Journal of Nuclear Medicine, published on May 22, 2020 as doi:10.2967/jnumed.119.240408

The prognostic value of quantitative bone scan SPECT/CT prior to 223Ra treatment in metastatic castration-resistant prostate cancer (mCRPC)

Dittmann Helmut[1], Kaltenbach Sabine[1], Weissinger Matthias[1], Fiz Francesco[1], Martus Peter[2], Pritzkow Maren[1], Kupferschlaeger Juergen[1], la Fougère Christian[1,3]

[1]Department of Nuclear Medicine and Clinical Molecular Imaging, University Hospital Tuebingen, Germany

[2]Institute for Clinical Epidemiology and Applied Biometry, University of Tuebingen, Germany

[3]iFIT-Cluster of Excellence, University of Tuebingen, Germany

CORRESPONDING AUTHOR:

Helmut Dittmann, MD

e-mail: helmut.dittmann@med.uni-tuebingen.de

ORCID: 0000-0001-6840-5571

KEYWORDS:

SPECT/CT, quantification, prostate cancer, bone scan, 223Ra

RUNNUNG TITLE

Quantitative SPECT/CT prior to 223Ra

Total word count: 4908

ABSTRACT

Rationale

Radiolabelled bisphosphonates such as 99mTc-DPD typically show intense uptake in skeletal metastases from metastatic castration resistant prostate cancer (mCRPC). Extensive bone involvement is regarded a risk factor for mCRPC patients treated with 223Ra-radiumdichloride (223Ra). Aim of this study was to quantify 99mTc-DPD uptake by means of SPECT/CT prior to 223Ra and compare results to the feasibility of treatment and overall survival (OS).

Methods

60 consecutive mCRPC patients were prospectively included into this study. SPECT/CTs of the central skeleton covering the scull to mid-femoral level were carried out before the first cycle of 223Ra. The bone compartment was defined by means of low-dose CT. Emission data were corrected for scatter, attenuation and decay supplemented by resolution recovery using dedicated software. The Kaplan-Meier estimator, U-Test and Cox regression analysis were employed for statistics.

Results

Total 99mTc-DPD uptake of the central skeleton varied between 11-56 percent of injected dose (%ID) or 1.8-10.5 %ID/1000 ml bone volume (%ID/L). SUVmean ranged from 1.9-7.4 while SUVmax range was 18-248. Patients unable to complete 223Ra treatment due to progression a/o. cytopenia (n=23) showed significantly higher uptake (31.9 vs. 25.4%ID; 6.0 vs 4.7x %ID/L, P <0.02). OS after 223Ra (median: 15.2 months) was reduced to 7.3 months in case of skeletal uptake ≥26 %ID as compared to 30.8 months if <26 %ID (p=0.008). Similar results were obtained for %ID/L and SUVmean. SUVmax was not correlated to survival. %ID/L was identified as an independent prognostic factor for OS (Hazard ratio 1.381 per unit) along with number of previous treatment lines.

Conclusion

Quantitative SPECT/CT of bone scans performed at baseline is prognostic for survival of mCRPC patients treated with 223Ra.

INTRODUCTION

Metastatic castration resistant prostate cancer (mCRPC) is a bone dominant disease with about 90% of patients affected by osseous involvement (*1*). Skeletal metastases are a major threat to patients' quality of life as they cause pain, pathological fractures and neurological dysfunctions. Depletion of the hematopoetic marrow by tumor expansion is recognized as the major cause of cancer-specific death in mCRPC (*2*). To overcome this, various new treatments have been developed including novel radiopharmaceuticals (*3,4*).

Bone scintigraphy using 99m-Technetium-labelled bisphosphonates is still considered the standard of choice for imaging of bone metastases in mCRPC (*5*). With introduction of SPECT/CT, sensitivity and diagnostic accuracy has been considerably improved as compared to 2D-imaging (*6*). The extent of bone involvement is usually reported applying qualitative or semi-quantitative measures such as the number of lesions. PET/CT with 18F-sodiumfluoride (NaF-PET/CT) is an alternative to bone scintigraphy that comes with superior image resolution and allows for absolute quantification (*7*). However, NaF-PET/CT suffers from limited availability and thus has not yet been recommended by guidelines (*8*). Moreover, it lacks reimbursement in most countries.

Osteotropic radiopharmaceuticals also allow for targeted irradiation following a Theranostic approach (*9*). The alpha-emitter 223Ra-radiumdichloride (223Ra) was shown to improve overall survival in mCRPC (*10*) and reduce skeletal-related events at favorable tolerability (*11*). Conversely, the optimal role of 223Ra in the growing instrumentarium against mCRPC has yet to be defined (*12,13*).

Earlier work has demonstrated that the extent of bone involvement as identified by bone scans is a risk factor for patients with mCRPC. In the pivotal 223Ra trial, A large number of skeletal lesions was associated with elevated risk for cytopenia (*14*). While the rate of anemia was comparable in the 223Ra and placebo group, thrombocytopenia was more frequent in 223Ra. High osseous tumor load as measured by NaF-PET/CT was shown to be associated with poor overall survival (OS) after

223Ra (*15*). More recently, semi-automated estimation of bone metastatic involvement creating a “bone scan index” has been shown to be related to poor survival of patients with great tumor burden (*16,17*). Since the latter approach involves only planar images, the projected two-dimensional anatomy may be subject to summation artifacts (*18*). As a result, differentiation of metastases from normal bone can be challenging in advanced tumor spread and a bone scan index might not be obtainable for all patients (*17*). Delineation of metastatic tumor load would be especially difficult in case of a “Superscan”finding (*19*).

