We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Targeted Therapy for Metastatic Prostate Cancer with Radionuclides

Hojjat Ahmadzadehfar

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64016>

Abstract

Progression to androgen-independent status is the main cause of death in patients with metastatic prostate cancer. Prostate-specific membrane antigen (PSMA) is anchored in the cell membrane of prostate epithelial cells. PSMA is highly expressed on prostate epithelial cells and strongly upregulated in prostate cancer. Therefore, it is an appropriate target for diagnosis and therapy of prostate cancer and its metastases. There is growing knowledge about promising response and low toxicity profile of radioligand therapy of metastatic castration-resistant prostate cancer using Lutetium-177-labeled PSMA ligands. For patients with only bone metastases, there are different radionuclides which have been used for decades. In this chapter, different methods of targeted radionuclide therapy of metastatic prostate cancer are described.

Keywords: PSMA, prostate cancer, radioligand therapy, metastatic disease, PSA, bone metastasis, radionuclide therapy

1. Introduction

Almost all patients with metastatic prostate cancer (PC) will initially respond to well-established and innovative anti-androgen treatments including the two recently approved hormone therapy agents, enzalutamide and abiraterone [1, 2], which significantly improve overall survival. However, progression to androgen-independent status is the main cause of death in these patients [3]. Most deaths related to PC are due to metastatic disease, which results from any combination of blood, lymphatic, or local spread. Targeted radionuclide therapy is an attractive and quickly developing therapy option for many different cancers, such as lymphoma, melanoma, and neuroendocrine tumors [4–7]. Radionuclide therapies should be

targeted, because this procedure always involves the administration of unsealed sources of radioactivity.

Most therapeutic tracers utilize β -particle emissions due to the ability of these particles to penetrate tissues. The deposition of energy in tissue by β -emitters results in cellular damage. Among the β -emitters, there are several choices regarding the energy of the β -emission. Lower energy β -particles can travel a few cell diameters, or at most in the submillimeter range. Higher energy β -particles, such as those emitted by Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu), have excellent tissue penetration with a range beyond the source of several millimeters [8, 9]. The only routinely used α -emitter for the treatment of metastatic disease is Radium-223 (^{223}Ra), which has been approved for the treatment of bone metastases in patients with prostate cancer and symptomatic disease with no known visceral metastases [10]. The physical half-life of therapeutic radionuclide is an important consideration and an underlying principle for therapy planning [11].

2. PSMA as a target

Prostate-specific membrane antigen (PSMA), also known as folate hydrolase I or glutamate carboxypeptidase II, is a type II transmembrane protein anchored in the cell membrane of prostate epithelial cells [12]. Several biological characteristics make PSMA an outstanding target for drug development. PSMA is highly expressed on prostate epithelial cells and strongly upregulated in PC. PSMA expression levels are directly correlated to androgen independence, metastasis, and PC progression [13]; thus, PSMA is an attractive target for the diagnosis and therapy of metastasized PC. Its target specificity is maintained after radiolabeling with ^{68}Ga [12, 14].

A commonly used radionuclide is ^{68}Ga -PSMA-11, which has been successfully used for the imaging of PC with high sensitivity and specificity, even in patients with very low prostate-specific antigen (PSA) levels ($<2\text{ ng/ml}$) [15]. Direct comparison studies support the superiority of ^{68}Ga -PSMA-11 in lymph node assessment over CT 3D volumetric-based lymph node assessments [16] and in overall disease assessment compared to ^{18}F -methylcholine, especially in patients with low PSA levels [17]. These positive results will lead to or have already led to a paradigm shift in the use of imaging in primary staging of PC. In a recent study by Hijazi et al., the diagnostic accuracy of ^{68}Ga -PSMA-11 in the preoperative assessment of nodal metastases was very high for macrometastases and even micrometastases in lymph nodes. Correlating imaging and tissue specimens of 213 removed nodes provided 94% sensitivity, 99% specificity, 89% positive predictive value, and 99.5% negative predictive value [18].

3. PSMA radioimmunotherapy

After rather unsuccessful therapy with the ^{90}Y -CYT-356 monoclonal antibody (mAb) recognizing the intracellular domain of PSMA [19], Phase I and II clinical trials utilizing the PSMA mAb J591, radiolabeled with ^{177}Lu or ^{90}Y , have shown promising results [20–23].

