
Prognostic Factors in Patients Treated with ^{223}Ra : The Role of Skeletal Tumor Burden on Baseline ^{18}F -Fluoride PET/CT in Predicting Overall Survival

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The purpose of this study was to evaluate outcome after ^{223}Ra dichloride therapy (^{223}Ra) and to determine whether skeletal tumor burden on whole-body ^{18}F -fluoride PET/CT can be used as a predictive biomarker of survival in patients treated with ^{223}Ra . **Methods:** Forty-two patients with hormone-refractory prostate cancer underwent ^{223}Ra and a baseline fluoride PET/CT scan. Fluoride PET/CT parameters were generated, including maximum standardized uptake value (SUV_{max}) of the hottest lesion (hSUV_{max}), average SUV of disease (Mean_{10}), and skeletal tumor burden indices of total fluoride skeletal metastatic lesion uptake (TLF_{10}) and total volume of fluoride avid bone metastases (FTV_{10}). Overall survival (OS) was the primary endpoint. Secondary endpoints were progression-free survival and skeletal-related event (SRE). **Results:** Skeletal tumor burden indices (TLF_{10} and FTV_{10}) derived from fluoride PET/CT at baseline were highly correlated and significant independent predictors of OS ($P = 0.0212$; hazard ratio = 5.990; 95% confidence interval = 1.306–27.475). A TLF_{10} cutoff value of 8,000 discriminated survivors from nonsurvivors after ^{223}Ra (with TLF_{10} values < 8,000, the median OS was not estimated, whereas with $\text{TLF}_{10} > 8,000$, the median OS was 6.67 mo). Visual analysis, Mean_{10} , and hSUV_{max} were not predictors of OS or progression-free survival. Mean_{10} was found to be a significant univariate predictor of the odds of having an SRE ($P = 0.0445$; odds ratio = 1.30; 95% confidence interval = 1.006–1.681), with a Mean_{10} greater than 19 increasing the risk of SRE. **Conclusion:** Skeletal tumor burden on baseline fluoride PET/CT is a predictive biomarker of OS and the risk of an SRE in patients treated with ^{223}Ra .

Key Words: ^{223}Ra ; fluoride PET/CT; NaF PET/CT; prostate cancer; skeletal tumor burden

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Several treatment modalities are used to control metastatic bone pain or prevent skeletal-related events (SREs) from prostate cancer, such as radiotherapy, bisphosphonates, denosumab,

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^{153}Sm -ethylene diamine tetramethylene phosphonate, ^{223}Ra -dichloride therapy (^{223}Ra), and other bone-seeking agents; however, only ^{223}Ra has demonstrated improved survival (1–6).

In daily clinical practice, ^{18}F -FDG PET/CT whole-body metabolic imaging is widely performed for staging, restaging, identifying responders, and predicting survival (7–10) and as a biomarker to assess tumor burden (11–14). One of the advantages of ^{18}F -FDG PET/CT imaging is the ability to objectively quantify tumor metabolism, providing prognostic or predictive information (15–17).

Whole-body fluoride PET/CT bone imaging is ideal for staging and restaging prostate cancer patients because of greater sensitivity, specificity, and accuracy than conventional bone scintigraphy (18). Beyond lesion detection and staging, it is feasible to quantify skeletal tumor burden using fluoride PET/CT. Tumor burden determined by skeletal scintigraphy has been shown to differentiate responders from nonresponders with some therapies (19).

We hypothesized that skeletal tumor burden determined by fluoride PET/CT will be correlated with clinical outcomes in patients treated with ^{223}Ra . By this determination, it may be possible to identify patients who will not respond to ^{223}Ra , thus reducing morbidity and unnecessary costs.

The purposes of this study were to evaluate outcome after ^{223}Ra and the potential of fluoride PET/CT to determine whole-body skeletal tumor burden as a prognostic biomarker of survival in patients treated with ^{223}Ra .

MATERIALS AND METHODS

Study Design

This study was approved by the Institutional Review Board (PA14-0848). The Waivers of Informed Consent and Authorization were granted for the retrospective analysis. We reviewed castrate-resistant prostate cancer (CRPC) patients metastatic to bone treated with ^{223}Ra who underwent baseline fluoride PET/CT scanning.

