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ORIGINAL ARTICLE

Bone marrow scintigraphy as a prognostic marker of overall survival in mCRPC patients treated with Radium-223 dichloride

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Abstract

Purpose To evaluate the potential prognostic value of pretherapeutic Bone Marrow Scintigraphy (BMS) in metastatic castration-resistant prostate cancer (mCRPC) patients treated with Ra-223 dichloride (Ra-223).

Methods We analyzed 28 mCRPC patients who performed BMS and treated with Ra-223. Visual image analysis was performed and defined as follows: normal distribution (uptake in the vertebral column and bony pelvis) vs. medullary expansion (uptake at the distal half of femoral and/or humeral diaphysis or more distally). Correlation between medullary expansion status and baseline laboratory factors was performed. Survival analyses for evaluating the association between medullary expansion and other variables with overall survival (OS) were conducted using cox regression hazard model and Kaplan Meier methods.

Results A total of 130 doses of Ra-223 were administered, with 17 (60%) patients received 6 cycles. BMS status was significantly correlated with hemoglobin levels ($p<0.001$), PSA levels ($p=0.008$), the number of prior systemic therapies ($p=0.032$) and radiotherapy ($p=0.01$). Median OS was 19 months, with 16 patients dead. Among variables tested, BMS status, hemoglobin, number of therapies, and number of Ra-223 cycles were significantly associated with OS (hazard ratios: 3.3, $p=0.02$; 0.75, $p=0.042$; 1.74, $p=0.019$; 4.6, $p=0.006$; respectively). Patients with normal BMS had a median OS of 33 months vs. 7.6 months in those with medullary expansion (log-rank 5.5, $p=0.019$).

Conclusion This study demonstrated a significant association between medullary expansion status on BMS and OS in mCRPC patients treated with Ra-223. Patients exhibiting medullary expansion have worse outcomes compared to those without expansion. Medullary expansion was correlated with adverse prognostic biomarkers commonly linked to worse outcomes in mCRPC.

Keywords Radium-223 · Prognosis · Bone marrow scintigraphy · Prostate cancer · Survival

Introduction

Prostate cancer is the most frequently diagnosed malignancy in men, with approximately 400,000 new cases reported in 2020, and it is the second leading cause of cancer-related death [1]. It is a heterogeneous disease with various clinical presentations, ranging from localized tumors to widespread metastatic disease at diagnosis. In metastatic castration-resistant prostate cancer (mCRPC), bone is the most common site of distant metastases, occurring in approximately 90% of cases, negatively impacting the patient's quality of life (QoL) [2, 3]. Different bone-targeted agents have been studied for the treatment of mCRPC patients with bone metastases; however, only Radium-223 dichloride (Ra-223) has shown both a survival benefit and improvement of QoL

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in a phase III clinical trial [4–6]. In practice, Ra-223 is recommended after two lines of systemic therapies or as first line for patients who are not eligible for taxane chemotherapy and presenting osteoblastic bone lesions on bone scintigraphy, with or without lymph nodes up to 3 cm in size, and no visceral metastases [4, 7]. Recently, the EORTC-1333 trial (PEACE-3) showed that adding six cycles of Ra-223 to enzalutamide in early asymptomatic or mildly symptomatic mCRPC patients delays progression-free survival and extends overall survival (OS), at the interim analysis [8].

Ra-223 is a calcium-mimicking alpha emitter that targets bone lesions with osteoblastic activity and induces double-stranded DNA breaks within both the tumor and nearby cells of the tumor microenvironment [9, 10]. Although Ra-223 exhibits minimal effects on healthy tissue, anemia and thrombocytopenia have been reported in 30% of mCRPC patients undergoing treatment [4]. Previous research have shown that approximately 50% of patients receiving Ra-223 dichloride do not complete the full course of six treatment cycles [4, 11]. However, there is a lack of pretherapeutic markers to guide the optimal initiation of Ra-223 therapy.

