



Quantitative assessment of ^{99m}Tc -methylene diphosphonate bone SPECT/CT for assessing bone metastatic burden and its prognostic value in patients with castration-resistant prostate cancers: initial results in a single-center retrospective study

Takashi Oya¹ · Yasutaka Ichikawa¹ · Satsohi Nakamura¹ · Yoya Tomita¹ · Takeshi Sasaki² · Takahiro Inoue² · Hajime Sakuma¹

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Abstract

Purpose To evaluate the prognostic value of the quantitative assessment of ^{99m}Tc -methylene diphosphonate (^{99m}Tc -MDP) bone SPECT/CT in castration-resistant prostate cancer (CRPC) patients with bone metastases.

Methods A total of 103 patients who underwent ^{99m}Tc -MDP bone SPECT/CT imaging from the neck to the proximal femur were included. First, in 65 patients without bone metastases, the normal range of standardized uptake value (SUV) of non-pathological bone was evaluated to determine an SUV threshold to reliably exclude most normal osseous activity. Then, in 38 CRPC patients with bone metastases, lesion uptake volume (LUV), which is the extracted volume of bone metastases exhibiting high accumulation above the SUV threshold, was calculated. The relation between LUV and prostate-related mortality was statistically evaluated.

Results Based on the SUV measurements of non-pathological bones, the optimal SUV threshold, which defines abnormal bone SPECT uptake, was determined to be 8. Median LUV was 39 mL (interquartile range 4.0–104.3 mL) in the CRPC subjects with bone metastases. Kaplan–Meier survival analysis showed a significant relation between prostate cancer-specific survival and LUV (cut-off value, 19.95 mL; $P=0.001$). Multivariate analysis revealed LUV as an independent prognostic factor for the survival ($P=0.008$, hazard ratio 23.424). Global chi-square test showed that LUV had significant incremental prognostic value in addition to prostate-specific antigen and the interval from progression to CRPC until bone SPECT/CT ($P=0.022$).

Conclusion Quantitative assessment of ^{99m}Tc -MDP bone SPECT images can provide valuable prognostic information in CRPC patients with bone metastases.

Keywords Bone scintigraphy · Single-photon emission tomography · Prostate cancer · Bone metastasis · Quantification · Prognosis

Introduction

Prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide, with an estimated 1,414,000 new cases

and 375,304 deaths in 2020 [1]. Men are at highest risk of prostate cancer death once the cancer becomes resistant to castration and distant metastases develop. Bone is the most common site of metastasis among patients with metastatic castration-resistant prostate cancer (mCRPC). Approximately, 90% of mCRPC patients are diagnosed with bone metastases during the treatment course [2]. Median survival for mCRPC patients with bone metastases is estimated at 16–40 months [3–5]. Identifying risk factors at this advanced stage is important in determining the appropriate course of treatment for patients.

Bone scintigraphy is the standard imaging modality for diagnosing bone metastases of prostate cancer. Several

✉ Yasutaka Ichikawa
yasutaka@med.mie-u.ac.jp

¹ Department of Radiology, Mie University Hospital, 2-174 Edobashi, Tsu, Mie 514-8507, Japan

² Department of Nephro-Urologic Surgery and Andrology, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan

methods have been proposed to assess the burden of skeletal metastases in bone scintigraphy. Extent of disease (EOD) classification is a visual assessment of the extent of bone metastases based on the number of lesions, and is reported to be useful for predicting survival in prostate cancer patients [6]. Although visual evaluation such as EOD still play an important role in bone scintigraphy, more objective and quantitative methods of assessing bone metastasis have recently been proposed. Bone scan index (BSI) is obtained using a computer-aided diagnostic system as a measure for objectively evaluating the severity of bone metastases, and is used clinically as a prognostic indicator for prostate cancer [7–9]. However, BSI is strongly influenced by tumor location and volume, since the index is based on two-dimensional planar images.

With the introduction of a scanner combining single-photon emission computed tomography (SPECT) and computed tomography (CT), the diagnostic performance of bone scintigraphy has been greatly improved as compared with two-dimensional imaging [10, 11]. SPECT/CT allows for the acquisition of three-dimensional data and the generation of attenuation correction maps that are necessary for accurate quantification of radionuclide uptake in tissues. Using quantitative analytical techniques for SPECT/CT, the standardized uptake value (SUV) of bone tissue can now be determined [12–14]. Recent studies have shown that quantitative evaluation using SUV on bone SPECT/CT is useful for differentiating bone metastases from benign lesions [15, 16]. However, the prognostic value of quantitative SPECT/CT assessment in prostate cancer patients with bone metastases has not yet been fully evaluated. This can be attributed to the fact that appropriate quantitative bone SPECT/CT indices to assess bone metastatic burden have yet to be established. Rohren et al. [17] developed a method for quantitatively assessing skeletal tumor burden using ^{18}F -labeled sodium fluoride (^{18}F -fluoride) positron emission tomography (PET)/CT. They identified an SUV threshold to exclude most bony activity on ^{18}F -fluoride PET/CT, then determined skeletal metastatic burden using volumetric parameters based on this SUV threshold. Adapting such methodologies may, thus, allow quantitative assessment of bone metastatic burden from SPECT/CT.

The purposes of this study were to determine a normal range of SUVs for bone on $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) SPECT/CT, to define a method for assessing skeletal tumor burden with an SUV threshold, and to evaluate the prognostic value of quantitative assessment in mCRPC patients with bone metastases.

