Radiol Oncol 2019

Research Article

Scintigraphic load of bone disease evaluated by DASciS software as a survival predictor in metastatic castration-resistant prostate cancer patients candidates to 223RaCl treatment

Viviana Frantellizzi1, Arianna Pani2, Maria Dea Ippoliti3, Alessio Farcomeni4, Irvin Aloise5, Mirco Colosi5, Claudia Polito6, Roberto Pani7, Giuseppe De Vincentis3

1 Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy
2 Postgraduate School of Clinical Pharmacology and Toxicology, University of Milan “Statale”, Milan, Italy
3 Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza University of Rome, Rome, Italy
4 Department of Public Health and Infectious Diseases, “Sapienza” University of Rome, Rome, Italy
5 Department of Computer, Control, and Management Engineering Antonio Ruberti, Sapienza University of Rome, Rome, Italy
6 Specialty School in Medical Physics, Department of Medico-Surgical Sciences and Biotechnologies, University La Sapienza, Rome, Italy
7 Department of Medico-Surgical Sciences and Biotechnologies, University La Sapienza, Rome, Italy

Radiol Oncol 2019

Received 18 June 2019
Accepted 22 October 2019

Correspondence to: Viviana Frantellizzi, Viale Regina Elena 324, 00161, Rome, Italy. E-mail: viviana.frantellizzi@uniroma1.it

Disclosure: No potential conflicts of interest were disclosed.

Background. Aim of our study was to assess the load of bone disease at starting and during Ra-223 treatment as an overall survival (OS) predictor in metastatic castration-resistant prostate cancer (mCRPC) patients. Bone scan index (BSI) is defined as the percentage of total amount of bone metastasis on whole-body scintigraphic images. We present a specific software (DASciS) developed by an engineering team of “Sapienza” University of Rome for BSI calculation.

Patients and methods. 127 mCRPC patients bone scan images were processed with DASciS software, and BSI was tested as OS predictor.

Results. 546 bone scans were analyzed revealing that the extension of disease is a predictor of OS (0–3% = 28 months of median survival (MoMS); 3%–5% = 11 MoMS, > 5% = 5 MoMS). BSI has been analyzed as a single parameter for OS, determining an 88% AUC. Moreover, the composition between the BSI and the 3-PS (3-variable prognostic score) determines a remarkable improvement of the AUC (91%), defining these two parameters as the best OS predictors.

Conclusions. This study suggests that OS is inversely correlated with the load of bone disease in mCRPC Ra-223-treated subjects. DASciS software appears a promising tool in identifying mCRPC patients that more likely take advantage from Ra-223 treatment. BSI is proposed as a predictive variable for OS and included to a multidimensional clinical evaluation permits to approach the patients’ enrollment in a rational way, allowing to enhance the treatment effectiveness together with cost optimization.

Key words: DASciS software; radium223 dichloride; bone scan index; bone disease; overall survival; mCRPC

Introduction

Bone metastasis is present in 90% of patients with metastatic castration-resistant prostate cancer (mCRPC).1 Radium-223 dichloride (Ra-223) is an alpha-emitter effective to relief bone metastasis’ pain and prolong survival. It is approved as treatment of mCRPC patients with symptomatic bone metastasis and no evidence of visceral metastatic involvement. Since 2018 The European Medicines
Agency (EMA) restricted the use of Ra-223. Today this treatment is reserved for those patients who have already followed two prior systemic treatments for bone-mCRPC or those who are ineligible for other treatments. The EMA also issued a contraindication for use in combination with abiraterone acetate plus prednisone/prednisolone. Ra-223 has a positive impact in limitation of osteoblastic cellular growth in the metastatic and in the bony environment. Ra-223 transfers a high amount of energy (80 keV/μm), in the form of alpha particles with a Linear Energy Transfer (LET) of 27.4 MeV, in a short action range (100 μm). It produces double strand’s breakings in tumor cells’ DNA with a cytotoxic effect. Thanks to the high LET and the short action range, this treatment has a limited hematological toxicity* associated with a reduction in pain and an improvement in quality of life.7,8

