

## A case report of image-based dosimetry of bone metastases with Alpharadin ( $^{223}\text{Ra}$ -dichloride) therapy: inter-fraction variability of absorbed dose and follow-up

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**Abstract** A 70-year-old man affected by bone metastases from castration resistant prostate cancer underwent Alpharadin ( $^{223}\text{Ra}$ -dichloride) therapy (6 administrations of 50 kBq per kg i.v., once every 4 weeks). The inter-fraction variability of the absorbed dose to lesions was evaluated for four injections. Dosimetric assessments were performed following the MIRD approach and a recently published methodology. The mean absorbed dose and standard deviation for 4 lesions [mean ( $\sigma$  %)] were: 434 mGy (15 %) and 516 mGy (21 %) for the right and left humeral head, 1205 mGy (14 %) and 781 mGy (8 %) for the right and left glenoid. The estimated total absorbed dose after the whole treatment, considering also the relative-biological effectiveness of alpha particles ( $\text{RBE} = 5$ ), yielded a  $D_{\text{RBE}}$  range of 13–36 Gy. A good correlation between

$^{99\text{m}}\text{Tc}$  and  $^{223}\text{Ra}$  uptake was obtained ( $R^2 = 0.7613$ ). The tumour–non-tumour (TNT) ratio of 8 lesions (those above, plus 4 additional), monitored by six  $^{99\text{m}}\text{Tc}$ -MDP bone scans over a period of about 10 months, evidenced a TNT reduction in two lesions (–42 and –48 %), but in most lesions the TNT remained fairly constant, evidencing that  $^{223}\text{Ra}$ -dichloride therapy tends to prevent further progression of osseous disease, leading to chronicity of the metastatic status.

**Keywords** Bone metastases ·  $^{223}\text{Ra}$ -dichloride · Radionuclide therapy · Dosimetry

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## Introduction

Clinical trials have shown the safety and efficacy of palliation of painful bone metastases in patients with castration resistant prostate cancer (CRPC) using  $^{223}\text{Ra}$ -dichloride. The ALSYMCA trial demonstrated significantly improved overall survival and a delay in the time to symptomatic skeletal metastases with very low toxicity, thus,  $^{223}\text{Ra}$ -dichloride has become a new standard of care for these patients [1–9]. Marketing authorisation from the European Commission was recently received for Alpharadin ( $^{223}\text{Ra}$ -dichloride) Xofigo®, solution for injection for the treatment of men with CRPC, symptomatic bone metastases and no visceral metastases. The standard administration protocol of  $^{223}\text{Ra}$ -dichloride consists of six monthly administrations of 50 kBq/kg.

$^{223}\text{Ra}$  emits useful photons for imaging, mainly at 81, 84 and around 95 keV (X-rays), and at 154, 269, 324, and 338 keV (gamma rays); however, due to the low number of photons, quantitative imaging was always considered challenging. Two previous studies addressed the possibility of in vivo assessment of pharmacokinetic and biodistribution [10], and quantitative planar imaging with gamma-camera [11]. Recently, two further studies reported the possibility of in vivo image-based macrodosimetric assessments. Chittenden et al. [12] evaluated absorbed dose to organs during a Phase 1, open-label study, administering 100 kBq per kg of body weight (twice the activity of the standard protocol). Pacilio et al. [13] presented a suitable methodology for dosimetry of bone metastases with a standard treatment protocol; 24 lesions from 9 patients affected by osseous metastases from CRPC were studied, assessing the absorbed dose to lesion by MIRD approach [14, 15]. The feasibility of macrodosimetric studies during routine treatments was also proven, but the variability of dosimetric assessments between fractions deserved to be studied, to establish if dosimetry after each administration is required to evaluate the total absorbed dose to lesion. Moreover, the usefulness of macrodosimetry should be still demonstrated, investigating the possibility of establishing dose–response correlations.

In the present case report, the inter-administration variability of absorbed dose to lesion was studied, and the lesion response was monitored in terms of radiopharmaceutical uptake.

