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# The Impact of Baseline PSMA PET/CT Versus CT on Outcomes of $^{223}$Ra Therapy in Metastatic Castration-Resistant Prostate Cancer Patients

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Imaging before $^{223}$Ra-dichloride ($^{223}$Ra) therapy is crucial for selecting metastatic castration-resistant prostate cancer (mCRPC) patients with bone-only disease. The purpose of this study was to evaluate if baseline prostate-specific membrane antigen (PSMA) PET/CT (bPSMA) versus CT is associated with outcomes of $^{223}$Ra therapy. **Methods:** A secondary analysis of the data of a prospective observational study (NCT04995614) was performed. Patients received a maximum of 6 $^{223}$Ra cycles and were retrospectively divided into the bPSMA or baseline CT (bCT) groups. All patients received baseline bone scintigraphy. Primary endpoints were alkaline phosphatase and prostate-specific antigen response. Secondary endpoints were overall survival (OS) and radiologic response. **Results:** Between 2017 and 2020, 122 mCRPC patients were included: 18 (14.8%) in the bPSMA group and 104 (85.2%) in the bCT group. All baseline characteristics were comparable. No significant differences in alkaline phosphatase or prostate-specific antigen response were found. The bCT group showed an OS significantly shorter than that of the bPSMA group (12.4 vs. 19.9 mo, $P = 0.038$). In 31 of 76 patients (40.1%) in the bCT group who also received posttherapy CT, lymph node or visceral metastases (soft-tissue involvement [STI]) were detected after $^{223}$Ra therapy, compared with 0 of 15 patients in the bPSMA group who received posttherapy PSMA PET/CT or CT. No significant difference in OS was found between patients in the bCT or posttherapy CT subgroup without STI (46/76) and the bPSMA group. **Conclusion:** bPSMA versus CT does not seem to impact biochemical response during $^{223}$Ra therapy in mCRPC patients. Nevertheless, patients in the bCT group had a significantly shorter OS, most likely due to underdetection of STI in this group. Therefore, replacing bCT with PSMA PET/CT appears to be a valuable screening method for identifying patients who will benefit most from $^{223}$Ra therapy.

**Key Words:** $^{223}$Ra; computer tomography; castration-resistant prostate cancer; overall survival; PSMA PET/CT

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Metastatic castration-resistant prostate cancer (mCRPC) is characterized as prostate cancer progression despite adequate androgen-deprivation therapy (*1*). Bone metastases are prevalent in over 90% of end-stage mCRPC (*2,3*) and a leading factor in skeleton-related events (SREs), morbidity, and mortality (*4,5*). Symptomatic bone metastases can be treated with $^{223}$Ra-dichloride ($^{223}$Ra), a radionuclide that actively incorporates into metastatic lesions, where it emits α-particles that induce tumor cell death (*6,7*). The phase 3 ALSYMPCA trial demonstrated that treatment with $^{223}$Ra compared with placebo significantly prolonged overall survival (OS), led to a more frequent decline in alkaline phosphatase (ALP), enhanced quality of life, and presented fewer SREs (*8–11*). $^{223}$Ra therapy should be withheld in patients with extensive malignant lymphadenopathy or visceral metastases (*12,13*), of which the latter is observed in up to 32% of mCRPC patients (*3*). Therefore, baseline imaging plays a crucial role in assessing eligibility for $^{223}$Ra therapy and currently consists of either baseline CT (bCT) or prostate-specific membrane antigen (PSMA) PET/CT, in addition to bone scintigraphy (*12,14*). PSMA PET/CT has a higher diagnostic sensitivity and specificity for detecting pelvic nodal or distant metastases than CT (*15–17*) and has been shown to be able to detect previously unknown visceral metastases in a small cohort of mCRPC patients who underwent screening for $^{223}$Ra therapy (*18*). To our knowledge, there is only one retrospective study available evaluating the impact

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of baseline PSMA PET/CT (bPSMA) compared with CT on outcomes of $^{223}$Ra therapy, and this study suggested that staging with PSMA PET/CT results in better therapeutic responses with greater declines in ALP and prostate-specific antigen (PSA) because of better patient selection (*19*). On the basis of the hypothesis that the higher diagnostic accuracy of PSMA PET/CT will lead to better patient selection and therefore outcomes of the proposed treatment, we studied the impact of bPSMA versus CT on outcomes of $^{223}$Ra therapy in mCRPC patients.