Patient Population

Three hundred eighty-nine doses were administered to 76 patients. Forty-two patients (Table 1) underwent baseline fluoride PET/CT imaging. Additionally, 38 of these 42 patients also underwent baseline bone scintigraphy and another 32 patients underwent bone scanning exclusively (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>). Eleven patients (14.5%) had initial Hb levels below 10.0 g/dL and received blood transfusion before ^{223}Ra .

TABLE 1
Clinical Characteristics of Patients at Initial Presentation Before First ^{223}Ra Dose

| Characteristic | <i>n</i> (median) | % (range) |
|---|-------------------|-------------|
| Age (y) | 71.7 | 43–88 |
| Time of last chemotherapy cycle (wk) (<i>n</i> = 22) | 6.5 | 0.9–53.9 |
| Time of last EBRT (wk) (<i>n</i> = 6) | 5.5 | 0.9–53.9 |
| PSA ($\mu\text{g/L}$) | 54.0 | 1.0–1,778.0 |
| ALP (U/L) | 137 | 48.0–913.0 |
| Hemoglobin (g/dL) | 11.0 | 6.6–15.1 |
| Platelets (K/uL) | 187 | 114–413 |
| Absolute neutrophil (K/uL) | 4.51 | 1.5–21.4 |

EBRT = external-beam radiation therapy.

^{223}Ra

^{223}Ra -dichloride (Xofigo; Bayer) was administered per clinical standard of care to 76 patients. Patients received between 1 and 6 doses of ^{223}Ra (50 kBq/kg or 1.4 $\mu\text{Ci/kg}$) intravenously, at monthly intervals.

Fluoride PET/CT

Fluoride PET/CT scans were obtained after the intravenous injection of 158–370 MBq of ^{18}F -sodium fluoride. Images were acquired on average 50–60 min after injection, from the vertex of the skull to the feet, on dedicated PET/CT scanners (Discovery STe, RX, VCT, 16- or 64-channel [GE Healthcare] or mCT Flow, 64-channel [Siemens Healthcare]). CT parameters included 3.75- or 2-mm axial reconstruction and 120 kV or Care kV tube voltage modulation (GE Healthcare or Siemens systems, respectively). PET was acquired in

3-dimensional mode using either 3–5 min/bed position or continuous bed motion (1 mm/s) according to the scanner platform. Images were reconstructed and displayed in the transverse, coronal, and sagittal planes using a MIM Vista workstation (MIM Vista).

Fluoride PET/CT Interpretation and Quantification

Baseline fluoride PET/CT images were analyzed by both visual and quantitative analyses by 2 board-certified nuclear medicine physicians. Visual analysis consisted of separating into 5 categories the number of bone metastatic lesions (1–6 lesions, 6–20, 20–50, above 50, and super scan).

Quantitative interpretation (using the MIM Vista workstation) was performed on all baseline fluoride PET/CT images to determine whole-body skeletal tumor burden (20). Briefly, the technique consists of drawing a rectangular semiautomatic volume of interest (VOI) in the whole-body image with caution to encompass all metastatic sites. After the whole-body VOI is drawn, the maximum standardized uptake value (SUV_{max}) threshold is set at 10, which excludes 99% of all normal bone uptake. Subsequently, the computer automatically generates individual VOIs surrounding only regions with an SUV_{max} of 10 or greater. Images are evaluated to manually exclude any sites of high uptake not related to bone metastases (such as the urinary activity in the renal collecting system, degenerative disease, and healing fractures). Afterward, volumetric parameters of skeletal fluoride uptake are automatically obtained from the statistics generated with the final volumetric extraction. The following parameters are obtained: highest SUV_{max} among all the metastases (hSUV_{max}), mean SUV_{max} of all metastases (Mean_{10}), and skeletal tumor burden. The latter is determined by calculating the total fluoride skeletal metastatic uptake as a product of mean $\text{SUV} \times \text{VOI}_{10}$ (TLF_{10}) and the total volume of fluoride bone metastases (FTV_{10}). Figure 1 is an example of the calculation of the skeletal tumor burden.