Recent development has allowed for quantification of SPECT/CT data similar to PET/CT (*20,21*). Here we report on quantitative bone SPECT/CT to analyze bisphosphonate uptake of the central skeleton. This approach is based on the notion that the higher overall bone uptake is, the higher the osteoblastic tumor load. We hypothesize that the resulting measure of bone metabolism may be prognostic in patients treated with 223Ra. A prospective clinical study was conceived, aiming to evaluate if quantitative bone scan imaging is correlated to completion of the subsequent 223Ra treatment course and survival.

PATIENTS AND METHODS

Patient Population

This prospective, observational study included mCRPC patients with symptomatic osseous metastases referred to our institution for 223Ra treatment. A bone scan including quantitative SPECT/CT was planned in all individuals lacking a recent pre-test (no longer than 2 months prior to the planned treatment). CT or MRI scans of the thorax, abdomen and pelvis region were performed to evaluate visceral and lymphonodal involvement. Lymph node metastases up to a maximum diameter of 3 cm were accepted while patients with visceral metastasis were excluded. This study was conceived as part of an extensive clinical protocol on SPECT/CT quantification registered in the German Registry for Clinical Studies (DRKS00013571) (*22*).The study was approved by the institutional review board (Decision No. 747/2014BO1) and all subjects signed a written informed consent.

223Ra Treatment

223Ra treatment was scheduled as a series of 6 cycles at 4 weeks interval with dose adapted to body weight (55 kBq/kg). In case of cytopenia, subsequent cycles could be postponed up to week 8 from the previous dose to allow for recovery. 223Ra treatment was considered completed in patients who received 5-6 cycles. Serum PSA level and blood cell counts were collected at baseline and blood cell counts were recorded appr. every two weeks during treatment. Cytopenia was classified according to CTCAE 4.03 criteria (*23*). Since osseous progression as well as treatment-related hematotoxicity may lead to reduced blood cell numbers, distinction between these causes can be challenging or even impossible in individual cases. In practice, decreased blood cell levels are often a combination of both. In this study, we report any reduction of blood cell elements corresponding to a CTCAE Grade 2 or higher as cytopenia irrespective of its possible cause.

Bone Scan Imaging

Imaging was performed within 30 d before the first cycle of 223Ra. Patients received on average 632 ± 56 MBq 99mTc-DPD (CIS Bio International, Gif-sur-Yvette, France) intravenously. A dual

detector SPECT/CT camera (GE Discovery NM/CT 670 Pro®; GE Healthcare, Chicago, USA) was used throughout. Approximately 3 hours from 99mTc-DPD injection, planar images of the whole body were acquired in anterior and posterior views (table feed 15 cm/min acquisition, 1028 x 256 matrix) followed by SPECT/CT. The SPECT acquisition parameters were: Camera heads in H-Mode, 3 fields of view (FOV) covering an area from the skull to mid-femoral level with arms adducted laterally to the body, 128 x 128 matrix, 30 steps and 15 sec. acquisition /step. Images were reconstructed with an ordered subset expectation maximization iterative protocol (4 iterations, 10 subsets) without pre- or postfiltering. Then, a non-contrast CT scan (dose-length product 358 to 462 mGy-cm, 120 kV, slice thickness 2.5 mm) was performed for attenuation correction and anatomical mapping. Finally, the reconstructed SPECT data were co-registered with CT images on a dedicated workstation (Xeleris 4®, GE Healthcare, Chicago, USA). Images were read by two experienced nuclear medicine specialists. Focal areas with increased uptake suspicious of osseous metastasis were recorded and classified as either less than 6 lesions, 6 and up to 20, more than 20 or Superscan as depicted on planar whole body images. Superscan was referred to as a bone scan showing diffuse, intense skeletal uptake without renal and background radioactivity.

Quantification

To quantify 99mTc-DPD uptake, tomographic SPECT data were corrected for attenuation, scatter and resolution recovery using a dedicated software algorithm (Evolution®, GE Healthcare, Chicago, USA). SPECT/CT of a cylindrical phantom (diameter x height 21x20 cm) filled with 99m-Tc and water at known activity concentration was used to calculate system sensitivity. This procedure was repeated after each system calibration (uniformity, energy, linearity) every 6 months. In addition, planar sensitivity using a point source was measured weekly to define a reference value (tolerance +/- 5%).

Volumes of interest (VOIs) were defined by means of a proprietary semi-automatic segmentation application (Q.metrix®, GE Healthcare, Chicago, USA). At first, the skeletal bone compartment was delineated using CT-measured density (lower threshold: +200 HU). Areas outside the skeletal compartment such as vessel calcifications or else were meticulously reviewed and manually excluded. The resulting VOI thus represented the entire central skeleton compartment from the

skull to mid-femoral level. Then, the following measures of tracer uptake in the bone VOI were extracted: percent injected dose (%ID), percent injected dose per 1000 ml bone volume (%ID/L), SUVmean and the maximum SUV in any of a patients tumor lesions (SUVmax).

Statistics

Differences in parameters between patient groups (complete vs. incomplete 223Ra treatment) were compared using Mann-Whitney U-Test. The Kaplan Meier Estimator and Log Rank test were used to assess patients' survival fraction consistent with quantitative SPECT/CT variables. Receiver operating characteristic (ROC) analysis was executed to analyze the performance of SPECT/CT to prognosticate early death and incomplete treatment. Simple and multiple Cox regression proportional hazards analysis and logistic regression were performed to analyze the influence of variables on OS and treatment completion. Stepwise forward variable selection was applied with inclusion / exclusion probabilities 0.05/0.10. All analyses were performed employing SPSS® 25 software (IBM, Armonk, NY, USA). An alpha level of 0.05 (two-sided) was considered significant. No correction for multiple testing was performed.