In oncology, hematopoietic status is crucial for initiating specific treatments. Impaired hematopoiesis may delay the initiation or necessitate discontinuation of potential therapies that could prolong survival and/or improve quality of life. Factors such as skeletal metastatic infiltration, prior chemotherapy, and external beam radiation therapy (EBRT) targeting the prostate or skeletal metastases can compromise hematopoietic capacity and alter the distribution of bone marrow (BM), often resulting in medullary expansion [12–15]. A few noninvasive imaging techniques have been used for the evaluation of BM, including magnetic resonance imaging (MRI) and bone marrow scintigraphy (BMS) [16]. BMS, using technetium-99 m (Tc-99 m)-labeled colloids, is employed to evaluate the functional marrow distribution and reserve. In adults over 25 years of age, red marrow is primarily distributed in the axial skeleton (spine and bony pelvis), sternum, ribs, and proximal femora and humeri [17]. Medullary expansion refers to the presence of functional marrow outside these normal regions. Reconversion from yellow to red marrow and BM expansion have been documented in multiple cases of hypoplasia secondary to metastatic involvement [14, 18]. BMS has been used to detect bone metastases [18–20], which appear as photopenic ("cold") areas, however, it remains inferior to bone scintigraphy in this context. Nowadays, BMS is primarily indicated for BM disorders and in conjunction with 111indium scintigraphy to evaluate suspected bone infections [15, 21]. However, the utility of BMS in the work-up of mCRPC patients eligible for Ra-223 is unknown.

Therefore, we aimed to assess the potential prognostic value of pretherapeutic BMS in mCRPC patients treated with Ra-223 dichloride.

Materials and methods

Patients

In this single-centre retrospective study, we screened our institutional database for patients with mCRPC who received Ra-223 (Ra-223) therapy between January 2014 and December 2024. Patients who underwent BMS before Ra-223 administration were included for the study analysis. Those who received combination therapy or did not undergo BMS were excluded. Figure 1 illustrates the patient selection and exclusion process. Demographic, clinical, and laboratory data were extracted from patients' electronic medical records. Baseline variables collected included age, prostate-specific antigen (PSA) levels, hemoglobin (Hb), platelet counts, alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and prior therapeutic interventions.

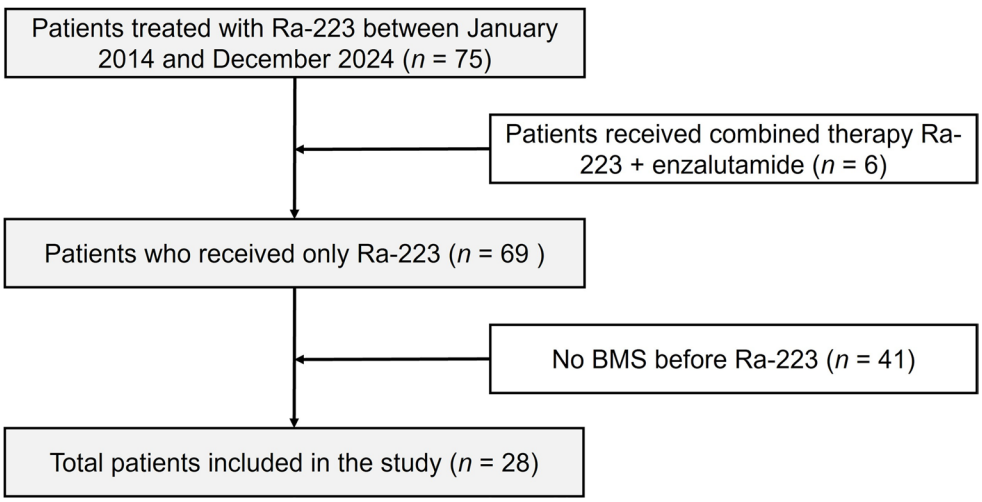

Fig. 1 Flowchart depicting the process of patient selection for study analysis BMS; bone marrow scintigraphy

The study was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. Due to the retrospective design, the requirement for informed consent was waived. The study protocol has been approved by our institutional ethical committee (ID: 2025/23MAI/202).

Radium-223 dichloride treatment

Patients eligible for Ra-223 treatment were discussed and selected at the multidisciplinary oncology meeting and treated according to local and international guidelines. A maximum of 6 cycles were administered at 4-weeks interval. A standard dose of 55 kBq/kg was administered as per manufacturer's instructions (Xofigo, Bayer AG, Leverkusen, Germany). Laboratory tests and clinical assessments were performed one week before each administration. The continuation or interruption of treatment was based on the clinical evolution and at the discretion of the treating physician.