## MATERIALS AND METHODS

### Study Design and Patient Population

We performed a secondary analysis of a prospective observational multicenter cohort study that evaluated mCRPC patients treated with $^{223}$Ra at 11 institutions throughout The Netherlands between April 2017 and July 2020 (NCT04995614) (*20*). Eligible patients had histologically proven mCRPC with symptomatic bone metastases and no visceral metastases. The study protocol was approved by the medical ethics committee (CMO 2017-3220) and the institutional review boards of all participating centers. Informed consent was obtained from all individual patients.

### Study Procedures and Follow-up

Patients were treated with $^{223}$Ra according to the standard of care at a dose of 55 kBq/kg of body weight injected intravenously every 4 wk, with a maximum of 6 injections. Every patient received a baseline bone scintigraphy to determine the extent and localization of bone metastases. Additionally, every patient received a contrast-enhanced high-dose CT of the thorax and abdomen or a low-dose $^{68}$Ga-PSMA-11 or $^{18}$F-PSMA-1007 PET/CT from the top of the skull down to the mid thigh to detect soft-tissue involvement (STI), defined as lymph or visceral node metastases. The choice for baseline imaging modality was made according to local standard clinical care in the respective hospitals. Baseline imaging was performed no more than 12 wk before the start of therapy. At least 1 wk before every $^{223}$Ra injection, laboratory evaluation was performed. Laboratory evaluation and posttherapy imaging (bone scintigraphy combined with either CT or PSMA PET/CT) were performed 4–8 wk after the last injection. All patients were followed until death or March 3, 2023.

### Subgroup Categorization

Patients were retrospectively allocated to the bPSMA or bCT group on the basis of imaging modality before $^{223}$Ra therapy. Additionally, patients were retrospectively allocated to the posttherapy PSMA PET/CT (pPSMA) or posttherapy CT (pCT) subgroups.

### Study Outcomes

The primary endpoint was biochemical response, defined as at least a 30% decline in ALP or PSA level from baseline during $^{223}$Ra therapy, as described in the ALSYMPCA trial (*9*). Any decline in PSA level from baseline during treatment was determined. ALP and PSA superresponders were defined as patients with at least a 50% decline from baseline during treatment.

Secondary endpoints were the best percentage change in ALP or PSA response from baseline during treatment, radiologic response, occurrence of SREs, and OS. Radiologic response after $^{223}$Ra therapy was evaluated by monitoring the presence of newly detected STI. Only patients who received identical baseline and posttherapy imaging techniques were eligible for radiologic response evaluation. RECIST version 1.1, the Prostate Cancer Working Group 3 criteria, and the PSMA PET progression criteria were used (*21–23*). SREs were defined as surgery or radiotherapy to the bone, spinal cord compression, and symptomatic pathologic fractures (*22*). OS was defined as the time from the start of $^{223}$Ra therapy to the date of death from any cause or the date of the last follow-up.

### Data Analysis

Statistical analysis was performed for the total cohort and the subgroups. Subgroups were compared using $\chi^2$ and Mann–Whitney $U$ tests for categoric and continuous variables, respectively. OS was analyzed for subgroups using Kaplan–Meier curves and the log-rank test. A 2-sided $P$ value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 27.0 (IBM Corp.), and figures were created using GraphPad Prism 9.0 (GraphPad Software Inc.).

## RESULTS

### Patient Characteristics

Of the 122 included patients, 18 patients (14.8%) underwent bPSMA and 104 patients (85.2%) underwent bCT imaging (Table 1). All patients received a baseline bone scintigraphy. Seventy-seven patients (63.1%) completed the full course of 6 $^{223}$Ra cycles. No significant differences in any of the baseline characteristics were found between the 2 groups.

### Biochemical Response

No significant differences in biochemical responses were found between the bPSMA and bCT groups (Table 2). ALP responses were found in 55.6% of bPSMA patients versus 62.5% of bCT patients ($P = 0.576$). More ALP superresponders were found in the bPSMA group than in the bCT group (50.0% vs. 28.8%, respectively; $P = 0.076$). In the bPSMA group, more patients had some PSA response than in the bCT group (44.4% vs. 29.8%, respectively; $P = 0.219$).