Materials and methods

Subjects

To determine a normal range of SUVs for non-pathological bone on $^{99\text{m}}\text{Tc}$ -MDP SPECT/CT, we retrospectively studied 65 cancer-bearing patients (56 men, 9 women; mean age, 71 ± 10 years), who had undergone $^{99\text{m}}\text{Tc}$ -MDP bone SPECT/CT at our institution for clinical purposes and had no evidence of bone metastasis on scintigrams. To assess the prognostic value of quantitative SPECT for bone metastatic burden, we also studied 38 patients (mean age, 74 ± 6 years) who had CRPC with bone metastases and underwent $^{99\text{m}}\text{Tc}$ -MDP bone SPECT/CT. At initial diagnosis, all patients had been histologically confirmed to have adenocarcinoma of the prostate. The 2016 TNM clinical staging system and 2014 International Society of Urographic Pathology Gleason grading system were used. The clinical stage was evaluated by chest and abdominal CT, and bone scans. All patients received androgen-deprivation therapy with surgical or pharmacologic castration (luteinizing hormone-releasing hormone agonist or antagonist) accompanied by a first-generation antiandrogen [combined androgen blockade (CAB)] and were followed up. The first-generation antiandrogen bicalutamide was initially used as CAB treatment. Prostate specific antigen (PSA) was serially measured during CAB treatment according to the decisions of the attending physicians. Imaging for metastatic disease was left to clinical judgement based on PSA and/or symptoms of recurrent disease. CRPC was defined as either progressively rising PSA (resulting in two 50% increases over the nadir, with PSA > 2.0 ng/mL), despite a castrate level (< 50 ng/dL) of testosterone according to a previous report [18]. After CRPC, the physician preferred the following treatments: antiandrogen treatments (flutamide, enzalutamide, and abiraterone), estrogen treatments (estramustine phosphate and ethinylestradiol), and chemotherapy (docetaxel and cabazitaxel). The current study was approved by our institutional review board and the need to obtain written informed consent was waived since this study used existing clinical data. The opportunity to opt out of inclusion in this study was given through a notice on the hospital website. No patient showed any intention to be excluded from this study.

Image acquisition

All subjects were injected with $^{99\text{m}}\text{Tc}$ -MDP at a mean dose of 752 MBq (range 510–878 MBq). Whole-body scintigraphy and SPECT/CT were performed at 2 h post-injection,

which took approximately 30 min. All data were acquired on a SPECT/CT scanner (Discovery NM/CT 670, GE Healthcare, Milwaukee, WI, USA) with a low-energy high-resolution collimator. SPECT data were acquired with 60 steps of 15 s/step, 360°, and a 128 × 128 matrix, covering from the cervical region to the proximal femur. The double-energy window method was used, with 140.5 keV \pm 10% for the main window and 120 keV \pm 5% for the sub-window. The sub-window was used for scatter correction. Non-contrast CT images were obtained for attenuation correction. CT parameters included: tube voltage, 120 kVp; tube current, 100 mA; rotation time, 0.5 s. SPECT images were reconstructed with attenuation correction, resolution recovery and scatter correction using ordered-subset expectation maximization algorithm (2 iterations, 10 subsets). Butterworth filtering with a cut-off of 0.50 cycles per pixel was also employed for SPECT image reconstruction.

Image analysis

Quantitative evaluation of SPECT images was performed using commercially available software (Q.Metrix, GE Healthcare). First, to assess the degree of accumulation in non-pathological bone, one experienced radiologist measured maximal SUV (SUV_{max}) at eight normal bone sites in each subject. Non-pathological bone was defined as a region of skeleton exhibiting mild diffuse uptake, without any focal uptake and without anatomical abnormalities identified on the CT portion of the scan. For analysis, cubic volumes of interest (VOIs) with 20 mm edges were placed over 8 sites of non-pathological bone: including the 4th cervical, 6th thoracic, and 3rd lumbar vertebral bodies, sacrum, sternum, right anterior and posterior iliac bone, and intertrochanteric right femoral bone, in each subject (Fig. 1). If abnormality such as fracture or degenerative disease was apparent at any of the bone sites on the CT portion of the scan, an alternative measurement was obtained on any of the following sites: the 3rd cervical, the 5th thoracic, and the 4th lumbar vertebral body, lower sacrum, lower sternum, left anterior and posterior iliac bone, and intertrochanteric left femoral bone, respectively. If neither the primary nor the secondary site was evaluable, measurement of that specific abnormal site was excluded for that particular patient. On the basis of the results for normal bone SUV_{max} , an SUV threshold slightly above most non-pathological bone values was then determined to allow reliable exclusion of most normal osseous activity and, thus, assess bone metastatic burden on ^{99m}Tc -MDP SPECT/CT images. Next, regions of hyperaccumulation that exceeded this SUV threshold were automatically segmented three-dimensionally using Q.Metrix software. Two radiologists with expertise in nuclear medicine then independently evaluated the segmentation and manually

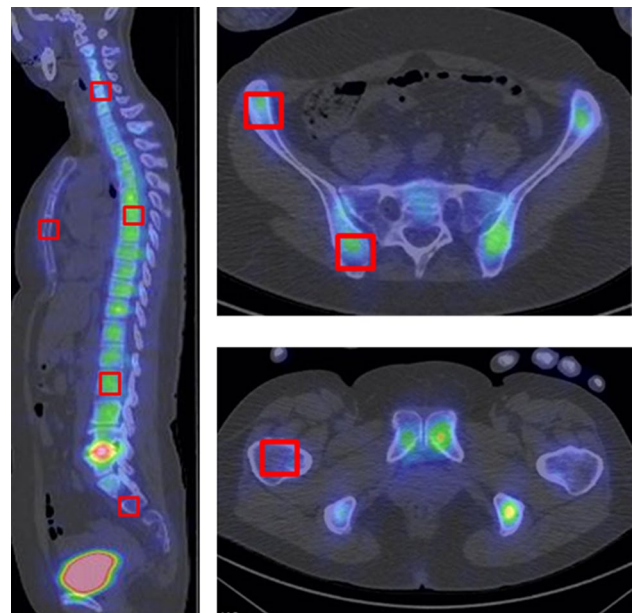


Fig. 1 Measurement of SUV_{max} for bone accumulation at 8 normal bone sites in subjects without bone metastases on ^{99m}Tc -methylene diphosphonate SPECT/CT. For this analysis, cubic volumes of interest with 20 mm edges were placed over 8 sites of normal bone, comprising the 4th cervical, 6th thoracic, and 3rd lumbar vertebral bodies, sacrum, sternum, right anterior and posterior iliac bone, and intertrochanteric right femoral bone, in each subject

excluded regions of hyperaccumulation due to physiological accumulation (e.g., urine in the renal collecting system) or benign bone lesions (e.g., degenerative disease) from the segmentation, referring to CT images, and extracted only regions of abnormal accumulation due to bone metastases from SPECT data. Lastly, the following two volumetric parameters were calculated: (1) lesion uptake volume (LUV) and (2) total lesion uptake (TLU). LUV was defined as the sum of the volumes of the regions extracted as bone metastases showing the SUV threshold or higher. TLU was calculated from LUV and the mean SUV in the hyperaccumulated regions extracted as bone metastases as follows:

$$\begin{aligned} \text{Total lesion uptake (TLU)} \\ = \text{meanSUV} \times \text{Lesion uptake volume (LUV)}. \end{aligned}$$