RESULTS

223Ra Treatment and Follow up

From 03/2015 until 06/2018, 65 consecutive patients fulfilled the inclusion criteria for this study and subsequently received at least one cycle of 223Ra. 60 of these individuals could be included. Reasons for inclusion failure were lacking or incomplete SPECT/CT data (n=4) while SPECT/CT could only be performed after the first 223Ra cycle in another patient. The clinical characteristics of involved patients are shown in (TABLE 1). The mean follow up after 223Ra treatment was 13.6 months (range 1 to 42). 35 patients died during the study period. Median OS since the first 223Ra therapy cycle was 15.2 months. Moderately decreased blood cell counts corresponding to CTCAE grade 2 were present in 7 patients before 223Ra (TABLE 1) while the vast majority of patients had no relevant myelosuppression. Newly onset cytopenia CTCAE grade 2-4 was observed in 21/53 patients (38.6%, 95% CI 26.5%-54.0%) during 223Ra. Severe myelosuppression grade 3/4 developed in 10 patients (n=9 newly evolved [6 anemias, no thrombocytopenia, 2 neutropenias, 1 leucopenia]; n=1 aggravation of preexisting bicytopenia in erythocytes and platelets (17%, 95% CI 8.1-29.9)). The scheduled 223Ra course could be completed in 36/60 individuals with 279 cycles applicated in total (6 cycles: n=36; 4 cycles: n=6; 3 cycles: n=7; 2 cycles: n=7; 1 cycle: n=4). Reasons for early termination (prevalence 40%, 95% CI 27.6% - 53.5%) were tumor progression (n=15), cytopenia grade 3/4 (n=5), or a combination of both (n=3). In one patient without evidence for myelosuppression or progression, 223Ra was terminated after 4 cycles following a novel reported contraindication against 223Ra combined with abiraterone and prednisolone. This case was excluded from analyses stratified for completed vs. incomplete 223Ra treatment. In total, 13 patients continued abiraterone or enzalutamide under 223Ra before contraindication for combination treatment was reported in 11/2017. No patient received 223Ra combined to novel anti-androgens in the remaining study period.Two patients developed pathological fractures during 223Ra treatment (one on 223Ra mono, one on 223Ra plus abiraterone), both of which were assigned to additional external beam irradiation before 223Ra was resumed.

Quantitative 99mTc-DPD Uptake as Prognosticator of Survival

Planar whole body scans revealed increased uptake in osseous metastases in all cases. The majority of scans visualized multiple bone lesions with increased tracer uptake classified as either >20 lesions or Superscan in about two thirds of patients (see TABLE 1). Quantification showed a mean total 99mTc-DPD uptake of 27.8 %ID in the central skeleton or 5.2 %ID/L (see TABLE 2) with considerable variance between individuals. The mean 99mTc-DPD uptake was calculated at SUVmean 4.1. Tumoral SUVmax showed particularly high variability in our patient cohort. Typical clinical examples are shown in (FIGURE 1 and 2).

Kaplan Meier analyses with thresholds set to median revealed significantly shortened OS of 7.3 months in patients with ≥26 %ID or >4.5 %ID/L, respectively (see FIGURE 3). The cohort of individuals with lower total uptake had favorable survival of 30.8 and 19.6 months, instead. A similar trend was also seen for SUVmean with threshold at 3.9 (7.3 vs. 17.8 months). In contrast, SUVmax was not associated with survival. The one-year OS rate after start of 223Ra was 55% (n=29/53, n=7 censored). ROC analysis of SPECT/CT variables demonstrated that high %ID and %ID/L were moderately accurate to prognosticate death during the first year (FIGURE 4). SUVmean showed only a trend for connection with first year mortality while SUVmax was not linked with early death.

Quantitative SPECT/CT variables and clinical characteristics (age, PSA level, tumor load categories, prior chemotherapy, number of previous treatment lines for mCRPC) were included as candidates in a Cox regression model for prediction of OS. Because PSA level was not distributed normally, decadic logarithm PSA was used instead. At univariate regression analyses, %ID, %ID/L, extent of bone disease, number of previous treatment cycles for mCRPC and history of chemotherapy were significantly associated with OS. Multiple Cox regression identified %ID/L and the number of previous therapy lines for mCRPC as independent predictors of survival (see TABLE 3).

Early Termination vs. Completed 223Ra Treatment

Median OS of patients unable to complete the full 223Ra treatment due to progression a/o cytopenia (n=23) was only 5.8 months while patients who received the complete course had a

median survival of 30.8 months (*P* <0.001; data not shown). Patients with early terminated treatment showed a significantly higher total 99mTc-DPD uptake (mean 31.9 %ID vs. 25.4, *P*= 0.017; %ID/L 6.0 vs. 4.7, *P*= 0.014) while SUVmean or SUVmax were not statistically different between groups. ROC analysis demonstrated an association of %ID and %ID/L with incomplete 223Ra, though considerable overlap limited discrimination from patients able to receive full treatment (see FIGURE. 5). Univariate regression analysis demonstrated %ID/L and the number of previous treatment lines as predictors of incomplete 223Ra therapy (TABLE 3). Multiple Logistic regression identified %ID/L as the sole independent predictor of incomplete 223Ra treatment.