Bone marrow scintigraphy and image analysis

BMS was performed on the same day, prior to Ra-223 administration to evaluate the BM reserve at treatment initiation. Whole body planar imaging was conducted 30–60 min after injection of ~ 7.5 mCi of (Tc-99 m)-labeled nanocolloids using a dual-head gamma camera (GE Infinia Hawkeye I or Philips Brightview XCT). The image interpretation was performed in consensus with, and under the supervision of a Nuclear Medicine expert with more than 30 years of experience in the field. The reader was blind to patient survival outcomes at the time of interpretation. Visual image analysis was performed using a 3-point scoring system as follows: a score of 0 indicated normal biodistribution, score 1 denoted mild expansion (discrete uptake outside regions of normal distribution), and score 2 represented moderate to extensive medullary expansion exemplified by uptake at the distal half of femoral and/or humeral diaphysis or more distally. Patients were subsequently dichotomized as those with scores of 0 or 1 versus those with 2. The classification criteria followed routine clinical practice and were in accordance with definitions described in prior publications [22]. Areas with reduced uptake due to local metastases or previous irradiation were not analyzed in this study. Figure 2 presents an example of patients with and without medullary expansion and their outcomes.

Statistics

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline characteristics. The Shapiro–Wilk test was applied to assess the normality of continuous variables. Normally distributed variables were reported as absolute numbers and frequencies and non-normally distributed variables as a median and interquartile range (IQR). To evaluate the relationship between the BMS and baseline variables, independent samples t-tests were

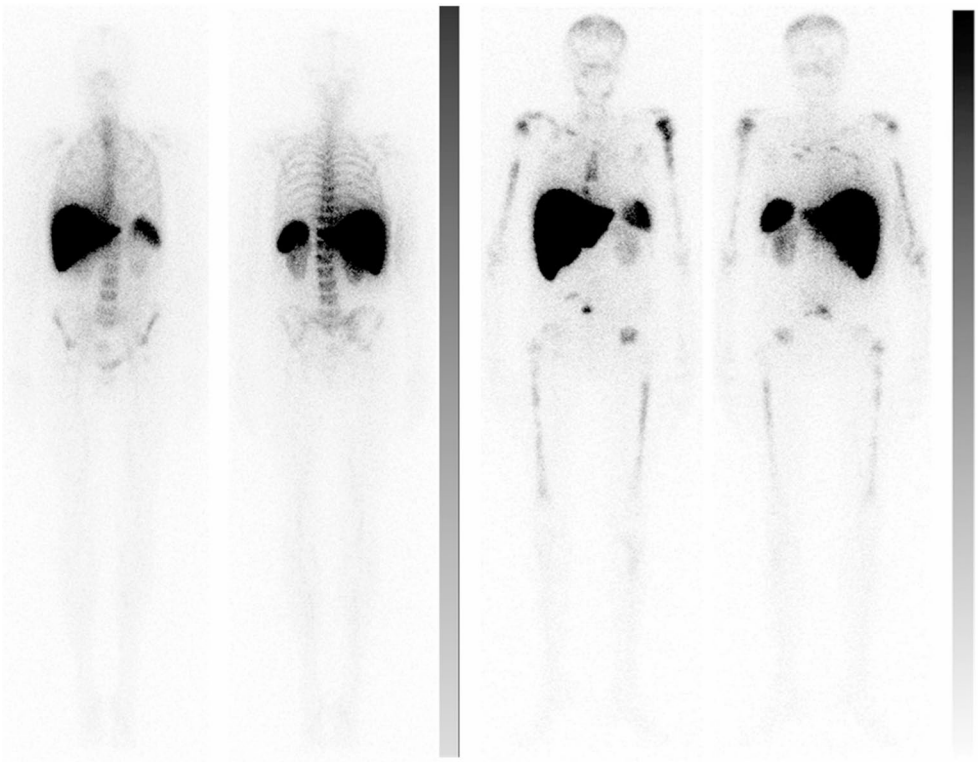

Fig. 2 Representative cases of bone marrow scintigraphy. The image on the left side for a patient with a normal distribution of red marrow, consistent with preserved bone marrow reserve. This patient had a hemoglobin level of 13.3 g/dL, received 6 cycles Radium-223 dichloride, and still alive at 35 months post therapy. The image on the right for a patient with bone marrow expansion, indicative of compromised marrow reserve. This patient had a hemoglobin level of 9.6 g/dL, received 3 treatment cycles, and died after 4 months

used for normally distributed data, and the Mann–Whitney U test was applied for non-normally distributed data. The association between baseline variables and OS was evaluated using the Cox proportional hazards regression model. Survival probabilities were estimated using the Kaplan–Meier method, and differences between survival curves were compared using the log-rank test. OS was estimated from the date of first Ra-223 till date of death or last follow-up. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patients