Whole-body bone scintigraphy of mCRPC patients was qualitatively evaluated with EOD scores based on the number and extent of bone metastases as follows [6]: 0, normal or abnormal due to benign bone disease; 1, fewer than six bony metastases, each less than 50% of the size of a vertebral body (one lesion approximately the size of a vertebral body was counted as two lesions); 2, 6–20 bone metastases, sized as described above; 3, more than 20 metastases, but fewer

than those observed in a “superscan”; and 4, a “superscan” or its equivalent (i.e., more than 75% of ribs, vertebrae, and pelvic bones showing metastasis). EOD was evaluated by consensus of two experienced nuclear medicine specialists, separate from the radiologists performing the SPECT evaluation. For mCRPC patients with bone metastases, BSI was also calculated as the percentage of the sum of all hotspots classified as bone metastases based on artificial neural network values. BONENAVI version 2 (Fujifilm RI Pharma, Co., Tokyo, Japan and Exini Bone, Exini Diagnostics, Lund, Sweden) was used for the calculation of BSI [19].

Statistical analysis

All continuous variables are expressed as mean \pm standard deviation or median and interquartile range (IQR). Uni- and multivariate analyses of prostate cancer-specific survival were performed using a Cox proportional hazards regression model, from which relative risks and 95% confidence intervals (95% CIs) were derived. In univariate analyses, the following variables were analyzed as binary variables: patient age, Gleason score, clinical TNM stage, PSA at initial and the time of bone SPECT/CT examination, alkaline phosphatase at bone SPECT/CT examination, EOD, LUV, TLU, and time interval from progression to CRPC until the ^{99m}Tc -MDP bone SPECT/CT study (TI from CRPC progression). PSA and alkaline phosphatase at the time of bone SPECT/CT examination were defined as data within 2 weeks of each SPECT/CT examination. Cutoff points for all continuous variables were determined using the method based on log-rank tests described by Contal and O’Quigley [20]. Multivariate analysis was performed using the variables showing values of $P < 0.1$ in univariate analyses. Before conducting the multivariate analysis, correlations between each factor were evaluated using Pearson product-moment correlation coefficients. If the correlation coefficient was > 0.7 , those factors were not used in the multivariate analysis at the same time due to multicollinearity. The Pearson product-moment correlation coefficient was used to measure the extent of linear dependence between mean bone SUV_{max} and age. The Mann–Whitney U test was used to compare gender differences in mean SUV_{max} at the eight normal bone sites. The Kaplan–Meier product-limit estimator was used to estimate the distribution of prostate cancer-related death. The log-rank test was used to analyze survival differences depending on the LUV. The incremental prognostic value of LUV over other clinical factors (BSI, PSA at bone SPECT/CT exam, and TI from CRPC progression) was evaluated using the global chi-square testing. Inter-observer reproducibility for measuring LUV and TLU was analyzed with the intraclass correlation coefficient (ICC). Statistical analysis was performed using R version 4.1.0. and SPSS version 25 (IBM

Corp.). Values of $P < 0.05$ were considered indicative of statistical significance.

Results

SUV_{max} at non-pathological bone sites on ^{99m}Tc -MDP SPECT/CT

Twenty-six bone sites, including 11 cervical vertebral bodies, 5 thoracic vertebral bodies, one lumbar vertebral body, one sacrum, one anterior iliac bone, 2 posterior iliac bone, 4 intertrochanteric femoral bone, and 2 sternum were excluded from analysis because of the presence of fracture or degenerative disease. Thus, SUV_{max} measurements were obtained from a total of 493 non-pathological bone sites (Fig. 2). Mean SUV_{max} of the non-pathological bone sites was 4.3 ± 1.2 for the cervical vertebral body, 5.1 ± 1.3 for the thoracic vertebral body, 5.1 ± 1.3 for the lumbar vertebral body, 3.8 ± 1.1 for the sacrum, 2.9 ± 0.8 for the sternum, 4.2 ± 1.4 for the anterior iliac bone, 4.7 ± 1.4 for the posterior iliac bone, and 2.7 ± 0.8 for the femoral bone. No relationship was apparent between mean bone SUV_{max} for each subject at the 8 measured sites and age (Pearson correlation coefficient, -0.06420 ; $P = 0.61$). No significant gender differences were found in mean bone SUV_{max} at the eight measurement sites (men, 4.1 ± 0.9 vs women, 4.1 ± 1.0 ; $P = 0.93$). The number of normal bone sites that would be erroneously included as abnormal uptake sites according to SUV thresholds is summarized in Table 1. At an SUV threshold of 6, 45 (9.1%) of 493 non-pathological bone sites would be erroneously included, whereas at a threshold of 8, 5 (1.0%) of the 493 non-pathological bone sites would be included. On the basis of these values, an SUV threshold of 8 was chosen as the lower boundary for volumetric extraction to exclude most non-pathological bone from the calculation of bone metastatic burden on ^{99m}Tc -MDP SPECT/CT.

