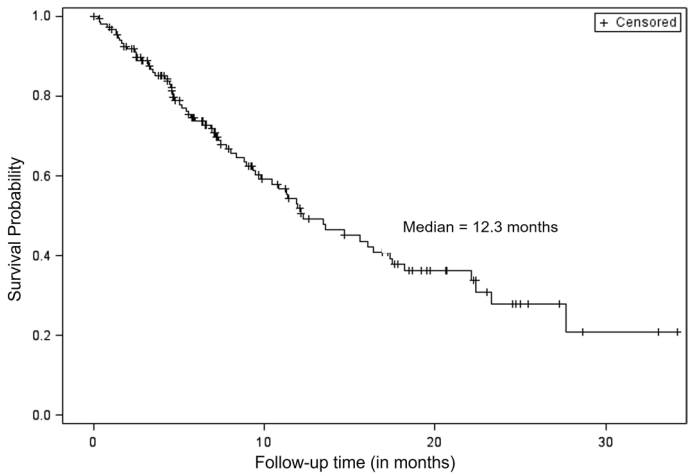

Fig. 8 Kaplan-Meyer curve for Skeletal-related event-free survival after Radium-223 therapy in 308 patients

There was a significant difference among the number of patients in using ^{223}Ra concomitant with other therapies compared to its use as monotherapy across the different centers ($p = 0.0003$, Table 6). Among the subset of 9 patients with off-label use of Radium-223 because of visceral metastases, 2 received concomitant chemotherapy, one received secondary hormonal therapy, and 6 were submitted to blood transfusion. Because of the limited number of patients, it was not possible to perform an analysis of overall survival compared to the remaining cohort of patients. Additionally, among the subset of 15 patients with hemoglobin levels below 10 g/dl, 6 of these patients died, and two were treated with concomitant chemotherapy.

The median PFS was 11.9 months (Fig. 7), and the median time to SRE was 12.3 months (Fig. 8). Table 7 displays the characteristics of the participating centers and survival times.

Table 7 Characteristics of the participating centers and OS, PFS and SRE data

Site	Region	Patients N (%)	Median OS (months)	Median PFS (months)	Median TTSRE (months)
A	NE	16 (5.2)	4.3	N/A	N/A
B	NE	22 (7.1)	6.6	N/A	N/A
C	C	28 (9.1)	10.3	5.2	9.5
D	C	45 (14.6)	16.1	N/A	N/A
E	SE	28 (9.1)	23.3	23.3	23.3
F	SE	14 (4.5)	14.5	13.4	13.5
G	SE	82 (26.6)	14.8	9.3	10.8
H	SE	47 (15.3)	30.2	14.9	N/A
I	S	26 (8.5)	6.4	3.7	N/A
Total		308 (100)	13.7	11.9	12.3

N, number; %, percentage; OS, overall survival; PFS, progression-free survival; TTSRE, time-to-skeletal related event; N/A, not applicable; NE, northeast; C, central; SE, southeast; S, south

Discussion

The introduction of ^{223}Ra therapy for mCRPC in Brazil in 2017 marked an important milestone in the treatment landscape for prostate cancer. Our investigation is the first real-world study regarding the Brazilian profile of ^{223}Ra treatment in mCRPC and the first to describe their outcomes. It brings objectively collected data and also sheds light on the disparate scenarios within this country of continental proportions. For example, treatment discontinuation occurred mainly after the first cycle and was related to a delay in oncologic referral and insurance company coverage approval. Additionally, changes in treatment were observed between the 2nd and 5th ^{223}Ra cycles, in patients with declining ECOG status, progression, hematologic toxicity or uncontrollable pain. These findings highlight the challenges within Brazil's healthcare system, where regional differences and delays in access to specialized care significantly impact treatment outcomes.

In our cohort, the median overall survival of the 308 patients submitted to 1402 cycles of ^{223}Ra was 13.7 months, similar to the overall survival of the patients from the ALSYMPCA trial (14 months) (Parker et al. 2013).