## Case report

A 70-year-old man affected by bone metastases from CRPC underwent treatment with  $^{223}\text{Ra}$ -dichloride. The patient was enrolled in a multicentre study (protocol 88-8223/16216) of the Bayer HealthCare Pharmaceuticals,

entitled “Radium-223 chloride in treatment of CRPC patients with bone metastasis”. According to the eligibility criteria, the patient provided written informed consent, had histologically confirmed, progressive bone predominant metastatic CRPC, with several bone metastases detected on  $^{99\text{m}}\text{Tc}$ -MDP bone scan, and no known visceral and/or brain metastases. The patient had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 [16], a life expectancy longer than 6 months, and adequate hematologic, renal, and liver function. Before the treatment with  $^{223}\text{Ra}$ -dichloride, the patient had not received external radiotherapy or systemic radionuclide therapy with other radioisotopes. He had no evidence of malignant lymphadenopathy that was more than 3 cm in the short-axis diameter, presence of visceral metastases, and imminent or established spinal cord compression. Treatment with  $^{223}\text{Ra}$ -dichloride followed the standard protocol: 6 injections of 50 kBq per kg of body weight (one every 4 weeks). Biokinetics and dosimetric evaluations were assessed for a total of 4 lesions (right and left humeral heads and right and left glenoids), whereas follow-up by  $^{99\text{m}}\text{Tc}$ -MDP whole-body (WB) scan was performed also for 4 additional lesions (right coxo femoral, right trochanter, right and left iliac wing).

A GE dual-head gamma-camera (Infinia Hawkeye 4 SPECT/CT), equipped with 3/8-in. crystal was employed. Proper gamma-camera calibrations, for both  $^{223}\text{Ra}$  and  $^{99\text{m}}\text{Tc}$ , were performed in terms of sensitivity (to convert image counts into activity) and transmission curve measurements (to correct image counts for attenuation and scatter by the methodology of the pseudo-extrapolation number) [14]. Further details about the calibration procedures can be found in Ref. [13].  $^{99\text{m}}\text{Tc}$ -MDP WB scans were performed with antero-posterior views, LEHR collimator, energy window centred at 140 keV (20 % wide), scan speed of 14 cm/min, and administration of 740 MBq. Patients’ images with  $^{223}\text{Ra}$  were collected acquiring antero-posterior planar static images with double-peak acquisition (two energy windows centred at 82 and 154 keV, 20 % wide), MEGP collimator, and an acquisition time of about 30 min. The patient underwent CT scan and first WB scan about 69 days before the first injection of  $^{223}\text{Ra}$ -dichloride. Immediately before the first injection, a static transmission image was also acquired (to perform attenuation correction) with a flood source filled with 185 MBq of  $^{99\text{m}}\text{Tc}$ , and an acquisition time of about 4 min, with and without the patient on the couch.

After the first, third, fifth, and sixth injection of  $^{223}\text{Ra}$ -dichloride, biokinetic studies were performed, acquiring antero-posterior planar static images at different times. The time scheduling was similar for the four studies: about 1 h, 1 day, between 2 and 4 days and between 7 and 9 days, after the  $^{223}\text{Ra}$ -dichloride administration. In two cases (first

and sixth injection), an additional late acquisition was performed between 11 and 13 days after the administration.

