

## Prognostic Value of Baseline [<sup>18</sup>F] Fluorodeoxyglucose Positron Emission Tomography and <sup>99m</sup>Tc-MDP Bone Scan in Progressing Metastatic Prostate Cancer

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### Abstract

**Purpose:** To compare the diagnostic and prognostic value of [<sup>18</sup>F] fluorodeoxyglucose positron emission tomography (FDG-PET) and bone scans (BS) in the assessment of osseous lesions in patients with progressing prostate cancer.

**Experimental Design:** In a prospective imaging trial, 43 patients underwent FDG-PET and BS prior to experimental therapies. Bone scan index (BSI) and standardized uptake value (SUV) on FDG-PET were recorded. Patients were followed until death ( $n = 36$ ) or at least 5 years ( $n = 7$ ). Imaging findings were correlated with survival.

**Results:** Osseous lesions were detected in 39 patients on BS and 32 on FDG-PET ( $P = 0.01$ ). Follow-up was available for 105 FDG-positive lesions, and 84 (80%) became positive on subsequent BS. Prognosis correlated inversely with SUV (median survival 14.4 versus 32.8 months if SUVmax > 6.10 versus  $\leq 6.10$ ;  $P = 0.002$ ) and BSI (14.7 versus 28.2 months if BSI > 1.27 versus < 1.27;  $P = 0.004$ ). Only SUV was an independent factor in multivariate analysis.

**Conclusion:** This study of progressive prostate cancer confirms earlier work that BSI is a strong prognostic factor. Most FDG-only lesions at baseline become detectable on follow-up BS, suggesting their strong clinical relevance. FDG SUV is an independent prognostic factor and provides complementary prognostic information. *Clin Cancer Res*; 16(24); 6093–99. ©2010 AACR.

The prognosis of patients with prostate cancer varies widely at all points in the disease. Even in the setting of progressive castration resistance, which represents the lethal variant of the disease, the survival of an individual patient can vary from months to years (1). To better define risk, several studies have focused on clinical or biological parameters, patterns of spread, and/or disease extent. Few of these analyses include quantitative measures of disease burden. PSA doubling time has been proposed as a potential surrogate of disease activity. However, a method that provides a direct measure of disease activity is clearly needed. For prostate cancer, this requires developing more reliable methods to assess disease in bone, the most common site of metastasis.

Several prognostic models have been reported on the basis of the number lesions on <sup>99m</sup>Tc-MDP bone scan (BS) or pattern of spread (axial or appendicular; refs. 2, 3). In previous work, we used standard man bone weights, and a semiquantitative estimation technique to develop a new parameter, the bone scan index (BSI), which provides a quantitative measure of the percentage of the adult skeleton involved by tumor (4). Using BSI, survival times vary inversely with disease extent. We also showed that the early spread of prostate cancer to bone is highly confined to regions of the skeleton that normally contain active red marrow in the adult male (5).

More recently, we have explored the use of [<sup>18</sup>F] fluorodeoxyglucose positron emission tomography (FDG-PET), which has the potential to provide a more direct measure of disease activity. In a pilot study of patients with progressive castrate resistant disease, we showed that at least 1 FDG-positive lesions was present in all the 14 patients with positive BS, and that the individual FDG-positive lesion was clinically relevant (6). Here, we expand on these findings in a larger group of patients studied under a prospective protocol, and investigate the utility of standardized uptake value (SUVmax), a measure of FDG accumulation in metastatic lesions, as a potential biomarker in progressive prostate cancer.

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### Translational Relevance

FDG-PET has incremental prognostic value in patients with progressive metastatic prostate cancer. There are currently only limited treatment options for this lethal form of the disease, and response assessment is difficult in particular for bone lesions. If confirmed in future studies, FDG-PET might serve as a prognostic, and potentially also predictive, imaging biomarker in prostate cancer.

## Materials and Methods

### Patients

From an ongoing prospective study approved by our Institutional Review Board, we identified 51 patients (median age: 68 years; range: 47–86 years) with progressive prostate cancer who were enrolled between June 1997 and December 2000 and who had follow-up for at least 5 years or until death. Study entry required histologically proven prostate adenocarcinoma and clinical evidence of disease progression as defined by a rising PSA and a detectable abnormality consistent with metastasis on a standard imaging study, such as a  $^{99m}\text{Tc}$ -MDP BS, computerized tomography (CT), or MRI. Written informed consent for this HIPPA-compliant study was obtained from all patients at the time of enrollment.