J591 is an anti-PSMA mAb that binds with 1 nM affinity to the extracellular domain of PSMA [24, 25]. Milowsky et al. [26] treated 29 patients in the ^{90}Y -J591 Phase I trial; patients received therapeutic doses of 185, 370, 555, 647.5, and 740 MBq/m² ^{90}Y -J591. Dose-limiting toxicity was seen at 740 MBq/m², with two patients experiencing thrombocytopenia with nonlife-threatening bleeding episodes requiring platelet transfusions. The 647.5 MBq/m² dose was determined to be the maximum tolerated dose (MDT).

Bander et al. [21] treated 35 patients with progressing androgen-independent PC with ^{177}Lu -J591, and 16 of these patients received up to three doses. Myelosuppression was dose-limiting at 2775 MBq/m², and the 2590 MBq/m² dose was determined to be the single-dose MTD. Repeat dosing at 1665–2220 MBq/m² was associated with dose-limiting myelosuppression [21]. The authors reported good targeting of all known sites of bone and soft tissue metastases in all patients. They found no clear relationship between a history of prior chemotherapy treatment and the degree of toxicity. Biological activity was seen with four patients experiencing $\geq 50\%$ declines in PSA levels lasting from 3 to 8 months. An additional 16 patients (46%) experienced PSA stabilization for a median of 60 days [21]. Tagawa et al. presented the results of a Phase II study of radionuclide therapy with the ^{177}Lu -PSMA mAb J591 [20], which was based on two published Phase I studies investigating this agent [21, 26]. In this study [20], 47 hormone-refractory patients (55.3% also had received chemotherapy) were treated with ^{177}Lu -J591. They compared two different doses (2405 vs. 2590 MBq/m²). About 11% of patients experienced a $\geq 50\%$ decline in PSA, 36.2% experienced a $\geq 30\%$ decline in PSA, and 59.6% experienced any PSA decline following a single therapy. All experienced reversible hematological toxicity, with Grade 4 thrombocytopenia occurring in 46.8% without significant hemorrhage. Grade 4 neutropenia happened in a total of 25.5% of patients, with one episode of febrile neutropenia. The 2590 MBq/m² dose resulted in not only 30% more of PSA decline (46.9 vs. 13.3%, $P = 0.048$) and longer survival (21.8 vs. 11.9 months, $P = 0.03$), but also more Grade 4 hematological toxicity and platelet transfusions. mAb are large molecules, and therefore show poor permeability in solid tumors and slow clearance from the circulation. This combination leads to suboptimal targeting and an increased absorbed dose in the bone marrow, narrowing the therapeutic window [27]. Thus, radionuclide treatment with ^{90}Y -J591 and ^{177}Lu -J591 is limited by myelosuppression and nonhematological toxicity, with a maximum tolerated activity per cycle of 650 and 2450 MBq/m², respectively.

4. PSMA radioligand therapy with a small-molecule inhibitor

The synthesis and design of a series of small-molecule inhibitors of PSMA have been described by Maresca et al. [28]. On the basis of the work of this group, Hillier et al. [29] performed a preclinical evaluation of two radiopharmaceuticals, ^{123}I -MIP-1072 and ^{123}I -MIP-1095, which were designed to target PSMA in PC cells and tissue. In a recent published study from the Heidelberg group, Zechmann et al. showed the utility of ^{131}I -MIP-1095 PSMA [27]. Therapy with ^{131}I -MIP-1095 PSMA was performed in 25 patients. The patients received a single therapeutic dose of ^{131}I -MIP-1095 (mean activity 4.8 GBq, range 2.0–7.2 GBq). Erythrocyte counts fell below the normal range at the nadir in 21 patients, with 17 patients having lower values prior to therapy. In 14 patients, white blood cell counts fell below the normal range after

therapy (one with Grade 3 toxicity). However, five of these 14 patients had levels below normal, prior to therapy (four Grade 1, one Grade 2); 11 patients had a reduction in platelet count below normal after therapy (two Grade 3), and one had a value below normal (Grade 2), prior to therapy. The changes in hematological parameters were not related to the activity administered. The onset of the myelosuppression occurred within 6 weeks after treatment with a quite variable time to recovery, in some cases requiring up to 3–6 months for recovery. White blood cells typically recovered within several weeks, whereas platelets required several months to recover [12, 27]. In contrast to mAb, the low-molecular-weight compounds, with higher permeability into solid tumors, offered a significant advantage in achieving higher uptake per gram of tumor tissue and a higher percentage of specific binding. Moreover, small molecules displayed more rapid tissue distribution and faster blood clearance compared with intact immunoglobulins. These properties often lead to a higher target to nontarget tissue ratio, which is important for successful application of therapeutic absorbed doses [27].