### Radiologic Response

Eleven of 18 bPSMA patients (61.1%) also received a pPSMA (bPSMA/pPSMA subgroup) (Fig. 1). Seventy-six of 104 bCT patients (73.1%) also received a pCT (bCT/pCT subgroup). Patients switched from bPSMA to pCT in 4 of 18 cases (22.2%) and from bCT to pPSMA in 7 of 104 cases (6.7%).

No significant differences were found in any of the baseline characteristics between the bPSMA/pPSMA and bCT/pCT subgroups (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). None of the 15 bPSMA patients who received posttherapy imaging were found to have newly detected STI. In 31 of 76 (40.1%) bCT/pCT patients, STI was newly detected after therapy (Table 3), with visceral metastases being detected in 16 patients (51.6%) and lymph node metastases in 20 patients (64.5%). In retrospect, small visceral metastases were already visible on bCT imaging in 2 patients. Among the bCT/pPSMA patients, newly detected STI was found in 6 of 7 patients (85.7%), with visceral metastases being detected in 4 patients (66.7%) and lymph node metastases in 6 patients (100%).

### SREs

SREs occurred during and after $^{223}$Ra therapy in 6 of 18 (36.4%) and 30 of 104 (28.8%) patients of the bPSMA and bCT groups, respectively ($P = 0.700$). External-beam radiotherapy to relieve skeletal symptoms was the most common SRE (61.5%) (Supplemental Table 2).

### OS

Median OS for the total cohort was 12.8 mo (95% CI, 3.3–46.4 mo). Patients in the bPSMA group had a significantly longer median OS of 19.9 mo (95% CI, 3.1 mo to not reached) than

**TABLE 1**
Baseline Patient Demographics and Clinical Characteristics

| Parameter | Total cohort ($n$ = 122) | bPSMA group ($n$ = 18) | bCT group ($n$ = 104) | $P$ |
|---|---|---|---|---|
| Age (y) | 73.1 (65.2–78.3) | 70.8 (63.7–76.2) | 73.2 (65.7–78.6) | 0.392 |
| Gleason score ≥ 8 | 80 (65.6) | 12 (66.7) | 68 (65.4) | 0.957 |
| Gleason score missing | 1 (0.8) | 0 (0) | 1 (1.0) | |
| ECOG performance score | | | | |
| ECOG 0 | 51 (41.8) | 8 (44.4) | 43 (41.3) | 0.161 |
| ECOG 1 | 53 (43.4) | 5 (27.8) | 48 (46.2) | |
| ECOG 2 and 3 | 18 (14.8) | 5 (27.8) | 13 (12.5) | |
| Prior SRE | 55 (45.1) | 11 (61.1) | 44 (42.3) | 0.139 |
| Prior life-prolonging drugs | | | | |
| Enzalutamide or abiraterone | 97 (79.5) | 15 (83.3) | 82 (78.8) | 0.663 |
| Docetaxel | 74 (60.7) | 6 (33.3) | 40 (38.50 | 0.679 |
| Cabazitaxel | 18 (14.8) | 11 (61.1) | 63 (60.6) | 0.966 |
| $^{177}$Lu-PSMA radioligand therapy | 1 (0.8) | 0 (0) | 1 (1.0) | 0.676 |
| None | 12 (9.8) | 2 (11.1) | 10 (9.6) | 0.844 |
| Time mCRPC to $^{223}$Ra (mo) | 21.4 (10.4–41.6) | 20.2 (7.4–46.2) | 21.8 (10.5–41.6) | 0.724 |
| Time since start last treatment to $^{223}$Ra (mo) | 10.5 (6.9–16.0) | 11.5 (5.6–16.7) | 10.4 (6.9–15.9) | 0.910 |
| Time since start last treatment to $^{223}$Ra missing (mo) | 20 (16.4) | 3 (16.7) | 17 (16.3) | |
| Time baseline imaging to $^{223}$Ra (mo) | 0.89 (0.66–1.58) | 1.02 (0.74–1.77) | 0.84 (0.67–1.57) | 0.154 |
| Hemoglobin (mmol/L) | 7.8 (7.3–8.3) | 7.9 (7.4–8.3) | 7.8 (7.3–8.3) | 0.908 |
| Lactate dehydrogenase (U/L) | 233.5 (204.0–280.0) | 222.5 (202.8–259.8) | 236.0 (206.0–287.3) | 0.494 |
| ALP (U/L) | 142 (102.0–233.5) | 136.0 (91.0–179.3) | 143.5 (102.8–241.8) | 0.495 |
| PSA (ng/mL) | 87.9 (29.4–256.3) | 99.5 (31.8–206.3) | 85.4 (27.4–257.5) | 0.718 |
| Lymph node metastases (≥15 mm) | 17 (13.9) | 3 (16.7) | 14 (13.5) | 0.717 |
| Extent of bone metastases | | | | |
| Low volume (<6 metastases) | 15 (12.3) | 4 (22.2) | 11 (10.6) | 0.655 |
| Intermediate volume (6–20 metastases) | 33 (27.0) | 2 (11.1) | 31 (29.8) | |
| High volume (>20 metastases) | 62 (50.8) | 12 (66.7) | 50 (48.1) | |
| Superscan | 12 (9.8) | 0 (0) | 12 (11.5) | |
| No. administered $^{223}$Ra injections | | | | |
| 1 − 3 | 22 (18.0) | 2 (11.1) | 20 (19.2) | 0.694 |
| 4 and 5 | 23 (18.9) | 4 (22.2) | 19 (18.3) | |
| 6 | 77 (63.1) | 12 (66.7) | 65 (62.5) | |
| Cause of discontinuation* | | | | |
| End of therapy | 77 (63.1) | 12 (66.7) | 65 (62.5) | 0.649 |
| Progression of disease | 28 (23.0) | 3 (16.7) | 25 (24.0) | |
| Myelotoxicity | 10 (8.2) | 2 (11.1) | 5 (4.8) | |
| Other | 7 (5.7) | 1 (5.6) | 9 (8.7) | |
| Death | 0 (0) | 0 (0) | 0 (0) | |
| Opioid use | 55 (45.1) | 7 (38.9) | 48 (46.2) | 0.567 |
| Bone health agent use | 82 (67.2) | 11 (61.1) | 71 (68.3) | 0.550 |
| Denosumab† | 57/82 (69.5) | 7/11 (63.6) | 50/71 (70.4) | |
| Bisphosphonates† | 25/82 (30.5) | 4/11 (36.4) | 21/71 (29.6) | |