Interestingly, the patients in our study who completed all 6 cycles of ^{223}Ra had survival benefits, with a significantly longer mean overall survival than patients completing less than 6 cycles (22.6 *vs* 6.4 months, respectively). Therefore, the 6-cycle completion rate appeared to be an important factor associated with improved outcomes, similar to prior investigations (Etchebehere et al. 2016; Dizdarevic et al. 2019; Sartor et al. 2015; McKay et al. 2017). Progression rates and skeletal-related events of our patient population also varied according to baseline ECOG status and pain scores and were greater in patients who did not complete all 6 cycles. Our findings are in line with the prospective, single-arm phase 3b study of 708 patients that received at least one ^{223}Ra injection, demonstrating that overall survival, time to disease progression, and time to first symptomatic skeletal event was also better in asymptomatic compared to symptomatic patients (20.5 *vs* 13.5 months) (Heidenreich et al. 2019).

The combination of ^{223}Ra with standard-of-care treatments such as abiraterone or enzalutamide showcased improved survival outcomes, emphasizing the potential synergistic effects of these therapies. In our population, 63% of patients received ^{223}Ra

concomitant with other treatments, such as chemotherapy or secondary hormonal therapy alongside bone-protective agents (BPA). In our study, patients who received ^{223}Ra concomitant with other treatments had consistently and significantly longer OS than patients who received ^{223}Ra exclusively (log-rank test, $p=0.0013$). Notably, ^{223}Ra exclusive therapy was associated with a 3.6-fold increased risk of mortality. This aligns with relatively wide OS rates and indicates the absence of precise or common criteria for treatment initiation. Recent advances in combination therapies for mCRPC patients have demonstrated significant survival improvements, and ongoing studies are expected to further refine and standardize treatment regimens for localized and metastatic disease (Jani et al. 2023). Several landmark phase III trials, such as ERA 223 (Smith et al. 2019), PEACE-3 (Gillessen et al. 2021) and DORA (Morris et al. 2021), have influenced treatment strategies by evaluating the safety and efficacy of combination therapies. Although the ERA 223 trial (NCT02043678) (Smith et al. 2019) assessed the combination of ^{223}Ra with abiraterone acetate and prednisone/prednisolone in asymptomatic or mildly symptomatic mCRPC patients with bone metastases highlighted a significantly increased fracture risk, patients were not treated with BPAs in that trial. Real-world studies with this combination and BPAs have proven OS benefit (Shore et al. 2020; Minekawa et al. 2021). Following the fracture risk findings from ERA 223, the PEACE-3 trial (NCT02194842) (Gillessen et al. 2021) implemented bone-protecting agents (BPAs) to mitigate skeletal complications. This trial compared the combination of ^{223}Ra and enzalutamide with enzalutamide alone in asymptomatic or mildly symptomatic mCRPC patients. Results demonstrated that fractures occurred more frequently without BPAs, particularly when enzalutamide was combined with ^{223}Ra, which highlights the critical role of BPAs in managing skeletal health during mCRPC treatments. The DORA trial (NCT03574571) (Morris et al. 2021) is another pivotal phase III study, enrolling 738 men across 32 sites in the US and Netherlands. This trial investigates the clinical benefit of combining ^{223}Ra with docetaxel in mCRPC patients. Early results from prior phases I and IIa, suggested that this combination provided greater reductions in PSA levels and bone markers, delayed PSA progression, and was better tolerated than docetaxel alone (Morris et al. 2019). These studies emphasize the need for randomized controlled trials to validate the efficacy and safety of combination therapies with radioisotopes, particularly for mCRPC. While progress has been made with the earlier integration of chemotherapy and androgen receptor signaling inhibitors, real-world evidence reveals that many patients are not receiving the recommended escalation in care, even with updated guidelines and approved therapies (Ryan et al. 2021).

Besides the independent predictive role of ^{223}Ra concomitant treatment for improved OS in our cohort, our study also demonstrated that higher baseline Hb levels were associated with better outcome. This finding aligns with previous studies (Etchebehere et al. 2016; Halabi et al. 2013; Sartor et al. 2018), which have also shown the prognostic significance of Hb levels.