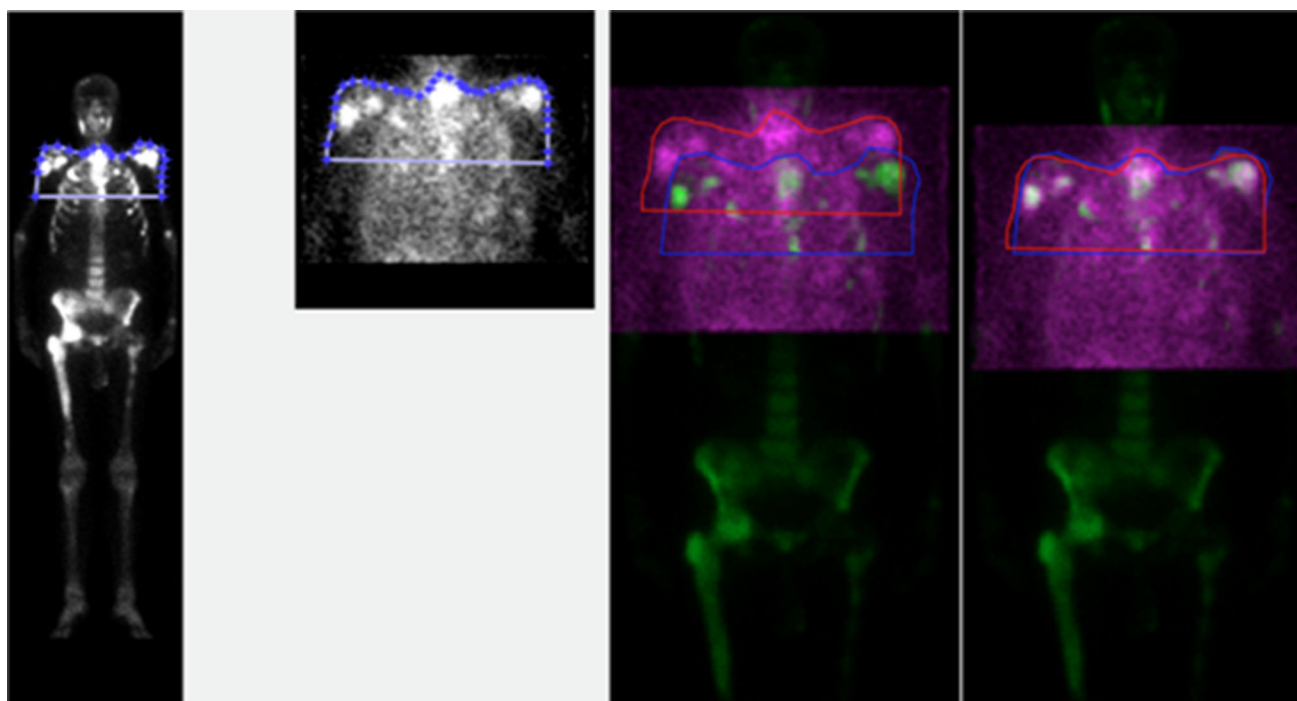
Due to the low quality of  $^{223}\text{Ra}$  images, the lesions were contoured on the WB scan, and then the regions-of-interest (ROIs) were overlapped on the  $^{223}\text{Ra}$  static images and transmission image. To improve the accuracy of the ROIs positioning, transmission and static images were coregistered with the WB scan by means of an in-house developed MATLAB (7.13.0.564, R2011b) toolkit. To further improve image co-registration (above all for the late acquisitions, having a low counting statistics),  $^{223}\text{Ra}$  images were processed with a Wiener filter to enhance contrast-ratio (CR) and signal-to-noise-ratio (SNR) [13]. Figure 1 reports an example of co-registration between WB and static image (anterior view, the static image was acquired at 1.5 h after the first administration), performed after filtering the static image. The activity of  $^{223}\text{Ra}$  in a source region at a given time was calculated following the methodology reported by MIRD Pamphlet No. 16 [14], performing background, attenuation, and scatter corrections. The background subtraction was performed with the Bujis method [14, 17], further details on the application of this methodology in the present study can be found in Ref. [13].

Biokinetics data were fitted with MATLAB, with a bi-exponential (when a wash-in phase was observed) or

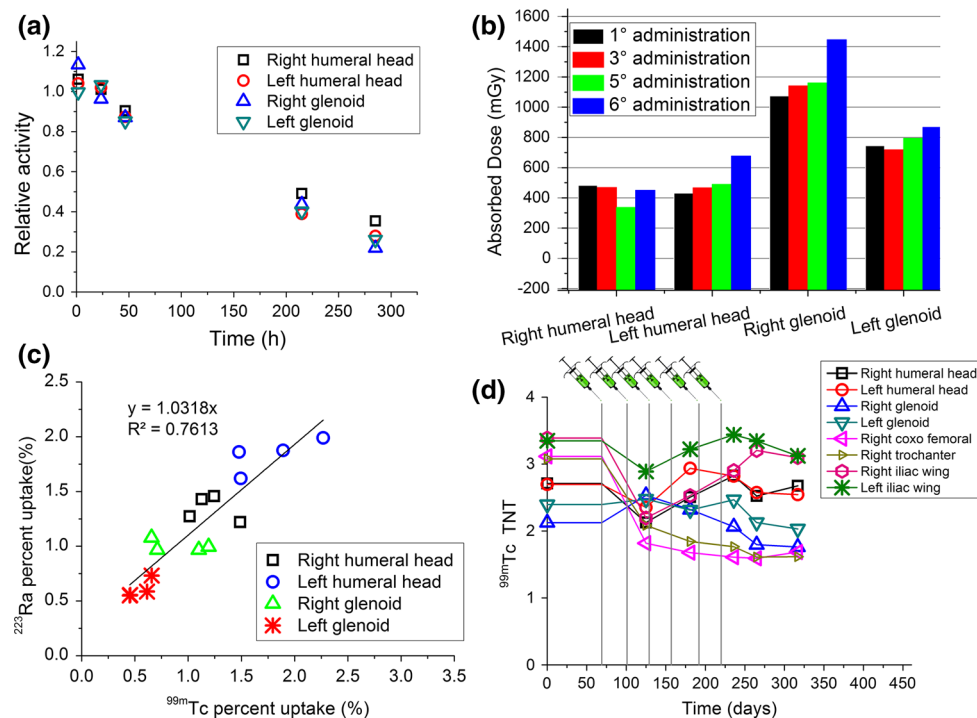
mono-exponential curve. The cumulated activity was calculated by analytic integration of the fitting curve from 0 to infinity. According to the MIRD approach [15], the absorbed dose to lesion was calculated as the product between the cumulated activity and the self-irradiation S factor for  $^{223}\text{Ra}$ , corresponding to the lesion mass. The lesion mass was estimated by delineation of CT images, considering a mean lesion density of  $1.4\text{ g/cm}^3$  [18]. The self-irradiation S factor for the given lesion mass was calculated from the OLINDA/EXM tabulations referred to spherical masses [19], by fitting the tabulated data with an inverse power law.