Once the images have been carefully analyzed, the process of calculating tumor burden is extremely fast because it is a semiautomatic measure, and the physician is not required to draw VOIs on all metastatic sites because, by establishing the threshold value for SUV_{max} of 10, the VOIs will automatically encircle the lesions and exclude all normal bone. If the amount of degenerative processes is minimal, the calculation of tumor burden takes less than 5 min.

Visual Interpretation of Other Imaging Modalities

Visual interpretation of $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) bone scintigraphy consisted of separating the number of bone metastases into the same 5 categories as with fluoride PET/CT (19). Nodal and visceral metastases were assessed visually on the images available (^{18}F -FDG PET/CT, fluoride PET/CT, body CT scans, ultrasound, or MR imaging).

Statistical Analyses

The primary endpoint was overall survival (OS), established from initial ^{223}Ra dose until date of death from any cause or last follow-up. Secondary aims were progression free-survival (PFS) and time-to-bone event (TTBE). PFS was established from initial ^{223}Ra dose until date of objective tumor progression, death of any cause, or last follow-up. Objective tumor progression was defined as a new lesion or

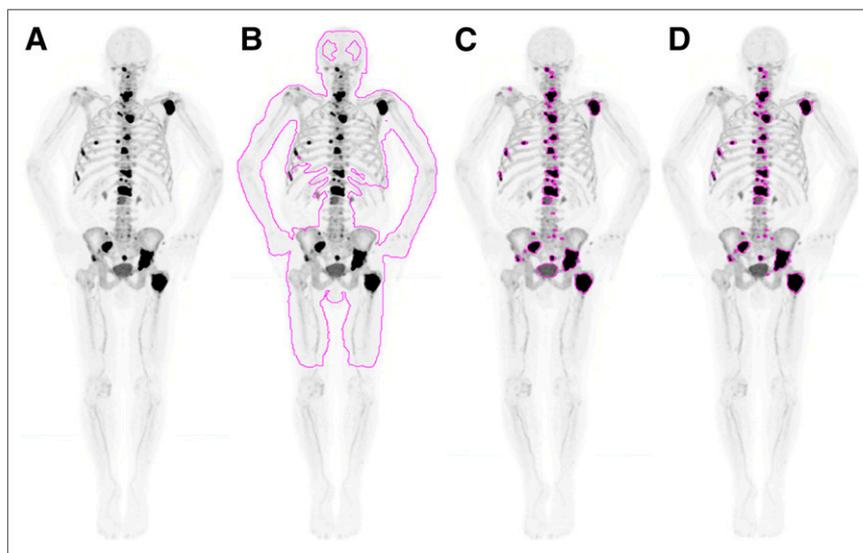


FIGURE 1. Calculation of hSUV_{max} , skeletal tumor burden (TLF_{10} and FTV_{10}), and Mean_{10} on fluoride PET/CT. (A) Fluoride PET/CT of CRPC patient being considered for ^{223}Ra . (B) Semiautomatic VOI is drawn in whole-body image. (C) With established threshold SUV_{max} of 10 or greater, all background activity is subtracted, leaving metastases and some nonmetastatic VOIs with high uptake. (D) All nonmetastatic VOIs (e.g., bladder and degenerative processes) are subtracted. Statistics demonstrate hSUV_{max} of 138 (L1 vertebral metastasis), TLF_{10} of 10,965, and Mean_{10} of 31.63. After 6 mo, patient developed multiple vertebral compression fractures and died after 8 mo.

a lesion that increased in size (Response Evaluation Criteria In Solid Tumors) in bone, node, or viscera leading to a change in current therapy or initiation of another therapy. TTBE was defined from initial ^{223}Ra dose until the date of a bone event (surgical intervention, spinal cord compression, pathologic fracture, bone pain, or rapid lesion progression requiring immediate intervention).