As already reported in other real-world studies (Higano et al. 2018; Poeppel et al. 2018; Badrising et al. 2020), ^{223}Ra was a safe and well-tolerated therapy in our population, rarely presenting severe side effects. The ECOG performance status of the patients was maintained through all 6 ^{223}Ra cycles. Saad et al. (Saad et al. 2016) studied safety and

overall survival in a similar clinical scenario to ours, with patients receiving other concomitant anticancer therapies. They found that among the 839 patients enrolled from 113 sites in 14 countries, overall survival was slightly greater than ours (16 months *vs* 14.3) but side effects behaved similarly. The overall survival was prolonged in patients who received ^{223}Ra plus abiraterone, enzalutamide, or both, and in patients with better baseline ECOG performance status. The interim analysis of the REASSURE study (Dizdarevic et al. 2019) demonstrated a similar safety profile of ^{223}Ra in clinical practice and in controlled studies. It also showed a lower proportion of treatment discontinuation in patients who had not previously received chemotherapy as they appeared to have a lower burden of disease at baseline.

The findings from our study, along with results from other real-world studies, suggest that the early incorporation of ^{223}Ra into the treatment paradigm for metastatic castration-resistant prostate cancer may play a crucial role in treatment escalation (McKay et al. 2017; Heidenreich et al. 2019). This was clearly noted in our patient population since increased overall survival was related to patients with higher baseline hemoglobin levels, lower baseline PSA levels, lower baseline alkaline phosphatase levels, lower pain scores, and good performance status. Therefore, as also evidenced by its safety profile and favorable outcomes ^{223}Ra treatment emerges as a promising therapy in Brazilian prostate cancer patients.

Our study had several limitations. The data was manually extracted from participant centers and therefore potential selection biases may have occurred. Although the investigation was a descriptive and retrospective study, it has sampled important data regarding geography, oncologist providers, and insurers/payers successfully. Our study did not evaluate the exact extent of skeletal metastasis, however, all patients had extensive disease when Radium-223 treatment commenced, as all were submitted to treatment in a late stage of the disease (60% after at least one chemotherapy regimen), as can be noted by median ALP levels of 114.5 IU/L. A specific analysis to assess outcomes based on skeletal metastases and explore how tumor burden was associated with survival may be the object of future analyses. Finally, our multicentric study analysis could not collect and analyze the differences in OS among patients who continued prior therapies, switched to newer agents, or discontinued all treatments. After the discontinuation of radium-223 therapy, patients were referred to oncology which, in our country, manages the patients independently. A standardized rollover study or post-discontinuation protocol across the centers could be subject of future studies to investigate this aspect.

Our study also uncovers notable regional discrepancies in patient outcomes within Brazil. Patients in the southeast and central regions experienced considerably longer overall survival benefits than patients in the southern and northeast regions of Brazil.

All patients received radium-223 treatment in the later stages of the disease (60% after at least one chemotherapy regimen); therefore, the baseline characteristics of patients did not differ and do not account for OS discrepancies among Brazilian regions. The regional discrepancies in OS in Brazil reflect significant inequities in economic resources, education, health insurance coverage, public hospital quality, and the level of professional training among healthcare providers. Brazil is divided into five regions, with the Southeast being the wealthiest, with notably higher-quality

healthcare infrastructure, more access to novel therapies, more patients with supplemental health insurance, better-equipped public hospitals, and superior logistics for transport and distribution of radiation therapies. These differences alone could lead to better outcomes because patients in the North, Northeast, South, and Midwest regions face limited access to advanced medical treatments. Many health insurance companies in these regions delay the approval of radium-223 treatments or only approve 1–2 cycles. Differences are also evident among traditional training centers, advanced private cancer hospitals, and public hospitals that are not affiliated with universities. Considering these regional discrepancies and that healthcare quality reflects the economic differences of a society, the observed variations in OS directly reflect healthcare quality across regions. For these reasons, patients from the Southeast region demonstrated longer OS compared to those in other Brazilian regions.

This regional variation raises important questions about healthcare accessibility, referral patterns, and the timing of ^{223}Ra initiation. These discrepancies were also seen across the profuse variation of imaging methods used, such as MRI and FDG PET/CT.

These findings highlight the need for further investigation into the reasons behind these regional disparities and the potential educational and healthcare system challenges contributing to suboptimal treatment timing in certain areas. Additionally, to investigate disparities in Brazil, studies could analyze regional differences in healthcare access, resource availability, and socioeconomic factors, while also examining treatment pathways and referral patterns across regions. Surveys of patients and providers could help identify barriers to care, such as financial or logistical challenges.