At the moment a validated standard technique to monitor mCRPC patients treated with Ra-223 does not exist, in spite several imaging techniques have been proposed such as PET and MRI.9,10 Bone scintigraphy is commonly used, thanks to its wide availability and low cost. Moreover, it represents a standard tool recommended for clinical trials designed for CRPC.11 This imaging technique allows to determine the skeletal disease burden in these patients, but it is a low accuracy modality to quantify disease or for demonstrating treatment effects because of its low spatial resolution.17 Indeed, it doesn’t specifically identify cancer and it can paradoxically worsen in the face of response (flare phenomenon). Moreover, it frequently shows a slow improvement during active treatments, or it doesn’t improve at all. Bone Scan Index (BSI), is defined as the percentage total amount of bone metastasis on whole-body scintigraphic images. It could be a valid tool to assess disease burden in patients with bone metastasis and to evaluate how disease burden changes during treatments. BSI allows to evaluate bone scintigraphy data as a single reproducible quantitative measure, so that it is possible to estimate the bone disease’s charge. BSI can be calculated with a specifically developed software, the EXINIBone (BONENAVI software in Japan) and has been validated as an OS predictor in some patient’s mCRPC treatment settings.13,15 However, at the moment EXINIBone is not commercially available in all European countries. In this study we present a newly developed software by an engineering team of “Sapienza” University of Rome for specific BSI calculation (DASciS software).

The aim of our study was to perform a BSI evaluation in a Ra-223 treated patients’ cohort, in order to calculate the load of bone disease at starting of treatment and to identify its variations during the treatment as an overall survival (OS) predictor. Another issue addressed in this study was to compare head to head and in association, the OS predictive ability of 3 variable Prognostic Score (3PS), a multidimensional predictive tool proposed by our group in this specific patient setting16, with BSI, both evaluated at baseline time. The 3-PS (3-variable prognostic score), is a multidimensional clinical evaluation based on: hemoglobin (Hb), Eastern Cooperative Oncology Group (ECOG) performance status (PS) and serum prostate specific antigen (PSA) baseline value. It has been demonstrated that the 3-PS is able to select those mCRPC subjects most suitable to receive the maximum benefit from Ra-223 treatment. It has also been tested as a predictor marker of OS16 resulting to have a higher accuracy than total alkaline phosphatase (tALP).

Patients and methods

This was an observational, retrospective cohort study performed in 127 mCRPC patients (all patients had biochemical progression of disease under Androgen Deprivation therapy, serum testosterone level < 50 ng/dL, a condition that is considered irreversible even if recently there is evidence of a radio-induced reversion17, with symptomatic bone metastases receiving Ra-223, enrolled at our Division of Nuclear Medicine. Informed consent was obtained from all individual participants included in the study. It was approved by the local ethical committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Baseline clinical data relevant to the survival analysis were collected, such as age, height and weight, Gleason Score, ECOG PS, number of systemic treatments prior to Ra-223 therapy. Body Mass Index (BMI) was calculated for each patient. Patients’ characteristics are summarized in Table 1.

After each therapy’s cycle and during the follow-up patient’s blood count, PSA and tALP were collected, in order to identify hematological toxicity and to monitor the therapy’s effectiveness. 76.6% of patients without visceral metastasis completed the Ra-223 treatment by administering 6 intravenous injections (55 kBq per kg of body weight) every 28 days (Table 1).18 A 99mTc-hydroxyethylene diphosphonate (HDP) bone scan was performed before starting the treatment, after 2 or 3 cycles of therapy and after the treatment’s end.
A scintigraphic image study was performed after 3 months, 6 months and 1 year from the end of the treatment. All the images were obtained 2 hours after an injection of 300-740 MBq of HDP. Bone scan images were then processed with a software (DASciS software) that calculated BSI, developed by an engineering team from the Sapienza University.

