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ORIGINAL ARTICLE

Prostate-specific antigen flare induced by $^{223}RaCl_2$ in patients with metastatic castration-resistant prostate cancer

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Abstract

Purpose Prostate-specific antigen (PSA) flare is a well-known phenomenon in patients with prostate cancer, but its impact during radium-223 dichloride ($^{223}RaCl_2$) therapy is still unclear. This radioisotope has shown to improve overall survival in metastatic castration-resistant prostate cancer (mCRPC). We sought to evaluate the impact of PSA flare on survival and its relation with metabolic parameters on ^{18}F-labeled sodium fluoride PET/CT.

Methods We conducted a retrospective study of 168 patients with mCRPC (median age 69; median PSA 29.7) receiving $^{223}RaCl_2$. Overall survival (OS) and progression-free survival (PFS), estimated by the Kaplan–Meier method and compared using a log-rank test, were evaluated for patient groups corresponding to different definitions of PSA flare. Metabolic ^{18}F-fluoride PET/CT data were analyzed as well.

Results Immediate PSA decline was observed in 49 patients (29.2%), whereas no PSA response was observed in 59 patients (35.1%). PSA flare (defined as rise after the first cycle followed by decrease below the baseline) was observed in 20 patients (11.9%) and PSA flare followed by a decrease from peak but not below baseline was observed in 40 (23.8%). The first flare subgroup had a median PFS and OS of 20.8 and 23.9 months, respectively. These outcomes were not significantly different from patients with immediate PSA decrease, but were significantly better than in patients with persistent PSA elevation (3.1 months for PFS and 11.5 months for OS, $p < 0.001$). Moreover, the PSA flare group showed an alkaline phosphatase (ALP) decrease significantly greater than non-responders ($p = 0.003$). Metabolic ^{18}F-fluoride PET/CT data were available in 35 patients at baseline and during $^{233}RaCl_2$ therapy. The tumor burden reduction, expressed by ΔTLF_{10} and ΔFTV_{10}, was more evident within PSA flare group below baseline than non-responders ($p = 0.005$ and 0.001, respectively).

Conclusions This report suggests that a flare does not necessarily indicate lack of response to $^{223}RaCl_2$ therapy.

Keywords Metastatic castration-resistant prostate cancer · ^{233}Ra-dichloride therapy · Bone metastases · Prostate-specific antigen flare · Fluoride PET/CT

Introduction

Prostate cancer is the second most common male cancer worldwide and the second cause of male cancer death in the USA. Bone is the main site of metastases, representing more than 90% of patients with metastatic disease. In addition, bone complications such as bone marrow failure, bone pain, pathological fracture, and spinal cord compression reduce significantly quality of life in these patients [1–3]. In the last decade, several advances in the treatment of metastatic castration-resistant prostate cancer (mCRPC) have been gained by the development of new drugs that have improved the overall survival (OS). ^{233}Ra-dichloride ($^{233}RaCl_2$) therapy, one of such new agents, has been shown to prolong OS, delay time to symptomatic skeletal events, and improve quality of life in mCRPC patients, regardless of previous docetaxel treatment. Thus, the US Food and Drug Administration (USFDA) approved $^{233}RaCl_2$ for treatment in mCRPC patients with symptomatic bone metastases [4–6].

Prostate-specific antigen (PSA) flare, which consists of an early and transient rise in the PSA level followed by a decline,

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is a well-known phenomenon observed in several studies during luteinizing hormone-releasing hormone (LHRH) agonist treatment and in almost 20% of patients in the course of systemic chemotherapy [7–10]. Nevertheless, at present, after an initial rise in PSA, there is no clear definition on the extent of the following PSA decline to be considered as a flare and its impact on treatment outcomes and patient management is still indeterminate. In literature, the phenomenon is defined as a decline of at least 50% from the baseline or from the PSA peak value, but also as an undefined PSA response [11, 12]. To our knowledge, there have been no studies investigating the PSA flare phenomenon during the course of $^{233}RaCl_2$ therapy.

The aim of our study was to evaluate the prognostic impact of the PSA flare in mCRPC patients treated with $^{233}RaCl_2$. We also investigated the possible correlation of this phenomenon with metabolic parameters by ^{18}F-fluoride PET/CT.