*Data summarized according to most important reason for discontinuation, with progression of disease being most important followed by myelotoxicity. Other causes of discontinuation included pain, SRE, adverse events, and patient wish.

†Data are number and valid percentage. Valid percentage is calculated percentage in case of subgroup analyses.

ECOG = Eastern Cooperative Oncology Group.

Qualitative data are number and percentage. Continuous data are median and interquartile ranges.

**TABLE 2**
Biochemical Response During $^{223}$Ra Therapy for Total Cohort and bPSMA and bCT Groups

| Parameter | Total cohort ($n$ = 122) | bPSMA group ($n$ = 18) | bCT group ($n$ = 104) | $P$ |
|---|---|---|---|---|
| ALP | | | | |
| Best response* (%) | −36.4 (−53.5 to −19.1) | −47.9 (−56.4 to −0.8) | −35.8 (−53.1 to −23.7) | 0.963 |
| Response*, decline ≥ 30% | 75 (61.5) | 10 (55.6) | 65 (62.5) | 0.576 |
| Superresponse*, decline ≥ 50% | 39 (32.0) | 9 (50.0) | 30 (28.8) | 0.076 |
| PSA | | | | |
| Best response* (%) | 19.8 (−10.5 to 69.7) | 1.1 (−15.3 to 52.6) | 21.5 (−6.1 to 73.6) | 0.486 |
| Any response*, any decline | 39 (32.0) | 8 (44.4) | 31 (29.8) | 0.219 |
| Response*, decline ≥ 30% | 18 (14.8) | 2 (11.1) | 16 (15.4) | 0.637 |
| Superresponse*, decline ≥ 50% | 10 (8.2) | 0 (0) | 10 (9.6) | 0.170 |

*ALP and PSA responses are compared with baseline. Negative value indicates decline in ALP or PSA values during or after $^{223}$Ra therapy.

Qualitative data are number and percentage. Continuous data are median and interquartile ranges in IU/L for ALP and ng/mL for PSA.

did those in the bCT group (12.4 mo, 95% CI, 3.3–37.2 mo; $P$ = 0.038) (Fig 2A).