^{131}I has a long half-life of 8.02 days and has a β -particle range in soft tissue of just 0.8 mm. Due to its γ -emitting properties and long half-life, ^{131}I is less attractive from a radiation safety point of view. ^{90}Y has a half-life of 64 h, but only undergoes high-energy β -emission, resulting in a long mean β -particle range of 3.6 mm and a maximum range of 10 mm in soft tissue. Due to its long β -particle range, collateral damage to surrounding tissues is quite high [30].

Recently, a novel theranostic drug, ^{177}Lu -PSMA 617, which is a DOTA-derivative of the Glu-urea-Lys motif, has been developed for the treatment of patients with metastatic PC [29, 31]. ^{177}Lu has a half-life of 6.7 days and undergoes low-energy β -particle emission with a mean range of 1 mm and a maximum range of 2–4 mm in soft tissue. So, the practical issues surrounding radiation safety with ^{131}I and the limited collateral damage to surrounding tissues compared to ^{90}Y make ^{177}Lu -labeled radionuclide treatment the most attractive option from a physics point of view. Ahmadzadehfar et al. [32] reported on the first 10 consecutive patients who were treated with ^{177}Lu -PSMA-617 in their department (University Hospital Bonn and Muenster, Germany). They showed that 8 weeks after the therapy in these 10 patients, seven patients showed a PSA decline, of whom six experienced a more than 30% and five a more than 50% decline. Three patients showed progressive disease according to the PSA increase. No patients experienced any side effects immediately after injection of ^{177}Lu -PSMA 617 [32]. Relevant hematotoxicity (Grade 3 or 4) occurred 7 weeks after the administration in just one patient. These encouraging results showed again the efficacy of radionuclide therapy in patients who have no other approved therapeutic option. A later study by the group from Bonn showed the efficacy and safety of ^{177}Lu -PSMA 617 therapy in patients who had undergone two cycles of therapy [8]. In this study, 46 cycles of ^{177}Lu -PSMA 617 were performed in 24 consecutive hormone and/or chemorefractory patients. Twenty-two patients received two cycles of therapy. Twenty-two patients had a history of or were on therapy with enzalutamide and/or abiraterone. Twelve patients had received ^{223}Ra (1–6 cycles; median 5 cycles). All patients had multiple bone metastases, and the majority of them also had lymph node metastases. The mean and median PSA levels prior to therapy were 628.3 and 522 ng/ml, respectively (range: 17.1–2360 ng/ml). It was found that 8 weeks after the first cycle of ^{177}Lu -PSMA therapy, 19/24 patients (79.1%) experienced a PSA decline, out of whom 13 experienced

a decline of more than 30% and 10 more than 50% (41.6%). Five patients showed progressive disease according to an increase in PSA. Two months after the second cycle in 22 patients who underwent two cycles of ^{177}Lu -PSMA therapy, 15/22 patients (68.2%) experienced a PSA decline in comparison to the baseline PSA value, of whom 15 experienced a decline of more than 30%, and 13 (60%) of more than 50%. Seven patients showed progressive disease according to an increase in PSA or disease progression. Again, in this study, the patients received radioligand therapy as the last therapeutic option [8]. Interestingly, although a majority of prostate cancer patients at such an advanced stage of disease with massive bone marrow infiltration suffer from anemia, relevant hematotoxicity (Grade 3) occurred during the observation period (within 2 months after the last cycle) in just two patients. Apart from some Grade 1 or 2 hematotoxicity, the majority of patients did not show any hematotoxicity during the observation period. Some patients who needed blood transfusions prior to the first cycle needed fewer transfusions after radioligand therapy with ^{177}Lu -PSMA 617 because of the regression of bone marrow involvement [33]. The Nordrhein–Westfalen study group recently published the results of single-dose administration of ^{177}Lu -PSMA 617 in 74 patients. They showed a PSA decline in 47 patients (64%); of these, 23 (31%) had a PSA decline >50%; 35 (47%) had stable disease with a PSA decline from <50% to an increase of <25%; and 17 (23%) showed progressive disease with a PSA increase >25%. Response and tolerability of a single dose of ^{177}Lu -PSMA-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis.