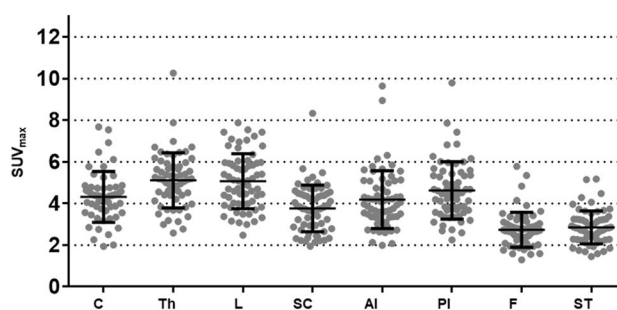


Fig. 2 SUV_{max} measurements for 8 normal bone sites in ^{99m}Tc -methylene diphosphonate SPECT/CT. Solid lines represent the mean and standard deviation of SUV_{max} at each bone site. C cervical vertebral body, Th thoracic vertebral body, L lumbar vertebral body, SC sacrum, AI anterior iliac bone, PI posterior iliac bone, F femoral bone, ST sternum

Table 1 Number of normal bone sites erroneously included as abnormal uptake sites due to SUV thresholds

SUV thresh- old	Cervical vertebral body <i>n</i> = 54	Thoracic vertebral body <i>n</i> = 60	Lumbar verte- bral body <i>n</i> = 64	Sacrum <i>n</i> = 64	Anterior iliac bone <i>n</i> = 64	Posterior iliac bone <i>n</i> = 63	Femoral bone <i>n</i> = 61	Sternum <i>n</i> = 63	Total <i>n</i> = 493
4	34 (63.0%)	47 (78.3%)	47 (73.4%)	27 (42.2%)	32 (50.0%)	40 (63.5%)	4 (6.6%)	5 (7.9%)	236 (47.9%)
5	10 (18.5%)	33 (55.0%)	32 (50.0%)	5 (7.8%)	16 (25.0%)	21 (33.3%)	2 (3.3%)	2 (3.2%)	121 (24.5%)
6	5 (9.3%)	13 (21.7%)	14 (21.9%)	1 (1.6%)	4 (6.3%)	8 (12.7%)	0 (0.0%)	0 (0.0%)	45 (9.1%)
7	2 (3.7%)	2 (3.3%)	7 (10.9%)	1 (1.6%)	2 (3.1%)	3 (4.8%)	0 (0.0%)	0 (0.0%)	17 (3.4%)
8	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	5 (1.0%)
9	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
10	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Bone metastatic burden on ^{99m}Tc -MDP SPECT/CT

The characteristics of mCRPC patients with bone metastases are listed in Table 2. In 28 patients (73.7%), metastases were found at the time of initial diagnosis prior to treatment [metastatic sites: bone in 26 patients (68.4%), lymph nodes in 5 patients (13.2%), and lungs in 3 patients (7.9%)]. Median duration of follow-up was 1008 days (IQR, 513–1285 days). Prostate cancer-related deaths occurred in 21 (55%) of 38 subjects. The median PSA at initial and bone SPECT/CT examination was 68.8 ng/mL (IQR, 25.4–380.1 ng/mL) and 6.05 ng/mL (IQR, 0.6–31.6 ng/mL), respectively. Median BSI, LUV and TLU was 0.25% (IQR, 0.04–0.71%), 39 mL (IQR, 4.0–104.3 mL) and 408.1 (IQR, 36.7–1347.3), respectively. ICCs between the two radiologists for measuring LUV and TLU was 0.997 (95% CIs 0.995–0.999) and 0.997 (95% CIs 0.994–0.999), respectively. A representative mCRPC patient with bone metastases who underwent SPECT/CT quantitative evaluation is shown in Fig. 3. Kaplan–Meier survival analysis revealed that both LUV and TLU were significantly associated with prostate cancer-specific survival ($P=0.001$) (Fig. 4). Cutoff values for LUV and TLU were 19.95 mL and 267.88, respectively. The Kaplan–Meier curves for LUV and TLU appeared identical. In univariate analysis, PSA at the time of bone SPECT/CT study, LUV and TLU were prognostic factors for prostate cancer-specific survival as shown in Table 3. [PSA at bone SPECT/CT study: $P<0.0001$, hazard ration (HR) 11.018 (95% CIs 3.029–40.083); LUV: $P=0.004$, HR 5.297 (95% CI 1.715–16.356); and TLU: $P=0.004$, HR 5.297 (95% CIs 1.715–16.356)] (Table 3). The indices other than TLU and LUV that showed $P<0.1$ in univariate analysis were TI from CRPC progression, PSA at the time of bone SPECT/CT study, and BSI. Since a strong linear correlation was found between LUV and TLU (Pearson correlation coefficient, 0.974; $P<0.0001$), the multivariate analysis did not include these two variables at the same time. The correlation

coefficients between the SPECT quantitative indices and the other indices were as follows: LUV vs TI from CRPC progression, -0.278 ; LUV vs PSA at the time of bone SPECT/CT study, -0.084 ; LUV vs BSI, 0.719; TLU vs TI from CRPC progression, -0.268 ; TLU vs PSA at the time of bone SPECT/CT study, 0.059; TLU vs BSI, 0.707. Because of the good linear correlation (correlation coefficient >0.7) between LUV and BSI and between TLU and BSI, BSI and these SPECT quantitative indices were not used simultaneously in multivariate analysis. In multivariate analysis, TI from CRPC progression, PSA at the time of bone SPECT/CT study, LUV, and TLU were independent prognostic factors for prostate cancer-specific survival (Table 4). Global chi-square testing revealed that PSA was of incremental prognostic value to TI from CRPC progression (3.4 vs 24.7, $P<0.0001$) (Fig. 5). Combining LUV or TLU with TI from CRPC progression and PSA at the time of bone SPECT/CT showed a significant increment in prognostic value (24.7 vs. 31.8, $P=0.022$). However, BSI did not confer significant incremental prognostic value in addition to TI from CRPC progression + PSA at the time of bone SPECT/CT (24.7 vs 36.9, $P=0.43$).

Discussion

The present study demonstrated that quantitative analysis of bone metastatic burden by ^{99m}Tc -MDP bone SPECT/CT provides prognostic value in mCRPC patients with bone metastases. The volumetric parameters derived from SPECT data offered higher prognostic value than conventional indices including EOD and BSI. In addition, the SPECT quantitative indices, LUV and TLU, appeared to provide incremental prognostic value over PSA levels and time interval from progression to CRPC until bone SPECT/CT. Utilizing the quantitative analysis of bone SPECT would permit more accurate assessment of bone metastatic burden and lead to better risk stratification in patients with mCRPC.