Twenty-eight patients with a median age of 75 years were analyzed. A total of 130 doses of Ra-223 were administered, with 17 (61%) patients having completed 6 cycles. Twenty-two patients have been treated with at least one line of androgen receptor pathway inhibitors, 14 with at least one line of chemotherapy, and 15 with at least two prior lines before Ra-223, and only one patient received 177Lu-PSMA-617. The median baseline Hb level was 12.6 g/dL (IQR: 10.9–13.5). Patients were followed up for a median of 13 months (IQR: 7–20). Details of patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Variable	Value
Age, years	75 (67–79)
Gleason score, *n* (%)	
5–6	4 (14)
7	6 (21)
8–10	10 (36)
missing	8 (29)
Primary treatment, *n* (%)	
Radical prostatectomy	8 (29)
Radical radiotherapy	8 (29)
Hormone therapy	10 (36)
Chemotherapy	1 (3.5)
Missing	1 (3.5)
Prior systemic therapies, *n* (%)	
ARPI	22 (79)
Chemotherapy	14 (50)
PSMA targeted therapy	1 (3.5)
Time from diagnosis to 1 st Radium-223 (years)	6.5 (3.2–15.8)
No. of radium cycles	6 (3–6)
Prostate-specific antigen (ng/mL)	51 (22–206)
Hemoglobin (g/dL)	12.6 (10.9–13.5)
Neutrophils (k)	4 (2.9–6.3)
Platelets (k)	260 (196–305)
Alkaline phosphatase (U/L)	123 (72–242)
Lactate dehydrogenase (IU/L)	215 (175–266)

Continuous data were reported as median and interquartile range, and non-continuous data in absolute numbers and frequencies. *ARPI* androgen receptor pathway inhibitors

Medullary expansion and its correlation with baseline factors

BM expansion was observed in 12 patients (43%). This group showed a significantly lower mean Hb level compared to those without expansion (10.8 ± 1.7 vs. 13.0 ± 1.2 g/dL, $p=0.001$) and higher baseline PSA level (median 199 [IQR:] vs. 24 [IQR:] ng/dL, $p=0.008$) (Table 2).

Additionally, medullary expansion was significantly associated with the number of prior systemic anti-cancer therapies. No expansion was observed in patients who received≤2 lines of treatment, while 50% of those who had undergone>2 lines of systemic treatment exhibited expansion (χ^2, $P=0.001$).

A significant association was also found between medullary expansion and prior exposure to salvage or metastasis-directed radiotherapy ($p=0.01$). No significant correlation was observed between the medullary expansion status and the number of Ra-223 administrations neither with prior radical radiotherapy, LDH, ALP, and platelet counts ($p>0.05$).

Table 2 The correlation between medullary expansion status on BMS and clinical variables

Variable	Expansion ($n=12$)	No expansion ($n=16$)	*p*-value
Hemoglobin (mean ± SD)	10.8 ± 1.7	13.0 ± 1.2	0.001
PSA (median)	199 ng/dL	24 ng/dL	0.008
Systemic therapy			
≤2 lines	6 (50%)	16 (100%)	0.001
>2 lines	6 (50%)	0 (0%)	
Salvage/metastatic RT			
Yes	7 (58%)	2 (12%)	0.010
No	5 (42%)	14 (88%)	
Radium-223 treatment[#]			
6 cycles	12 (43%)	5 (18%)	0.074
1–3 cycles	4 (14%)	7 (25%)	

PSA prostate-specific antigen, *RT* radiotherapy

[#] Number of patients

Association of baseline variables with overall survival

The median OS of the entire patient cohort was 19 months (95%CI 10–27), with 16 patients deceased at the time of study analysis. A significant association was observed between medullary expansion status and OS (HR 3.28, 95% CI 1.16–9.27), as shown in Table 3. Patients with medullary expansion had a shorter median OS compared to those without expansion (7.6 months, 95%CI 1–15 vs. 33 months, 95%CI 7–58), Fig. 3. Furthermore, the number of Ra-223 cycles was significantly associated with OS (HR 4.6, 95%CI

Table 3 Cox regression hazard model analyses of the association of the clinical variables and BMS with patient OS