Figure 1. (A) ^{68}Ga -PSMA PET scan of a 66-year-old hormone- and chemorefractory patient with multiple bone and lymph node metastases (pink arrows), with a history of chemotherapy, abiraterone, and ^{223}Ra therapies. (B) The follow-up PET scan prior to the second cycle shows a partial response with regression of the metastases and PSA decline. (C) The PET scan, 2 months after the third cycle of Lu-PSMA therapy, which shows a very good response with further decline of PSA.

Rahbar K, Schmidt M, Heinzl A, Eppard E, Bode A, Yordanova A, Claesener M, Ahmadzadehfah H. J Nucl Med. 2016 Apr 7. pii: jnumed.116.173757. [Epub ahead of print]

Further research into the efficacy of this therapy is needed. Rahbar et al. showed for the first time the overall survival benefit of RLT in comparison to a historical collective. They showed that the estimated median survival was 29.4 weeks, significantly longer than the survival in the historical control group at 19.7 weeks [hazard ratio: 0.44 (95% confidence interval: 0.20–0.95); $P = 0.031$] [34] (**Figure 1**).

5. Treatment of bone metastases with radionuclides

Bone metastases, a major cause of morbidity and mortality in patients with castration-resistant prostate cancer, are associated with pain, pathological fractures, spinal cord compression, and decreased survival [35]. The major mechanism of pain from small metastases appears to be the stimulation of nerve endings in the endosteum by a variety of chemical mediators. Larger bone metastases produce stretching of the periosteum, which leads to pain [36]. The incidence of bone metastases in patients with prostate cancer, according to autopsy studies, is 65–85% [37].

Bone pain palliation with radionuclides has a very long history of using different β -emitters such as phosphorus-32 (^{32}P) [38], strontium-89 (^{89}Sr) [38], rhenium-186-hydroxyethylidene diphosphonate (^{186}Re -HEDP) [39], ^{188}Re -HEDP, samarium-153-EDTMP (^{153}Sm -EDTMP) [39], and recently, lutetium-177-EDTMP (^{177}Lu -EDTMP) [40] and ^{177}Lu -BPAMD [41]. The only approved α -emitter is radium-223 (^{223}Ra) [42].

Calcium analogues	Attached to phosphate
Strontium-89	Phosphorus-32
Radium-223	Samarium-153-EDTMP
	Rhenium-186-HEDP
	Rhenium-188-HEDP
	Lutetium-177-EDTMP
	Lutetium-177-BPAMD

Table 1. Different radionuclides for bone palliation.

Bone-seeking radionuclides are classified into two groups: calcium analogues and radionuclides attached to phosphate (**Table 1**). Different radionuclides have different physical characteristics, which are shown in **Table 2**.

	Emission type	$t_{1/2}$ (days)	Maximum energy (MeV)	Max tissue penetration range (mm)
Phosphorus-32	β	14.3	1.7	8.5
Strontium-89	β	50.5	1.46	7
Samarium-153	β and γ	1.9	0.81	4
Rhenium-186	β and γ	3.7	1.07	5
Rhenium-188	β and γ	0.7	2.1	10
Lutetium-177	β and γ	6.7	0.498	1.8
Radium-223	α and γ	11.4	27.78	0.1

All, but Radium-223, are β -emitters.

Table 2. Summary of the main physical properties of different radionuclides in clinical use for pain palliation.

5.1. ³²P

³²P decays by 1.7 MeV ($E_{\max}$) β -emission and has a physical half-life of 14.3 days, with a maximum tissue penetration of 8.5 mm (**Table 2**) [43]. During treatment with ³²P, pain relief was reported by 50–87% of patients treated with 200–800 MBq of ³²P administered daily in 20–80 MBq fractions after androgen priming. Pain reduction occurred within 5–14 days, with a mean response duration of 2–4 months [38, 44, 45] (**Table 3**). The main disadvantage of ³²P therapy is dose-limiting myelosuppression with reversible pancytopenia maximal at 5–6 weeks after administration [46].

Radiopharmaceutical	activity	Typical response time	Typical response duration	Retreatment interval
Phosphorus-32	444 MBq (fractionated)	14 days	10 weeks	<3 months
Strontium-89 chloride	150–200 MBq	14–28 days	12–26 weeks	<3 months
Samarium-153-EDTMP	37 MBq/kg	2–7 days	8 weeks	<2 months
Rhenium-186-HEDP	1.3 GBq	2–7 days	8–10 weeks	<2 months
Rhenium-188-HEDP	1.3–4.4 GBq	2–7 days	8 weeks	2 months
Refs. [93–95].				