DISCUSSION

Quantitative measures of bone metastatic disease are desirable for risk stratification in patients considered for 223Ra treatment. The current prospective study on quantitative bone scan SPECT/CT demonstrated shortened overall survival of mCRPC patients with high bisphosphonate uptake prior to 223Ra. All measures of average bone uptake in the central skeleton (%ID, %ID/L and SUVmean) were associated with survival. In particular, %ID at a threshold ≥26 showed the strongest separation of prognostic groups (7.3 months vs. more than 30 months survival). Multiple regression identified %ID/L as an independent prognostic variable of overall survival along with the number of previous treatment lines. Furthermore, high uptake was associated with inability to complete the planned 223Ra sequence, due to progression or cytopenia. In fact, %ID/L was the only independent prognosticator of completion failure at multivariate analysis. The observed relations should not lead to denial of 223Ra treatment, as patients unable to complete the course may still benefit from 223Ra. While overlap between prognostic groups may limit the use of quantitation for individual decision making, risk stratification could be helpful for clinical studies on mCRPC treatment. In contrast, SUVmax of the most intensive lesion seems to be independent of cumulative tumor load. According to NaF-PET/CT(*15*) and current results, SUVmax was not correlated to survival. Thus, maximum uptake does not seem to be of value to define a reference lesion that might prognosticate outcome.

Our results correspond to the findings of retrospective studies demonstrating poor survival in extensive metastatic burden expressed as a “bone scan index” (*17*) or high tumor volume estimated by quantitative NaF-PET/CT (*15*). Recently, a similar approach has been suggested using quantification by SPECT/CT of bone scans (*24*). It has also been shown that bisphosphonate uptake as measured by quantitative SPECT/CT is closely correlated to that of NaF (*25*). Methodology in the previous studies differed from our approach in that cut-offs, either based on SUV or count-rates, were hitherto used to separate metastatic from normal bone so as to define the osseous tumor load. Overlap between uptake of normal and metastatic bone (*26*) is a potential limitation of cut-offs which may lead to false positive results. This might be circumvented by using a relatively high cut-off, possibly at the price of underestimating tumor volume. In addition, cut-offs will

have to be individually established for the scanner used for imaging (*27*). By omitting any cut-off, our approach does not call for individual adaption and should be independent of scanner features. Obviously, the hereby presented method does not provide a measure of tumor volume.

Median OS in our cohort is in keeping with the results of the pivotal Phase III trial (15.2 vs. 14.9 month) (*10*). Compared to the latter, the proportion of patients with extensive bone disease (i.e. more than 20 tumor lesions or Superscan) was considerably higher in the current study (65 vs 41%). Equal outcome in our study may be due to the availability of further treatment options introduced since the previous trial which may be used after 223Ra, in particular abiraterone and enzalutamide. In comparison, OS was shorter in the retrospective studies of PET/CT(*15*) and bone scan imaging (*17*). Most probably, this might be explained by more advanced tumor burden.

As mathematical tumor models suggest that 223Ra targets only a fraction of bone tumor areas (*28*), there is a need to improve our understanding of 223Ra distribution. Imaging with 223Ra for the purpose of dosimetry is limited by the low number of photons (*29*). It has been shown that uptake of bisphosphonates is correlated to that of 223Ra (*30*). Though quantitative SPECT/CT cannot be used to clarify the unknown microdistribution, it is obvious that further studies should adress individual dosimetry in patients with advanced disease.

Recently, the indication for 223Ra was restricted by the European Medicines Agency, as in a prospective study the combination of 223Ra with abiraterone and prednisone or prednisolone was associated with an increased risk for fractures (*31*). Since no quantitative analysis of bone scans was performed in this study, the potential influence of bisphosphonate uptake can only be speculated about.

Limitations

Our survey included a relatively small cohort of patients, thus it has to be considered hypothesis-generating and a larger study is desirable to confirm the results. However, we could include all patients in the observational period, thus we should not expect bias in the selection of our sample.

Due to the small absolute number of grade 3/4 cytopenia, our study was not powered to explore the relationship between quantitative imaging parameters and clinically relevant myelosuppression. In the current study, alkaline phosphatase, a potential risk factor for survival in mCRPC patients (*32*), was not systematically recorded at baseline, thus it could not be included in the multivariate analysis.

CONCLUSION

This study indicates that bisphosphonate uptake of the central skeleton as quantified by SPECT/CT prior to 223Ra is prognostic of outcome. Our results should encourage further studies on possible prognostic markers including tumor-volume based quantitation to identify the best approach for risk stratification in mCRPC.

FINANCIAL DISCLOSURE

This study was in part funded by a grant from GE Healthcare (received by author CLF). HD and CLF received honoraria for advisory boards and training lectures on the use of 223Ra from Bayer Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is baseline bone scan quantification by SPECT/CT associated with survival in patients starting 223Ra treatment?

PERTINENT FINDINGS: In a prospective clinical cohort study of 60 mCRPC patients assigned for 223Ra treatment, high total skeletal bisphosphonate uptake at baseline was associated with significantly shortened survival. Conversely, survival of patients with low uptake was superior to that observed in earlier studies.

IMPLICATIONS FOR PATIENT CARE: Quantitative bone scan SPECT/CT may be useful for risk stratification in mCRPC.

LITERATURE

1. Bubendorf L, Schopfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol.* 2000;31:578-583.

2. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. What do prostate cancer patients die of? *Oncologist.* 2011;16:175-181.

3. Chandrasekar T, Yang JC, Gao AC, Evans CP. Mechanisms of resistance in castration-resistant prostate cancer (CRPC). *Transl Androl Urol.* 2015;4:365-380.

4. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol.* 2017;71:630-642.

5. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol.* 2016;34:1402-1418.