Table 2 Characteristics of CRPC patients with bone metastases

Patient age, years	Median, 73 (IQR, 70–79)
Observation period, days	Median, 1008 (IQR, 512.5–1285.25)
Time interval from progression to CRPC until bone SPECT/CT exam, days	Median, 370 (IQR, 122.75–1148)
TNM classification at initial diagnosis	
<i>T</i> , <i>n</i> (%)	
T1	0 (0.0%)
T2	4 (10.5%)
T3	15 (39.5%)
T4	19 (50.0%)
<i>N</i> , <i>n</i> (%)	
N0	14 (36.8%)
N1	24 (63.2%)
<i>M</i> , <i>n</i> (%)	
M0	10 (26.3%)
M1	28 (73.7%)
Gleason score, <i>n</i> (%)	
7	3 (7.9%)
8	11 (28.9%)
9	18 (47.4%)
10	6 (15.8%)
Initial PSA (ng/mL)	Median, 68.85 (IQR, 25.40–380.14)
PSA at bone SPECT/CT exam (ng/mL)	Median, 6.05 (IQR, 0.57–31.64)
ALP at bone SPECT/CT exam, IU/L	Median, 213.5 (IQR, 157.75–283.25)
EOD, <i>n</i> (%)	
Scale 0	6 (15.8%)
Scale 1	17 (44.7%)
Scale 2	9 (23.7%)
Scale 3	3 (7.9%)
Scale 4	3 (7.9%)
BSI, %	Median, 0.25 (IQR, 0.04–0.71)
Quantitative indices of bone SPECT/CT	
LUV, mL	Median, 39.0 (IQR, 4.03–104.34)
TLU	Median, 408.06 (IQR, 36.75–1347.25)

IQR interquartile range, *CRPC* castration-resistant prostate cancer, *SPECT/CT* single-photon emission computed tomography/computed tomography, *PSA* prostate-specific antigen, *ALP* alkaline phosphatase, *EOD* extent of disease, *BSI* bone scan index, *LUV* lesion uptake volume, *TLU* total lesion uptake

Accurate assessment of bone metastatic burden in patients suffering from cancer leads to the selection of more appropriate treatment strategies and monitoring of treatment efficacy. BSI, which utilizes a computer-aided diagnostic system for bone scintigraphy, is an objective and quantitative clinical tool for evaluating bone metastatic prostate cancer and has previously been reported as useful in predicting prognosis among men with prostate cancers [7–9]. Miyoshi et al. retrospectively evaluated the association between overall survival and pretreatment clinicopathologic characteristics including patients' age, PSA value, Gleason scores, clinical TNM stage, and BSI in 60 patients with hormone-naïve prostate cancer and bone metastases who underwent whole-body bone scintigraphy (median observation period

21.4 months) [8]. They found that BSI and patient age were independent prognostic factors in multivariate analysis (BSI: > 1.9 vs $\leq 1.9\%$, HR 4.676, 95% CIs 1.238–17.661, $P = 0.023$; patient age: ≤ 72 vs > 72 years old, HR 5.811, 95% CIs 1.656–20.386, $P = 0.006$) [8]. A retrospective study by Mitsui et al. [7] of 42 consecutive CRPC patients with bone metastases treated with taxane chemotherapy found that the change in BSI between baseline and 16 weeks after the start of chemotherapy was a significant prognostic factor. Thus, BSI provides useful information for assessing bone metastatic burden and prognosis. However, BSI is based on planar images, and so is inherently limited in the quantitative assessment of the three-dimensional spread of bone metastases.

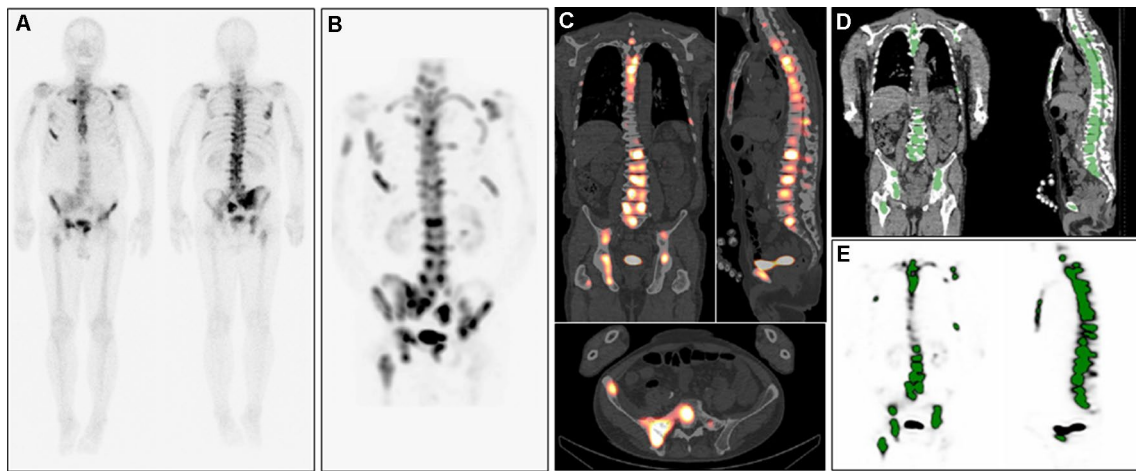
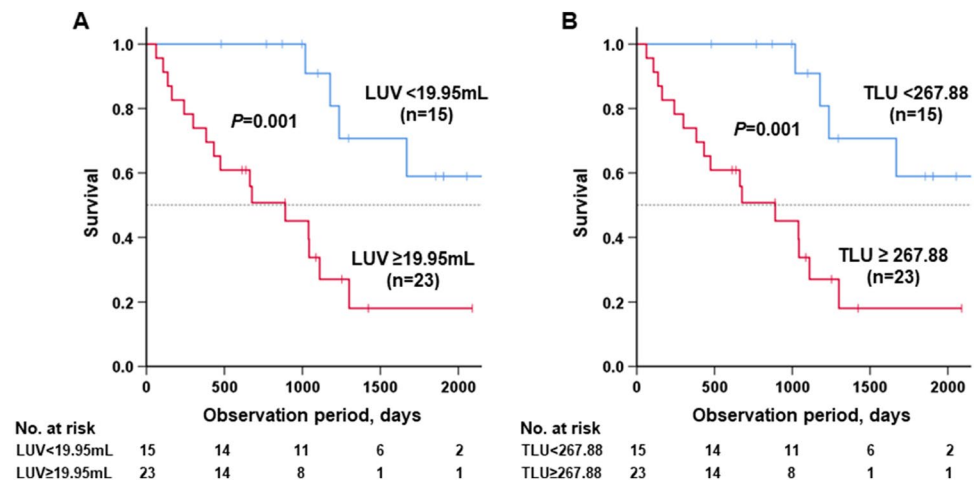


