27 Targeted Therapy with Radium-223 of Bone Metastases

Sergio Baldari, Alessandro Sindoni, Laura Evangelista, and Emilio Bombardieri

Abstract

^{223}Ra is a targeted alpha therapy approved for treatment of metastatic prostate cancer with symptomatic bone metastases and without known visceral metastases. It documented an overall survival benefit, increased time to symptomatic skeletal event, improved quality of life and good safety profile in the pivotal trial ALSYMPCA.

The patient suitable for treatment must present at least two sites of osseous localization at bone scan, with no visceral involvement and lymph nodal disease within 3 cm diameter (short axis).

First data from clinical practice and from expanded access program confirmed safety and efficacy and highlighted that early use is related to completion of six cycles and better clinical outcome.

During treatment, it is important to evaluate pain response, clinical outcome, complete blood count and ALP at each cycle, while PSA must be assessed only every three cycles. Imaging modalities should be repeated at baseline (to select the right patient) and after at least 8 weeks from last administration (to assess the disease response); only in case of clinical suspicion of relapse, the same modalities could be repeated during treatment to exclude a disease progression.

S. Baldari (✉) • A. Sindoni
Department of Biomedical and Dental Sciences, and of Morphological and Functional Images, University of Messina, Messina, Italy
e-mail: sbaldari@unime.it

L. Evangelista
Veneto Institute of Oncology IOV – IRCCS, Padua, Italy

E. Bombardieri
Department of Nuclear Medicine, Humanitas Gavazzeni Hospital, Bergamo, Italy

27.1 Physical and Biological Properties of ^{223}Ra

^{223}Ra is a targeted alpha therapy that documented a survival benefit in metastatic castration-resistant prostate cancer [1]; it is an alpha-emitting radionuclide, with a calcium mimetic behaviour, which belongs to the alkali earth metals in the periodic table. Emitted energy distribution is α-energy (average) = 5.78 MeV (accounts for

E. Bombardieri et al. (eds.), *Clinical Applications of Nuclear Medicine Targeted Therapy*,
https://doi.org/10.1007/978-3-319-63067-0_27

93.5% of emitted energy), <4% as beta particles and <2% as γ radiation. Combined energy for the complete decay of ^{223}Ra and daughters is equal to 28 MeV; some γ (0.9 MeV total) is also emitted.

Tissue range for ^{223}Ra is inferior to 100 μm (α) with respect to several mm for β-particles, and it is characterized by a higher linear transfer energy ranging 100–200 keV/μm with respect to that of β-particles, which is inferior to 1 keV/μm: this high energy deposition of α-particles in a very small tissue range is able to cause irreversible double-strand DNA breaks [2, 3]. Other than DNA damage, the high energy determines the production of highly toxic radicals and chemicals for cells. Since energy of α-particles is released in a very short range in tissue, the targeted cells receive higher absorbed radiation doses than adjacent healthy cells, which permit to spare near-critical structure and, in particular, bone marrow [4].

In vitro experiments have demonstrated that the lethal effect is not cell type specific and is also delivered on multidrug resistant cells; moreover, it produces G2 arrest and causes a dose-dependent inhibition of differentiation of the osteoclasts [5–7]. In mice model bearing intratibial LNCaP or LuCaP 58 tumours and administered with ^{223}Ra, the inhibition of tumour-induced osteoblastic bone growth and protection of normal bone architecture leading to reduced bone volume were documented. ^{223}Ra resulted in lower PSA values and reduced total tissue and tumour areas.

A decreased number of osteoblasts and osteoclasts and reduced level of the bone formation marker PINP were observed. ^{223}Ra therapy exhibits a dual targeting mode of action that induces tumour cell death and suppresses tumour-induced pathological bone formation, both essential players in the destructive vicious cycle of osteoblastic bone metastasis in prostate cancer [8].

27.2 Castration-Resistant Prostate Cancer

Prostate cancer is the most common solid malignant tumour in men and represents the second cause of cancer-related deaths in this sex [9]. Men with localized prostate cancer are treated with surgery or radiation therapy. However, at follow-up, biochemical recurrence (increase in PSA levels) can occur, and, in this setting, localization of disease is important for patients' management, which may include active surveillance, systemic therapy, localized salvage therapy or both systemic and localized treatments. The term "castration resistant" is used when a measurable progression of disease occurs in the setting of castrate levels of testosterone, manifesting itself with PSA increase or imaging abnormalities at computed tomography, magnetic resonance imaging or nuclear medicine techniques. Up to 20% of patients with metastatic prostate cancer develop CRPC within 5 years; prevalence CRPC has been estimated to be 17.8% among patients with prostate cancer [10]. In the majority of patients affected by CRPC, bone is the site of metastatic involvement. Bone metastases are cause of decreased quality of life, pain and disability with increased treatment cost and, finally, also death. The major concerns in these patients are skeletal-related events (SREs), manifesting with spinal cord compression and pathological fractures. Available treatments for metastatic CRPC (mCRPC) include chemotherapy with docetaxel or cabazitaxel, androgen synthesis inhibitors abiraterone acetate, androgen receptor blocker enzalutamide and immunotherapy with sipuleucel-T [11]. Although these drugs have provided interesting results, additional studies are needed to define potential combinations and optimal sequencing. Since bone is a frequent site of metastatic involvement, significant efforts in developing approaches for bone metastases have been made and are ongoing with the aim to reduce pain and limit complications and SREs. Bisphosphonates, zoledronic acid [12] and mostly antibodies to RANKL (denosumab) have demonstrated to delay SREs [13], but they have not shown significant impact in patients' survival.

Palliative therapy using [^{186}Re]hydroxyethylidene diphosphonate (HEDP) was extensively performed in patients with bone metastases from prostate and breast cancers [14].

^{89}Sr-chloride showed significant results when used with the aim of palliating pain from

bone metastases, in particular metastatic prostate or breast cancer, resulting in pain relief in 60–92% of patients [15–21]. Since ^{153}Sm alone has no affinity for bone, the isotope is chelated to ethylene diamine tetramethylene phosphonate (EDTMP) for targeting bone.