Table 3. Bone-seeking radionuclides.

5.2. ⁸⁹Sr

⁸⁹SrCl₂ is an element that behaves like calcium and localizes in bone, primarily in areas of osteoblastic activity. It decays by 1.4 MeV ($E_{\max}$) β -emission, with a long physical half-life of 50.5 days. The maximum penetration range in tissue is about 7 mm. Excretion is predominantly renal, dictated by the skeletal tumor burden and glomerular filtration rate [47, 48].

The biological half-life in normal bone is around 14 days, compared with more than 50 days in osteoblastic metastases. The first studies using ⁸⁹Sr demonstrated efficacy for pain reduction

as high as 80%. Complete response rates vary widely among studies and have been reported in 8–77% of cases. The overall response rate varied from 33 to 82% [49–54]. It was the first radiopharmaceutical to be approved for systemic radionuclide therapy in the palliation of painful bone metastases. The standard recommended dose of ^{89}Sr is 150–200 MBq (**Table 3**). It was shown to be as effective as both local field and hemibody external-beam radiotherapy in relieving existing bone pain, but delayed the development of new pain at preexisting, clinically silent sites [45, 55].

Toxicity is limited with the common development of thrombocytopenia, with the nadir between the 4th and 6th weeks. Recovery is typically slow over the next 6 weeks, dictated by skeletal tumor extent and bone marrow reserve [45].

The largest study was published by Robinson et al. In this study, 622 patients were included (466 with prostate cancer). About 15% of patients showed complete pain relief, and a partial response was documented in 81% [56–58]. Tu et al. [59] reported improved survival using six weekly administrations of $^{89}\text{SrCl}_2$ combined with doxorubicin after induction chemotherapy, compared with six weekly administrations of doxorubicin alone; however, the follow-up Phase II trial of the same study group did not confirm the positive effect of this combination therapy on overall survival [60].

A nonrandomized study using 12 weekly administrations of estramustine phosphate, vinblastine, and $^{89}\text{SrCl}_2$ recorded effective, durable symptom palliation, more than a 50% reduction in PSA in 48% of treated patients, and reduced demand for subsequent palliative radiotherapy [61]. Several patient characteristics could predict a favorable response to ^{89}Sr . A normal serum hemoglobin level prior to treatment is associated with a higher pain response rate [62]. Other predictors of a poor pain response were low performance status, higher serum PSA, more extensive osseous metastases, and a poor PSA response [63–66].

5.3. ^{186}Re -HEDP

^{186}Re is a medium-energy β -emitter with a physical half-life of 89 h. ^{186}Re -1,1-hydroxyethylidene diphosphonate (^{186}Re -HEDP) is a surface bone-seeking radiopharmaceutical used for internal radiotherapy. The maximum tolerated activity is 2960 MBq, but for routine use the recommended activity is 1285 MBq. Peak skeletal uptake occurs 3 h after intravenous administration [67, 68]. An early study by Maxon et al. [69] using 1285 MBq of ^{186}Re -HEDP documented overall pain relief in 80% of patients, with a mean duration of 7 weeks in hormone refractory PC patients (**Table 3**) [70]. Eighty to ninety percent of patients reported improved symptoms after a single ^{186}Re -HEDP administration. The response was typically rapid, occurring within 24–48 h of activity administration. Placebo-controlled, randomized studies have confirmed the efficacy of ^{186}Re -HEDP [70, 71]. ^{186}Re -HEDP undergoes rapid urinary excretion and rapid blood clearance (plasma half-life of 41 h) [70]. For the standard applied activity of 1285 MBq, ^{186}Re -HEDP provided a median radiation-absorbed dose of 26 Gy to bone metastases and 1.73 Gy to the red bone marrow [70]. The tumor to marrow dose ratios had a high therapeutic index, with a mean value of 34:1 [69]. Toxicity was limited to temporary myelosuppression, with platelet and neutrophil nadirs at 4 weeks after therapy. Recovery occurred within 8 weeks and was usually complete [72].