6. Helyar V, Mohan HK, Barwick T, et al. The added value of multislice SPECT/CT in patients with equivocal bony metastasis from carcinoma of the prostate. *Eur J Nucl Med Mol Imaging.* 2010;37:706-713.

7. 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;34:1295-1316.

8. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate cancer, Version 1.2016. *J Natl Compr Canc Netw.* 2016;14:19-30.

9. Goyal J, Antonarakis ES. Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases. *Cancer Lett.* 2012;323:135-146.

10. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213-223.

11. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol.* 2014;15:738-746.

12. Jacene H, Gomella L, Yu EY, Rohren EM. Hematologic toxicity from radium-223 therapy for bone metastases in castration-resistant prostate cancer: Risk factors and practical considerations. *Clin Genitourin Cancer.* 2018;16:e919-e926.

13. Den RB, George D, Pieczonka C, McNamara M. Ra-223 treatment for bone metastases in castrate-resistant prostate cancer: practical anagement issues for patient selection. *Am J Clin Oncol.* 2019;42:399-406.

14. Vogelzang NJ, Coleman RE, Michalski JM, et al. Hematologic safety of radium-223 dichloride: baseline prognostic factors associated with myelosuppression in the ALSYMPCA trial. *Clin Genitourin Cancer.* 2017;15:42-52.e48.

15. Etchebehere EC, Araujo JC, Fox PS, Swanston NM, Macapinlac HA, Rohren EM. Prognostic factors in patients treated with 223Ra: The role of skeletal tumor burden on baseline 18F-Fluoride PET/CT in predicting overall survival. *J Nucl Med.* 2015;56:1177-1184.

16. Ulmert D, Kaboteh R, Fox JJ, et al. A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the Bone Scan Index. *Eur Urol.* 2012;62:78-84.

17. Fosbol MO, Petersen PM, Kjaer A, Mortensen J. (223)Ra therapy of advanced metastatic castration-resistant prostate cancer: Quantitative assessment of skeletal tumor burden for prognostication of clinical outcome and hematologic toxicity. *J Nucl Med.* 2018;59:596-602.

18. Agrawal K, Marafi F, Gnanasegaran G, Van der Wall H, Fogelman I. Pitfalls and limitations of radionuclide planar and hybrid bone imaging. *Semin Nucl Med.* 2015;45:347-372.

19. Constable AR, Cranage RW. Recognition of the superscan in prostatic bone scintigraphy. *Br J Radiol.* 1981;54:122-125.

20. Bailey DL, Willowson KP. Quantitative SPECT/CT: SPECT joins PET as a quantitative imaging modality. *Eur J Nucl Med Mol Imaging.* 2014;41 Suppl 1:S17-25.

21. Bailey DL, Willowson KP. An evidence-based review of quantitative SPECT imaging and potential clinical applications. *J Nucl Med.* 2013;54:83-89.

22. DRKS. German Clinical Trials Register (DRKS). https://www.drks.de/drks_web/setLocale_EN.do Accessed 3 April, 2020.

23. CTCAE. CTCAE Files. https://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed 3 April, 2020.

24. Umeda T, Koizumi M, Fukai S, et al. Evaluation of bone metastatic burden by bone SPECT/CT in metastatic prostate cancer patients: defining threshold value for total bone uptake and assessment in radium-223 treated patients. *Ann Nucl Med.* 2018;32:105-113.

25. Arvola S, Jambor I, Kuisma A, et al. Comparison of standardized uptake values between (99m)Tc-HDP SPECT/CT and (18)F-NaF PET/CT in bone metastases of breast and prostate cancer. *EJNMMI Res.* 2019;9:6.

26. Kuji I, Yamane T, Seto A, Yasumizu Y, Shirotake S, Oyama M. Skeletal standardized uptake values obtained by quantitative SPECT/CT as an osteoblastic biomarker for the discrimination of active bone metastasis in prostate cancer. *Eur J Hybrid Imaging.* 2017;1:2.

27. Matheoud R, Goertzen AL, Vigna L, Ducharme J, Sacchetti G, Brambilla M. Five-year experience of quality control for a 3D LSO-based whole-body PET scanner: results and considerations. *Phys Med.* 2012;28:210-220.

28. Moreira HMR, Guerra Liberal FDC, O'Sullivan JM, McMahon SJ, Prise KM. Mechanistic Modeling of Radium-223 Treatment of Bone Metastases. *Int J Radiat Oncol Biol Phys.* 2019;103:1221-1230.

29. Hindorf C, Chittenden S, Aksnes AK, Parker C, Flux GD. Quantitative imaging of 223Ra-chloride (Alpharadin) for targeted alpha-emitting radionuclide therapy of bone metastases. *Nucl Med Commun.* 2012;33:726-732.

30. Pacilio M, Ventroni G, De Vincentis G, et al. Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting (223)Ra-dichloride. *Eur J Nucl Med Mol Imaging.* 2016;43:21-33.

31. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20:408-419.

32. Pinart M, Kunath F, Lieb V, Tsaur I, Wullich B, Schmidt S. Prognostic models for predicting overall survival in metastatic castration-resistant prostate cancer: a systematic review. *World J Urol.* December 17, 2018 [Epub ahead of print].