Materials and methods

Waivers of informed consents and institutional board authorization were granted for this study. Clinical records of 168 patients with mCRPC and treated with $^{233}RaCl_2$ at MD Anderson Cancer Center between August 2013 and February 2017 were retrospectively analyzed. All patients receiving at least one cycle of $^{223}RaCl_2$ therapy were considered for the analyses. The following parameters were recorded for all patients: age, Gleason score (GS), treatment history, sites of metastases, Eastern Cooperative Oncology Group (ECOG) performance status, baseline serum PSA, PSA trend during treatment, and duration of $^{233}RaCl_2$ treatment. Whole-body skeletal ^{18}F-fluoride PET/CT was performed to determine eligibility for $^{233}RaCl_2$ therapy and/or to restage the patients every three or after six cycles at the physician's discretion. Nodal and visceral metastases were assessed visually on the images available (^{18}F-fluorodeoxyglucose PET/CT, ^{18}F-fluoride PET/CT, body CT scans, ultrasound, or MR imaging). Baseline characteristics of the patient population are displayed in Table 1.

At present, as no official definition is available for PSA flare, we considered different definitions described in previous reports, although with chemotherapy drugs [10, 13]. A flare was defined as an increase of PSA after the first cycle of $^{233}RaCl_2$ therapy followed by a decrease which could be: (1) a decrease less than baseline, (2) a ≥ 50% decrease from baseline, and (3) a decrease from the peak of PSA during treatment. Patients with persistent PSA rise during therapy with radium were considered non-responders, whereas immediate responders were those with an immediate and continue decrease of PSA after the first cycle.

The primary endpoint of the study was to evaluate OS, which was established from $^{233}RaCl_2$ cycle start until date of death, and PFS, which was defined as the interval from beginning of $^{233}RaCl_2$ therapy until date of death of any cause, or disease progression according the recommendations of the Prostate Cancer Working Group 3 (PCWG3) [14]. All deceased patients underwent complete follow-up until death. The secondary endpoint was to assess semi-quantitative parameters by ^{18}F-fluoride PET/CT during $^{233}RaCl_2$ therapy.

Table 1 Demographics and clinical characteristics of patients at baseline

Characteristic	Median	Range
Age (y)	69	42–88
PSA (μg/L)	29.7	1.0–7207.4
ALP (U/L)	109	48–1134
Hemoglobin (g/dL)	11.6	5.7–15.6
Platelets (K/uL)	187	114–413
Absolute neutrophil (K/uL)	4.5	1.5–21.4
Gleason score	***n (%)***	
8–10	116 (69)	
≤ 7	38 (22.7)	
NA	14 (8.3)	
Eastern Cooperative Oncology Group performance status		
0	88 (52.4)	
1	61 (36.3)	
≥ 2	19 (11.4)	
World Health Organization pain scale		
0	93 (55.4)	
1	29 (17.3)	
≥ 2	46 (27.4)	
Metastatic sites		
Lymph nodes	47 (28)	
Visceral	16 (9.6)	

PSA prostate-specific antigen, *ALP* alkaline phosphatase

$^{233}RaCl_2$ treatment

$^{233}RaCl_2$ (Xofigo®, Bayer Healthcare Pharmaceuticals Inc.) treatment was administered per clinical standard of care to 168 mCRPC patients, all of them with bone metastases; additionally, 34% of these patients had visceral and/or nodal metastases. Eligibility criteria for treatment with $^{233}RaCl_2$ consisted of being older than 18 years and signing the informed consent. Treatment was given if: hemoglobin (Hb) level >10 g/dL, absolute neutrophil count (ANC) ≥1.5 × 10^9/L, and platelet count ≥100 × 10^9/L. Patients with initially low levels of Hb (<10 g/dL) received a blood transfusion prior to $^{233}RaCl_2$ therapy being started.

The used activity dose of $^{223}RaCl_2$ was 50 kBq/kg body weight (1.4 μCi/kg) given at monthly intervals for 6 cycles [15]. The volume administered was calculated using the patient's body weight (kg), the dosage level (50 kBq/kg body weight), the radioactivity concentration of the product at the

reference date, and the decay correction factor provided with each vial. After each $^{233}RaCl_2$ cycle, the patients were counseled regarding expected side effects and precautions of the radiopharmaceutical.

Semi-quantitative assessment of ^{18}F-fluoride PET/CT

Images were acquired after 50–60 min of ^{18}F-sodium fluoride injection (158–370 MBq), from the vertex of the skull to the feet. MIM Vista workstation (MIM Vista) was used for reconstruction and displaying images in the three different planes (transverse, coronal, and sagittal).