5.4. ¹⁸⁸Rhenium-HEDP

¹⁸⁸Re has a short physical half-life of 16.8 h and a maximum β -particle energy of 2.1 MeV with a 15% γ -component of 155 keV. The maximum β -range in tissue is approximately 10 mm [73]. Blood clearance is rapid after injection, with 41% renal clearance within 8 h of administration. Absorbed doses for bone metastases are in the range of 3.83 ± 2 mGy/MBq, in comparison with 0.61 ± 0.2 mGy/MBq for bone marrow and 0.07 ± 0.02 mGy/MBq for the whole body. The mean effective whole-body half-life is 11.6 ± 2.1 h compared with 15.9 ± 3.5 h in bone metastases [45]. ¹⁸⁸Re is of special interest in clinical applications because of its excellent availability and cost-effectiveness, as it is the product of a ¹⁸⁸W (¹⁸⁸W/¹⁸⁸Re) generator [74].

The short physical half-life and high dose rate are predicted to lead to a rapid symptom response. Fractionated therapy has been shown to prolong response duration and progression-free survival (PFS). Palmedo et al. [73] randomly assigned 64 patients to two different groups for radionuclide therapy with ¹⁸⁸Re-HEDP; patients in group A received a single injection, while patients in group B received two injections with an 8-week interval. In both groups, toxicity was low, with moderate thrombopenia and leukopenia. Repeated ¹⁸⁸Re-HEDP therapies (group B) were more effective for pain palliation compared to group A, with a response rate and time of response of 92% and 5.66 months, respectively ($P = 0.006$ and $P = 0.001$). In group B, 11/28 patients (39%) had a PSA decline of more than 50% for at least 8 weeks, compared with 2/30 patients (7%) in group A. The median times to progression in group A and group B were 2.3 months (0–12.2 months) and 7.0 months (0–24.1 months), respectively ($P = 0.0013$), and the median overall survival times were 7.0 months (range, 1.3–36.7 months) and 12.7 months (range, 4.1–32.2 months), respectively ($P = 0.043$) [74].

Liepe et al. [75] reported moderate transient bone marrow toxicity with a decrease in the number of platelets from a baseline value of $286 \pm 75 \times 10^9/l$ to a maximum of $218 \pm 83 \times 10^9/l$ with the nadir at 3 weeks. This study group found no evidence of either local or systemic intolerance to treatment with ¹⁸⁸Re-HEDP, while a flare reaction with an increase in pain within 14 days after therapy was noted in 16% of patients [75].

Biersack et al. [76] also showed the positive effect of repeated therapy on overall survival. They retrospectively analyzed 60 hormone-refractory patients classified into three different groups according to the number of therapies. Group A comprised patients who had received only one therapy (19 patients), group B included patients who had received two therapies (19 patients), and group C included patients who had received three or more therapies (22 patients). All patients had bone pain and presented with more than five lesions documented by a bone scan. Mean survival after the initial therapy improved from 4.5 months in group A to 9.98 months in group B and 15.7 months in group C [76].

5.5. ¹⁵³Samarium-EDTMP

¹⁵³Sm-EDTMP has a lower β -emission energy [0.81 MeV (20%), 0.71 MeV (49%), and 0.64 MeV (30%)], a 28% abundance of γ -emission at 103 keV (28%) and a physical half-life of 46.3 h. ¹⁵³Sm forms a stable complex with ethylenediamine tetramethylene phosphonate (EDTMP).

Clearance is bi-exponential after administration, comprising rapid bone uptake (half-life of 5.5 min) and plasma renal clearance (half-life of 65 min) [77].

A dose escalation study with 10–36 MBq/kg of ^{153}Sm -EDTMP reported a pain relief rate of 65%, with a duration range from 4 to 35 weeks [78]. A further dose escalation study in 52 patients using administered activities from 37 to 111 MBq/kg had a response rate of 74% with a median duration of 10 weeks [79]. Larger studies with more than 100 patients showed a median therapeutic efficacy of 80%. In a randomized, double-blind, placebo trial ($n = 152$), pain relief was found in 65% of patients after ^{153}Sm -EDTMP treatment compared to 45% in the placebo group [80]. A significant decrease in pain between ^{153}Sm -EDTMP and placebo was reported after 1 week, and the analgesic intake was significantly reduced after 3 and 4 weeks. Two large studies using ^{153}Sm -EDTMP with more than 550 patients reported response rates of 73 and 86% [81, 82].