The absorbed dose and relative biological effectiveness (EBR) of ^{223}Ra to lesions per unit administered activity was much higher than that of other bone-seeking radiopharmaceuticals, but considering a standard administration of 21 MBq (six injections of 50 kBq/kg to a 70-kg patient), the mean cumulative value of absorbed dose and relative biological effectiveness was about 19 Gy and was therefore in the range of those of other radiopharmaceuticals [20].

In the wave of novel therapies for mCRPC which has characterized the last years, a renewed attention towards the potential role of targeted α-therapy has been established in the set of patients affected by bone metastases from mCRPC.

27.3 ^{223}Ra in Symptomatic Prostate Cancer Clinical Trial

In phase I and II studies involving patients with bone metastases [22, 23], safety and tolerability of ^{223}Ra had been previously evaluated. The first phase I trial enrolled breast and prostate cancer patients with skeletal metastases (15 prostate and 10 breast cancer ones) for receiving a single IV injection of ^{223}Ra: five patients were included at each of the dosages, 46, 93, 163, 213 or 250 kBq/kg, and followed for 8 weeks [22]. A phase II trial enrolled patients with hormone-refractory prostate cancer and bone pain needing external-beam radiotherapy, who were randomized to four administrations of ^{223}Ra (50 kBq/kg, 33 patients) or placebo (31 patients), given every 4 weeks [23].

In 2013, Parker et al. [24] assessed efficacy and safety of ^{223}Ra compared to placebo, in addition to the best standard of care, in men with CRPC and bone metastases. In this phase III study, they randomly assigned 921 patients who had received, were not eligible to receive, or declined docetaxel, in a 2:1 ratio, to receive six injections of ^{223}Ra (50 kBq/kg b.w. intravenously) or matching placebo. Time interval between each injection was 4 weeks. The primary end point was overall survival; the main secondary efficacy end points were the time to the first symptomatic skeletal, time to PSA and ALP progression, PSA and ALP responses, safety and quality of life. At the interim analysis, which involved 809 patients and was performed when 314 deaths had occurred, ^{223}Ra significantly improved overall survival with respect to placebo (median, 14.0 months vs. 11.2 months; $P = 0.002$). The updated analysis, performed when 528 deaths had occurred and involving 921 patients, confirmed the ^{223}Ra survival benefit (median, 14.9 months vs. 11.3 months; $P < 0.001$). Also considering all main secondary efficacy end points, a benefit of radium-233 with respect to placebo was found. ^{223}Ra significantly prolonged the time to the first symptomatic skeletal event (median, 15.6 months vs. 9.8 months; $P < 0.001$), the time to an increase in the total alkaline phosphatase level ($P < 0.001$) and the time to an increase in the PSA level ($P < 0.001$). More patients in the ^{223}Ra group than in the placebo group experienced a decrease in the total alkaline phosphatase and PSA levels. About safety, ^{223}Ra was associated with low myelosuppression rates and few adverse events.

^{223}Ra demonstrated to prolong median OS with respect to placebo, regardless of previous docetaxel use. However, patients previously treated with docetaxel had a higher incidence of grades 3–4 thrombocytopenia with ^{223}Ra with respect to placebo, whereas the incidences of grades 3–4 anaemia were associated with bone involvement at baseline in both arms of treatment. In ^{223}Ra and placebo patients who received subsequent chemotherapy (142 patients for ^{223}Ra and 64 placebo), evaluation of haemoglobin, neutrophils and thrombocytes showed similar findings up to 18 months following the start of chemotherapy, and only a low percentage of cases in both groups showed grades 3–4 haematological toxicities: from this evaluation, chemotherapy after ^{223}Ra, regardless of prior docetaxel treatment, is well tolerated in patients with CRPC and symptomatic bone metastases [25].

Recently, Alva et al. [26] identified potential clinical variables associated with outcomes after ^{223}Ra therapy in 145 patients. 74/145 (or 51%) received six cycles of treatment. In their study, survival was highly associated with receiving all six doses, and the receipt of six doses was also associated with ECOG PS of 0–1, lower baseline PSA and pain level, no prior abiraterone/enzalutamide, <5 bone scan index value and normal alkaline phosphatase. In 72 patients with baseline pain evaluation, pain declined in 51% after one dose and increased in 7%. PSA declined ≥50% in 16% of cases, whereas alkaline phosphatase declined ≥25% in 48% and ≥50% in 23% of patients. Bone scan index declined in 17/25 (or 68%) who had bone scan available at treatment follow-up. Grade ≥ 3 neutropenia, anaemia and thrombocytopenia occurred in 4% (n = 114), 4% (n = 125) and 5% (n = 123), respectively. They concluded that patients earlier in their disease course with <5 bone scan index, low pain score and good ECOG performance status are optimal candidates for ^{223}Ra.

27.4 ^{223}Ra Dichloride: Indication and Patient Management

^{223}Ra is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

Before considering a patient for this treatment modality, it is mandatory to check eligibility and verify osseous metastases on a recent bone scan. Patients must present at least two sites of bone metastases demonstrated at bone scintigraphy[a] with ^{99m}Tc-diphosphonate performed before to start therapy with ^{223}Ra. As an alternative, ^{18}F-NaF PET/CT can be used because it has demonstrated a higher diagnostic performance than bone scintigraphy. To exclude visceral metastases, a computed tomography (CT) imaging and/or positron emission tomography (PET)/CT after administration of ^{18}F/^{11}C-choline or ^{68}Ga-prostate-specific membrane antigen (PSMA) in selected cases must be performed. These imaging modalities consent to verify also the presence of nodal disease (the presence of malignant lymph nodes greater than 3 cm short axis represents exclusion criteria for treatment) (Table 27.1). Diagnostic examinations have to be done within 3 months before starting treatment.

Pain must be assessed through specific questionnaires and scales; according to ALSYMPCA inclusion criteria and approved label, patient must present a WHO pain ≥1 (=assumption of nonsteroidal anti-inflammatory or antalgic EBRT in the previous 12 weeks; in the ALSYMPCA trial, 44% of enrolled pts presented a WHO pain = 1). According to Brief Pain Inventory-Short Form (BPI-SF) question 3, the referred pain in the last 24 h must be ≥2 (the score 2–3 corresponds to a mildly symptomatic disease, while the score from 4 to 10 is from moderate to severe pain) (Tables 27.1 and 27.4).