In an exploratory analysis, OS was compared for patients in the bCT/pCT subgroup with and without newly detected STI after therapy. The patients in the bCT/pCT subgroup with newly detected STI had a significantly shorter OS than that in those without newly detected STI (median OS, 10.6 vs. 14.9 mo, respectively; $P < 0.01$) (Table 3; Fig. 2B). No significant OS difference was found between the bCT/pCT subgroup without newly detected metastases and the overall bPSMA group ($P$ = 0.456).

## DISCUSSION

In this prospective cohort study, we investigated the impact of bPSMA versus bCT on the outcomes of $^{223}$Ra therapy in mCRPC patients. Patients who received bCT had a significantly shorter OS than those who underwent bPSMA. We did not observe significant differences in biochemical response rates.

Our study found ALP and PSA responses similar to those in the ALSYMPCA trial and previous retrospective studies on $^{223}$Ra therapy in mCRPC patients (*8,24–26*). To date, only Ahmadzadehfar et al. reported outcomes on biochemical response during $^{223}$Ra therapy based on different baseline imaging modalities (*26*). In this study, both ALP and PSA response rates were significantly higher when using bPSMA than when using bCT. Although we did not observe significant differences, the bPSMA group showed more ALP superresponders and PSA responses (any decline) than did the bCT group.

Overall, the OS of 12.8 mo found in our study is in line with other real-world studies evaluating $^{223}$Ra therapy (*20,27*). We found a remarkably longer median OS for patients in the bPSMA

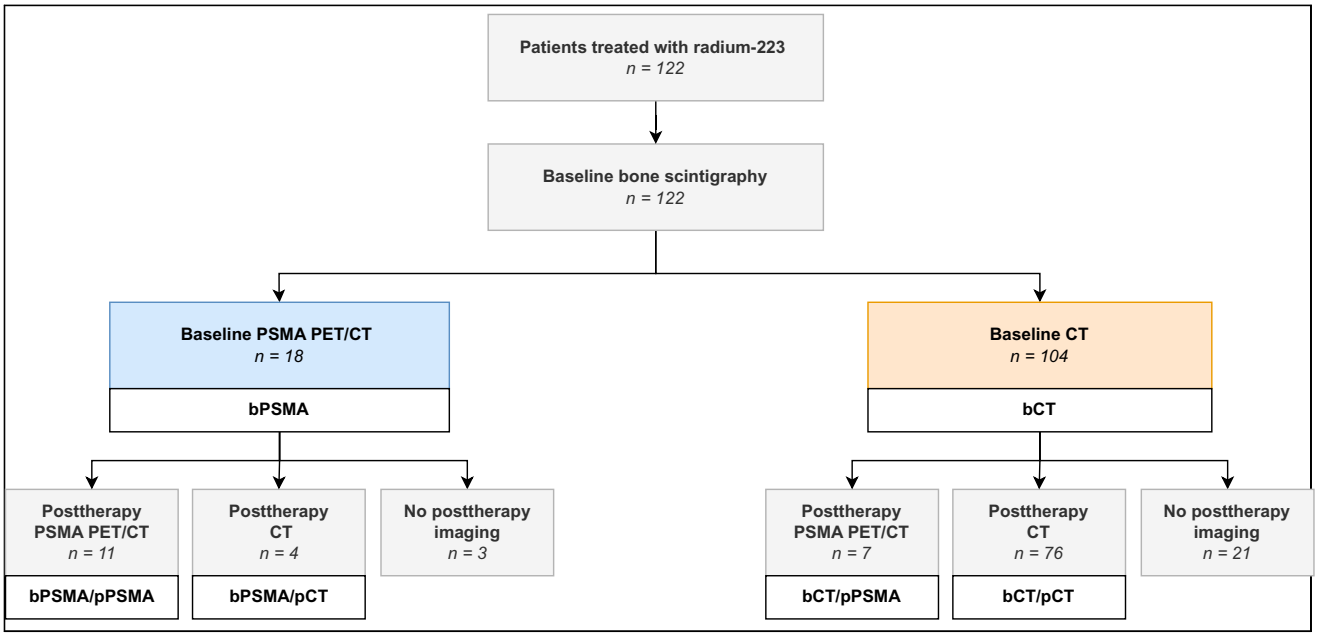


**FIGURE 1.** CONSORT (Consolidated Standards of Reporting Trials) diagram. Stratification of study population was based on baseline and posttherapy imaging methods used for radiologic response evaluation.