^{18}F-Fluoride PET/CT images were analyzed by two board-certified nuclear medicine physicians. Whole-body skeletal tumor burden was determined by semi-quantitative analysis, with MIM Vista, on baseline and restaging fluoride images. The technique, already described by Etchebehere et al. [16], consists of drawing a rectangular semiautomatic volume of interest (VOI) in the whole-body image with caution to encompass all metastatic sites. When the whole-body VOI is drawn, the maximum standardized uptake value (SUVmax) threshold is set at 10, in order to exclude 99% of all normal bone uptake. Hence, only regions with a SUVmax of 10 or greater generated VOIs automatically by the computer and images were revised to manually exclude any sites of high uptake not related to bone metastases (i.e. urinary activity or degenerative disease). Subsequently, the following parameters were obtained: highest SUVmax among all the metastases, mean SUVmax of all metastases ($mean_{10}$), and skeletal tumor burden, obtained by calculating the total fluoride skeletal metastatic uptake as a product of mean SUV *x* VOI_{10} (TLF_{10}) and the total volume of fluoride bone metastases (FTV_{10}).

Statistical analysis

Patient and clinical characteristics were summarized using descriptive statistics. Frequencies and percentages were provided for categorical variables; mean (SD) and median (range) were provided for continuous variables. For the statistical analysis, we divided our cohort in three categories: responders, which included patients who experienced flare (definitions 1, 2, and 3 mentioned above), non-responders, and immediate responders.

Kaplan–Meier survival curves demonstrated survival time distributions and log-rank tests for comparison between groups. The Wilcoxon signed rank test (paired, two-tailed) was applied for the comparison of the different response parameters for continuous variables and chi-square test or Fisher's exact test for categorical variables. All statistical tests used a significance level of 5%. Statistical analyses were performed using the Statistical Package for Social Sciences, version 22.0, for Windows (SPSS, Chicago, IL, USA).

Results

$^{233}RaCl_2$ doses were completed in 108 (64.2%) patients, 6 (3.7%) patients were still undergoing $^{233}RaCl_2$ therapy, and 54 (32.1%) patients did not complete all 6 doses because of either progression, hematologic toxicity, or deteriorating ECOG status. Median age at the first cycle of $^{233}RaCl_2$ therapy was 69 years. The mean number of doses performed was five (median, six doses). Only two patients performed one cycle, but due to persistent increase of PSA, were considered non-responders. After treatment, median follow-up was 8.4 months (range 0.5–36.7). The median OS time was 12.2 months (range 1.4–41.6). The median PFS was 6.2 months (range 0.6–41.6). Population characteristics and outcomes are shown in Tables 1 and 2.

The incidence of the PSA flare, according to different definitions, ranged from 9.5 to 35.7%. According to definition 1 (flare after the first cycle followed by a decrease below the baseline), 18 patients had a flare after the first cycle and 2 after the second cycle. On the other hand, among patients with flare until the peak of PSA (definition 3, which includes also patients from definition 1), 32 had a flare after the first cycle, 18 after the second, 6 after the third, and 4 after the fourth. The median initial PSA increase from the baseline was +20% in patients where flare persisted only for the first cycle and +39% in those who experienced a longer flare period. In this latter group, median interval to the PSA flare was 1.7 months, whereas it was 0.9 months in the first group with flare persisting only for the first cycle. Patients who experienced a flare only after the first dose showed a median PFS and OS of 20.8 and 23.9, respectively, while patients with a longer flare PFS and OS were shorter (9.8 and 18.3, respectively; Table 3). When we considered PSA flare with decrease below the baseline (definition 1), OS and PFS were considerably better than non-responders (PFS: 20.8 vs. 3.1 months, $p < 0.001$; OS: 23.9 vs. 11.5 months, $p < 0.001$; Fig. 1). Furthermore, patients with decline from the peak but not below baseline had a longer PFS and OS than non-responders (PFS: 7.9 vs. 3.1 months, $p < 0.001$; OS: 14.5 vs. 11.5 months, $p = 0.04$; Fig. 2). In contrast, no significant differences in PFS and OS were found among patients with flare, regardless of definition, and those with immediate decline in PSA level. Indeed, according to definition 1, PFS was 20.8 vs. 12.9 months [p = non-significant (ns)] and OS was 23.9 vs. 37.2 months (p = ns), respectively. According to definition 3, PFS was 9.8 vs. 12.9 months (p = ns) and OS 18.3 vs. 37.2 months (p = ns), respectively (Fig. 3). Finally, when stricter definition of PSA flare was used, such as PSA decline ≥50% less than baseline, similar OS and PFS results were obtained (data not shown). Additionally, we also evaluated alkaline phosphatase (ALP) trend during $^{223}RaCl_2$ treatment and found that ALP reduction was significantly higher in the flare group compared to non-responders (median reduction: −25% and −7.6%, respectively,