Haematological evaluation must be performed at baseline and prior to every radiopharmaceutical administration. Before the first administration, the absolute neutrophil count should be ≥1.5 × 10^9/l, the platelet count ≥100 × 10^9/l and haemoglobin ≥10.0 g/dl. Before subsequent administrations, the absolute neutrophil count should be ≥1.0 × 10^9/l and the platelet count ≥50 × 10^9/l. In patients with persistent impairment in these values within 6 weeks after the last administration of ^{223}Ra despite receiving standard of care, treatment with ^{223}Ra should only be continued after a benefit/risk balance [27].

In the presence of compromised bone marrow functionality related to prior cytotoxic therapies (chemotherapy and/or radiotherapy) or prostate cancer patients with advanced diffuse bone infiltration, treatment should be performed with caution because these patients have a higher risk of haematological toxicity. In "superscan" condition, patients can be treated with ^{223}Ra after careful evaluation. Other comorbidities have to be evaluated, such as inflammatory bowel disease (a condition that can be worsened because of faecal ^{223}Ra excretion) and spinal cord compression and fractures (which have to be stabilized before starting treatment). Osteonecrosis of the jaw, often related to previous treatment with zoledronic acid or denosumab, is not an absolute contraindication to ^{223}Ra administration, but it represents a condition to be carefully evaluated.

There aren't any known interactions with other drugs nor contraindication in patients with renal or hepatic impairment. No dosage adjustment is required in older patients, and no differences in

Table 27.1 Characteristics of patients suitable for ^{223}Ra treatment

Characteristics	Definition
Bone-dominant castrate-resistant prostate cancer (CRPC)	At least two sites of bone metastases were demonstrated at bone scintigraphy[a] with ^{99m}Tc-diphosphonate performed before to start therapy with ^{223}Ra
Presence of symptomatic bone metastasis	Identified by: – The assumption of specific pharmacologic agents, such as FANS or opioids (WHO scale ≥1;) and/or – BPI-SF ≥2 (the score 2–3 corresponds to a mild pain, the score ≥4 is an intense pain)
Adequate medullary function	Before the administration of ^{223}Ra, please check: – Absolute neutrophil count (ANC) (should be ≥1.5 × 10^9/l) – Platelet count (should be ≥100 × 10^9/l) – Haemoglobin (should be ≥10.0 g/dl) Before the administration of ^{223}Ra (after the first cycle), please check: – ANC (should be ≥1.0 × 10^9/l) – Platelet count (should be ≥50 × 10^9/l) (If the above-mentioned values remain abnormal until 6 weeks from the last administration, Ra223 should be continued after a benefit/risk balance
No visceral metastases[b] (an absolute contraindication to the treatment)	Liver, lung and central nervous system (CNS)
Presence of lymph node metastases[b]	Only lymph node metastases with a diameter <3 cm are allowed

[a]Bone scintigraphy is useful because the uptake of ^{99m}Tc-phosphonate is similar to that of ^{223}Ra, therefore similar to calcium. As an alternative, ^{18}F-NaF PET/CT can be used because it has demonstrated a higher diagnostic performance than bone scintigraphy

[b]To exclude the presence of visceral metastases or to assess the presence of lymph node dissemination, it is recommended to perform a thorax-abdominal computed tomography (CT) with contrast enhancement or a PET/CT with radiolabelled choline. The examination should be performed at least 3 months before to start ^{223}Ra treatment. PET/CT does not exclude the execution of bone scintigraphy, before to start ^{223}Ra treatment

terms of efficacy in patients <65 years vs. >65 years resulted in the ALSYMPCA trial.

^{223}Ra is contraindicated in patients who experience life-threatening complications despite supportive care approaches. In fact, therapeutic decision-making should consider all the aspects of the patient's overall clinical state, such as age, performance status, comorbidities, other available therapeutic options in the disease setting and patient's choice. Attention must be taken considering disease aggressiveness in accordance with extent of metastases, presence of visceral metastases, presence of pain, time from diagnosis, PSA kinetic and ADT response duration. The most appropriate patients may be those with lower burden of bone disease and good bone marrow reserve [28] since ^{223}Ra administration is limited only by haemoglobin levels <10 mg/dl. In chemo-naïve patients, physician should consider the presence of pain: in symptomatic patients, the use of abiraterone acetate and enzalutamide is not indicated [28], and in this set of patients, excluding those with visceral metastases and/or with relevant nodal involvement (nodes ≥3 cm), mCRPC patients may receive docetaxel or ^{223}Ra [28]. Ideal candidates for ^{223}Ra treatment are patients with mildly symptomatic bone metastasis, limited burden of disease and a long PSA doubling time (e.g. ≥6 months), or with comorbidities contraindicating the use of chemotherapy, or in patients refusing chemotherapy [28]: interestingly, as mentioned above,^{223}Ra allows subsequent docetaxel therapy [29]. In patients already treated with docetaxel, physician should consider its toxicities: for example, patients experiencing relevant toxicities may be not good candidates for cabazitaxel, while the toxicity profiles of the new hormonal agents or ^{223}Ra could favour their use in the setting of symptomatic patients without visceral metastases and relevant nodal involvement (nodes ≥3 cm) [28]. By contrast, in patients with aggressive disease after docetaxel failure, cabazitaxel could be proposed. If abiraterone or enzalutamide was administered as first-line therapy for mCRPC, valid therapeutic options include docetaxel and ^{223}Ra if indicated [28]. Additionally, if the choice is between ^{223}Ra and a new generation hormonal agent, the presence of relevant comorbidities

should be evaluated, since the use of enzalutamide may be limited by either clinical history of seizure or concomitant administration of drugs that act on CYP3A4, CYP2C9 and CYP2C19 [28], and the presence of severe cardiovascular disease or uncontrolled diabetes suggests caution in the use of abiraterone: in this setting, ^{223}Ra is an alternative valid approach [28]. Moreover, consideration about sequencing of the available active agents in mCRPC is needed: medical literature suggests a relationship between the development of resistance to new hormonal agents and the upregulation of androgen receptors; ^{223}Ra efficacy is not related to androgen receptor pathways and to the known pathways involved in drugs' resistance [28].