All 51 patients had evidence of progressing metastatic prostate cancer: 39 patients had castrate resistant disease, and 12 had noncastrate disease. Progressing cancer was defined as a rising PSA on 3 observations taken at least 1 week apart (with a total rise of more than 50% from baseline) or an increase in preexisting lesions on bone scintigraphy or in measurable soft tissue disease by CT or MRI within 6 weeks of study entry or development of new lesions. Patients were considered castrate if testosterone levels were less than 50 ng/dL in blood.

### Image acquisition

FDG-PET and BS were performed at baseline (30 days before to 7 days after first treatment). All 51 patients had BS prior to treatment initiation; FDG-PET was performed in 43 patients before and in 8 patients (1–20 days) after treatment initiation. Because of the possibility of confounding results of FDG-PET after treatment, these 8 patients were eliminated from further analysis, and the FDG-PET information in this article was derived from this 43 patient subset. Follow-up BS were performed in 36 of these patients 3 to 6 weeks after the initiation of therapy.

For the PET scan, patients fasted for at least 6 hours before FDG injection, but liberal intake of water was allowed. Plasma glucose levels were measured before FDG injection and were found to be in the acceptable range (<200 mg/dL) in all patients. Following intravenous injection of 555 MBq FDG (15 mCi) and an approximately

45 to 60 minutes uptake period, images were acquired from the level of the auditory meatus to the level of the mid thighs on an Advance (GE Medical Systems) whole body PET scanner. Emission and transmission images were both obtained for 4 minutes per bed position. Transmission data were used for attenuation correction in all cases and an iterative reconstruction with segmented attenuation corrections algorithm was employed.

BS were obtained approximately 2 to 3 hours after the intravenous injection of 925 MBq (25 mCi) of  $^{99m}\text{Tc}$ -MDP in the anterior and posterior projections (and spot views of selected body regions when indicated) using a dual-head gamma camera (ADAC Laboratories) equipped with a low-energy, high-resolution collimator at a scan speed of 20 cm/min.

### Image analysis

Attenuation-corrected PET images were reviewed by a radiologist and a nuclear medicine physician who were unaware of patients' clinical data (except that all had progressive prostate cancer) and laboratory findings. Interpretation was performed on a dedicated workstation displaying 3 orthogonal planes and a maximum intensity projection image. SUVmax was calculated for the lesion with the most intense FDG uptake in a given PET scan.

BS were reviewed on dedicated workstations by the same observers. The BSI was calculated as described previously (4).

For both image modalities, abnormal tracer accumulation in bones consistent with metastasis was defined as focal or linear in shape, and of intensity greater than that in adjacent normal skeleton. These bone lesions were recorded on the basis of a consensus between the 2 readers. Discrepant cases were discussed with senior nuclear medicine physicians and then classified as either benign or malignant. When available, plain films, CT, and MRI were used for a better understanding of findings on PET and BS. The behavior of lesions with discrepant findings on baseline FDG-PET and BS was assessed on follow-up BS.

### Statistical analyses

The McNemar test was employed to compare the number of osseous metastases on FDG-PET and BS, adjusted for clustering (7). As the skull was not usually included in the PET field of view, skull lesion on the BS was not considered for this analysis. Recognizing that tissue diagnosis rather than imaging findings should represent the gold standard for detection of bone metastases, sensitivity and specificity of PET and BS were not estimated; instead, the total number of lesions and their concordance on FDG and BS were compared. Survival probabilities were estimated by Kaplan–Meier method and compared with the logrank test. Multivariate analyses were performed by proportional hazards regression. Prognostic values were dichotomized around the observed medians when necessary. This method of analysis permitted for reasonably sized groups in each category. All analyses were performed using SAS (version 9.1, Cary, NC). Two-tailed *P* values of less than 0.05 were considered significant.

**Table 1.** Number of patients with bone lesions on FDG-PET versus bone scan

|                    | Negative<br>FDG-PET                             | Positive<br>FDG-PET | Total              |
|--------------------|---|---------------------|--------------------|
| Negative bone scan | 6   | 0                   | 6 (13.9%)          |
| Positive bone scan | 6 (all BS remained positive on follow-up scans) | 31                  | 37 (86.1%)         |
| <b>Total</b>       | <b>12 (27.9%)</b>                               | <b>31 (72.1%)</b>   | <b>43 (100.0%)</b> |

$P = 0.01$ .