Table 2 Summary of treatment outcomes with $^{233}RaCl_2$

	Number of patients (%)
$^{233}RaCl_2$ doses ($N = 168$)	
Completed	108 (64.2)
Stopped	54 (32.1)
In progress	6 (3.7)
Median follow-up after $^{233}RaCl_2$, mo [range],	8.4 [0.5–36.7]
PSA decline ≥50%	49/168 (29.2)
Median OS, mo [range]	12.2 [1.4–41.6]
Median PFS, mo [95% CI]	6.2 [0.6–41.6]

PSA prostate specific antigen, *mo* months, *OS* overall survival, *PFS* progression-free survival

$p = 0.003$; Fig. 4), whereas we did not find a similar ALP flare phenomenon in our cohort. No significant differences between patients with visceral metastases and the other groups in terms of either survival or side effects to therapy were observed.

Semi-quantitative analysis by ^{18}F-fluoride PET/CT

Semi-quantitative parameters on ^{18}F-fluoride PET/CT were obtained at baseline and after $^{233}RaCl_2$ therapy in 35 patients, 10 with PSA flare below baseline (definition 1), and 25 non-responders. Nine out of 10 patients completed all 6 cycles, and only 1 patient stopped after the fourth. Among non-responders, 16 patients completed all cycles, while 3 and 6 patients stopped after five and four cycles of radium, respectively.

The mean shrinkage of tumor lesions was significantly greater in the flare group, as demonstrated by ΔTLF_{10} (−44.4% for flare patients vs. +13.3% within non-responders, $p = 0.005$) and ΔFTV_{10} (−35.5% vs. +22.8% in non-responders, $p = 0.001$). On the other hand, no significant differences for ΔSUVmax and $\Delta SUVmean_{10}$ were found (Table 4).

A typical example of flare during treatment with $^{233}RaCl_2$ is illustrated in Fig. 5.

Discussion

Our study highlights a better OS and PFS in mCRPC patients experiencing PSA flare in $^{233}RaCl_2$ therapy than those with progressive PSA increase, most of whom were already treated with androgen deprivation therapy, cytotoxic chemotherapy, hormone therapy, and palliative radiotherapy. We also included patients with visceral metastases because they were previously treated and felt to be quiescent. Moreover, Etchebehere et al. [17] previously demonstrated a benefit to radium therapy in patients with more advanced disease, including visceral metastases.

Although the phenomenon has been described only in two case reports [18, 19], where patients had a significant pain response to treatment and stable bone disease after six cycles of $^{233}RaCl_2$therapy, to our knowledge, this is the first large study which demonstrates a survival advantage in PSA flare patients during bone-targeted therapy. As the first study of PSA flare during $^{233}RaCl_2$, comparison to other reports of PSA response is difficult because of differences in treatment dose, schedule, and concomitant therapies. Previously, PSA flare has been described during first-line docetaxel, cabacitaxel chemotherapy, and abiraterone treatment [11–13, 20, 21] with an incidence ranging from 8.3 to 30.6%. In our study, the incidence of PSA flare was comprised between 9.5 and 35.7%, depending upon the definition used for flare. When we defined flare with stricter criteria, i.e. a rise followed by a decrease of 50% from baseline, median PFS and OS were not significantly different from those in patients incurring an immediate PSA response. Similar results were observed in the abovementioned studies as well. Although our study has highlighted the relation between PSA flare and survival, a clear definition of PSA flare is still a matter of debate. In our opinion, for an accurate comparison, it is preferable to define a

Table 3 Incidence of PSA flare according to various definitions

PSA response	Patients N (%)	Median PSA rise from baseline (%)	Median time to peak PSA level, months (range)	Median PFS, months (95%CI)	Median OS, months (95%CI)
PSA Increase after the 1st cycle followed by:					
1) Decline below the baseline	20 (11.9)	19.8	0.9 (0.8–1.9)	20.8 (8.6–33.0)	23.9 (14.3–33.5)
2) Decline ≥50% than baseline	16 (9.5)	19.8	0.9 (0.8–1.9)	20.8 (17.1–24.4)	23.9 (16.4–31.4)
3) Decline from PSA peak value	60 (35.7)	39.1	1.7 (0.8–4.5)	9.8 (7.6–12.1)	18.3 (15.6–20.9)
Immediate decline					
Any	49 (29.2)	NA	NA	12.9 (5.9–19.8)	37.2 (12–62.3)
≥ 50% Decline	31 (19.6)	NA	NA	20.5 (13.9–27.1)	37.2 (12.2–62.3)
Non-responders	59 (35.1)	NA	NA	3.1 (2.2–4.0)	11.5 (7.6–15.2)