Fig. 3 Images from bone scintigraphy of a 69-year-old CRPC patient with multiple bone metastases. Whole-body planar images (A) show multiple abnormal uptake in the spine, bilateral acetabula, ribs, right humerus, left scapula, and right femur, suggesting multiple bone metastases. Abnormal accumulation due to multiple bone metastases are clearly identified on an anterior-view maximal intensity projection of SPECT images from the neck to the proximal thigh (B). SPECT/CT fusion images with coloring of regions above SUV 8 (C). Using Q.Metrix software (GE Healthcare), multiple bone metastases with

SUV ≥ 8 were segmented three-dimensionally and colored green on CT images (D) and on SPECT images (E). Physiologic hyperaccumulation of urine in the bladder and renal pelvis was removed from the segmentation using the software. Lesion uptake volume (LUV; defined as the extracted volume of bone metastases), and total lesion uptakes (the product of LUV and mean SUV of the regions of hyperaccumulation extracted as bone metastases) was 1183.7 mL and 14,798.9, respectively, in this patient

Fig. 4 Prognostic value of quantitative assessment of ^{99m}Tc -MDP bone SPECT/CT. Kaplan–Meier survival analysis revealed that lesion uptake volume (LUV) (A) and total lesion uptake (TLU) (B) were significantly associated with prostate cancer-specific survival (log-rank $P=0.001$). Cutoff points for indices were determined using the method of Contal and O’Quigley (Reference [20]). Kaplan–Meier curves for LUV and TLU were identical



Recent developments have allowed the quantification of bone SPECT/CT data [12–14]. Quantitative bone SPECT/CT analysis has been shown to be useful in differentiating bone metastases from other benign lesions [15, 21]. In a recent prospective study by Dittmann et al. [22], 60 mCRPC patients with bone metastases referred for ^{223}Ra therapy underwent pretreatment ^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid bone SPECT/CT to assess the accumulation rate and SUV of the radiopharmaceutical in bone tissue and the association between these indices and subsequent overall survival. According to that study, which followed patients for a mean of 13.6 months (range 1–42 months), both bone accumulation rate and mean SUV

showed significant associations with overall survival, suggesting that quantitative assessment of bone SPECT/CT may have prognostic value for mCRPC patients. However, evidence regarding the prognostic value of quantitative assessment of bone SPECT remains limited. The current study is the first to suggest that volumetric data from SPECT quantitative analysis may provide a more prognostic indicator than conventional BSI or EOD in mCRPC patients with bone metastases. These findings suggest that three-dimensional SPECT data are more useful for assessing bone metastatic burden than two-dimensional planar images.

PET/CT with ^{18}F -fluoride is an alternative to bone scintigraphy that comes with superior image resolution and

Table 3 Univariate analysis using a Cox proportional hazards regression model

	Univariate analysis			
	<i>P</i> value	Hazard ratio	95% confidential interval	
			Lower	Upper
Patient age (< 73 vs ≥ 73 years)	0.819	1.109	0.457	2.688
Time interval from progression to CRPC until bone SPECT/CT exam (< 343 vs ≥ 343 days)	0.073	2.407	0.921	6.292
T factor (2–3 vs 4)	0.264	0.604	0.250	1.462
N factor (0 vs 1)	0.116	2.279	0.815	6.374
M factor (0 vs 1)	0.162	0.500	0.189	1.321
Gleason score (≤ 8 vs 9–10)	0.296	1.677	0.635	4.427
Initial PSA (< 1603 vs ≥ 1603 ng/mL)	0.133	2.216	0.785	6.255
PSA at bone SPECT/CT exam (< 5.84 ng/mL vs ≥ 5.84 ng/mL)	<0.0001	11.018	3.029	40.083
ALP at bone SPECT/CT exam (< 155 IU/L vs ≥ 155 IU/L)	0.202	1.790	0.732	4.377
EOD scale (0–1 vs 2–4)	0.169	1.859	0.768	4.501
BSI (< 0.69 vs ≥ 0.69%)	0.084	2.234	0.898	5.560
LUV (< 19.95 vs ≥ 19.95 mL)	0.004	5.297	1.715	16.356
TLU (< 267.88 vs ≥ 267.88)	0.004	5.297	1.715	16.356

HR hazard ratio, *CI* confidential interval, *CRPC* castration-resistant prostate cancer, *SPECT/CT* single-photon emission computed tomography/computed tomography, *PSA* prostate-specific antigen, *ALP* alkaline phosphatase, *EOD* extent of disease, *BSI* bone scan index, *LUV* lesion uptake volume, *TLU* total lesion uptake

*TLU was excluded from the multivariate analysis because of its strong linear correlation with LUV (Pearson correlation coefficient, 0.974; $P < 0.0001$).

allows more accurate quantification [23]. Rohren et al. [17] determined a SUV threshold for obtaining volumetric data from ^{18}F -fluoride PET/CT for assessing bone metastatic burden by excluding most normal bone accumulations in 98 consecutive patients (90 men; mean age, 65.7 ± 14.2 years). According to that study, mean normal SUV_{max} on ^{18}F -fluoride PET/CT for all 543 bone sites, including the 12th thoracic vertebra, 5th lumbar vertebra, sacrum, ilium and femur, was 5.32 ± 0.99 [17]. Based on SUV measurements, they reported that an SUV threshold of 10 would exclude most normal bone and allow the calculation of volumetric parameters to assess bone metastatic burden from ^{18}F -fluoride PET/CT. A similar approach reported for ^{18}F -fluoride PET/CT was applied to $^{99\text{m}}\text{Tc}$ -MDP bone SPECT/CT in the current study to determine the optimal SUV threshold to exclude most normal bone sites. Using this SUV threshold, we showed that volumetric parameters representing bone metastatic burden can be measured in $^{99\text{m}}\text{Tc}$ -MDP bone SPECT/CT with excellent interobserver reproducibility (ICCs for both LUV and TLU were 0.997). Bone scintigraphy with $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals is still considered the imaging standard for assessing bone metastases in mCRPC [24]. The present study therefore demonstrated that volumetric parameters derived from $^{99\text{m}}\text{Tc}$ -MDP bone SPECT/CT for assessing bone metastatic burden represent promising imaging biomarkers with prognostic relevance for the

routine clinical workflow of mCRPC patients with bone metastases.