Variable	Hazard ratio	95% CI	*p*-value
Hemoglobin (cont.)	0.75	0.56–0.99	0.043
Medullary expansion (yes vs. no)	3.28	1.16–9.27	0.025
Radium-223 (1–3 vs. 6 cycles)	4.6	1.53–13.91	0.006
Prior systemic therapies (cont.)	1.74	1.13–2.67	0.011
Lactate dehydrogenase (cont.)	1.01	1.004–1.016	0.001
Prostate-specific antigen (cont.)	1.001	1.000–1.001	0.053

CI confidence interval

1.53–13.91, $p=0.006$) (Table 3; Fig. 3). Moreover, results from Cox regression showed that low Hb levels, number of prior systemic therapies, and high LDH levels were also significantly associated with worse OS ($p=0.043$, 0.011, and 0.001, respectively) (Table 3). Baseline ALP and PSA levels were not significantly associated with OS ($p>0.05$).

Discussion

The identification of prognostic factors is crucial for guiding therapeutic decision-making in patients with mCRPC. In this study, we investigated the prognostic value of medullary expansion observed on pretherapeutic BMS in patients with mCRPC treated with Ra-223. Our findings demonstrate that medullary expansion is significantly associated with worse OS, highlighting its potential value as a non-invasive imaging prognostic marker in mCRPC.

Most patients with mCRPC receive chemotherapy and/or palliative radiotherapy, treatment modalities that frequently compromise BM function. Under conditions of increased hematopoietic demand, yellow marrow may undergo reconversion to red marrow, reversing the typical age-related marrow conversion pattern. This phenomenon, known as medullary expansion, can be visualized using BMS. Widespread bone metastases physically replace and disrupt the normal hematopoietic microenvironment, whereas prior treatments, such as chemotherapy and external beam radiotherapy, further deplete the hematopoietic stem cell pool. Our data support this hypothesis, showing that medullary expansion was significantly more prevalent among patients who had received >2 lines of systemic therapy or prior radiotherapy. Additionally, patients exhibiting medullary expansion showed higher PSA levels, which may reflect a greater tumor burden, although PSA is not a universally reliable surrogate marker. Therefore, the presence of medullary expansion may serve as an indicator of widespread disease dissemination. Furthermore, our findings demonstrated a higher incidence of anemia among patients with medullary expansion, consistent with previously published data [18]. Aside from bone marrow infiltration or scarring/fibrosis secondary to active or treated metastases, chronic anemia itself may serve as a stimulus for marrow expansion/reconversion.

Although Ra-223 is generally considered to have a minimal impact on healthy BM, myelotoxicity is nonetheless reported in nearly 30% of treated patients. The precise pathophysiological mechanism underlying this myelotoxicity remains incompletely understood. In this context, BMS may offer valuable insights into the functional BM reserve, potentially aiding in the identification of patients at increased risk of hematologic adverse events prior to initiation of Ra-223 treatment. Preliminary results from our study suggest that patients exhibiting medullary expansion tend to tolerate treatment less well. Patients with medullary expansion received fewer Ra-223 treatment cycles compared to those without expansion. While the exact mechanism remains to be elucidated, medullary expansion may