NA, not applicable

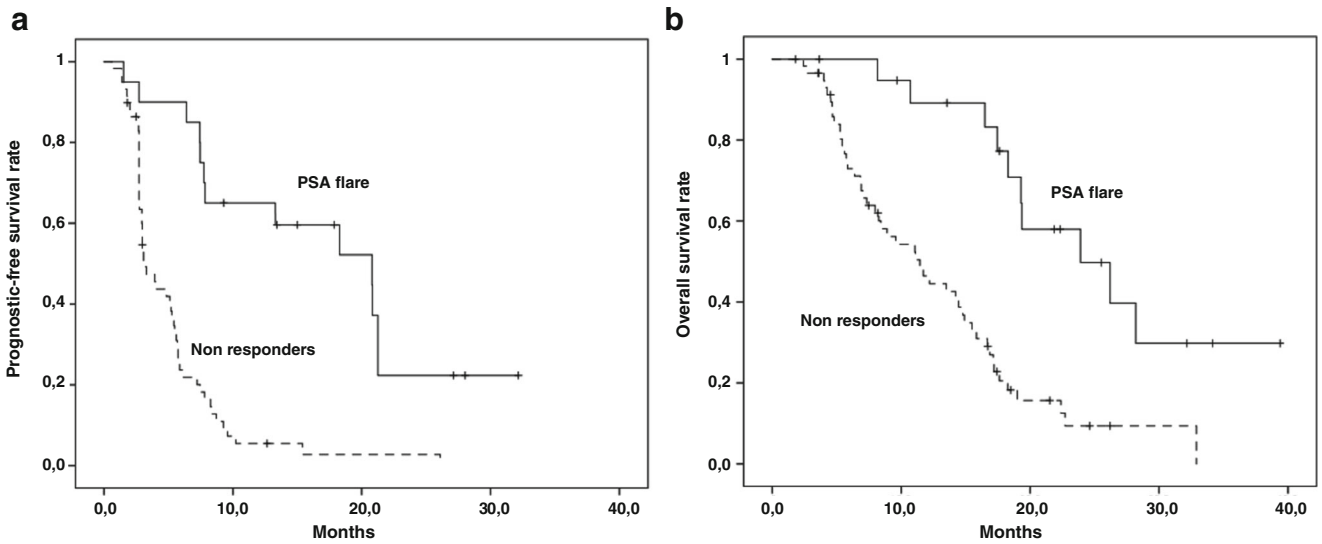

Fig. 1 **a.** PFS in patients with PSA flare followed by a decrease below the baseline compared to patients with disease progression. **b.** OS in patients with PSA flare followed by a decrease below the baseline compared to patients with disease progression

PSA flare only if the decrease is below the baseline (definition 1). On the other hand, a decrease from peak but not below the baseline could be mixed with phenomena of tumor progression. Additionally, a reduction of PSA flare ≥50% seems to be easier and faster to calculate in daily practice. The mechanism of a PSA flare induced by $^{233}RaCl_2$, abiraterone, and other chemotherapeutic prostate drugs has not yet been understood. Our opinion, supported by data, is that the phenomenon is related to tumor response. $^{233}RaCl_2$ is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases, particularly into newly formed bone stroma, and emits high-energy alpha particles of short range. The high-energy alpha-particle radiation induces mainly DNA damage that result in a potent and highly localized cytotoxic effect in the target areas [22]. As such, we hypothesize that the observed PSA flare during $^{233}RaCl_2$ treatment is due to PSA release from tumor cell lysis. Based on this mechanism of action, PSA flare may correspond to a high degree of tumor cell death and may be associated with more complete and more durable response. On the other hand, minor bone metastases or micro-metastases that are present before treatment could not be sufficiently irradiated and may progress during $^{233}RaCl_2$ therapy. This might explain, together with any change in the tumor microenvironment, the persistent increase of PSA in a part of our patients and the different survival results.