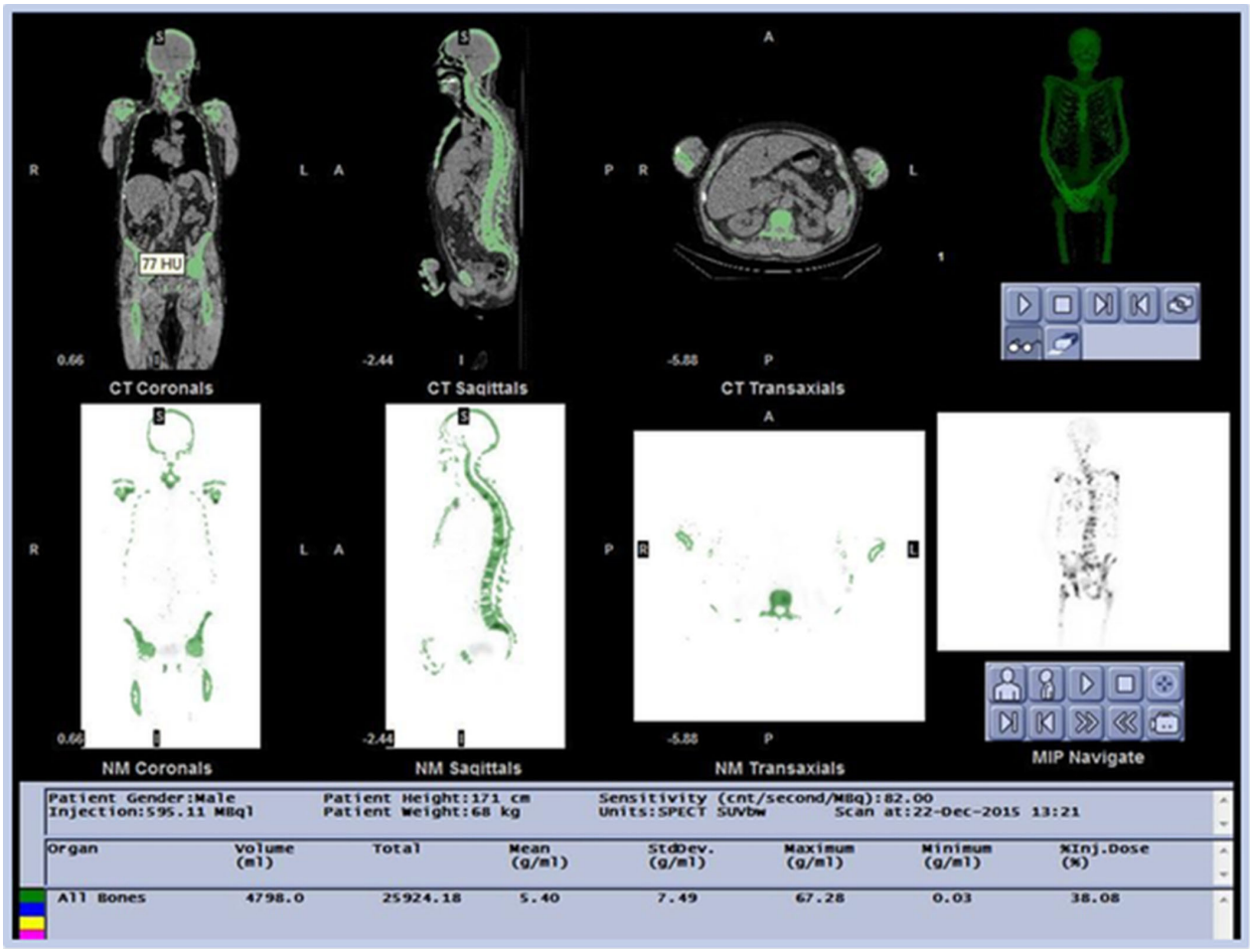


FIGURE 1: The bone compartment as defined by CT and quantitative data for 99mTc-DPD uptake in a mCRPC patient with osseous metastases.