## Results

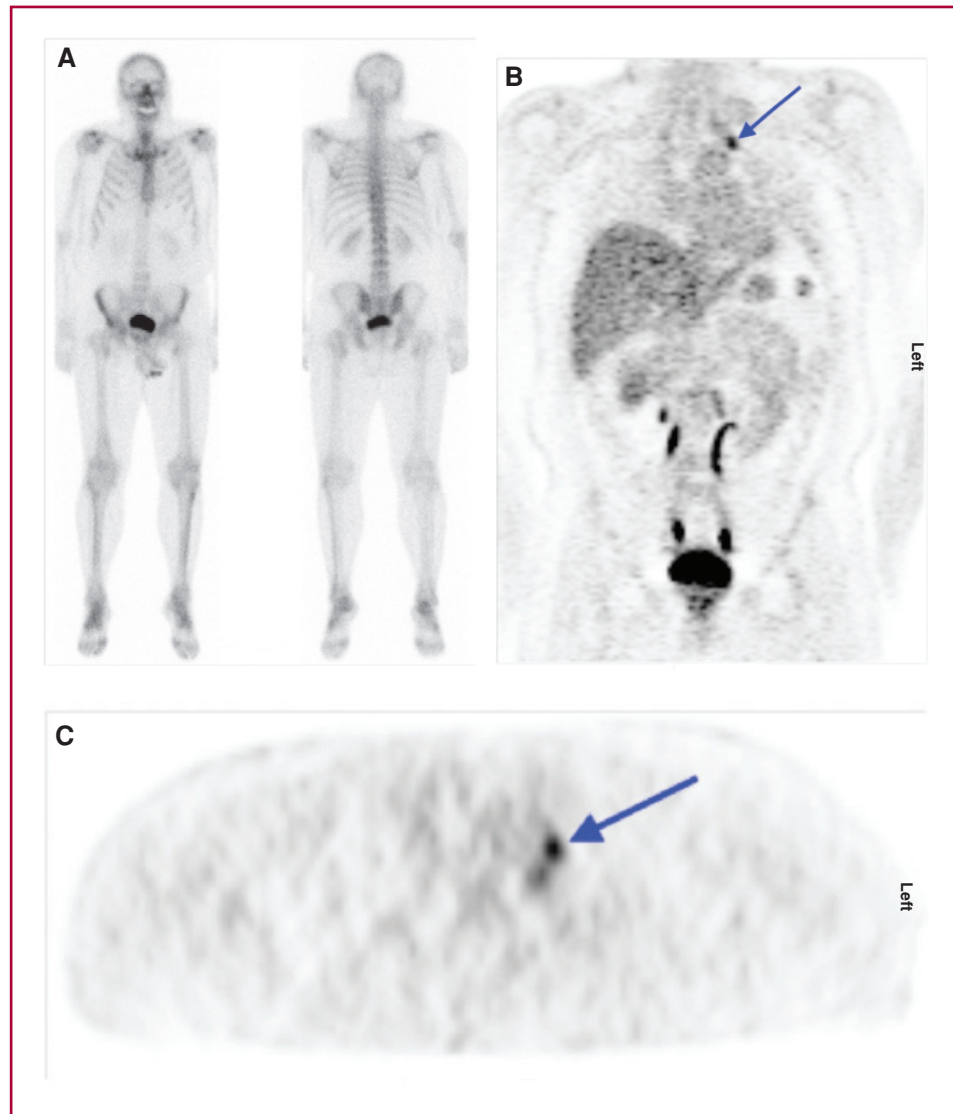
### Imaging findings

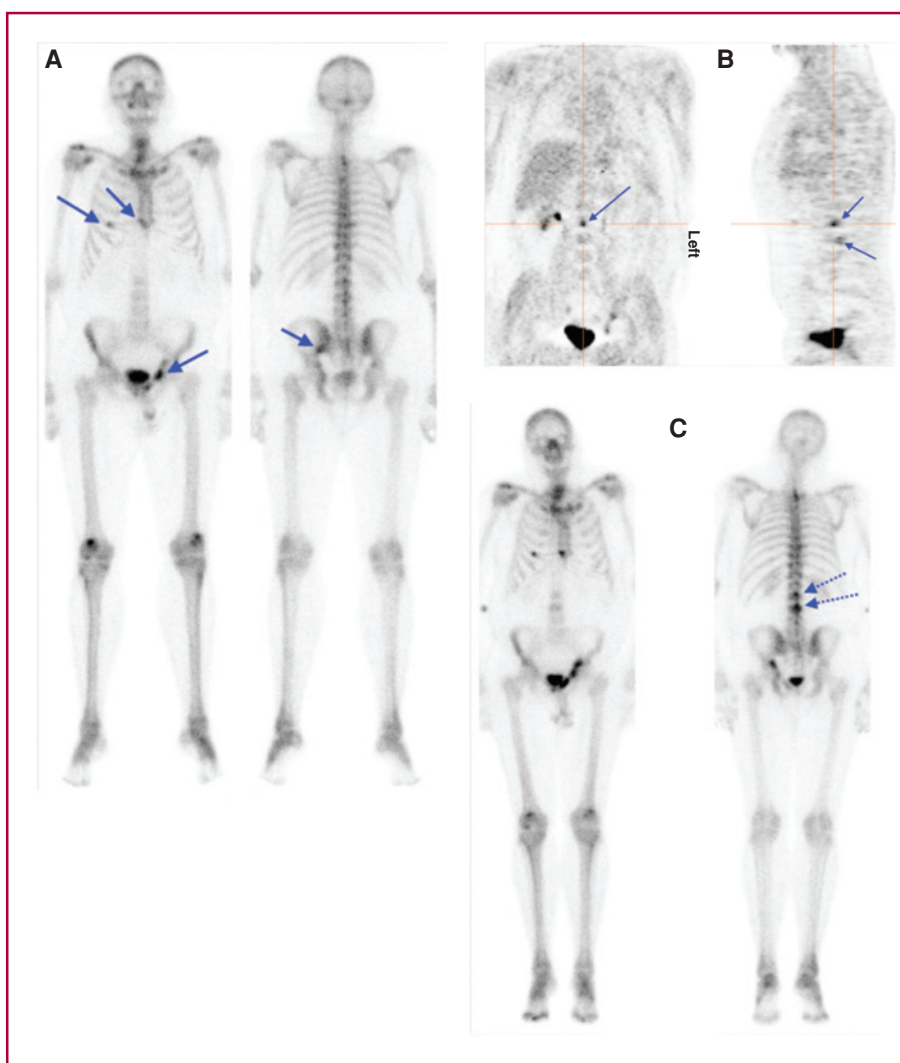
The median time between BS and PET scan was 11.6 days (maximum of 46 days). Overall, 37 of the 43 patients were thought to have osseous metastases, based on BS positivity,

and FDG-PET was positive in 31 of these 43 patients. The BS indicated metastases in significantly more patients than did the FDG-PET ( $P = 0.01$ ; Table 1).

Among the 31 patients with *osseous metastases on both BS and FDG-PET*, the PET also showed lymph node involvement in 8 patients and lymph node plus organ involvement

**Fig. 1.** A, negative bone scan, except for foci of degenerative joint disease in the shoulders. B and C, coronal and sagittal FDG-PET does not show skeletal lesions, but metastatic lymph node (arrows) is identified in the left supraclavicular region.





**Fig. 2.** A 53-year-old male with castrate resistant metastatic prostate cancer. A, the initial bone scan shows several osseous metastases in the right fifth rib, sternum, left iliac bone, and acetabulum. B, FDG-PET scan 4 days later shows the same lesions and in addition 2 metastatic foci in the lumbar spine (arrows). C, a bone scan 6 months later shows abnormal tracer uptake in these lumbar vertebrae (dotted arrows).

(lung, pleura, or liver) in another 4 patients. Of the 6 patients with *positive BS but no osseous lesions on PET*, 2 were found to have lymph node metastases by PET.

All of the 6 patients with *negative BS* also showed normal distribution of FDG throughout the skeleton on PET.