Our study has some limitations that should be kept in mind when interpreting the results. First, the study population was relatively small, and the research was conducted retrospectively on participants from a single institution. Despite the small number of cases, however, quantitative measures derived from bone SPECT were significantly associated with subsequent prostate cancer-related survival in mCRPC patients with bone metastases. Although prospective studies involving multiple centers with large numbers of patients are needed before quantitative bone SPECT analysis can be applied in clinical practice, this study provides promising data as a preliminary step toward more rigorous investigation in the future. Second, this study did not include blood data other than alkaline phosphatase and PSA, which are considered to be directly related to bone metastasis. Previous studies have reported a number of other blood data as predictors of survival for prostate cancer patients, including serum hemoglobin, white blood cell counts, lactate dehydrogenase, and C-reactive protein [25–27]. Third, only one SUV threshold setting was examined in this study; changing the SUV threshold setting may alter LUVs and TLUs, and affect their prognostic value.

In conclusion, quantitative analysis of bone metastatic burden by $^{99\text{m}}\text{Tc}$ -MDP bone SPECT/CT has the potential to provide prognostic value for mCRPC patients with bone

Table 4 Multivariate analysis

	Model 1			Model 2			Model 3		
	P value	Hazard ratio	95% confidential interval	P value	Hazard ratio	95% confidential interval	P value	Hazard ratio	95% confidential interval
			Lower			Lower			Lower
			Upper			Upper			Upper
Time interval from progression to CRPC until bone SPECT/CT exam (< 343 vs \geq 343 days)	0.008	4.529	1.492	13.744			0.023	3.228	1.171 8.895
PSA at bone SPECT/CT exam (< 5.84 vs \geq 5.84 ng/mL)				0.018	4.302	1.285 14.41			
BSI (< 0.69 vs \geq 0.69%)							0.026	3.107	1.147 8.416
LUV (< 19.95 vs \geq 19.95 mL)/TLU (< 267.88 vs \geq 267.88)	< 0.001	9.681	2.568	36.49	0.001	10.203			
	Model 4			Model 5					
	P value	Hazard ratio	95% confidential interval	P value	Hazard ratio	95% confidential interval	P value	Hazard ratio	95% confidential interval
			Lower			Lower			Lower
			Upper			Upper			Upper
Time interval from progression to CRPC until bone SPECT/CT exam (< 343 vs \geq 343 days)	0.011	3.852	1.355	10.951					
PSA at bone SPECT/CT exam (< 5.84 vs \geq 5.84 ng/mL)	< 0.001	16.488	4.027	67.513			10.588	2.832	39.576
BSI (< 0.69 vs \geq 0.69%)							1.753	0.673	4.563
LUV (< 19.95 vs \geq 19.95 mL)/TLU (< 267.88 vs \geq 267.88)									

Abbreviations as in Table 3

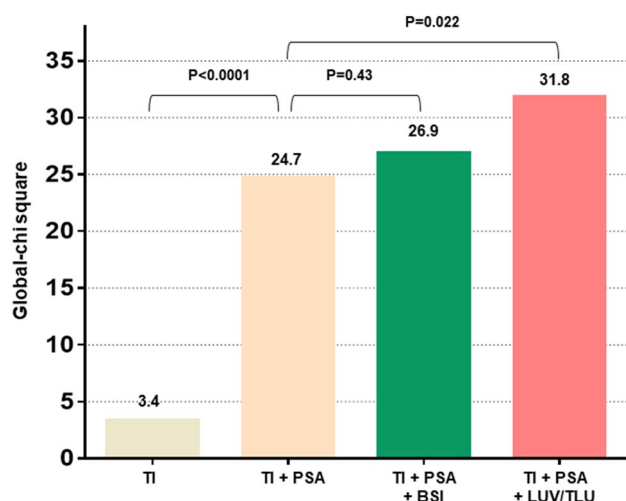


Fig. 5 Incremental prognostic value of quantitative assessment of bone SPECT/CT over time interval from progression to CRPC until the bone SPECT/CT study (TI) and prostate-specific antigen (PSA) at bone SPECT/CT study. Global chi-square testing reveals that PSA is of incremental prognostic value for TI. Combining LUV or TLU with TI and a PSA study shows a significant increment in prognostic value, while BSI does not contribute a significant increment in prognostic value as compared to TI+PSA

metastases. Volumetric parameters derived from SPECT data are significantly more associated with prostate-related survival than conventional planar image-based indices, including EOD and BSI. The SPECT quantitative indices LUV and TLU were found to have incremental prognostic value over PSA values and the time interval between progression to CRPC and bone SPECT/CT examination. Quantitative analysis of bone SPECT could be utilized to more accurately assess bone metastatic burden and provide better risk stratification of mCRPC patients.

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

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval and consent to participate The current study was approved by our institutional review board and the need to obtain written informed consent was waived since this study used existing clinical data (approval number: H2019-085). The opportunity to opt out of inclusion in this study was given through a notice on the hospital website. No patient showed any intention to be excluded from this study.