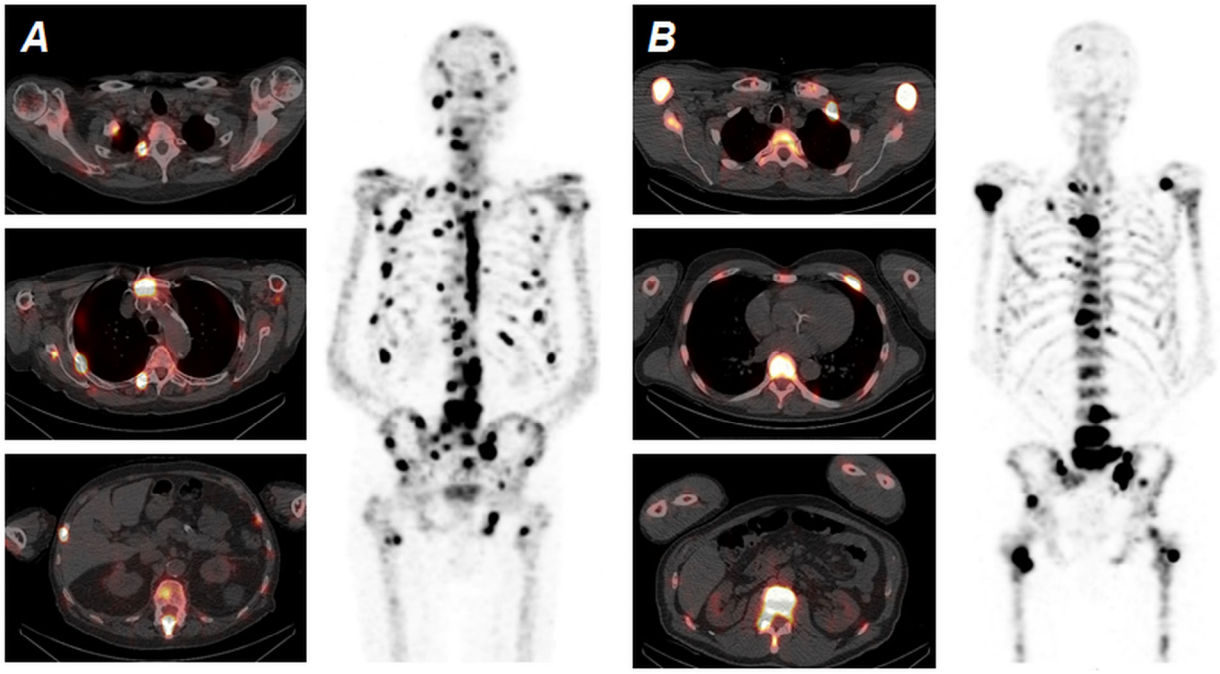


FIGURE 2: Typical case studies in two patients with disseminated bone metastasis. Quantitative SPECT/CT revealed low to moderate parameters of 99mTc-DPD uptake except for pronounced SUVmax in patient *A* [left] while all measures were markedly high in patient *B* [right]. Both patients subsequently received 6 cycles of 223Ra. OS survival in patient *A* (85 y) was 13 months while patient *B* (72 y) only survived for 7 months after the start of 223Ra.

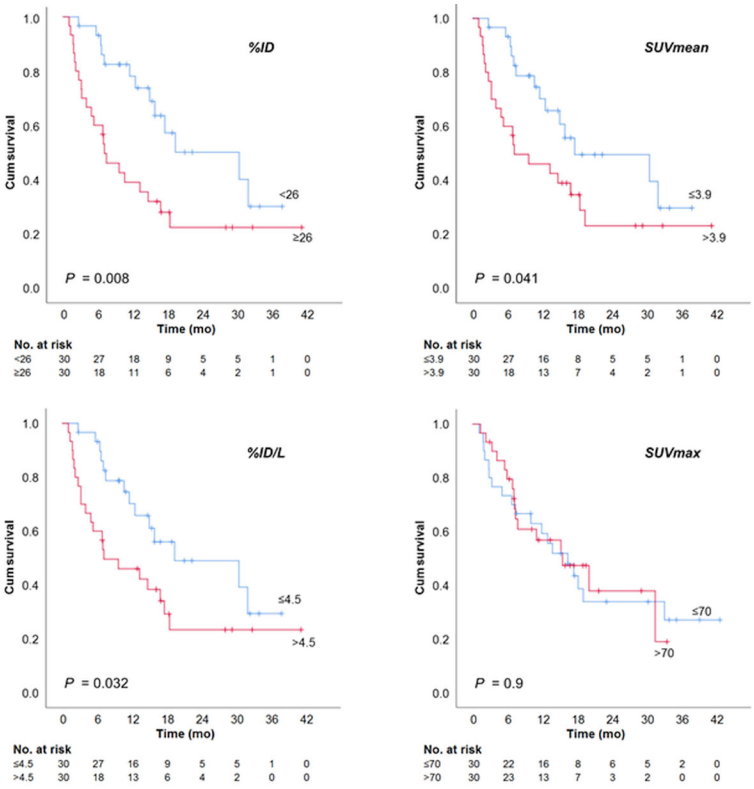
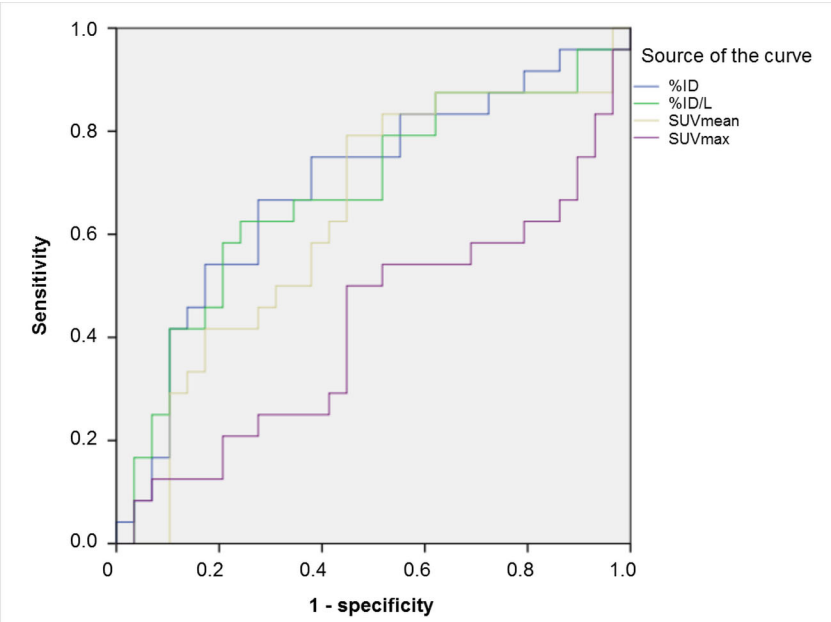
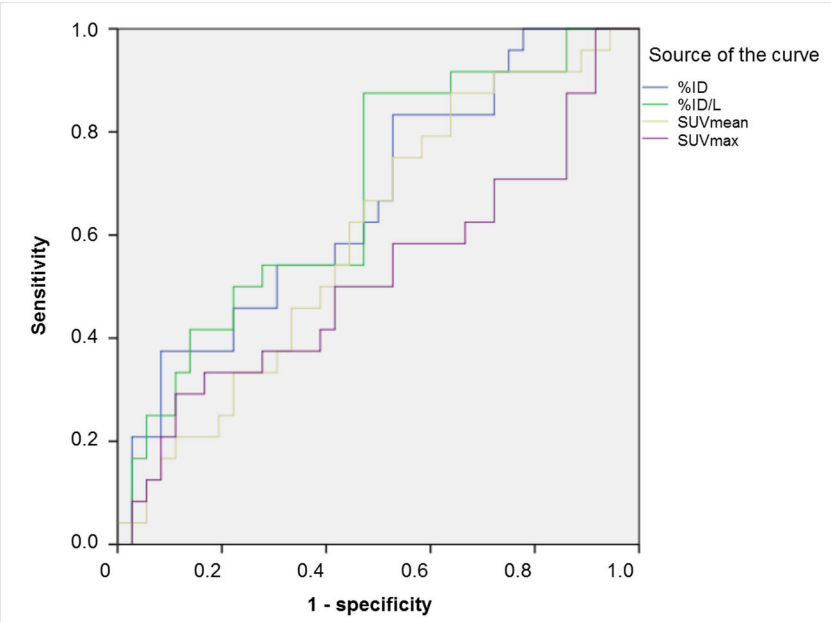