DASciS software – which stands for Dicom Analyzer Scintigraphy Software – is an automatic tool for bone scan quantitation. Gamma Cameras usually output images in DICOM format. The output file contains the actual images together with all the metadata gathered during the exam. Through DASciS software, we can visually analyze those files, computing the area relative to the ill portions of the patient skeleton. The software performs the computation based on the intensity of the pixels. More specifically, once the operator has selected a pixel on the image that has been recognized as portion of ill skeleton, the software automatically selects all the pixels in the image whose intensity is equal or higher to the picked one. All those pixels are clustered into - potentially - multiple region of interests (ROIs). To avoid false positives - e.g. spot due to benign pathologies - and to refine the clustering process, it is possible to manually remove ROIs that are not interesting and to perform fine tuning over the pixel intensity threshold. Once the operator has successfully analyzed the file, DASciS outputs a file containing the statistics and the relevant metadata of the investigation. More specifically, the statistics include the cumulative percentage of ill regions computed with respect to the total image area of the patient over multiple sessions - i.e. corresponding to different scintigraphy acquisitions. The metadata, instead, contain patient generalities and the date of acquisition. From a more technical point of view, the software has been developed in Java to grant cross-compatibility with all the most used Operating Systems (Windows, MacOS, Linux) and to easily prototype an effective Graphical User Interface (GUI). Image processing is performed using the well-known OpenCV library while DICOM files are handled using the open source PixelMed library. The OpenCV library implements several efficient Computer Vision algorithms, like the ones used in DASciS to perform intensity-based clustering of pixels – based on the well-known approach of Suzuki - and to compute the cluster area – through the Green’s theorem.

Summarizing, the DASciS software semi-automatically identifies all the areas of increased fixation of bone targeted radiotracer, that appear as

### TABLE 1. Baseline patients’ characteristics

| Baseline variable                      | Patients (n = 127) | %     |
|----------------------------------------|--------------------|-------|
| Age (years)                            | Mean (range)       | 73.82 (59–90) |
| Heigth (m)                             | Mean (range)       | 1.71 (1.58–1.95) |
| Weight (kg)                            | Mean (range)       | 78.60 (59–120) |
| BMI                                     | Mean (range)       | 26.75 (19.57–39.18) |
| Gleason score                          | Mean (range)       | 6.3 (5–10) |
| ECOG Performance status                | Mean (range)       | 0.86 (0–3) |
| Extent of skeletal disease             | < 6 metastases     | 18 14.17 |
|                                      | 6–20 metastases    | 46 36.22 |
|                                      | > 20 metastases    | 63 49.61 |
| No. of previous systemic treatments after castration resistance (Docetaxel, Cabazitaxel, Abiraterone, Enzalutamide) | 0 46 32 21 20 16.53 |
| No. of therapy’s cycles administered   | Mean (range)       | 5.56 (2–6) |
| No. of systemic treatments after Radium223 | Docetaxel  | 11 8.6 |
|                                        | Cabazitaxel        | 0 0 |
|                                        | Abiraterone        | 2 1.5 |
|                                        | Enzalutamide       | 6 4.7 |
| Baseline Hb                            | Median (range)     | 12.14 (7.5–15) |
|                                        | < 12 g/dl          | 54 42.51 |
|                                        | ≥ 12 g/dl          | 73 57.48 |
| Baseline tALP*                         | Median (range)     | 300 (34–1750) |
|                                        | < 226 U/l          | 79 62.2 |
|                                        | ≥ 226 U/l          | 48 87.8 |
| Baseline PLT (10^3/mm³)                | Median (range)     | 249 (74–763) |
|                                        | < 20 ng/ml         | 42 33.07 |
|                                        | ≥ 20 ng/ml         | 85 66.92 |

*Cut-off value validated in a previous study14

BMI = Body mass index; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; tALP = total alkaline phosphatase; PLT = platelets count; PSA = serum prostate specific antigen
spots on the image, only requiring the operator to identify one of these areas. With this method it is possible to make a quantitative analysis of the ROIs representing the metastatic bone towards the whole body bone mass, obtaining a percentage of bone metastatic load. Reproducibility of this method was examined by comparing results obtained by three independent, blinded operators, with different degrees of expertise in nuclear medicine techniques. BSI data obtained from images acquired before, during and after the treatment were then analyzed in an OS prediction’s perspective. Aiming to evaluate a further correlation with OS, the baseline 3-PS was adopted. This is a predictor of OS, including Hb value, PSA and ECOG PS pre-therapy as variables, that in our experience it has proved superior to tALP. 16  In this study, 3-PS was calculated for each patient and compared to BSI data as a predictor of OS.