We also found that serum ALP after $^{233}RaCl_2$therapy was significantly lower in the flare groups compared to non-

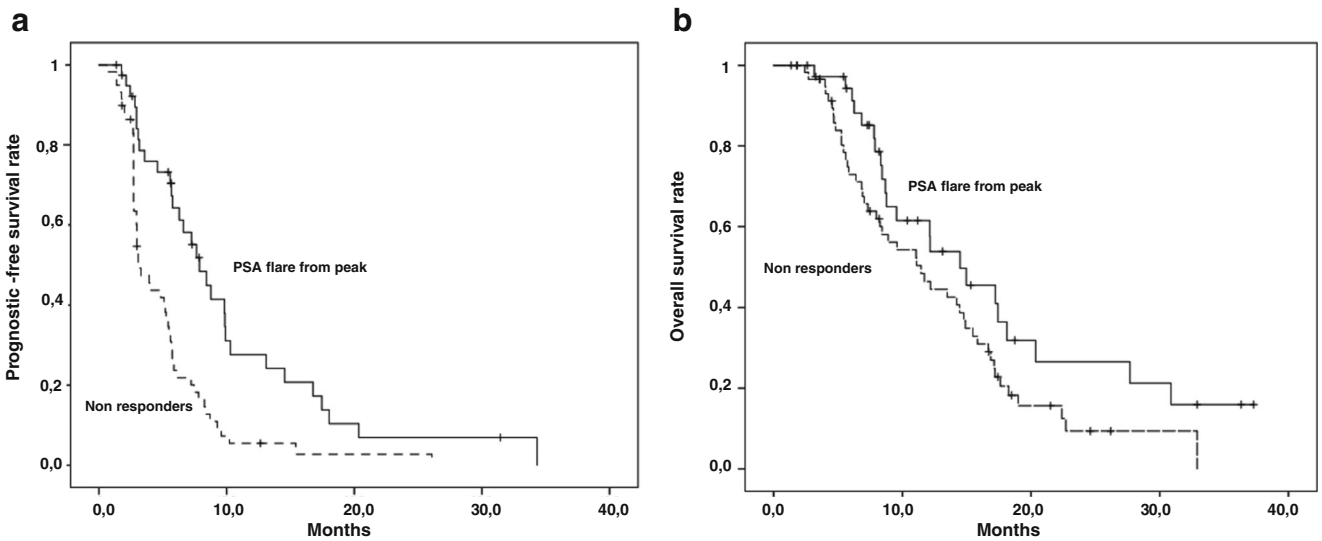

Fig. 2 **a.** PFS in patients with PSA flare from the peak compared to PFS and OS in patients with disease progression. **b.** OS in patients with PSA flare from the peak compared to PFS and OS in patients with disease progression

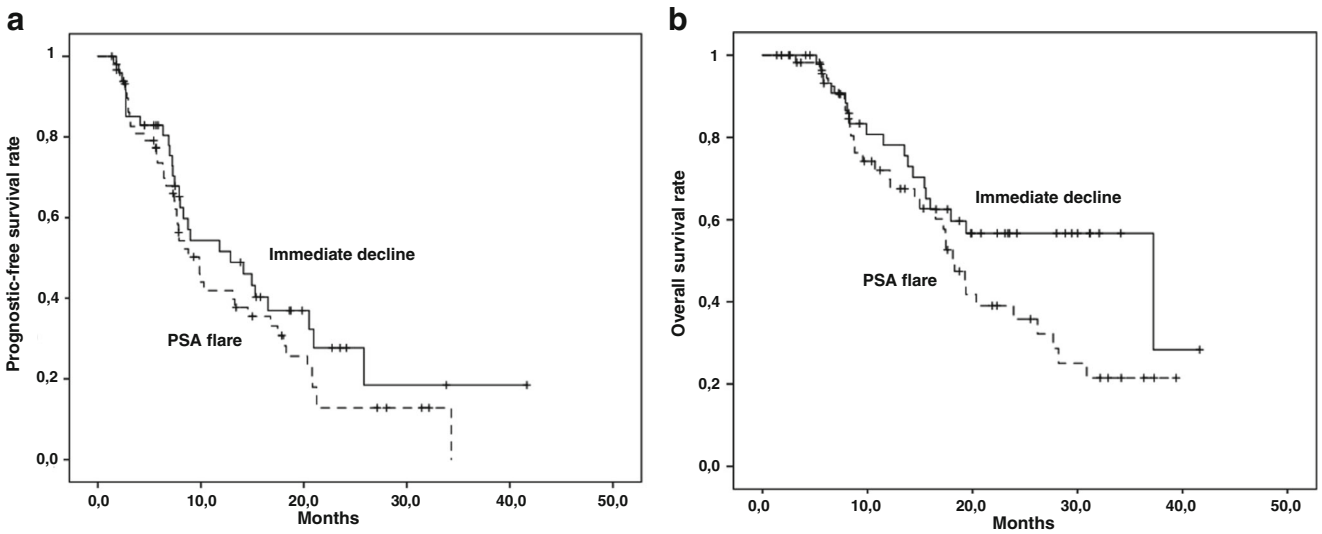

Fig. 3 **a.** PFS in patients with PSA flare (definition 3) compared to OS and PFS in patients with immediate PSA response. **b.** OS in patients with PSA flare (definition 3) compared to OS and PFS in patients with immediate PSA response

responders. Recently, Han and Hong [23] reported that ALP kinetics can identify PSA flare among men with mCRPC, although in patients treated with different chemotherapies, suggesting a potential role of ALP as a biomarker for treatment response. Indeed, ALP is an osteoblastic activity marker, so that variations in ALP levels might reflect changes in bone metastases more accurately than PSA levels in mCRPC, where PSA promoter/enhancer activity of metastatic cancer cells is not overexpressed [24, 25].