Before starting treatment, a complete bone disease staging must be performed as described above. Pain evaluation, dosage of alkaline phosphatase and complete blood count should be repeated at baseline and each cycle; PSA should be tested at baseline and, during treatment, only if clinically indicated (Table 27.2).

Imaging must be repeated at the end of six cycles, after at least 8 weeks from last administration, to avoid the phenomenon of bone flare at scan. Visceral status of disease with CT scan or choline PET is generally repeated at the same time (+8 weeks from last cycle), but if clinically suggested, it could be performed also after third cycle, in case of clinical suspicion of disease progression. It is mandatory to use the same imaging modalities applied at baseline (Table 27.2).

A signed consent form should be obtained after showing the features of the treatment to the patient or patient's caregiver and answering all their questions. ^{223}Ra should be handled following both radiation safety and pharmaceutical quality requirements. Aseptic precautions should be taken. Dose calibrator measurement may be required. The volume to be administered is calculated on the basis of patient's body weight (kg), dosage level (55 kBq/kg body weight according to National Institute of Standards and Technology [30]), activity at reference date (6.6 MBq or 1100 kBq/ml) and decay correction factor to correct for physical decay of ^{223}Ra. Double gloves should be worn. Floor, chair and table have to be protected from eventual contamination. Saline flushes and an IV pole with 500 ml saline and primed tubing should be available. The saline flow has to be connected through a

Table 27.2 Preparation of patients for the treatment with ^{223}Ra

Biochemical analysis	Imaging evaluation	Medical condition
Baseline serum ALP Baseline serum PSA	Bone scintigraphy	In older patients, the dosage should not be rearranged (no differences in terms of efficacy in patients aged <65 years vs. aged >65 years, in the ALSYMPCA trial)
Serum testosterone (in order to confirm the presence of *castration-resistant disease*)	CT scan or radiolabelled choline PET/CT scan[a]	In patients with liver dysfunction, the dosage should not be rearranged, because ^{223}Ra is not metabolized by the liver and it is not eliminated by the bile
		In patients with renal failure, the dosage should not be rearranged because the urinary excretion is minimal (<5%)
		In patients with inflammatory bowel disease (Crohn disease or ulcerative colitis), the risk/benefit ratio should be considered, because ^{223}Ra has an intestinal elimination (>75%)
		In patients with a "superscan," ^{223}Ra is not contraindicated, but a careful evaluation of the performance status and medullary reserve is required
		In patients with a potential medullary compression or bone fracture, the stabilization is recommended before to start the treatment with ^{223}Ra
		There are no limitations regarding previous treatments, like chemotherapy or others. In accordance with phase II trial (ALSYMPCA), both patients before and after chemotherapy are eligible for the therapy with ^{223}Ra

ALP alkaline phosphatase, *PSA* prostate-specific antigen
[a]*See* Table 27.1

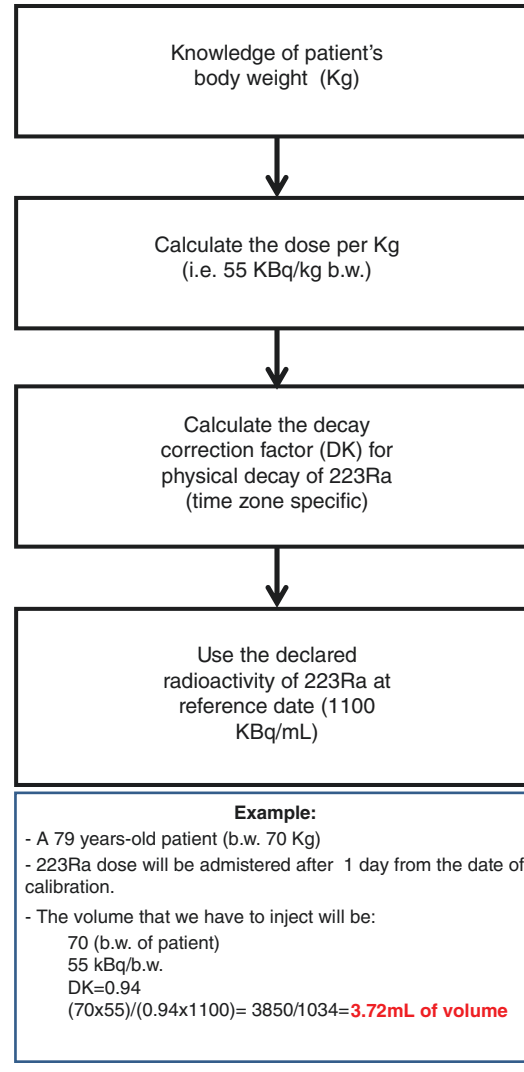
three-way stopcock and should be stopped, and then ^{223}Ra should be administered up to 1 min by the physician. Also central venous catheter could be used for administration. A therapeutic activity of 55 kBq per kg body weight is recommended. Then saline flushes are connected and pushed. Then all the tubing and the radioisotope syringe are placed in an appropriate container and left in a red biohazard bag for measuring eventual residual. Technologist's and physician's hands and feet have also to be preserved from potential contamination. Before patient demission, general status evaluation with heart rate and blood pressure has to be performed. A report indicating cycle's number administered activity and basic information on clinical indication and laboratory data. The patient is scheduled for the next cycles 28 days later. The most frequently observed adverse reactions (≥10%) in patients receiving ^{223}Ra were diarrhoea, nausea, vomiting and thrombocytopenia. Rare serious adverse reactions were thrombocytopenia and neutropenia. It is mandatory to evaluate complete blood count and other markers such as serum alkaline phosphatase (ALP), serum PSA, lactate dehydrogenase and bone-specific alkaline phosphatase. Restaging is recommended after the completion of six cycles of ^{223}Ra, but the revaluation can be performed earlier if suspicious clinical symptoms occur.

The patient should avoid prolonged contact with children and pregnant women during the first week after each administration. It is recommended that he follows behavioural norms to avoid contamination (by using gloves if it is necessary to clean urine, stool or vomit and when touching or washing dirty clothes). Toilet should be flushed twice after each use. Possible incontinence must be checked by physicians, to give complete information to patients and their caregivers. Underwear used during the first week after each ^{223}Ra administration and any clothing soiled with urine, stool or blood should be washed separately).