Frequencies and percentages were provided for categorical variables; mean (SD) and median (range) were provided for continuous variables. Kaplan–Meier survival curves demonstrated survival time distributions. Cox proportional hazards regression was used to analyze predictors of survival. Backward stepwise selection was performed for multivariable Cox models. Logistic regression modeled the odds of a bone event as a function of fluoride PET/CT variables. Spearman correlation assessed the amount of agreement between fluoride PET/CT variables. All statistical analyses were performed using SAS 9.3 for Windows (SAS Institute).

RESULTS

^{223}Ra Doses in Relation to OS, PFS, and TTBE

^{223}Ra doses were completed in 44 (57.9%) patients, 1 patient was still undergoing ^{223}Ra , and 31 (40.8%) patients did not complete all 6 doses because of either progression, hematologic toxicity, declining Eastern Cooperative Oncology Group (ECOG) status by 2 points, or a bone event (Table 2). The mean number of doses performed was 5 (median, 6 doses). The median OS time was 11.93 mo (95% confidence interval [CI] = 8.12–censored). The median PFS was 3.68 mo (95% CI = 3.02–5.09), and the median TTBE could not be estimated (only 6 patients had bone events) (Tables 3 and 4).

There was a significant correlation between OS and the number of ^{223}Ra doses administered, with improved survival in patients treated with a greater number of doses, especially in patients receiving all 6 doses. The number of ^{223}Ra doses was an independent predictor of OS, was beneficial, and reduced the risk of death.

Likewise, the risk of progression was lower in patients receiving more ^{223}Ra doses, and PFS was higher in patients who received all 6 doses. Additionally, more ^{223}Ra doses was an independent predictor of PFS. There was no correlation between TTBE and the continuous number of ^{223}Ra doses delivered to patients.

Visual Imaging Analysis in Relation to OS and PFS

Visual analyses were performed on 42 patients who underwent fluoride PET/CT and on 70 patients who underwent bone scintigraphy. Among these 70 patients, 32 underwent only bone scintigraphy and 38 underwent bone scintigraphy and fluoride PET/CT. There were no differences in the clinical characteristics among patients who underwent only bone scintigraphy versus patients who underwent both scans (Supplemental Table 2). OS strongly correlated with the presence of bone metastases on visual analysis only on fluoride PET/CT scans. On multivariate analysis, however, neither visual analysis of fluoride PET/CT scans nor the presence of nodal or visceral metastases were predictors of OS.

PFS had a strong correlation to visual analysis of both fluoride PET/CT and bone scintigraphy after ^{223}Ra and to the presence of nodal or visceral metastases. For example, patients with more than 50 bone metastases had twice the risk of progression when compared with a patient with fewer than 20 bone metastases. The risk of progression increased 2.7 times for patients with nodal metastases and 2.1 times for the presence of visceral metastases. However, on a multivariate model, only the presence of nodal metastases at initial diagnosis was a significant predictor of PFS ($P = 0.0080$).

Quantitative Imaging Analysis in Relation to OS, PFS, and TTBE

Quantitative analyses were performed on baseline fluoride PET/CT in 42 patients. The parameters Mean₁₀, hSUV_{max}, TLF₁₀, and FTV₁₀ were correlated to OS, PFS, and TTBE.

OS was strongly predicted by both TLF₁₀ and FTV₁₀. Because TLF₁₀ and FTV₁₀ were shown to be highly correlated ($\rho = 0.95$; $P < 0.0001$), all further analyses were performed solely with TLF₁₀ values. TLF₁₀ was shown to be significant independent predictor of OS. When establishing the TLF₁₀ cutoff value at 8,000 (Fig. 2), it was possible to generate survival curves and identify which patients would most likely benefit from ^{223}Ra . There were fewer than 50% of deaths with TLF₁₀ less than 8,000; thus, the median OS was not estimated (95% CI = 8.90–not estimated). However, with a TLF₁₀ greater than 8,000, the median OS was 6.67 mo (95% CI: 4.73–8.57). Mean₁₀ and hSUV_{max} were not predictors of OS.

PFS did not correlate with TLF₁₀, FTV₁₀, Mean₁₀, or hSUV_{max}.