The correlation between the activity of  $^{99\text{m}}\text{Tc}$  (“ $^{99\text{m}}\text{Tc}$  percent uptake”) and that of  $^{223}\text{Ra}$  ( $^{223}\text{Ra}$  percent uptake) contained in each lesion was studied by linear regression analysis. The methodology for estimating  $^{99\text{m}}\text{Tc}$  and  $^{223}\text{Ra}$  percent uptakes has been previously reported [13].

To monitor the response of the lesions during and after treatment, the patient underwent additional WB scans: 4 days before the third injection, 11 days before the fifth injection, and three more at 16, 45, and 93 days after the last injection. Uptake of the lesions was assessed in terms of uptake ratio between lesion and normal bone (hereinafter called TNT), calculated dividing the mean counts in the lesion by mean counts in the normal bone (both corrected for attenuation and scatter). The normal bone considered here was a part of the left crest of ilium.



**Fig. 1** Example of coregistration between a  $^{99\text{m}}\text{Tc}$ -MDP WB image and a static  $^{223}\text{Ra}$  image (acquired at 1.5 h after administration, anterior view), performed with the MATLAB toolkit, delineating shoulders and body contour



**Fig. 2** Data deriving from quantification on images: **a** activities normalized at  $t = 24$  h, as a function of time after the first injection of  $^{223}\text{Ra}$ -dichloride, for right and left humeral head, right and left glenoid (for each lesion, the 24-h normalization value was calculated from the corresponding biokinetics fit); **b** dose assessments for right and left humeral head, right and left glenoid, performed after the first, third, fifth, and sixth injection of  $^{223}\text{Ra}$ -dichloride; **c** correlation

Figure 2 reports all data deriving from quantification on scintigraphic images. Figure 2a shows the activity normalized at  $t = 24$  h, as a function of acquisition time, for right and left humeral head, and right and left glenoid, after the first injection of  $^{223}\text{Ra}$ -dichloride. For each lesion, the 24-h normalization value was calculated from the corresponding biokinetics fit. Figure 2b reports the dose assessments after the first, third, fifth, and sixth administration. For each lesion, mean value of absorbed dose to lesion and corresponding percent standard deviation was [mean ( $\sigma$  %): right humeral head, [434 mGy (15 %)]; left humeral head, [516 mGy (21 %)]; right glenoid, [1205 mGy (14 %)]; left glenoid, [781 mGy (8 %)]. The correlation between  $^{99\text{m}}\text{Tc}$  and  $^{223}\text{Ra}$  percent uptakes is reported in Fig. 2c for the four lesions for which absorbed dose was assessed, reporting data from all the biokinetics studies. Unfortunately, the acquisitions of WB scans acquired during the treatment did not correspond exactly to the  $^{223}\text{Ra}$  injections times, so the  $^{99\text{m}}\text{Tc}$  percent uptakes were associated to  $^{223}\text{Ra}$  ones using the WB scan temporally closest to the instant of the  $^{223}\text{Ra}$  administration. Nevertheless, the  $R^2$  is 0.7613, showing a significant correlation between the uptakes of the two radiopharmaceuticals. Figure 2d reports the TNT values, calculated on