If a patient dies within 7 days from last administration, cremation must be postponed or burial used instead [31].

Diagnostic imaging workup in CRPC includes nuclear medicine (bone scintigraphy, PET/CT) and radiological techniques (CT, magnetic resonance imaging). Nuclear medicine techniques may be used to assess response in bone metastases treated with ^{223}Ra, either with bone scintigraphy or with PET/CT imaging. Among last techniques, changes in large metastatic deposits after ^{223}Ra therapy have been reported, with a dramatic drop of radiopharmaceutical lesions' accumulation either of ^{18}F-choline [11] or ^{68}Ga-PSMA [32, 33] in responders together with a reduction of PSA and ALP. This phenomenon cannot be simply explained by tumour cell irradiation but also by an effect on the microenvironment including vessels and stroma, which induces tumour regression in both osteolytic and osteoblastic tumours [7], opening the way for the use of ^{223}Ra also for other malignancies.

How to calculate 223Ra dose



27.5 Response Evaluation

Response evaluation after ^{223}Ra therapy can be followed by several biomarkers and bone scintigraphy (Table 27.3). ALP is a biomarker of osteoblastic activity and its serum levels are often incremented in mCRPC patients. High serum ALP levels are related to an increased risk of SREs and mortality. It can be used for evaluating treatment response, disease progression and survival in mCRPC patients [34–39]. Major reduction of ALP levels with respect to PSA ones reflects the differences between the two biomarkers: in fact, if ALP levels are linked to bone metabolism and are therefore influenced by a bone-targeted treatment as ^{223}Ra, serum PSA is an expression of overall disease evolution and is less influenced by a targeted therapy.

Considering disease markers for response evaluation, such as serum PSA and bone metabolism indices (bone and total ALP) together with bone scan, it has been found that ALP represents the most accurate marker for evaluating response to treatment, whereas in some patients serum PSA levels can increase at the end of the treatment. Bone scan is accurate and has a high sensibility in detection of bone metastases. Additionally, it can show new findings, since some lesions can be characterized by metabolic response, whereas new lesions can appear after the end of ^{223}Ra therapy. In this setting, combination with other medical approaches can be useful. It should be considered that flare response can occur, since some patients can experience an increase in disease biomarkers (PSA and ALP) together with a worsening of pain after the starting of the treatment, but followed by an improvement at bone scintigraphy and a subsequent reduction of disease biomarkers and pain:

Table 27.3 Evaluation of response to ^{223}Ra treatment

Test	Time
ALP	Baseline After 3 months At the end of therapy
Complete blood count (CBC)	Every 1 month before ^{223}Ra administration[a]
PSA	Baseline During treatment, if requested by nuclear medicine physician, only for monitoring the presence of visceral involvement[b]
CT or radiolabelled choline PET/CT	Only in case of visceral progression
Bone scintigraphy	Baseline After 2–3 months from the end of treatment
Pain score test	*See* Table 27.4

ALP alkaline phosphatase, *PSA* prostate specific antigen
[a]CBC is suggested at each cycle for assessing the eligible of patients (*see* Table 27.2)
[b]PSA can falsely increase during ^{223}Ra therapy (flare phenomena), but it represents a marker of a potential visceral progression

Table 27.4 Pain scales for the assessment of life quality

Method	Grade	Meaning
ECOG	0	Fully active, able to carry on all pre-disease performance without restriction
	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
	2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
	3	Capable of only limited self-care; confined to bed or chain more than 50% of waking hours
	4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
	5	Dead
WHO	0	No pain at rest on movement
	1	No pain at rest, mild on movement (mild analgesic action, i.e. paracetamol)
	2	Mild pain at rest, moderate on movement (weak opiate/NSAID and consider paracetamol)
	3	Continuous pain at rest, severe on movement (morphine or other strong agent; and consider weak opiate/NSAID/paracetamol)
EQ-5D	1	Mobility
	2	Self-care
	3	Usual activities
	4	Pain/discomfort
	5	Anxiety/depression

flare phenomenon can occur up to 12 weeks after the starting of ^{223}Ra therapy. On this way, progression of disease should be considered at least in cases with ≥2 bone lesions after flare occurrence and should be confirmed by a bone scan performed 6 weeks later [40]. An interesting aspect of bone scan is represented by the calculation of the bone scan index, which allows to assess more precisely the extent of metastatic disease [41].

On the other hand, patients who underwent multiple prior chemotherapy schemes, ECOG ≥2 and lower haemoglobin levels have more advanced disease and are less likely to reach the recommended six administrations; oppositely, the completion of treatment is associated with higher efficacy (Fig. 27.1) and longer overall survival [42].

Even if CT is the classical imaging technique used to detect cancer and to assess disease status through "Response Evaluation Criteria In Solid Tumors" (RECIST criteria), it cannot be used to assess response to therapy in bone metastases: in fact, even if it permits to evaluate osseous architecture, bone structure rarely normalizes even with completely effective therapy [43]. Additionally, the occurrence of worsening bone sclerosis on CT is occasionally and erroneously classified as disease progression, without considering CT flare response [43]. The superiority of MRI for detection of bone metastases with respect to CT has been demonstrated. Diffusion-weighted imaging (DWI) sequences are able to detect changes in water diffusion: if normal fatty marrow is replaced with highly dense cellularity, normal water movements among cell membranes