Mean₁₀ was found to be a significant univariate predictor of the odds of having an SRE ($P = 0.0445$; odds ratio = 1.30; 95% CI = 1.006–1.681), with a Mean₁₀ greater than 19 increasing the risk of SRE (sensitivity = 0.83; specificity = 0.67). It was not possible to predict TTBE or the odds of having a bone event by TLF₁₀, FTV₁₀, or hSUV_{max}. Figure 3 shows an example of fluoride PET/CT skeletal tumor burden determination and patient outcome.

DISCUSSION

To our knowledge, this is the first study to demonstrate that volumetric semiautomatic quantification of whole-body skeletal tumor burden on fluoride PET/CT is an independent predictor of OS in CRPC patients treated with ^{223}Ra . OS has been shown to improve after ^{223}Ra in CRPC patients with bone metastases (1–3). We found that more ^{223}Ra doses were an independent predictor of OS, reducing the risk of death by 60% for each continuous increase in dose. However, although ^{223}Ra has been shown to improve survival, there is heterogeneity of response, with some patients showing limited or poor response.

As with any therapy, it is important to identify factors that may influence response. In the phase III study of ^{223}Ra in CRPC, improvements in time to first SRE and OS occurred in the ^{223}Ra arm (vs. placebo arm). Although time to total alkaline phosphatase (ALP) and prostate-specific antigen (PSA) progression and ALP response were significantly longer in the ^{223}Ra arm, unfortunately these markers were not predictors of response or predictors of OS. In our study, fluoride PET/CT skeletal tumor burden correlated with OS, similar to prior studies using ^{18}F -FDG PET/CT (21,22). Fluoride PET/CT skeletal tumor burden (TLF₁₀) with a cutoff value of 8,000 discriminated survivors from nonsurvivors after ^{223}Ra . The risk of death after ^{223}Ra was increased by 76.5% for each unit increase in TLF₁₀. Evaluation of target lesions with ^{18}F -FDG PET/CT have demonstrated strong correlation to OS (17,23–25). We were not able to predict OS, PFS, or TTBE by evaluation of a target lesion (hSUV_{max}), because patients had widespread metastases, whereas target lesions usually were applicable for evaluation of the primary tumor.

Although previous reports have demonstrated the ability of predicting OS with bone scintigraphy, either visually or semi-quantitatively, this can be a time-consuming process (19,26,27). Visual analysis of fluoride PET/CT and $^{99\text{m}}\text{Tc}$ -MDP bone scinti-

TABLE 2
Demographics and Clinical Characteristics of 42 Patients at Initial Presentation Before First ²²³Ra Dose

| Characteristic | <i>n</i> | % | Range |
|---|----------|------|-------------|
| ²²³ Ra doses (<i>n</i> = 201) | | | |
| Completed | 19 | 45.2 | |
| In progress | 1 | 2.4 | |
| Stopped | 22 | 52.4 | |
| Gleason score | | | |
| 10–8 | 27 | 64.3 | |
| 7–6 | 14 | 33.3 | |
| NA | 6 | 14.3 | |
| Tumor stage | | | |
| T4 | 0 | 0 | |
| T3 | 23 | 54.7 | |
| T2 | 4 | 9.6 | |
| NA | 15 | 35.7 | |
| Clinical stage | | | |
| IV | 16 | 38.1 | |
| III | 20 | 47.6 | |
| IIB | 4 | 9.5 | |
| NA | 2 | 4.8 | |
| Eastern Cooperative Oncology Group performance status | | | |
| 0 | 10 | 24.4 | |
| 1 | 15 | 36.6 | |
| 2 | 12 | 29.3 | |
| 3 | 4 | 9.8 | |
| 4 | 0 | 0.0 | |
| World Health Organization pain scale | | | |
| 0 | 13 | 31.7 | |
| 1 | 7 | 17.1 | |
| 2 | 16 | 39.0 | |
| 3 | 5 | 12.2 | |
| 4 | 0 | 0.0 | |
| Additional data | | | |
| Age (y) | 71.7 | | 43–88 |
| Time of last chemotherapy cycle (wk) (<i>n</i> = 22) | 6.5 | | 0.9–53.9 |
| Time of last EBRT (wk) (<i>n</i> = 6) | 5.5 | | 0.9–53.9 |
| PSA (μg/L) | 54.0 | | 1.0–1,778.0 |
| ALP (U/L) | 137 | | 48.0–913.0 |
| Hemoglobin (g/dL) | 11.0 | | 6.6–15.1 |
| Platelets (K/uL) | 187 | | 114–413 |
| Absolute neutrophil (K/uL) | 4.51 | | 1.5–21.4 |