FIGURE 3: Kaplan Meier analysis of overall survival since start of 223Ra treatment stratified for quantitative SPECT/CT measures of 99mTc-DPD uptake.



Variable	Area under the ROC curve	SE	95%-CI	*P*-Value
%ID	0.694	0.075	0.547 - 0.841	0.016
%ID/L	0.681	0.076	0.532 - 0.830	0.024
SUVmean	0.634	0.079	0.479 - 0.788	0.097
SUVmax	0.421	0.081	0.262 - 0.580	0.326

FIGURE 4: ROC analyses showing the sensitivity and specificity of quantitative SPECT/CT variables in prognosticating death within the first year after 223Ra.



Variable	Area under the ROC curve	SE	95%-CI	*P*-Value
%ID	0.668	0.071	0.529 - 0.806	0.029
%ID/L	0.684	0.070	0.547 - 0,821	0.016
SUVmean	0.602	0.074	0.457 - 0.746	0.184
SUVmax	0.520	0.080	0.363 - 0.676	0.798

FIGURE 5: ROC analyses showing the sensitivity and specificity of quantitative SPECT/CT variables in prognosticating failure to complete the subsequent 223Ra therapy.

Patient and tumor related variable	***n* or median (range)**	**%**
Age - years	71 (55-90)	
Gleason score		
≤7	17	28
≥8	36	60
unknown	7	12
PSA Level - µg/l	65 (1.1-9375)	
Preexisting cytopenia grade 2	7	12
anemia	5	8
neutropenia	1	
thrombocytopenia	1	
Prior treatment lines for mCRPC		
0	17	28
1	20	33
2	14	23
3 or more	9	15
Prior chemotherapy	26	43
Extent of bone disease		
<6 metastases	4	7
6-20 metastases	17	28
>20 metastases	32	53
Superscan	7	12

TABLE 1: Baseline characteristics of included patients. Note: Percentages may not sum up to 100 due to rounding.

Parameter	Mean	Median	Range
Skeletal volume - ml	5447	5491	4161 - 7720
%ID	27.8	25.7	11 - 56
%ID/L	5.2	4.5	1.8 - 10.5
SUVmean	4.1	3.9	1.9 - 7.4
SUVmax	82.4	70.2	18 - 248

TABLE 2: Results of quantitative SPECT/CT of bone scans prior to 223Ra treatment.

Overall Survival

	univariate Regression			Cox multiple Regression		
Variable	***P*-Value**	**Hazard Ratio**	**95%-CI**	***P*-Value**	**Hazard Ratio**	**95%-CI**
%ID; *per 1 unit*	0.005	1.046	1.014 - 1.079			
%ID/L; *per 1 unit*	0.003	1.259	1.083 - 1.464	<0.001	1.381	1.162 - 1.643
SUVmean; *per 1 unit*	0.068	1.225	0.985 - 1.523			
SUVmax; *per 1 unit*	0.920	1.00	0.991 - 1.008			
Age; *per year*	0.159	1.033	0.987 - 1.080			
Tumor load; *per 1 category*	0.015	1.744	1.112 - 2.736			
prior treatment lines; *1, 2, 3 or more*	0.007	1.488	1.116 - 1.984	<0.001	1.676	1.258 - 2.234
prior chemotherapy; *yes vs no*	0.039	2.031	1.038 - 3.974			
log_{10}PSA; *per 1 unit*	0.476	1.175	0.754 - 1.829			

223Ra terminated early

	univariate Regression			multiple logistic Regression		
Variable	***P*-Value**	**Hazard Ratio**	**95%-CI**	***P*-Value**	**Hazard Ratio**	**95%-CI**
%ID; *per 1 unit*	0.03	1.059	1.005 - 1.114			
%ID/L; *per 1 unit*	0.029	1.346	1.032 - 1.757	0.029	1.346	1.032 - 1.757
SUVmean; *per 1 unit*	0.158	1.311	0.9 - 1.910			
SUVmax; *per 1 unit*	0.582	1.003	0.992 - 1015			
Age; *per year*	0.591	1.019	0.95 - 1.094			
Tumor load; *per 1 category*	0.112	1.839	0.867 - 3.904			
prior treatment lines; *1, 2, 3 or more*	0.927	0.98	0.629 - 1.525			
prior chemotherapy; y*es vs no*	0.499	1.44	0.5 - 4.147			
log_{10}PSA; *per 1 unit*	0.238	1.561	0.745 - 3.268			

TABLE 3: *Top:* Cox proportional hazard regression analysis on the association of multiple variables and overall survival after 223Ra treatment.

Bottom: Logistic regression analysis for incomplete 223Ra therapy depending on multiple variables.