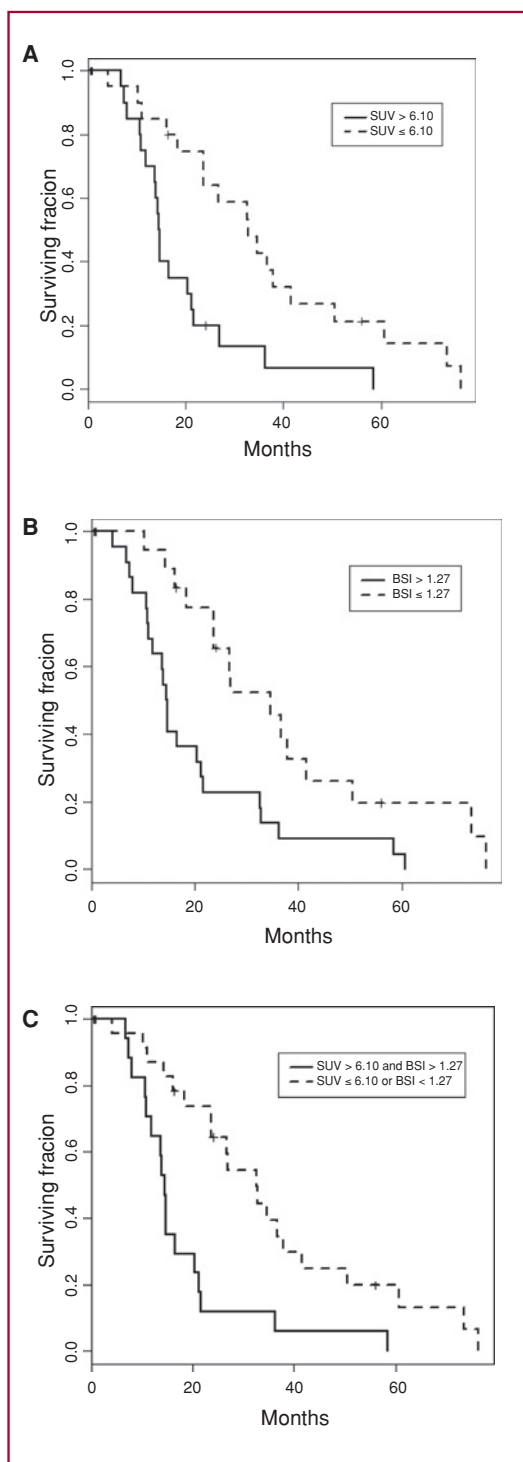
However, 1 of these patients showed abnormal FDG uptake in lymph nodes and prostate bed. An example of a patient is shown in Fig. 1.

Twelve of the 43 patients (27.8%) had *no evidence for osseous metastases on FDG-PET*; in 6 of these individuals, the

**Table 2.** FDG-PET versus bone scan for the detection of bone lesions as a fraction of all bones assessed

|                           | Negative<br>FDG-PET   | Positive<br>FDG-PET   | Total             |
|---------------------------|---|---|-------------------|
| <b>Negative bone scan</b> | 1,079   | 121 [BS follow-up for 105 lesions: 84 (80%)<br>became positive] | 1,200<br>(69.8%)  |
| <b>Positive bone scan</b> | 120 (BS follow-up for 83 lesions:<br>all remained positive) | 400   | 520<br>(31.2%)    |
| <b>Total</b>              | 1,199 (69.8%)   | 521 (30.2%)   | 1,720<br>(100.0%) |

*P* = 0.75 (N.S.).



**Fig. 3.** A, Kaplan–Meier survival curves: FDG–PET SUV—survival curves for 22 patients with low ( $\leq 6.10$ ) and 21 patients with high ( $>6.10$ ) SUVmax,  $P = 0.002$ . B, Kaplan–Meier survival curves: Bone scan index (BSI)—survival curves for 22 patients with low ( $\leq 1.27$ ) and 21 patients with high ( $>1.27$ ) BSI,  $P = 0.004$ . C, joint analysis of SUVmax and BSI showing 2 patient groups with distinct prognosis. In the low SUV and low BSI group, median survival is 32.6 months; in the "high" SUV and BSI group, survival was 14.4 months and there is a distinct difference between the curves ( $P = 0.001$ ).

BS was also negative, but BS showed abnormal sites interpreted as metastases in the other 6 patients, including axial skeleton and/or thoracic cage ( $n = 5$ ) or widespread lesions throughout the skeleton (pelvis, spine, thoracic cage, and skull;  $n = 1$ ).