**TABLE 3**
OS Among Subgroups

| Baseline imaging | Posttherapy imaging | *n* | OS (mo) | *P* |
|---|---|---|---|---|
| bPSMA | Total | 18 | 19.9 (12.7–29.0) | 0.038 vs. bCT |
| | pPSMA | 11/18 | | |
| | STI | 0/11 | | |
| | No STI | 11/11 | 21.2 (6.7–NR) | |
| | pCT | 4/18 | | |
| | STI | 0/4 | | |
| | No STI | 4/4 | 20.3 (13.8–NR) | |
| | No imaging | 3/18 | 4.9 (3.1–NR) | |
| bCT | Total | 104 | 12.4 (7.9–18.2) | 0.038 vs. bPSMA |
| | pPSMA | 7/104 | 16.0 (12.4–23.2) | |
| | STI | 6/7 | 14.6 (8.9–NR) | |
| | No STI | 1/7 | 21.5 (NR) | |
| | pCT | 76/104 | 12.7 (8.4–20.4) | |
| | STI | 31/76 | 10.6 (2.9–35.0) | <0.01 vs. bCT/pCT no STI |
| | No STI | 45/76 | 14.9 (5.9–54.8) | 0.456 vs. bPSMA |
| | No imaging | 21/104 | 9.2 (1.6–45.7) | |

NR = not reached.
OS data are median and 95% CI.

group than for patients in the bCT group (19.9 vs. 12.4 mo, respectively), whereas all baseline characteristics were comparable. The most probable explanation for this finding is the absence of newly detected STI in any of the 15 patients in the bPSMA/pPSMA and bPSMA/pCT subgroups, whereas STI was frequently detected after therapy in the bCT/pCT and bCT/pPSMA subgroups (40.1% and 85.7%, respectively). Our exploratory analysis confirmed a significant difference in OS between bCT/pCT patients with and without newly detected STI after therapy. Conversely, the OS of patients in the bCT/pCT subgroup without newly detected STI did not significantly differ from the OS of the bPSMA group. These findings are supported by data in the literature that suggest mCRPC patients with visceral metastases have a significantly shorter OS than patients without visceral metastases (*28,29*).

It seems unlikely that the newly detected STI after treatment in the bCT group was not already present at the start of $^{223}$Ra therapy, since development of visceral disease takes approximately 1.6 y from CRPC diagnosis (*3*). In retrospect, the posttherapy-detected STI was already visible at the bCT in 2 patients. We encountered a lower proportion of patients with a PSA decline in the bCT group than in the bPSMA group, possibly due to the presence of STI (*3*). The presumed underdetection of STI at the start of $^{223}$Ra therapy in the bCT group might have caused the treatment to be less effective. However, as there was no control group, our results may still be explained by the natural history of the disease and unrelated to $^{223}$Ra therapy itself.

Our study has several limitations that should be considered when interpreting the results. The retrospective allocation of patients into the bPSMA and bCT groups might have led to selection bias. However, the groups did not significantly differ in any of the baseline characteristics, and the baseline imaging modality choice was made according to local standards of care in the respective hospitals. To the best of our knowledge, patient characteristics did not influence the imaging modality of choice. In addition, none of the patients received both imaging modalities at baseline. Furthermore, the small sample size of the subgroups may have contributed to the lack of statistical significance in biochemical response analyses. Because of these limitations, conclusions should be drawn with caution.

Our study fills a gap of knowledge as little research has been done on the impact of using PSMA PET/CT instead of CT when selecting mCRPC patients for $^{223}$Ra therapy. To our knowledge, our population is the largest cohort of patients addressing this research question. It is probable that the OS benefit associated with PSMA PET/CT as a therapeutic eligibility assessment modality can be extrapolated to other therapies for metastatic prostate cancer. Patients who might benefit less from $^{223}$Ra monotherapy because of the presence of STI may be redirected to other treatments, such as the combination of docetaxel plus $^{223}$Ra therapy (DORA trial, NCT03574571). Additionally, the outcomes of this study raise the question whether existing evidence-based guidelines are still valid for current daily practice, as PSMA PET/CT appears to become a potential replacement of CT in the management of mCRPC. For instance, a recently published article on the use of $^{68}$Ga-PSMA PET/CT for response evaluation of $^{223}$Ra therapy demonstrated that total tumor volume within the bone at baseline $^{68}$Ga-PSMA PET/CT was associated with treatment response and development of extraosseous disease during treatment (*30*). This emphasizes the need for prospective randomized clinical trials, preferably incorporating masking of the practitioner, to assess the impact of PSMA PET/CT compared with CT on therapeutic choices and outcomes (*31*).