Statistical analysis

The marginal and stratified survival distributions were estimated through the Kaplan-Meier product-limit estimator. The association between OS and predictors was evaluated by means of Cox regression. At multivariate analysis, for assessment of the independent prognostic performance of BSI, we first performed model selection through forward stepwise based on AUC, and then included all possible confounders. The prognostic performance of BSI alone and in addition to the 3-PS score was evaluated by means of time-dependent ROC curves and related AUC. In order to derive a simple scoring system based on the 3-PS and BSI, we dichotomized BSI and established the optimal number of points by rounding and scaling the log-hazard ratio coefficients in a bivariate model including 3-PS and BSI. To choose the optimal threshold for dichotomization of BSI we evaluated a grid of possible thresholds and maximized the final AUC in order to choose the best one. In order to assess reproducibility among three operators, the intra-class correlation coefficient was used. A significance level of 5% was specified before data analysis. All analyses are conducted in R version 3.4.0.

Results

546 bone scans, collected in the period between October 2013 and September 2018, were analyzed with the DASciS software. During the Ra-223 treatment, for all the 127 patients had a baseline bone scan (Figure 1). 122 of these patients had a second bone scan and 89 of them a third intermediate image. 87 patients had a final bone scan at the end of the treatment. During the follow-up, 60 images were available as a 3 month-after-treatment control, 38 after 6 months from the treatment’s end and 23 patients completed the 1-year follow-up. Among 127 patients, 79 died in a period between the starting of the therapy and the year after its end. Exploring the inter-observer reproducibility of the DASciS software evaluation, the intraclass correlation coefficient for BSI was 0.815 (95% CI: 0.776–0.865; p < 0.001).

The primary endpoint of this study was to evaluate the association between baseline BSI and OS. OS cumulative incidence is reported in Figure 2. Available data were analyzed, revealing that the baseline percentage of disease is a predictor of OS (Table 2).

This results came from both the univariate analysis (HR: 1.8, 95% CI 1.61–2.02, p < 0.001) and the multivariate analysis (HR: 1.79, 95% CI 1.59–2.01, p < 0.001) and are also confirmed from the adjusting for all possible confounders measured (HR: 1.82, 95 CI 1.57–2.10, p < 0.001). As clearly shown in Table 3

| % BSI | Patients number (n = 127) | Median survival (months) | 0.95 LowCL (months) | 0.95 UpCL (months) |
|-------|----------------------------|--------------------------|---------------------|-------------------|
| 0–3   | 59                         | 28                       | 19                  | NA                |
| 3–5   | 33                         | 11                       | 9                   | 12                |
| > 5   | 35                         | 5                        | 5                   | 7                 |

CL = confidence level
at multivariate analysis only the load of bone disease and EOGP PS resulted statistically related with OS (Table 3).

In our series, only 19 patients received further lines of treatments after Ra-223 (11 received Docetaxel, 2 Abiraterone and 6 Enzalutamide), consequently, our sample does not lend itself to a detailed analysis of the role of the position of the Ra-223 in the sequence of treatment lines on OS.

The baseline BSI was analyzed as a single parameter for OS, determining an 88% AUC. A comparison between BSI and 3-PS was performed, revealing a superiority of BSI in term of OS prediction (the 3-PS AUC was 73%, while the BSI one was 88%). Moreover, the addition of the BSI to the 3-PS determines a remarkable improvement of the AUC (91%). In order to add BSI to the 3-PS we set a cutoff of 3, where patients with a BSI above the cutoff were given 4 points, and zero otherwise. From these data, it can be inferred that, the baseline BSI, used as a single parameter is better than baseline 3-PS in OS prediction. At the same time, using both BSI and 3-PS is the best way to predict the OS.