NA = Data not available; EBRT = external-beam radiation therapy.

graphy demonstrated that only fluoride PET/CT scans were a significant univariate predictor of OS (visual analysis of ^{99m}Tc-MDP scans were not, although there was a tendency [*P* = 0.0871] in patients with multiple metastases). Possibly we did not reach statistical significance in bone scanning because of the small number of

patients studied. On the other hand, fluoride PET/CT imaging has a high impact on management of CRPC patients when compared with body CT or MR imaging (28). In addition, ¹⁸F-fluoride uptake is 2-fold higher than ^{99m}Tc-MDP, leading to improved lesion detectability (29,30). Furthermore, although fluoride PET/CT

TABLE 3
Correlation to OS

| Variable | Hazard ratio | 95% CI | P |
|---|--------------|--------------|---------|
| Univariate | | | |
| Total no. of ²²³ Ra doses | 0.397 | 0.292–0.539 | <0.0001 |
| All six ²²³ Ra doses vs. < six doses | 0.158 | 0.069–0.358 | <0.0001 |
| Nodal metastases | 1.829 | 0.830–4.031 | 0.1342 |
| Visceral metastases | 1.874 | 0.798–4.405 | 0.1496 |
| Visual analysis | | | |
| Fluoride PET/CT scan | | | |
| 20–50 | – | – | – |
| >50 | 2.520 | 0.507–12.530 | 0.2587 |
| Super scan | 7.484 | 1.557–35.979 | 0.0120 |
| Bone scan | | | |
| 20–50 | – | – | – |
| >50 | 2.619 | 0.869–7.891 | 0.0871 |
| Super scan | 1.360 | 0.501–3.690 | 0.5466 |
| Qualitative analysis | | | |
| TLF ₁₀ | 1.765 | 1.038–3.001 | 0.0361 |
| FTV ₁₀ | 1.920 | 1.111–3.317 | 0.0194 |
| hSUVmax | 1.003 | 0.983–1.022 | 0.7989 |
| Mean ₁₀ | 0.928 | 0.795–1.083 | 0.3443 |
| Multivariate | | | |
| Total no. of ²²³ Ra doses | 0.386 | 0.252–0.591 | <0.0001 |
| All six ²²³ Ra doses vs. < six doses | 0.120 | 0.034–0.427 | 0.0011 |
| TLF ₁₀ | 5.990 | 1.306–27.475 | 0.0212 |

has a higher cost, acquisition time is faster and spatial resolution higher, and images may be acquired earlier (31–33). All these factors lead to a better performance of fluoride PET/CT to detect bone lesions and to define equivocal bone metastases (18,34,35). For

example, in our patient population, among the cases in which fluoride PET/CT detected above 20 bone metastases, bone scintigraphy detected less in 63% of the patients, although we cannot be certain if this difference of lesion detectability could affect

TABLE 4
Correlation to PFS

| Variable | Hazard ratio | 95% CI | P |
|---|--------------|-------------|---------|
| Univariate | | | |
| Total no. of ²²³ Ra doses | 0.447 | 0.340–0.587 | <0.0001 |
| All six ²²³ Ra doses vs. < six doses | 0.359 | 0.213–0.603 | 0.001 |
| Nodal metastases | 2.749 | 1.429–5.286 | 0.0024 |
| Visceral metastases | 2.167 | 1.081–4.345 | 0.0293 |
| Qualitative analysis | | | |
| TLF ₁₀ | 1.081 | 0.772–1.515 | 0.6486 |
| FTV ₁₀ | 1.104 | 0.775–1.573 | 0.5825 |
| hSUVmax | 1.005 | 0.993–1.017 | 0.4308 |
| Mean ₁₀ | 0.977 | 0.902–1.057 | 0.5608 |
| Multivariate | | | |
| Total no. of ²²³ Ra doses | 0.456 | 0.344–0.603 | <0.0001 |
| Nodal disease | 2.451 | 1.264–4.756 | 0.0080 |