Summarizing PET-FDG versus BS in these 43 patients, 37 had a positive BS as an indicator of bony disease involvement; 31 of 43 had corresponding FDG+ in bone; 3 of 43 had FDG+ only in nodal or soft tissue. Thus, 8 of 43 (18.6%) patients with progressing prostate cancer by our criteria had no site that was positive on PET-FDG.

Table 2 shows the findings in individual bones. Discrepancies between BS and PET-FDG were noted in 241 bones. Overall, slightly fewer metastases were noted on BS than on the FDG-PET. The median BSI was 1.3 (mean: 6.44, range: 0.0–55). This amounts to about 3.4% of the red marrow containing skeleton in the average adult male. Fifteen patients showed focal abnormal radiotracer accumulation on the BS in sites not included in the PET field of view. In 14 cases, this involved the skull with or without simultaneous disease in the extremities, and in 1 case the tibia. However, none of these patients had lesions exclusively in those sites, and in each case the PET revealed osseous metastases in other locations. Eight additional patients showed solitary abnormalities in the mandible on BS, which were considered unlikely to represent metastatic prostate cancer. The median SUVmax was 6.1 (range: 2.2–16.8).

Follow-up BS were available in 36 subjects with at least 1 discrepancy between number and distribution of osseous lesions on BS versus FDG-PET, involving a total of 214 bones. Of note, of the 105 bones with lesions seen on PET, 84 (80%) became positive on follow-up BS and 21 (18.4%) remained negative (Fig. 2). All lesions identified only on BS remained positive on subsequent BS.

### Prognostic value of imaging findings

Median survival of the entire sample was 21.3 months (95% CI: 14.7–32.8). The hazard ratio of FDG SUVmax in bone, when used as a continuous variable, was estimated to be 1.11; that is, a 11% increase in risk of death is expected for each unit increase in SUV (95% CI for hazard ratio: 1.03–1.19;  $P = 0.007$ ). Kaplan–Maier curves for SUVmax  $\leq 6.10$  against SUVmax  $> 6.10$  (observed median), are shown in Figure 3A. In the 22 patients whose metastases had a SUVmax  $\leq 6.10$ , the median survival was 32.8 months (95% CI: 23.6–41.6). By comparison, in the 21 patients whose metastases had a SUVmax  $> 6.10$ , the median survival was only 14.4 months (95% CI: 13.9–21.7;  $P = 0.002$ ). The hazard ratio for BSI versus prognosis was estimated at 1.02 (95% CI: 1.00–1.04;  $P = 0.120$ ). Median survival was 27.0 months (95% CI: 23.6–50.5) for the 26 patients with a BSI  $\leq 1.27$  as compared with 14.4 months (95% CI: 11.1–24.9) for the 25 patients with a BSI  $> 1.27$  ( $P = 0.004$ ; Fig. 3B). When both SUVmax and BSI were used in a multivariate analysis, SUVmax retained its significance ( $P = 0.010$ ; hazard ratio = 1.098; 95% CI: 1.024–1.177), and BSI showed a trend toward significance ( $P = 0.215$ ;

**Table 3.** Results of the univariate and multivariate survival analysis

| Variable                     | Hazard Ratio     | P     |
|------------------------------|------------------|-------|
| <i>Univariate analysis</i>   |                  |       |
| SUV (continuous)             | 1.11 (1.03–1.19) | 0.007 |
| SUV > 6.10                   | 2.90 (1.43–5.91) | 0.003 |
| BSI (continuous)             | 1.02 (0.99–1.04) | 0.116 |
| BSI > 1.27                   | 2.71 (1.35–5.43) | 0.004 |
| <i>Multivariate analysis</i> |                  |       |
| Model 1                      |                  |       |
| SUV (continuous)             | 1.10 (1.02–1.19) | 0.009 |
| BSI (continuous)             | 1.02 (0.99–1.04) | 0.202 |
| Model 2                      |                  |       |
| SUV > 6.10                   | 1.63 (0.67–3.97) | 0.278 |
| BSI > 1.27                   | 1.54 (0.63–3.74) | 0.345 |

hazard ratio = 1.019; 95% CI: 0.981–1.040). We further noted that dichotomized versions of these 2 variables formed 2 distinct groups: among the 26 patients with SUVmax  $\leq$  6.10 and BSI  $\leq$  1.27, the median survival was 34.6 months (95% CI: 23.6–NR). On the contrary, among the 19 patients who had metastases with either SUVmax > 6.10, a BSI > 1.27, or both, the median survival was only 14.7 months (95% CI: 13.8–27.0). The corresponding survival curves are shown in Figure 3C, and the statistical summary is shown in Table 3.