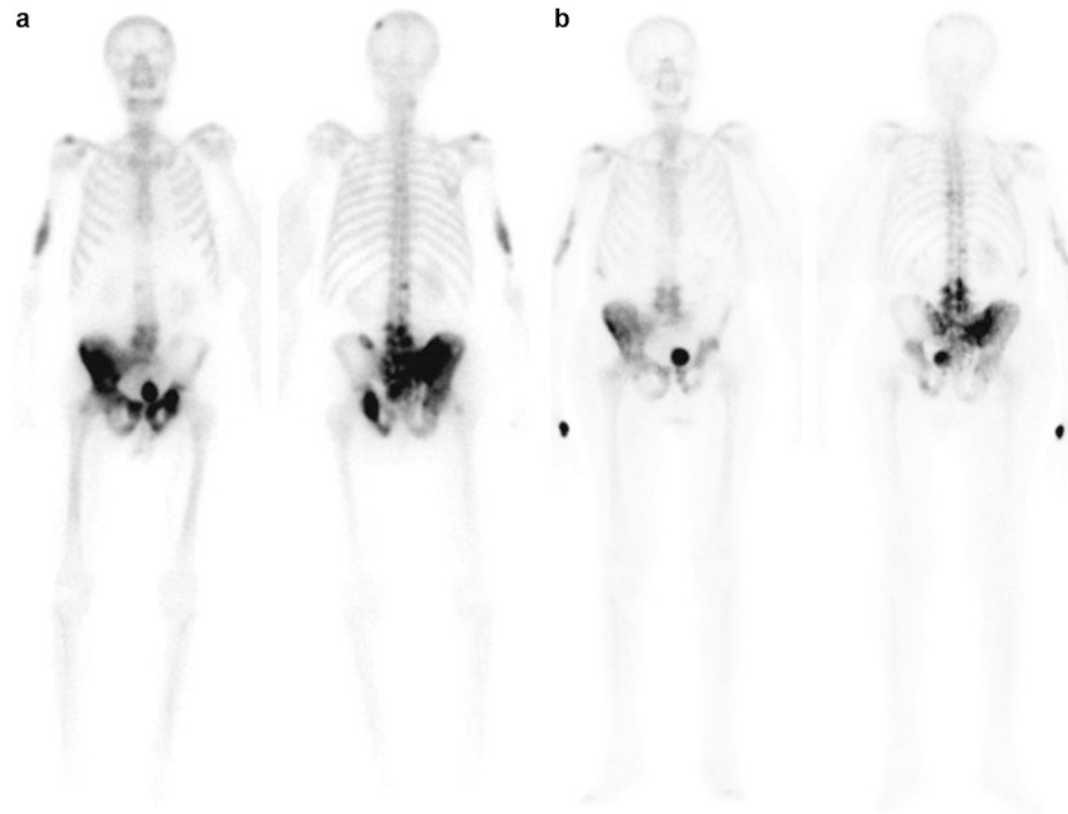


Fig. 27.1 Pretreatment (**a**) and post-treatment (**b**) bone scintigraphy of a 73-year-old patient affected by castration-resistant prostate cancer (Gleason 9) with bone metastases who underwent six administrations of $^{223}RaCl_3$ at the therapeutic activity of 55 kBq/kg b.w

are limited. Moreover, changes in water mobility occur in response to treatment. However, benign conditions may show high signal intensity on DWI images, and, on the contrary, false-negative findings may occur, mainly in sclerotic or calcified metastases. On this way, MRI is a reliable tool for confirming stable disease or corroborating progressive disease if new lesions appear or if a sclerotic lesion has a new peripheral halo [43].

New nuclear imaging techniques are now available to better assess patients' condition and treatment response. First of all, ^{18}F-fluoride may be considered, since it is a bone-seeking radiopharmaceutical which is used for PET/CT imaging: in particular, it has shown higher sensibility, higher specificity and higher accuracy than bone scintigraphy [44]. The spreading of nuclear medicine centres using new tracers, such as ^{18}F-choline/^{11}C-choline and ^{68}Ga-PSMA, offers additional opportunities to better evaluate disease status of patients.

Choline PET/CT has demonstrated agreement with PSA changes in patients with progressive disease but has some limitations in identifying patients with partial or complete response to therapy: in fact, the uptake normalization is not always related to the disappearance of the cancer lesion, since it could represent the effect of a stable or nonmetabolic lesion [43]. In contrast, the appearance of new areas of uptake does not always correlate with certain progression, but they can be an expression of the well-known flare phenomenon [43]. So, choline PET/CT should be repeated within 3 months if a flare phenomenon is suspected. Advantages of ^{68}Ga-PSMA PET/CT are the sensitive detection of lesions, even at low PSA levels (i.e. PSA <1 ng/ml), small lymph node metastases and central bone and liver metastases due to tumour/non-tumour ratio [43].

Finally, the main markers to be used for monitoring the response to treatment are:

- Pain reduction: its evaluation is mandatory, in association with quality of life evaluation.
- Serum PSA: it should not be used as specific marker for treatment response, since it reflects the general evolution of the disease.
- Serum ALP: it should be considered the most important marker.
- Bone scintigraphy: its usefulness is indisputable, not only to evaluate the patient at the end of the treatment but also in an "ad interim" intent in cases which elicit strong clinical suspicion of bone disease progression.

During treatment, diagnostic imaging should not be performed systematically but in the set of a multidisciplinary evaluation which considers also clinical and laboratory data. However, a clear worsening clinical condition justifies evaluation by means of imaging modalities.

On the basis of clinical evidence, the following lines have to be followed:

- Continue treatment and stop it only in cases with major side effects or clinical deterioration.
- Consider all available clinical sign and symptoms.
- Keep an eye on overall patients' conditions.

Conclusions

^{223}Ra is a calcium mimetic targeted alpha therapy and permits delivery of high radiation energy at sites of active bone turnover due to metastatic spreading. Literature experiences have demonstrated increased overall survival and decreased time to skeletal-related events with ^{223}Ra-dichloride, with additional benefits involving also other disease biomarkers. The integration of ^{223}Ra into the management of mCRPC may improve OS also by the additional and sequential chemotherapy. This leads to consider what is the best sequence of drugs or if a combined therapy could be used. The nonoverlapping mechanism of action and the safety of ^{223}Ra may allow new combination strategies in an era of releasing of novel innovative drugs, moving from symptomatic and more diffuse bone disease to an earlier phase characterized by asymptomatic/limited bone disease or in the set of patients with visceral disease and bone involved. Finally, further studies are needed in the metastatic bone setting from other solid malignancies besides prostate cancer. These questions require a more accurate evaluation of ^{223}Ra's action and a dosimetric approach beyond activity/weight

criteria: interestingly, lesions with ^{99m}Tc-MDP contrast ratio higher than 10, not overlapping the gastrointestinal tract, are generally visible on ^{223}Ra images acquired at 24 h after the administration, and possibly eligible for dosimetric studies [45].