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–49. <https://doi.org/10.3322/caac.21660>.
- Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol*. 2000;31:578–83. <https://doi.org/10.1053/hp.2000.6698>.
- Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424–33. <https://doi.org/10.1056/NEJMoa1405095>.
- Sturge J, Caley MP, Waxman J. Bone metastasis in prostate cancer: emerging therapeutic strategies. *Nat Rev Clin Oncol*. 2011;8:357–68. <https://doi.org/10.1038/nrclinonc.2011.67>.
- Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351:1502–12. <https://doi.org/10.1056/NEJMoa040720>.
- Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway S, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer*. 1988;61:195–202. [https://doi.org/10.1002/1097-0142\(19880101\)61:1%3c195::aid-cnrcr2820610133%3e3.0.co;2-y](https://doi.org/10.1002/1097-0142(19880101)61:1%3c195::aid-cnrcr2820610133%3e3.0.co;2-y).
- Mitsui Y, Shiina H, Yamamoto Y, Haramoto M, Arichi N, Yasumoto H, et al. Prediction of survival benefit using an automated bone scan index in patients with castration-resistant prostate cancer. *BJU Int*. 2012;110:E628–34. <https://doi.org/10.1111/j.1464-410X.2012.11355.x>.
- Miyoshi Y, Yoneyama S, Kawahara T, Hattori Y, Teranishi J, Kondo K, et al. Prognostic value of the bone scan index using a computer-aided diagnosis system for bone scans in hormone-naïve prostate cancer patients with bone metastases. *BMC Cancer*. 2016;16:128. <https://doi.org/10.1186/s12885-016-2176-6>.
- Poulsen MH, Rasmussen J, Edenbrandt L, Høiland-Carlson PF, Gerke O, Johansen A, et al. Bone Scan Index predicts outcome in patients with metastatic hormone-sensitive prostate cancer. *BJU Int*. 2016;117:748–53. <https://doi.org/10.1111/bju.13160>.
- Utsunomiya D, Shiraishi S, Imuta M, Tomiguchi S, Kawanaka K, Morishita S, et al. Added value of SPECT/CT fusion in assessing suspected bone metastasis: comparison with scintigraphy alone and nonfused scintigraphy and CT. *Radiology*. 2006;238:264–71. <https://doi.org/10.1148/radiol.2373041358>.
- Palmedo H, Marx C, Ebert A, Kreft B, Ko Y, Türler A, et al. Whole-body SPECT/CT for bone scintigraphy: diagnostic value and effect on patient management in oncological patients. *Eur J Nucl Med Mol Imaging*. 2014;41:59–67. <https://doi.org/10.1007/s00259-013-2532-6>.
- Cachovan M, Vija AH, Horneberger J, Kuwert T. Quantification of ^{99m}Tc -DPD concentration in the lumbar spine with SPECT/CT. *EJNMMI Res*. 2013;3:45. <https://doi.org/10.1186/2191-219x-3-45>.
- Kaneta T, Ogawa M, Daisaki H, Nawata S, Yoshida K, Inoue T. SUV measurement of normal vertebrae using SPECT/CT with Tc-99m methylene diphosphonate. *Am J Nucl Med Mol Imaging*. 2016;6:262–8.
- Yamane T, Fukushima K, Shirotake S, Nishimoto K, Okabe T, Oyama M, et al. Test-retest repeatability of quantitative bone SPECT/CT. *Ann Nucl Med*. 2021;35:338–46. <https://doi.org/10.1007/s12149-020-01568-2>.

15. Qi N, Meng Q, You Z, Chen H, Shou Y, Zhao J. Standardized uptake values of (99m)Tc-MDP in normal vertebrae assessed using quantitative SPECT/CT for differentiation diagnosis of benign and malignant bone lesions. *BMC Med Imaging*. 2021;21:39. <https://doi.org/10.1186/s12880-021-00569-5>.
16. Tabotta F, Jreige M, Schaefer N, Becce F, Prior JO, Nicod LM. Quantitative bone SPECT/CT: high specificity for identification of prostate cancer bone metastases. *BMC Musculoskelet Disord*. 2019;20:619. <https://doi.org/10.1186/s12891-019-3001-6>.
17. Rohren EM, Etchebehere EC, Araujo JC, Hobbs BP, Swanston NM, Everding M, et al. Determination of skeletal tumor burden on 18F-fluoride PET/CT. *J Nucl Med*. 2015;56:1507–12. <https://doi.org/10.2967/jnumed.115.156026>.
18. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65:467–79. <https://doi.org/10.1016/j.eururo.2013.11.002>.
19. Koizumi M, Wagatsuma K, Miyaji N, Murata T, Miwa K, Takiguchi T, et al. Evaluation of a computer-assisted diagnosis system, BONENAVI version 2, for bone scintigraphy in cancer patients in a routine clinical setting. *Ann Nucl Med*. 2015;29:138–48. <https://doi.org/10.1007/s12149-014-0921-y>.
20. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Anal*. 1999;30:253–70. [https://doi.org/10.1016/S0167-9473\(98\)00096-6](https://doi.org/10.1016/S0167-9473(98)00096-6).
21. Zhang Y, Li B, Yu H, Song J, Zhou Y, Shi H. The value of skeletal standardized uptake values obtained by quantitative single-photon emission computed tomography-computed tomography in differential diagnosis of bone metastases. *Nucl Med Commun*. 2021;42:63–7. <https://doi.org/10.1097/mnm.0000000000001311>.
22. Dittmann H, Kaltenbach S, Weissinger M, Fiz F, Martus P, Pritzkow M, et al. The prognostic value of quantitative bone SPECT/CT before (223)Ra treatment in metastatic castration-resistant prostate cancer. *J Nucl Med*. 2021;62:48–54. <https://doi.org/10.2967/jnumed.119.240408>.
23. Bastawrous S, Bhargava P, Behnia F, Djang DS, Haseley DR. Newer PET application with an old tracer: role of 18F-NaF skeletal PET/CT in oncologic practice. *Radiographics*. 2014;34:1295–316. <https://doi.org/10.1148/rg.345130061>.
24. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, 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;34:1402–18. <https://doi.org/10.1200/jco.2015.64.2702>.
25. Machidori A, Shiota M, Kobayashi S, Matsumoto T, Monji K, Kashiwagi E, et al. Prognostic significance of complete blood count parameters in castration-resistant prostate cancer patients treated with androgen receptor pathway inhibitors. *Urol Oncol*. 2021;39:365.e1–e7. <https://doi.org/10.1016/j.urolonc.2020.09.036>.
26. Thurner EM, Krenn-Pilko S, Langsenlehner U, Stojakovic T, Pichler M, Gerger A, et al. The elevated C-reactive protein level is associated with poor prognosis in prostate cancer patients treated with radiotherapy. *Eur J Cancer*. 2015;51:610–9. <https://doi.org/10.1016/j.ejca.2015.01.002>.
27. Yamada Y, Sakamoto S, Rii J, Yamamoto S, Kamada S, Imamura Y, et al. Prognostic value of an inflammatory index for patients with metastatic castration-resistant prostate cancer. *Prostate*. 2020;80:559–69. <https://doi.org/10.1002/pros.23969>.

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