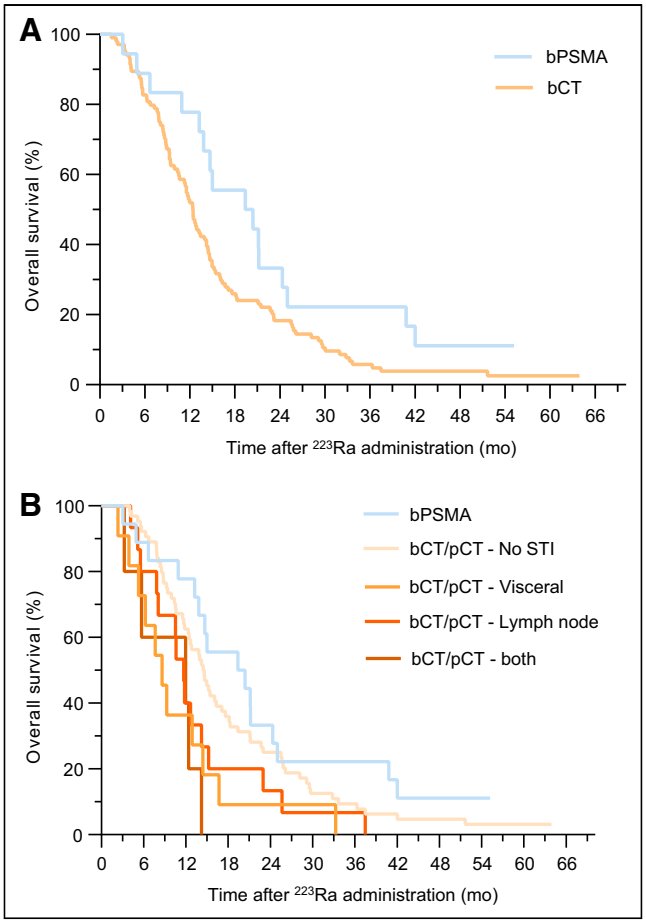


**FIGURE 2.** OS among subgroups: OS of bPSMA and bCT groups (A) and OS of bPSMA and bCT/pCT subgroups (B). Latter are divided into further subgroups: without STI, with lymph node metastases, with visceral metastases, and with both lymph node and visceral metastases.

## CONCLUSION

bPSMA does not appear to be a strong predictor of biochemical response during $^{223}$Ra therapy when compared with CT. However, patients who underwent bCT had a significantly shorter OS, most likely due to underdetection of STI before the start of $^{223}$Ra therapy. Therefore, replacing bCT with bPSMA appears to be a valuable screening method to identify the patients who will benefit most from $^{223}$Ra therapy.

## DISCLOSURE

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**KEY POINTS**

**QUESTION:** How does using PSMA PET/CT instead of CT to select patients for $^{223}$Ra therapy impact the outcome?

**PERTINENT FINDINGS:** In this prospective cohort study, we found a significantly longer median OS for patients who received bPSMA compared than for those who received bCT, most likely due to underdetection of STI at the start of $^{223}$Ra therapy.

**IMPLICATIONS FOR PATIENT CARE:** PSMA PET/CT appears to be a valuable screening method to identify the patients who will benefit most from $^{223}$Ra therapy.

## REFERENCES

1. Sartor O, de Bono JS. Metastatic prostate cancer. *N Engl J Med.* 2018;378:645–657.
2. Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol.* 2000;31:578–583.
3. Pezaro C, Omlin A, Lorente D, et al. Visceral disease in castration-resistant prostate cancer. *Eur Urol.* 2014;65:270–273.
4. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev.* 2001;27:165–176.
5. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer.* 2007;110:1860–1867.
6. Henriksen G, Breistøl K, Bruland ØS, Fodstad Ø, Larsen RH. Significant antitumor effect from bone-seeking, alpha-particle-emitting $^{223}$Ra demonstrated in an experimental skeletal metastases model. *Cancer Res.* 2002;62:3120–3125.
7. Suominen MI, Fagerlund KM, Rissanen JP, et al. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. *Clin Cancer Res.* 2017;23:4335–4346.
8. Sartor O, Coleman RE, Nilsson S, et al. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223. *Ann Oncol.* 2017;28:1090–1097.
9. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213–223.
10. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol.* 2014;15:738–746.
11. Nilsson S, Cislo P, Sartor O, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. *Ann Oncol.* 2016;27:868–874.
12. Poeppel TD, Handkiewicz-Junak D, Andreeff M, et al. EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2018;45:824–845.