ALP flare is a well-established phenomenon during endocrine therapy in metastatic prostate cancer [26, 27]. However, we did not find any significant correlations between ALP flare and PSA flare, as most patients with PSA flare had decrease in ALP levels, suggesting a different mechanism of flare between these two markers.

Moreover, our data suggest a possible correlation between PSA flare and a lower tumor burden as shown by ΔTLF_{10} ΔFTV_{10} on ^{18}F-fluoride PET/CT, which was recently

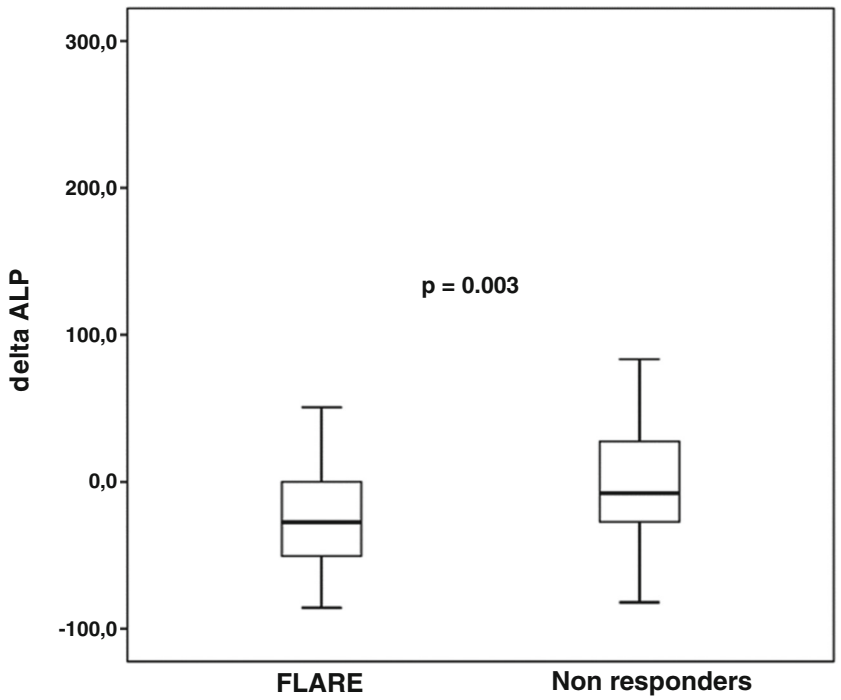

Fig. 4 Variation in serum alkaline phosphatase (ALP) after radium between PSA flare patients and non-responders

Table 4 ^{18}F-fluoride PET/CT parameters in PSA flare and non-responder patients after $^{233}RaCl_2$therapy

Metabolic parameters	PSA flare below baseline % (range) $N = 10$	Non-responders % (range) $N = 25$	p
ΔSUVmax	−52.6 (−390.8 + 48)	−46.1 (−170.5 + 47)	n.s.
$\Delta SUVmean_{10}$	−9.3 (−77.8 + 16.2)	−13.5 (−65 + 19.3)	n.s.
ΔTLF_{10}	−44.4 (−247.1 + 12.7)	+13.3 (−161.2 + 88.7)	0.005
ΔFTV_{10}	−35.5 (−288.2 + 10.7)	+22.8 (−84 + 90)	0.001

SD standard deviation; *ΔSUVmax* delta maximum standardized uptake value; *ΔSUVmean* delta mean standardized uptake value; ΔTLF_{10} delta total fluoride skeletal metastatic uptake; ΔFTV_{10} delta total volume of fluoride bone metastases; *n.s.* not significant

identified as a prognostic factor of outcome in $^{233}RaCl_2$ therapy [28]. Our observations are in line with those reported by Modi et al. [29], where a significant correlation with number of bone metastases was found.