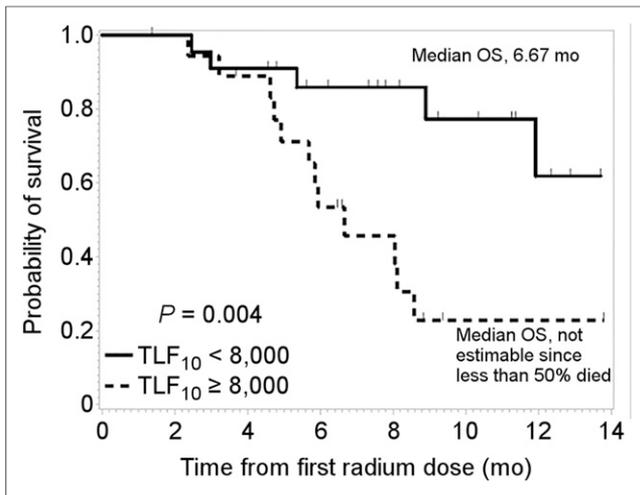


FIGURE 2. OS according to TLF₁₀ on fluoride PET/CT.

patient management. However, because visual analysis of fluoride PET/CT was not an independent predictor of OS, the findings in our study support the idea that objective skeletal tumor burden quantification is an important parameter to independently predict OS.

Bone-related laboratory parameters in CRPC patients have also been described as predictors of survival (36). Worse survival has been associated with ALP greater than 146 U/L, pain score greater than 3, SREs, PSA greater than 10 ng/mL, hemoglobin less than 12.8 g/dL, visceral metastases, ECOG greater than 1, and older age. In our patient group, we did not evaluate these parameters because our cohort was composed of patients in whom most of these parameters already indicated advanced disease. Among the patients with a TLF₁₀ greater than 8,000, PSA levels were high in 83% (mean = 211 ng/mL). Interestingly, though, 4 patients in our study had a PSA less than 10 ng/mL, with surprisingly high TLF₁₀ (>8,000). One patient had a PSA of 2.3 ng/mL with a TLF₁₀ of 22,969 whereas the other had a PSA of 7.5 ng/mL with a TLF₁₀ of 25,841, both having deceased after 5 mo of beginning ²²³Ra. ALP may reflect more accurately than PSA levels the extent of bone disease (37); however, in our study, 9 patients with an ALP less than 146 U/L had a TLF₁₀ greater than 8,000 and 6 of them were deceased after an average of 6.9 mo. In addition, as with other studies, visceral and nodal metastases were also univariate predictors of OS. Because the number of ²²³Ra doses in itself is a strong predictor of OS, the fact that skeletal tumor burden was an even a stronger predictor establishes fluoride PET/CT as an important imaging modality to guide treatment strategies, combined with laboratory results, which sometimes may be misleading.

Many of the patients progressed during ²²³Ra (median time to progression = 3.68 mo). We found that the risk of progression (including death) was reduced by 55.3% with more ²²³Ra doses, and patients who received all 6 doses had a 65% reduction of PFS. Although it seems logical that PFS would be longer in patients who received more ²²³Ra doses in comparison to those who did not receive doses because of death, this was not the case. Among the patients who progressed during ²²³Ra, only 20% died immediately after ²²³Ra, whereas the other 80% continued ²²³Ra (with the addition of chemotherapy) or discontinued ²²³Ra (and were