13. Summary of product characteristics: Xofigo. European Medicines Agency website. https://www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_en.pdf. Published November 28, 2013. Updated October 30, 2023. Accessed February 5, 2024.
14. Parker C, Heidenreich A, Nilsson S, Shore N. Current approaches to incorporation of radium-223 in clinical practice. *Prostate Cancer Prostatic Dis.* 2018;21:37–47.
15. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet.* 2020;395:1208–1216.
16. Hope TA, Goodman JZ, Allen IE, Calais J, Fendler WP, Carroll PR. Metaanalysis of $^{68}$Ga-PSMA-11 PET accuracy for the detection of prostate cancer validated by histopathology. *J Nucl Med.* 2019;60:786–793.
17. Heinzel A, Boghos D, Mottaghy FM, et al. $^{68}$Ga-PSMA PET/CT for monitoring response to $^{177}$Lu-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2019;46:1054–1062.
18. Bräuer A, Rahbar K, Konnert J, Bögemann M, Stegger L. Diagnostic value of additional $^{68}$Ga-PSMA-PET before $^{223}$Ra-dichloride therapy in patients with metastatic prostate carcinoma. *Nucl Med (Stuttg).* 2017;56:14–22.
19. Ahmadzadehfar H, Azgomi K, Hauser S, et al. $^{68}$Ga-PSMA-11 PET as a gatekeeper for the treatment of metastatic prostate cancer with $^{223}$Ra: proof of concept. *J Nucl Med.* 2017;58:438–444.
20. van der Doelen MJ, Oving IM, Wyndaele DNJ, et al. Health-related quality of life, psychological distress, and fatigue in metastatic castration-resistant prostate cancer patients treated with radium-223 therapy. *Prostate Cancer Prostatic Dis.* 2023;26:142–150.
21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.
22. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016;34:1402–1418.
23. Fanti S, Hadaschik B, Herrmann K. Proposal for systemic-therapy response-assessment criteria at the time of PSMA PET/CT imaging: the PSMA PET progression criteria. *J Nucl Med.* 2020;61:678–682.
24. van der Doelen MJ, Stockhaus A, Ma Y, et al. Early alkaline phosphatase dynamics as biomarker of survival in metastatic castration-resistant prostate cancer patients treated with radium-223. *Eur J Nucl Med Mol Imaging.* 2021;48:3325–3334.
25. Badrising SK, Louhanepessy RD, van der Noort V, et al. A prospective observational registry evaluating clinical outcomes of radium-223 treatment in a nonstudy population. *Int J Cancer.* 2020;147:1143–1151.
26. Kuppen MC, Westgeest HM, van der Doelen MJ, et al. Real-world outcomes of radium-223 dichloride for metastatic castration resistant prostate cancer. *Future Oncol.* 2020;16:1371–1384.
27. Frantellizzi V, Monari F, Mascia M, et al. Validation of the 3-variable prognostic score (3-PS) in mCRPC patients treated with $^{223}$radium-dichloride: a national multicenter study. *Ann Nucl Med.* 2020;34:772–780.
28. Armstrong AJ, Garrett-Mayer E, de Wit R, Tannock I, Eisenberger M. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res.* 2010;16:203–211.
29. Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2014;32:671–677.
30. de Jong AC, Segbers M, Ling SW, et al. $^{68}$Ga-PSMA PET/CT for response evaluation of $^{223}$Ra treatment in metastatic prostate cancer. *J Nucl Med.* 2023;64:1556–1562
31. Kelly R, Jensen A, Karunaratna N, et al. Prostate-specific membrane antigen positron emission tomography-computed tomography use prior to systemic therapy in metastatic castration-resistant prostate cancer. *BJU Int.* 2023;131:179–182.