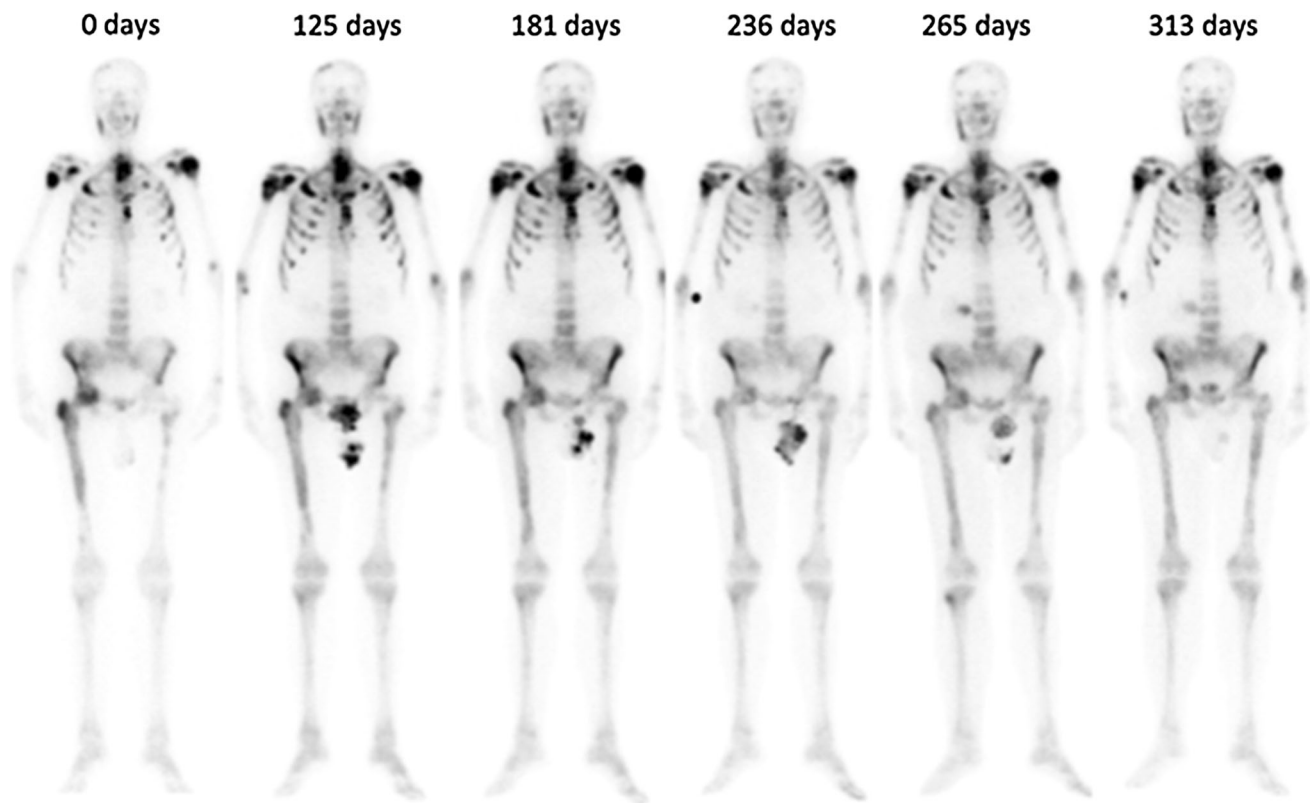
between  $^{99\text{m}}\text{Tc}$  uptake and  $^{223}\text{Ra}$  activity extrapolated at time  $t = 0$ , for the four lesions for which absorbed dose was assessed, reporting data from all the biokinetics studies; **d**  $^{99\text{m}}\text{Tc}$  uptake ratio between lesion and normal tissue (TNT) at different time before, during, and after the cycle of administrations of  $^{223}\text{Ra}$ , as a function of the time elapsed after the first scan (the instants of  $^{223}\text{Ra}$  administrations are indicated in the figure with vertical lines)

serial WB scans, as a function of the time elapsed after the first WB scan. The instants of  $^{223}\text{Ra}$  administrations are also indicated in the figure with vertical lines. The percent difference between the first TNT value (before the first  $^{223}\text{Ra}$  injection) and that temporally closest to the last administration, for the 8 lesions observed, ranged from  $-48$  to  $4$  %. Two lesions evidenced a TNT decrease: right trochanter and right coxofemoral, with reductions of 42 and 48 %, respectively. For other lesions, TNT remained about constant, varying between  $-14$  and  $4$  %. Two successive scans after that temporally closest to the last administration of  $^{223}\text{Ra}$  confirmed a fairly constant trend of TNT values.