In a clinical setting, our findings have useful implications because an initial PSA rise is not necessarily signal disease progression, but may be either a non-response or may represent a prognostic favorable flare. It is essential for oncologists to recognize flare phenomenon in order to avoid a premature interruption of $^{233}RaCl_2$ therapy. Then, as the PSA trend is only a part of the anticancer therapy response, new monitoring means are being developed (circulating tumor cells and circulating DNA) and new drugs appear to be effective without determining PSA variance [30–33].

The main limitation of this study was the retrospective design. Second, approximately one third of patients discontinued $^{233}RaCl_2$ therapy and were switched to chemotherapy (or secondary hormone therapy) according to the oncologist's decision, although it is well known that switching to another therapy has worse outcomes compared to patients who continued with $^{233}RaCl_2$ therapy despite progression [28]. Finally, the timing of PSA measurements and scanning intervals during the alpha emitter therapy varied among the patients, although this aspect is similar to the real-world clinical practice.

Conclusion

In summary, for the first time, our study confirms the PSA flare phenomenon in a large series of mCRPC patients treated with $^{233}RaCl_2$. Patients who experienced PSA flare had significantly better survival than those with persistent PSA increase ("non-responders") and similar to those with immediate PSA decline. Thus, we strongly recommend that $^{233}RaCl_2$ therapy should not be discontinued after an early and transient PSA rise. In particular, physicians should be aware of the possibility of PSA flare induced by $^{233}RaCl_2$therapy during, at least, the first 2 months of treatment, which does not represent a sign of disease

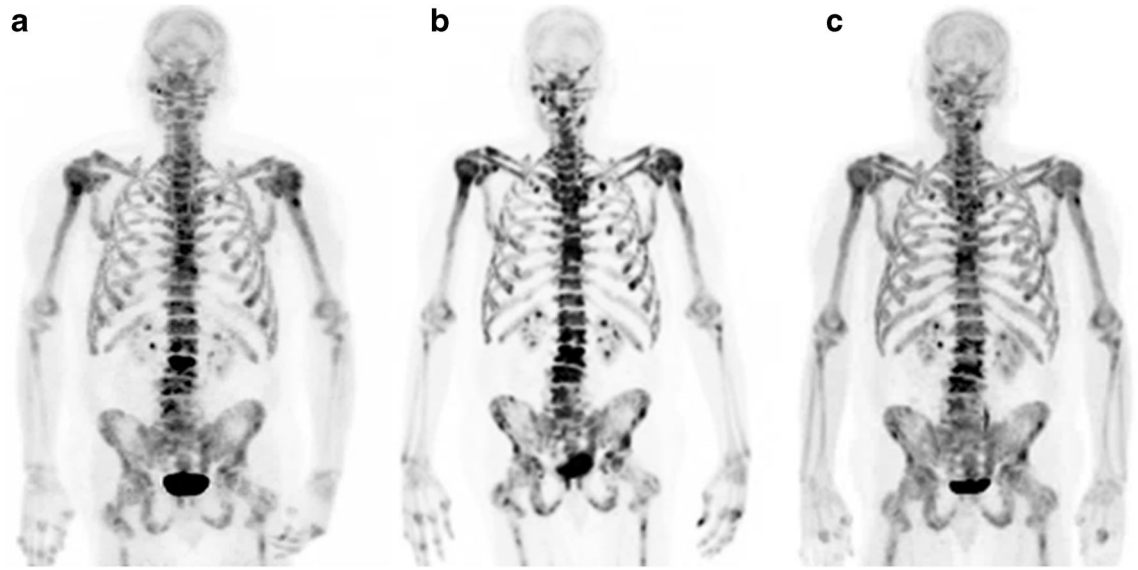

Fig. 5 Example of flare: ^{18}F–NaF PET/CT scans performed at baseline (**a**), after the third $^{223}RaCl_2$ cycle (**b**), and after the sixth $^{223}RaCl_2$ cycle (**c**). The baseline scan demonstrates osteoblastic metastases with TLF_{10} of 3.391 and the interim scan demonstrated an increase in uptake of some bone lesions, particularly the sternum, left humerus, lumbar spine, and pelvis with a TLF_{10} of 5.437. The scan after radium therapy demonstrated improvement of bone lesions (TLF_{10} of 2170) and reduction in ALP and PSA levels. The patient was still alive 20 months after $^{223}RaCl_2$ therapy was started

progression. However, our study highlights the need to find a standard and validate PSA flare definition and thresholds to ensure homogeneity among studies.

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Compliance with ethical standards

The study herein presented was approved by the local review board and performed in accordance with the principles of good clinical practice, with the Declaration of Helsinki, and with the national regulations regarding clinical trials. Waivers of informed consent and authorization were granted for the retrospective analysis.

Conflicts of interest The authors have declared no conflicts of interest.

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