FIGURE 3. Baseline fluoride PET/CT images of patient with castrate-resistant prostate cancer prior to ²²³Ra show widespread bone metastases (PSA = 36.0 ng/mL and ALP = 109 U/L). Skeletal tumor burden measurements were: TLF₁₀ = 14,643 and Mean₁₀ = 21.1. Patient developed compression fracture after 2 mo of ²²³Ra and died after 4 mo.

switched to chemotherapy). Those patients who continued ²²³Ra benefitted from more doses as opposed to those who discontinued the treatment. We did not find a correlation between skeletal tumor burden and PFS. On the other hand, nodal or visceral metastases were strong univariate predictors of shorter PFS, which could be expected, because ²²³Ra does not target extraskelatal metastases. However, on a multivariate analysis, only the presence of nodal metastases at the first ²²³Ra treatment was an independent predictor of shorter PFS. Because chemotherapy and hormonal therapy has improved OS of prostate cancer patients with visceral metastases (38–41), our patients with visceral metastases were treated with combination ²²³Ra and chemotherapy (cyclophosphamide [6 patients], paclitaxel [3 patients], doxorubicin [1 patient], docetaxel [1 patient], and mitoxantrone [1 patient]) or secondary hormonal agents (abiraterone or enzalutamide). The concomitant use of chemotherapy with ²²³Ra may account for the fact that the presence of visceral metastases was not an independent predictor of PFS.

A 30% increase in the risk of a bone event occurred in patients with a higher Mean₁₀. Bone events occurred only in 6 patients (spinal cord compression [1 patient], pathologic bone fracture [4 patients], and intractable bone pain [1 patient]). Therefore, knowledge up front that a Mean₁₀ greater than 19 on a baseline fluoride PET/CT before ²²³Ra increases the risk of a bone-related event should heighten awareness of potential complication and may prompt close surveillance.

When our results were compared with the ALSYMPCA trial (1), we found that our median OS was lower (11.93 vs. 14.9 mo, respectively), which may be due to patient characteristics. We also found that the percentages of patients with super scans (27.6% vs. 9%), with ECOG status greater than 2 (32.9% vs. 13%), and with fewer than 6 bone metastases (5.3% vs. 16%) were lower. Combined, these indicate a higher skeletal tumor burden in our population, which likely accounts for the reduced OS in comparison to the ALSYMPCA trial. The greater proportion of patients in our group with high skeletal tumor burden was not based on a specific selection criteria, and many patients underwent ²²³Ra in a compassionate setting.

A high Gleason score normally accounts for patients having high skeletal tumor burden. It could be that the outcome we observed was related to most of our patients having a high Gleason

score. Maybe, in patients with lower Gleason scores (6 and 7) the outcome might have been better and a study evaluating patients only with low Gleason score is necessary to confirm our findings. However, in our study, a low Gleason score was also related to a high tumor burden. All patients in our study were already castrate-resistant, with progression, and had already undergone multiple lines of chemotherapy before ^{223}Ra . There was a similar percentage of deaths among patients with a Gleason score of 8–10 and Gleason 6 and 7 (45% vs. 40%, respectively). The comparable outcome is not surprising because patients with low Gleason scores tend to develop castrate-resistance after many years of initial diagnosis when compared with patients with higher Gleason score: the mean time to perform ^{223}Ra from initial diagnosis of prostate cancer was 11 y for patients with a Gleason score of 6 or 7 and 7 y for patients with Gleason 8–10.

CONCLUSION

Fluoride PET/CT skeletal tumor burden is a powerful and novel predictive biomarker of OS and of the risk of a bone event in CRPC patients treated with ^{223}Ra . Fluoride PET/CT skeletal tumor burden before ^{223}Ra may be able to separate responders from nonresponders in a reproducible and objective manner and identify patients at most risk of SREs during or after ^{223}Ra therapy.

It might be that fluoride PET/CT is a robust prognostic predictive imaging biomarker for other therapies in CRPC. Its use could extend beyond CRPC, as well, providing determination of skeletal tumor burden in patients with breast cancer and sarcomas. Further work is needed to assess whether fluoride PET/CT measures of skeletal tumor burden in these other settings impart similar predictive value with OS and other outcomes as with ^{223}Ra .

DISCLOSURE

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