Key Points

- ^{223}Ra delays time to symptomatic skeletal-related events and prolongs overall survival in men affected by metastatic castration-resistant prostate cancer (mCRPC) and more than two painful bone metastases.
- $^{223}RaCl_2$ is the only radiopharmaceutical that has demonstrated to give a benefit in overall survival, regardless of previous docetaxel use.
- Patients earlier in their disease course with <5 bone scan index, low pain score and good ECOG performance status are optimal candidates for ^{223}Ra.
- Men who underwent multiple prior chemotherapy schemes, ECOG ≥2 and lower haemoglobin levels have more advanced disease and are less likely to reach the recommended six administrations; on the other hand, the completion of treatment is associated with higher efficacy and longer overall survival.
- Prostate-specific antigen trend should not be used to determine response or duration of treatment, whereas ALP represents the most accurate marker for evaluating response to treatment.

References

1. Picciotto M, Franchina T, Russo A, Ricciardi GRR, Provazza G, Sava S, Baldari S, Caffo O, Adamo V. Emerging role of Radium-223 in the growing therapeutic armamentarium of metastatic castration-resistant prostate cancer. Expert Opin Pharmacother. 2017;18:899–908.
2. Kassis AI. Therapeutic radionuclides: biophysical and radiobiologic principles. Semin Nucl Med. 2008;38:358–66.
3. Harrison MR, Wong TZ, Armstrong AJ, George DJ. Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease. Cancer Manag Res. 2013;5:1–14.
4. Logothetis CJ, Gallick GE, Maity SN, et al. Molecular classification of prostate cancer progression: foundation for marker-driven treatment of prostate cancer. Cancer Discov. 2013;3:849–61.
5. Henriksen G, Breistøl K, Bruland ØS, Fodstad Ø, Larsen RH. Significant antitumor effect from bone-seeking, alpha-particle emitting (223)Ra demonstrated in an experimental skeletal metastases model. Cancer Res. 2002;62:3120–5.
6. Suominen MI, Rissanen JP, Käkönen R, Fagerlund KM, Alhoniemi E, Mumberg D, Ziegelbauer K, Halleen JM, Käkönen SM, Scholz A. Survival benefit with radium-223 dichloride in a mouse model of breast cancer bone metastasis. J Natl Cancer Inst. 2013;105:908–16.
7. Abou DS, Ulmert D, Doucet M, Hobbs RF, Riddle RC, Thorek DL. Whole-body and microenvironmental localization of Radium-223 in naïve and mouse models of prostate cancer metastasis. J Natl Cancer Inst 2016; 108: pii: djv380.
8. Suominen MI, Fagerlund KM, Rissanen JP, Konkol YM, Morko JP, Peng ZQ, Alhoniemi EJ, Laine SK, Corey E, Mumberg D, Ziegelbauer K, Käkönen SM, Halleen JM, Vessella RL, Scholz A. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. Clin Cancer Res. 2017;23(15):4335–46.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.
10. Alemayehu B, Buysman E, Parry D, Becker L, Nathan F. Economic burden and healthcare utilization associated with castration-resistant prostate cancer in a commercial and medicare advantage US patient population. J Med Econ. 2010;13:351–61.
11. Ritch CR, Cookson MS. Advances in the management of castration resistant prostate cancer. BMJ. 2016;355:i4405.
12. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Chen B. Zoledronic acid prostate cancer study group: a randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94:1458–68.
13. Fizazi K, Beuzeboc P, Lumbroso J, Haddad V, Massard C, Gross-Goupil M, Di Palma M, Escudier B, Theodore C, Loriot Y, Tournay E, Bouzy J, Laplanche A. Phase II trial of consolidation docetaxel and samarium-153 in patients with bone metastases from castration-resistant prostate cancer. J Clin Oncol. 2009;27:2429–35.
14. Minutoli F, Herberg A, Spadaro P, Restifo Pecorella G, Baldari S, Aricò D, Altavilla G, Baldari S. [186Re] HEDP in the palliation of painful bone metastases from cancers other than prostate and breast. Q J Nucl Med Mol Imaging. 2006;50:355–62.
15. Fuster D, Herranz D, Vidal-Sicart S, et al. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. Nucl Med Commun. 2000;21:623–6.