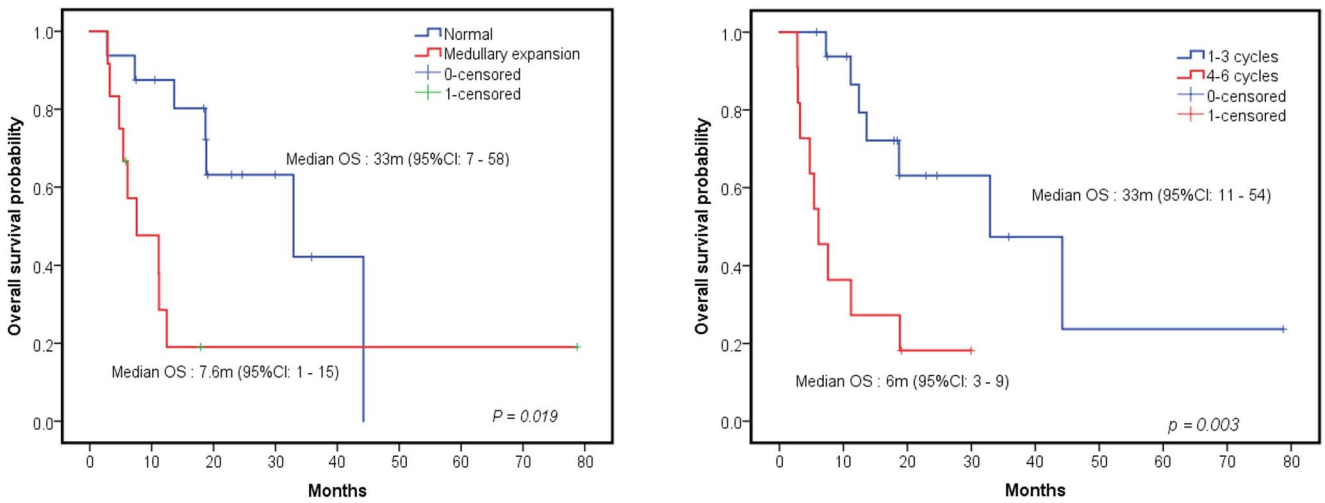

Fig. 3 Kaplan-Meier plots for bone marrow expansion (left) and the number of Ra-223 cycles (right). *P*-values of the log-rank tests

reflect an already compromised hematopoietic reserve, e.g., in patients with limited marrow capacity, Ra-223, despite its targeted mechanism, may further exacerbate marrow insufficiency, increasing the likelihood of treatment-limiting toxicity.

Multiple baseline prognostic biomarkers have been identified in mCRPC. Previous studies have shown that Hb levels and LDH are significant predictive biomarkers of OS in patients with mCRPC receiving systemic therapies, including chemotherapy, androgen receptor pathway inhibitors, and Ra-223 [23, 24]. In line with these reports, our findings demonstrate that high LDH and low Hb levels are associated with poorer OS. LDH is widely recognized as a marker of high tumor burden and rapid cellular turnover, while low Hb has been linked to depleted BM reserve and reduced tolerance for current and future treatment regimens. Moreover, the number of Ra-223 cycles has been reported as a prognostic factor for OS [25, 26]. Our results support this observation, revealing that patients who completed 6 cycles had improved OS compared to those who received only 1–3 cycles.

While advanced molecular imaging with PSMA-PET has revolutionized the staging of prostate cancer by accurately evaluating tumor extension and burden, it does not provide information on BM function. Whole-body MRI can evaluate red marrow distribution [27] however its clinical utility is limited by prolonged acquisition times and restricted availability. In contrast, BMS offers the advantage of whole-body assessment, including the appendicular skeleton which is often excluded in other imaging modalities. Although BMS is an older and less commonly used technique, it may occupy a unique role in the Ra-223 setting by enabling direct visualization of functional red marrow distribution. It can reveal medullary expansion, although a patient fulfills standard eligibility criteria, suggesting a fragile bone marrow reserve. Such findings could have implications for treatment tolerance and overall survival. However, this hypothesis needs to be validated in larger prospective studies.

This study has some limitations inherent to its retrospective nature. BMS was not performed systematically in all patients, as it is not part of routine practice, hereby introducing a potential selection bias. However, all patients who underwent BMS were included in this analysis. Moreover, BMS was not used in the selection of eligible patients for Ra-223 treatment. Additionally, the lack of standardized and validated criteria for interpreting BMS, combined with challenges in applying an objective and reproducible quantitative assessment method. The lack of inter-observer agreement could be a potential limitation. To reduce the effect of these limitations, the interpretation followed the routine clinical practice and was performed under the supervision of NM expert with more than 30yrs experience in the field. Despite these limitations, this study provides a valuable basis for future studies to overcome these challenges and further explore the clinical utility of BMS in the setting of Ra-223 treatment in mCRPC.

Conclusion

This study demonstrated a significant association between medullary expansion status on BMS and OS in mCRPC patients treated with Ra-223. Patients exhibiting medullary expansion have worse outcomes compared to those without expansion. In addition, medullary expansion was correlated with adverse prognostic biomarkers commonly linked to worse outcomes in mCRPC. These findings underscore the potential value of BMS in identifying patients at higher risk of poor prognosis before Ra-223 treatment. Further validation in larger prospective cohorts is warranted to confirm these observations.

Author contributions All authors contributed to the study conception and design. Material preparation and analysis were performed by QA Shagera. Data collections were performed by QA Shagera and E. Jonard. The first draft of the manuscript was written by QA Shagera, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval This study was performed according to the principles of the Declaration of Helsinki and its later amendments. Approval was granted by the Cliniques universitaires Saint-Luc Ethics Committee (ID: 2025/23MAI/202).

Informed consent The requirement for written informed consent was waived due to the retrospective design of the study.

Conflict of interest The authors declare no conflicts of interest.

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