Scintigraphic data were collected during treatment and follow-up, however the BSI variation trend over time is not significant as a OS predictor (p = 0.36), as shown in Figure 3, where patients BSI values related to the time when they performed bone scans are represented in the boxplot. Index that takes in account BSI and 3-PS appears to be the best OS predictor (Figure 4).

| TABLE 3. Univariate and multivariable analysis of overall survival (OS) in relation to baseline variables |
| Clinical covariates | Univariate models HR (95% CI) | p-value | Multivariable model HR (95% CI) | p-value |
|---------------------|-----------------------------|---------|-------------------------------|---------|
| BSI                 | 1.80 (1.61–2.02)            | < 0.001 | 1.79 (1.59–2.01)              | < 0.001 |
| Age (years)         | 1.02 (0.99–1.05)            | 0.184   |                               |         |
| BMI                 | 0.94 (0.89–1.00)            | 0.057   |                               |         |
| Gleason Score       | 0.97 (0.91–1.04)            | 0.414   |                               |         |
| ECOG Performance Status | 1.97 (1.48–2.64)        | < 0.001 | 1.74 (1.29–2.36)              | < 0.001 |
| N of previous systemic treatments | 1.35 (1.12–1.164)       | 0.002   |                               |         |
| Baseline Hb         | 0.73 (0.64–0.84)            | < 0.001 |                               |         |
| Baseline PLT / 100  | 1.51 (1.19–1.92)            | < 0.001 |                               |         |
| Baseline PSA / 100  | 1.06 (1.02–1.12)            | 0.006   |                               |         |
| Baseline tALP /100  | 1.11 (1.06–1.17)            | < 0.001 |                               |         |

BMI = body mass index; BSI = bone scan index; CI = Confidence interval; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; HR = hazard ratio; PLT = platelets count; PSA= serum prostate specific antigen; tALP = total alkaline phosphatase
Discussion

Evaluating the overall survival in mCRPC patients treated with Ra-223, several markers were analyzed (ECOG PS, tALP, Hb, PSA, number of previous systemic treatments), however, it was not possible to identify a predictive clinical variable assessing the Ra-223 therapeutic benefit.²³

PSA can’t be considered a valid marker of clinical benefit for this treatment, because Ra-223 acts directly on bone metastases microenvironment, rather than on prostate cancer cells: this can explain why there’s a minor decline of this marker during the therapy.²⁴ On the other hand, this value can sometimes grow despite a good symptomatologic outcome of the treatment: this could be linked to a “flare phenomenon”, similar to the one that’s find in the administration of other anticancer drugs.²⁵,²⁶

tALP is generally considered the most reliable marker in in patients receiving Ra-223. The tALP generally declines at 4 weeks during this therapy. This pharmacodynamic trend was studied in a recent exploratory analysis on LDH, PSA and tALP dynamics.²⁷ Baseline tALP levels are not correlated to the efficacy of Ra-223, that’s why tALP can’t be considered as a predictive value in this setting. Data coming from literature have shown that baseline tALP level is prognostic for OS.²⁸ Anyway, an increased risk of death, time to progression, skeletal- related events, and bone marrow failure are possibly related to pre-treatment tALP levels (≥146 U/L): this admits to hypothesize a predicting role for this marker.²⁹ In addition to that, from a retrospective analysis of data from the ALSYMPCA trial emerged that patients treated with Ra-223 and with confirmed decline in tALP at week 12 had a significantly longer OS.³⁰ The 3-PS seems to fulfill this necessity of a predictor marker of OS.¹⁶

A further implementation of the OS prediction comes from BSI evaluation of bone disease that we propose in our study. Although PET with 18F-sodium fluoride has been shown to be more sensitive in assessing the burden of bone disease in this kind of patients³⁷, the authors evaluated bone scintigraphy with diphosphonates because it is available for all the Nuclear Medicine Centers, it is significantly cheaper and is the recommended test for enrolling patients in 223-Radium therapy. Interestingly our data are comparable with results available from literature, where, by applying a similar evaluation method, BSI inversely correlated with OS.¹²,³² Indeed, the baseline BSI has a better predictive power than 3-PS. However, it is possible to obtain a major effectiveness of the marker by combining it with the 3-PS itself.