16. Kraeber-Bodéré F, Campion L, Rousseau C, et al. Treatment of bone metastases of prostate cancer with strontium-89 chloride: efficacy in relation to the degree of bone involvement. Eur J Nucl Med. 2000;27:1487–93.
17. Ashayeri E, Omogbehin A, Sridhar R, et al. Strontium 89 in the treatment of pain due to diffuse osseous metastases: a university hospital experience. J Natl Med Assoc. 2002;94:706–11.
18. Gunawardana DH, Lichtenstein M, Better N, et al. Results of strontium-89 therapy in patients with prostate cancer resistant to chemotherapy. Clin Nucl Med. 2004;29:81–5.
19. Liepe K, Kotzerke J. A comparative study of 188Re-HEDP, 186Re-HEDP, 153Sm-EDTMP and 89Sr in the treatment of painful skeletal metastases. Nucl Med Commun. 2007;28:623–30.
20. Pacilio M, Ventroni G, De Vincentis G, Cassano B, Pellegrini R, Di Castro E, Frantellizzi V, Follacchio GA, Garkavaya T, Lorenzon L, Ialongo P, Pani R, Mango L. Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting (223)Ra-dichloride. Eur J Nucl Med Mol Imaging. 2016;43:21–33.
21. Correa-González L, Arteaga de Murphy C, Pichardo-Romero P, Pedraza-López M, Moreno-García C, Correa-Hernández L. (153)Sm-EDTMP for pain relief of bone metastases from prostate and breast cancer and other malignancies. Arch Med Res. 2014;45:301–8.
22. Nilsson S, Larsen RH, Fosså SD, Balteskard L, Borch KW, Westlin JE, Salberg G, Bruland OS. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. Clin Cancer Res. 2005;11:4451–9.
23. Nilsson S, Franzén L, Parker C, Tyrrell C, Blom R, Tennvall J, Lennernäs B, Petersson U, Johannessen DC, Sokal M, Pigott K, Yachnin J, Garkavij M, Strang P, Harmenberg J, Bolstad B, Bruland OS. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol. 2007;8:587–94.
24. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen DC, Hoskin P, Bottomley D, James ND, Solberg A, Syndikus I, Kliment J, Wedel S, Boehmer S, Dall'Oglio M, Franzén L, Coleman R, Vogelzang NJ, O'Bryan-Tear CG, Staudacher K, Garcia-Vargas J, Shan M, Bruland ØS, Sartor O, ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213–23.
25. Sartor O, Hoskin P, Coleman RE, et al. Chemotherapy following radium-223 dichloride treatment in ALSYMPCA. Prostate. 2016;76:905–16.
26. Alva A, Nordquist L, Daignault S, George S, Ramos J, Albany C, Isharwal S, McDonald M, Campbell G, Danchaivijitr P, Yentz S, Anand A, Yu EY. Clinical correlates of benefit from Radium-223 therapy in metastatic castration resistant prostate cancer. Prostate. 2017;77:479–88.
27. ema.europa.eu. Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/002653/WC500156172.pdf. Accessed Mar 2017.
28. Baldari S, Boni G, Bortolus R, CAffo O, Conti G, De Vincentis G, Monari F, Procopio G, Santini D, Seregni E, Valdagni R. Management of metastatic castration-resistant prostate cancer: a focus on radium-223. Crit Rev Oncol Hematol. 2017;113:43–51.
29. Sartor AO, Heinrich D, Mariados N. Radium-223 (Ra-223) re-treatment (Re-tx): first experience from an international, multicenter, prospective study in patients (Pts) with castration-resistant prostate cancer and bone metastases (mCRPC). J Clin Oncol. 2016;34(Suppl 2S):197. Dent Abstr
30. Zimmerman BE, Bergeron DE, Cessna JT, Fitzgerald R, Pibida L. Revision of the NIST standard for (223) Ra: new measurements and review of 2008 data. J Res Natl Inst Stand Technol. 2015;120:37–57.
31. Prior JO, Gillessen S, Wirth M, Dale W, Aapro M, Oyen WJG. Radiopharmaceuticals in the elderly cancer patient: practical considerations, with a focus on prostate cancer therapy: a position paper from the International Society of Geriatric Oncology Task Force. Eur J Cancer. 2017;77:127–39.
32. Miyazaki KS, Kuang Y, Kwee SA. Changes in skeletal tumor activity on (18)F-choline PET/CT in patients receiving (223)radium radionuclide therapy for metastatic prostate cancer. Nucl Med Mol Imaging. 2015;49:160–4.
33. Ahmadzadehfar H, Schlenkhoff CD, Rogenhofer S, Yordanova A, Essler M. 68Ga-PSMA-11 PET represents the tumoricidal effect of 223Ra in a patient with castrate-resistant metastatic prostate cancer. Clin Nucl Med. 2016;41:695–6.
34. Seibel MJ. Biochemical markers of bone turnover: part I: biochemistry and variability. Clin Biochem Rev. 2005;26:97–122.
35. Jung K, Lein M, Stephan C, Von Hösslin K, Semjonow A, Sinha P, Loening SA, Schnorr D. Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: diagnostic and prognostic implications. Int J Cancer. 2004;111:783–91.
36. Berruti A, Tucci M, Mosca A, Tarabuzzi R, Gorzegno G, Terrone C, Vana F, Lamanna G, Tampellini M, Porpiglia F, Angeli A, Scarpa RM, Dogliotti L. Predictive factors for skeletal complications in hormone-refractory prostate cancer patients with metastatic bone disease. Br J Cancer. 2005;93:633–8.
37. Smith MR, Cook RJ, Coleman R, Brown J, Lipton A, Major P, Hei YJ, Saad F. Predictors of skeletal complications in men with hormone-refractory metastatic prostate cancer. Urology. 2007;70:315–9.
38. Cook RJ, Coleman R, Brown J, Lipton A, Major P, Hei YJ, Saad F, Smith MR. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clin Cancer Res. 2006;12(11 Pt 1):3361–7.

39. Som A, Tu SM, Liu J, Wang X, Qiao W, Logothetis C, Corn PG. Response in bone turnover markers during therapy predicts overall survival in patients with metastatic prostate cancer: analysis of three clinical trials. Br J Cancer. 2012;107:1547–53.
40. Fox JJ, Morris MJ, Larson SM, Schöder H, Scher HI. Developing imaging strategies for castration resistant prostate cancer. Acta Oncol. 2011;50(Suppl 1):39–48.
41. Dennis ER, Jia X, Mezheritskiy IS, Stephenson RD, Schoder H, Fox JJ, Heller G, Scher HI, Larson SM, Morris MJ. Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer. J Clin Oncol. 2012;30:519–24.
42. Sartor O, Coleman RE, Nilsson S, et al. 3-year follow-up of chemotherapy following radium-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients (Pts) with symptomatic bone metastases (Mets) from ALSYMPCA. Presented at: European Cancer Congress 2015. Vienna, Austria: Poster session. Abstract 2510.
43. Evangelista L, Bertoldo F, Boccardo F, Conti G, Menchi I, Mungai F, Ricardi U, Bombardieri E. Diagnostic imaging to detect and evaluate response to therapy in bone metastases from prostate cancer: current modalities and new horizons. Eur J Nucl Med Mol Imaging. 2016;43:1546–62.
44. Withofs N, Grayet B, Tancredi T, Rorive A, Mella C, Giacomelli F, Mievis F, Aerts J, Waltregny D, Jerusalem G, Hustinx R. ^{18}F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers. Nucl Med Commun. 2011;32:168–76.
45. Pacilio M, Cassano B, Chiesa C, Giancola S, Ferrari M, Pettinato C, Amato E, Fioroni F, Lorenzon L, Pellegrini R, Di Castro E, Pani R, Cremonesi M. The Italian multicentre dosimetric study for lesion dosimetry in (223)Ra therapy of bone metastases: calibration protocol of gamma cameras and patient eligibility criteria. Phys Med. 2016;32:1731–7.