International guidelines can direct the best scenarios possibilities, whereas national guidelines may suggest proper and homogenous alternatives considering local healthcare systems and resource availability.

Additionally, the incorporation of multidisciplinary teams comprising urologists, oncologists, nuclear medicine physicians, radiologists, and palliative care specialists can ensure comprehensive patient care and optimal treatment outcomes. The current body of evidence supports the need for new studies and clinical trials to monitor the combined use of ^{223}Ra with other therapies closely. There's a compelling rationale for further exploration with growing evidence of ^{223}Ra's safety and potential efficacy, particularly when used alongside standard treatments like abiraterone or enzalutamide. In spite of territorial discrepancies, these findings collectively reassure the safety and efficacy of ^{223}Ra treatment while advocating for the early integration of ^{223}Ra into the treatment landscape of mCRPC, offering a promising avenue for improving patient outcomes and redefining treatment escalation strategies. Additionally, investigating the feasibility and benefits of initiating ^{223}Ra at earlier disease stages could offer valuable insights into optimizing treatment approaches for metastatic castration-resistant prostate cancer.

Conclusions

Treatment with ^{223}Ra presents itself as a valuable option as a life-prolonging agent in the Brazilian population with mCRPC, with few adverse effects. Further analyses of Brazilians' vast and complex scenarios, especially related to patient referral, may bring more valuable information on how ^{223}Ra might be even more efficient if sequencing becomes more consistent.

Abbreviations

µCi	Microcurie of radioactivity
^{18}F	Fluoride-18
^{68}Ga	Gallium-68
^{177}Lu	Lutetium-177
^{223}Ra	Radium-223
ALSYMPCA	Apharadin in Symptomatic Prostate Cancer
ANC	Absolute neutrophil count
ANVISA	National Health Surveillance Agency
ALP	Alkaline phosphatase
BPAs	Bone-protecting agents
CI	Confidence interval
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter (SI)
ECOG	Eastern Cooperative Oncology Group
EDTMP	Ethylene-diamine-tetramethylene-phosphonic acid
FDG	Fluorodeoxyglucose
g	Gram (SI)
G1	Grade 1
G2	Grade 2
Hb	Hemoglobin
HR	Hazard ratio
kb	Kilogram (SI)
kBq	Kilobecquerel (SI)
LDH	Lactate dehydrogenase
LET	Linear Energy Transfer
mCRPC	Metastatic castrate-resistant prostate cancer
MeV	Mega electron-volt
mm^3	Cubic millimeter (SI)
MRI	Magnetic resonance imaging
n	Number
OS	Overall survival
PARP	Poly adenosine diphosphate-ribose polymerase
PET	Positron emission tomography
PFS	Progression-free survival
PLT	Platelets
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
SAS	Statistical Analysis System
SRE	Skeletal-related event
TTSRE	Time to skeletal-related events
WHO	World Health Organization

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Author contributions

Conceptualization: Elba Etchebehere, Allan Santos, Mariana Lima, André Moraes, and André Sasse; Methodology: Marcelo Tavares, Flávia Lopes, Sumara Matedi, Renata Fockink, Dalton Anjos, Gustavo Gomes, Ana Teixeira, Raul Martins, Adelina Sanches, Nilton Hanaoka, Rafael Tavares, Felipe Villela-Pedras, and Paulo Almeida; Formal analysis and Investigation: Marcelo Tavares, Stephan Souza, Felipe Ribeiro, Ana Brito, Thaís Minekawa, Laura Silva, Mariana Camacho, Whemberton Araújo and Felipe Mourato; Writing—original draft preparation: Stephan Souza, Felipe Ribeiro, Ana Brito, and Thaís Minekawa; Writing—review and editing: Elba Etchebehere, Allan Santos, Caroline Torricelli and Thiago Alves; Funding acquisition: Elba Etchebehere, Allan Santos, Mariana Lima and Caroline Torricelli; Resources: N/A; Supervision: Elba Etchebehere and Allan Santos. All authors read, reviewed and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy concerns but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Ethics Review Board (IERB)—CAAE: 28788220.0.1001.5404. As this is a retrospective study analyzing previously collected clinical data, the requirement for informed consent was waived by the IERB.

Consent for publication

Not applicable.

Competing interests

The authors have no financial or non-financial interests to disclose.

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