According to the EMA recommendations and Pharmacovigilance Risk Assessment Committee (PRAC), the administration of Ra-223 treatment, should be started only after the failure of 2 different therapeutic strategies and in the presence of ≥6 bone metastasis. A treatment with Abiraterone acetate plus chemotherapy (Docetaxel, Cabazitaxel) or Enzalutamide should be performed before starting a therapy with Ra-223.³³ In addition to this, is recommended to not start Ra-223 treatment together with Abiraterone administration, because both these drugs act on bone metabolism (ERA 223 – NCT 02043678). Finally, there’s an indication for Ra-223 treatment when no other therapeutic strategies are available.³³ At the end of study it can be concluded, in line with O’Sullivan et al.,³⁴ that Ra-223 cannot be only reserved for third or later lines of therapy in mCRPC, moreover that is wrong considering the presence of ≥6 bone metastasis as an inclusion criterion for its use. This study indeed suggests that OS is inversely correlated with the baseline BSI (the longer OS is expected with the lowest BSI value). Independently from the number of previously administered therapies, from this analysis we can infer that the best OS can be obtained when the load of bone disease is ≤5% of the whole skeletal mass. This results show that, it might be more appropriate to consider the percentage of disease burden than concentrating on the number of metastatic lesions drawing up the treatment’s directions (Figure 5). A new interesting point of view could be carried by these results, towards the necessity of a re-evaluation of the Ra-223 therapeutic indications. Despite this, the limited number of our sample does not consent us to state definitive conclusions; indeed, a larger number of cases should be considered to confirm these results.

FIGURE 5. ⁹⁹mTc-HMDP Bone scan, example of evaluation of load of the disease. (A) Few but very extensive bone metastases. Bone scan index [BSI] value = 6.13%. (B) numerous but small bone metastases. BSI value = 3.4%.
In addition to this, another limitation of this study could come from the follow-up time we considered. In fact we observed patients during a limited period of time, with a maximum survival of 38 months: a longer time frames and larger sample sizes are required to appropriately draw conclusions about overall survival. Anyway, the DASiS software, despite having a theoretical limitation in those lesions with much lower tracer absorption that could be lost, in our experience it does not affect the clinical performance of the software itself, and it appears a promising tool that can help in identifying mCRPC patients that more likely will take advantage from Ra-223 treatment.

From literature data it’s known that, in terms of ability to prolong survival, Ra-223 therapy is more effective on patients that are able to receive almost all of the six cycles currently administered according to the treatment scheme. In this context, it’s necessary to find a way to stratify the patients at the time of enrollment for this treatment, aiming to select patients that are more likely to benefit from it. In our study, the imaging assessment, in terms of bony disease percentage burden, is proposed as a predictive variable for OS that can be added to a multidimensional clinical evaluation in order to highlight those mCRPC patients that will more probably take advantage from Ra-223 therapy. Approaching the patients’ enrollment this way, it might be possible to enhance the treatment effectiveness together with cost optimization.