Figure 3 shows all WB scans (only anterior views), acquired before, during, and after the  $^{223}\text{Ra}$  treatment, reporting also, on the top of each image, the time elapsed from the first WB scan.

## Discussion

Figure 2a shows that the wash-in phase of radiopharmaceutical uptake is rapid, resulting in a negligible impact on the calculation of the cumulated activity. So it would be possible to avoid the early acquisition, to limit the



**Fig. 3** The WB scans (*anterior views*), acquired before, during, and after the  $^{223}\text{Ra}$  treatment, reporting the time elapsed from the first WB scan on the *top* of each image

discomfort in patients with pain. The level of variability for repeated inter-fraction absorbed dose assessments indicates that measurements after each administration of  $^{223}\text{Ra}$  would be advisable for accurate dosimetry, even though an analysis of experimental uncertainty would also be required to come to this conclusion. However, a good enough estimation could also be obtained multiplying by 6 the mean value of absorbed dose derived from some (not necessarily all) administrations, distributed during the whole treatment. In the present study, the estimated total absorbed dose to lesion, after a full cycle of administrations, accounting also for the suggested value of relative biological effectiveness for alpha particles ( $\text{RBE} = 5$ ) [20], yields a  $D_{\text{RBE}}$  ranging from about 13 to 36 Gy.

Despite the non-perfect temporal matching between the WB scan acquisitions and the  $^{223}\text{Ra}$  injections, the very good correlation between  $^{99\text{m}}\text{Tc}$  and  $^{223}\text{Ra}$  percent uptakes reported in Fig. 2c indicates that the  $^{223}\text{Ra}$ -dichloride lesion uptake is well enough represented by  $^{99\text{m}}\text{Tc}$ -MDP WB scans, so the lesions can be confidently delineated on  $^{99\text{m}}\text{Tc}$ -MDP WB images. The correlation between  $^{99\text{m}}\text{Tc}$  and  $^{223}\text{Ra}$  percent uptakes may suggest that, for a given lesion, the variation of the absorbed doses with respect to the first dosimetric assessment could be estimated by the

variation of uptake of  $^{99\text{m}}\text{Tc}$ -MDP, but this would occur as long as the biokinetics of the lesions remains the same from one injection to another. Unfortunately, it was not always the case. For instance, the increase of absorbed dose to the right glenoid at the sixth injection, 19 % with respect to the mean value (see Fig. 2b), is mostly explained by the increase of 12 % of the effective half time. Similarly for the left humeral head, the absorbed dose increase at the sixth injection of about 31 % is mainly due to an increment of about 27 % of the effective half time. The follow-up of uptake in lesions represented by Fig. 2d shows a sensible uptake reduction for the right trochanter and the right coxofemoral. Moreover, Fig. 3 also shows a visible reduction for the right femur (not quantified in Fig. 2d). However, for most lesions, a stabilization of the level of uptake was noticed: this is a direct indication that  $^{223}\text{Ra}$ -dichloride therapy tends to stop the progression of the osseous disease, leading to chronicity of the metastases. Thus, radiopharmaceutical uptake of metastatic bone could be inadequate as endpoint for studying dose–response correlation. However, time to radiological progression, or, even more importantly, time to symptomatic skeletal events (defined as: the need of radiation therapy to relieve symptoms, new symptomatic pathological bone fractures,

tumor-related orthopaedic surgical intervention, or spinal cord compression), and overall survival could be more appropriate as endpoints.

## Conclusions

The feasibility of *in vivo* quantitative imaging and macrodosimetry of bone lesions is confirmed. The follow-up of the level of uptake of the  $^{223}\text{Ra}$  can be efficiently and quantitatively performed by  $^{99\text{m}}\text{Tc}$ -MDP imaging. For about 1 year, the level of uptake of the radiopharmaceuticals remained stable for most lesions. This does not testify in favour of the uptake in lesion for studying the dose–response correlation, but symptomatic skeletal event-free survival, or overall survival, could also be considered as endpoints.

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## Compliance with ethical standards

**Conflict of interest** None.

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