## Discussion

Our study shows for the first time that FDG-PET SUVmax, a measure of the tumor glycolytic rate and Warburg effect, is strongly related to adverse prognosis in patients with progressive prostate cancer. Thus, progressing prostate cancer must now join the relatively long list of tumors for which FDG glycolytic rate, as captured by the baseline SUVmax, yields important prognostic information (8–20).

This study also confirms several important observations that were made on a preliminary basis in earlier pilot trials. First, BSI was confirmed as a prognostic factor (5), but in this study, even a relatively modest tumor involvement of 1.3% (the median in our data set) conferred a poor prognosis. Of note, in adult, males bone marrow is confined to about 38% of the skeleton (axial skeleton, pelvis, variably the humeral and femoral heads, less commonly also the skull). Because osseous metastases initially localize to normal red marrow, a BSI of 1.3% corresponds to approximately 3.8% of the bones containing red marrow. Although a BSI of 1.3% then indicates a relatively modest involvement of marrow containing bone, in this group of patients with documented progressing prostate cancer, even this relatively low degree of involvement is an ominous sign. Second, we confirm our earlier observation from a smaller group of patients (6) that BS-positive but FDG-

negative bone lesions are essentially static. On the contrary, the FDG-positive but BS-negative lesions at baseline eventually become detectable on follow-up BS. This supports the hypothesis that FDG-positive lesions are biologically active and aggressive, whereas lesions detectable on BS only (with negative FDG-PET) have been treated successfully and tend to be stable, because active tumor has been removed. Thus, we believe that in patients with progressive disease, FDG-PET outperforms bone scanning for the detection of clinically active disease in the skeleton. Finally, we show that both FDG SUVmax and BSI were inversely correlated with survival, but only SUVmax was an independent predictor of survival in the multivariate analysis.

We recognize that our study plan also had limitations. For example, for purposes of accrual, 6 of 51 patients had FDG scans performed from 1 to 7 days after a change in therapy as permitted by protocol. Also, the SUV measurement itself can be quite variable, and the scans were performed, according to a protocol that permitted considerable variation in blood glucose (200 mg/dL) and time after injection (target of 60 minutes, but a broad range of 60–90 minutes). Also, the size of small lesions may have limited count recovery, and size of lesions is notoriously difficult to assess particularly in the bone. It is our view that all of these technical features of SUV response would be likely to increase random variation of the measure and reduce the predictive power of SUV, and in fact it is all the more remarkable that SUV was such a powerful predictor of survival, given its technical limitations.

On the basis of our results, we therefore believe that FDG SUV, when used in proper clinical context, can serve as a biomarker of prognosis in progressing metastatic prostate cancer.

In previous studies in mixed or smaller groups of patients with metastatic prostate cancer, FDG-PET showed detection rates of suspicious bone lesions between 18% (21) and 65% (22). We consider it a serious problem that the patient

populations in many of these earlier studies were not uniformly defined with regard to disease progression and distinct clinical states (1), which carry a different prognosis and require different therapies and imaging strategies (23). This assessment also includes treated tumors. Of note, in the initial states of the disease, prostate cancer responds to antiandrogen therapies. These hormone-responsive tumors likely have a very low glycolytic rate, so that FDG-PET may not be a useful test in nonprogressing patients with metastatic prostate cancer. In contrast, we have previously shown that in patients with progressing castrate resistant disease, FDG-PET can be highly useful for assessing treatment response, because a high positivity rate on baseline FDG can be evaluated as a useful indicator of response (24).

## Conclusion

In conclusion, in patients with progressing prostate cancer, osseous metastases are readily detected on FDG-

PET. Although the extent of osseous disease, as quantified by BSI, is by itself a prognostic marker, SUV is a stronger prognostic indicator in progressing prostate cancer. In castrate-resistant patients, the subset with the most aggressive disease, SUV adds incremental prognostic information. FDG-PET provides clinically relevant information that may improve the management of patients with progressing metastatic prostate cancer.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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