References
1. Den RB, George D, Pieczonka C, McNamara M. Ra-223 treatment for bone metastases in castrate-resistant prostate cancer: practical management issues for patient selection. J Am Clin Oncol 2019; 42: 399-406. doi: 10.1097/JCO.0000000000000528
2. De Vincentis G, Gerritsen W, Gschwend JE, Hacker M, Lewington V, O’Sullivan JM, et al. Advances in targeted alpha therapy for prostate cancer. Ann Oncol 2019; 0: 1-12. doi: 10.1093/annonc/mdz270
3. Logothetis C, Morris MJ, Den R, Coleman RE. Current perspectives on bone metastases in castrate-resistant prostate cancer. Cancer Metastasis Rev 2018; 37: 189-96. doi: 10.1007/s10555-017-9719-4
4. Bruald OS, Nilsson S, Fisher DR, Larsen RH. High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter 223Ra: adjuvant or alternative to conventional modalities? Clin Cancer Res 2006; 12: 6250-7s. doi: 10.1186/1748-0171-6-06-0841
5. Henrekson G, Fisher DR, Roeske JC, Bruald OS, Larsen RH. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. J Nucl Med 2003; 44: 252-9. PMID: 12571218
6. De Vincentis G, Follacchio GA, Frantellizzi V, Prelaj A, Farcomeni A, Giulì A, et al. 223Ra-dichloride therapy in an elderly metastatic castration-resistant prostate cancer patient: a case report presentation and comparison with existing literature. Aging Clin Exp Res 2017; 30: 677-80. doi: 10.1007/s40520-017-0826-4
7. De Vincentis G, Monari F, Baldari S, Salgarello M, Frantellizzi V, Salvi E, et al. Narrative medicine in metastatic prostate cancer reveals ways to improve patient awareness & quality of care. Future Oncol 2018; 14: 1621-32. doi: 10.2217/fon-2018-0318
8. De Vincentis G, Frantellizzi V, Follacchio GA, Farcomeni A, Pani A, Samaritani R, et al. No evidence of association between psychological distress and pain relief in patients with bone metastases from castration-resistant prostate cancer treated with 223Ra. Eur J Cancer Care 2019; 28: e13112. doi: 10.1111/ecc.13112
9. Lecouvet FE, Talbot JN, Messiou C, Bourguet P, Liu Y, de Souza NM. Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: a review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer 2014; 50: 2519-31. doi: 10.1016/j.ejca.2014.07.002
10. Pyka T, Okamoto S, Dahlbender M, Tauber R, Retz M, Heck M, et al. Comparison of bone scintigraphy and (68)Ga-PSMA PET for skeletal staging in prostate cancer. Eur J Nucl Med Mol Imaging 2016; 43: 2114-21. doi: 10.1007/s00259-016-3435-0
11. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26: 1148-56. doi: 10.1200/jco.2007.12.4487
12. Dennis EA, Jia X, Moshetsiisky I, Stephansson RO, Schoder H, Fox J, et al. Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer. J Clin Oncol 2012; 30: 519-24. doi: 10.1200/jco.2011.36.5791
13. Anand A, Morris MJ, Larson SM, Minarik D, Josefsson A, Helgstrand JT, et al. Automated Bone Scan Index as a quantitative imaging biomarker in metastatic castration-resistant prostate cancer patients being treated with enzalutamide. EANMMI Res 2016; 6: 21. doi: 10.1186/s13550-016-0173-z
14. Fosbol MO, Petersen PM, Kjaer A, Mortensen J. (223)Ra therapy of advanced metastatic castration-resistant prostate cancer: quantification and assessment of skeletal tumor burden for prognostication of clinical outcome and hematologic toxicity. J Nucl Med 2018; 59: 596-602. doi: 10.2997/jnumed.117.195677
15. Uemura K, Miyoshi Y, Kawahara T, Yoneyama S, Hattori Y, Teranishi J, et al. Prognostic value of a computer-aided diagnosis system involving bone scans and hematologic toxicity. J Nucl Med 2018; 59: 596-602. doi: 10.2997/jnumed.117.195677
16. Ricci M, Frantellizzi V, Bulzonetti N, De Vincentis G. Reversibility of castration resistance status after Radium-223 dichloride treatment: clinical evidence and review of the literature. Int J Radiat Biol 2019; 95: 554-61. doi: 10.1080/09553002.2019.1558301
17. Kelch M, Frantelli Z, Bulzonetti N, De Vincentis G. Reversibility of castration resistance status after Radium-223 dichloride treatment: clinical evidence and review of the literature. Int J Radiat Biol 2019; 95: 554-61. doi: 10.1080/09553002.2019.1558301
18. Baldari S, Boni G, Bortolus R, Caffo O, Corli G, De Vincentis G, et al. Management of metastatic castration-resistant prostate cancer: a focus on radium-223: opinions and suggestions from an expert multidisciplinary panel. Crit Rev Oncol Hematol 2017; 113: 43-51. doi: 10.1016/j.critrevonc.2017.03.001
19. Van den Wyngaert S, Strobel K, Kampen WU, Kuwert T, van der Bruggen W, Mohan HK, et al. The EANM practice guidelines for bone scintigraphy. Eur J Nucl Med Mol Imaging 2016; 43: 1723-38. doi: 10.1007/s00259-016-3415-4
20. Bradski G. The OpenCV Library. Dr Dobbs’s Journal of Software Tools 2000; 122: 125-5. citeulike-article-id:2236121
21. Suzuki S. Topological structural analysis of digitized binary images by border following. Comput Vision, Graphics Image Process 1985; 30: 32-46. doi: 10.1016/0734-189X(85)90016-7
22. Green G. An Essay on the application of mathematical analysis to the theories of electricity and magnetism. Journal fur die Reine und Angewandte Mathematik 1854; 1854: 161-221. doi: 10.1515/err-1854.47.161
23. Du Y, Carrio I, De Vincentis G, Fanti S, Ilhan H, Mommers C, et al. Practical recommendations for radium-223 treatment of metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2017; 44: 1671-8. doi: 10.1007/s00259-017-3756-7

Radiol Oncol 2019
Unauthentifiziert | Heruntergeladen 20.12.19 07:23 UTC
24. Osvaldo GF, Salvador MS, Zael SR, Nora SM. Radium-223 in metastatic hormone-sensitive high-grade prostate cancer: initial experience. Am J Nucl Med Mol Imaging 2017; 7: 236-45. PMID: 29181271

25. Castello A, Macapinlac HA, Lopci E, Santos EB. Prostate-specific antigen flare induced by 223RaCl2 in patients with metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2018; 45: 2256-63. doi: 10.1007/s00259-018-4051-y

26. De Vincentis G, Follacchio GA, Frantellizzi V, Liberatore M, Monteleone F, Cortesi E. Prostate-Specific Antigen flare phenomenon during 223Ra-dichloride treatment for bone metastatic Castration-Resistant Prostate Cancer: a case report. Clin Genitourin Cancer 2016; 14: e529-e533. doi: 10.1016/j.clgc.2016.04.014

27. Sartor O, Coleman RE, Nilsson S, Heinrich D, Helle SI, O’Sullivan JM, et al. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223. Ann Oncol 2017; 28: 1090-7. doi: 10.1093/annonc/mdx044

28. Heinrich D, Bruland O, Guise TA, Suzuki H, Sartor O. Alkaline phosphatase in metastatic castration-resistant prostate cancer: reassessment of an older biomarker. Future Oncol 2018; 14: 2543-2556. doi: 10.2217/fon-2018-0087

29. Gravis G, Boher J-M, Fizazi K, Joly F, Priou F, Marino P, et al. Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the glass model and development of a novel simplified prognostic model. Eur Urol 2015; 68: 196-204. doi: 10.1016/j.eururo.2014.09.022

30. Parker C, Nilsson S, Heinrich D, Helle SI, O’Sullivan JM, Fosså SD, et al. Alpha emitter Radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213-23. doi: 10.1056/nejmoa1213755

31. Liu Y, Sheng J, Dong Z, Xu Y, Huang Q, Pan D, et al. The diagnostic performance of (18)F-fluoride PET/CT in bone metastases detection: a meta-analysis. Clin Radiol 2019; 74: 196-206. doi: 10.1016/j.crad.2018.12.011

32. Sabbatini P, Larson SM, Kremer A, Zhang ZF, Sun M, Yeung H, et al. Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. J Clin Oncol 1999; 17: 948-57. doi: 10.1200/JCO.1999.17.3.948

33. Smith M, Parker C, Saad F, Miller K, Tombal B, Ng QS, 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. doi: 10.1016/s1470-2045(18)30860-x

34. O’Sullivan JM, Heinrich D, James ND, Nilsson S, Ost P, Parker CC, et al. The case against the European Medicines Agency’s change to the label for Radium-223 for the treatment of metastatic castration-resistant prostate cancer. Eur Urol 2018; 75: e51-2. doi: 10.1016/j.eururo.2018.11.003

35. van der Doelen MJ, Mehra N, Hermens R, Janssen MIR, Gerritsen WR, van Oort IM. Patient selection for Radium-223 therapy in patients with bone metastatic castration-resistant prostate cancer: new recommendations and future perspectives. Clin Genitourin Cancer 2019; 17: 79-87. doi: 10.1016/j.clgc.2018.11.008