5.6. Comparing the pain response between different radionuclides

Dickie et al. compared ^{89}Sr with ^{153}Sm in 57 prostate cancer patients. They found no difference in the pain response rate and toxicity [83]. van der Poel et al. compared ^{186}Re with ^{89}Sr and reported no differences in the response rate or toxicity [54]. A nonrandomized comparison of ^{188}Re -HEDP and ^{153}Sm -EDTMP in patients with painful metastases from prostate and breast cancer by Liepe et al. [84] showed a comparable response and toxicity with both agents. Liepe et al. also performed a comparative study of ^{188}Re -HEDP, ^{186}Re -HEDP, ^{153}Sm -EDTMP, and $^{89}\text{SrCl}_2$ in the treatment of painful bone metastases. They reported that all radiopharmaceuticals were effective in pain palliation, without the induction of severe side effects or significant differences in therapeutic efficacy or toxicity [39].

5.7. $^{223}\text{Radium}$ dichloride

^{223}Ra , an α -emitter, has a half-life of 11.4 days, with a total emitted energy of about 28 MeV. It is the only FDA-approved radiopharmaceutical for the treatment of bone metastases of PC with positive impact on overall survival according to a prospective randomized study [10]. It is a bone stromal-targeted radiopharmaceutical that undergoes α -emission. The α -particle is considerably more destructive to tumor cells than the β -particle. ^{223}Ra has a very high linear energy transfer, and only one to five hits per cell can be fatal. Double-strand breaks are induced even in quiescent cells and at low oxygen levels [85].

The penetration range of α -particles ($<100\ \mu\text{m}$) in tissue is much smaller than that of previously described β -emitters in this chapter; so, despite the high energy, because of the short penetration range, bone marrow damage is minimal [86]. Nonhematological toxicities are more commonly observed, and are mild to moderate in intensity. The most common side effects are diarrhea, fatigue, nausea, vomiting, and bone pain, some of which are dose-related [87–89]. These side effects are easily manageable with symptomatic and supportive treatments [90].

Parker et al. [89] performed a randomized, double-blind, dose-finding, Phase II study that included 122 PC patients who were randomized to be treated with three injections of ^{223}Ra at 6-week intervals, at doses of 25 kBq/kg ($n = 41$), 50 kBq/kg ($n = 39$), or 80 kBq/kg ($n = 42$). They

compared the proportion of patients in each group with confirmed PSA decline of $\geq 50\%$. No patient in the 25 kBq/kg dose group showed a significant PSA decline $\geq 50\%$. In the 50 kBq/kg dose group, only two patients (6%) showed a significant PSA decline, whereas in five patients (13%) in the 80 kBq/kg dose group, a significant PSA decline was reported ($P = 0.0297$). A $\geq 50\%$ decrease in the bone alkaline phosphatase level was reported in 6 patients (16%), 24 patients (67%), and 25 patients (66%), in the 25, 50, and 80 kBq/kg dose groups, respectively ($P < 0.0001$). The most common treatment-related adverse events ($\geq 10\%$) occurring up to week 24 across all dose groups were diarrhea (21%), nausea (16%), and anemia (14%). No difference in the incidence of hematological events was seen among the dose groups. They concluded that ^{223}Ra had a dose-dependent effect on serum markers of PC activity, suggesting that controlling bone disease with ^{223}Ra may affect cancer-related outcomes [89].

The ALSYMPCA trial (ALpharadin in SYMptomatic Prostate CANcer) is the first randomized Phase III study demonstrating improved survival with a bone-seeking radioisotope [42]. The number of PC patients recruited was 921. All patients were required to have progressed with symptomatic bone metastases, with at least two or more metastases on bone scintigraphy with no known visceral metastases. Randomization was 2:1 in a double-blind fashion to receive six cycles of intravenous ^{223}Ra every 4 weeks with best standard of care or six infusions of placebo with best standard of care. This study demonstrated a significant prolongation of survival (14.9 vs. 11.3 months, respectively; $P < 0.001$). Apart from this, the frequency of skeletal-related events was reduced in the ^{223}Ra group, and the median time to a skeletal-related event increased (15.6 vs. 9.8 months; $P < 0.001$). ^{223}Ra was well-tolerated with low rates of grade 3/4 neutropenia (1.8 vs. 0.8%) and thrombocytopenia (4 vs. 2%) [42].

Etchebehere et al. retrospectively reviewed 110 patients with metastatic PC treated with ^{223}Ra . The end points of this study were overall survival, bone event-free survival, progression-free survival (PFS), and bone marrow failure. They evaluated the following parameters prior to the first therapy cycle: hemoglobin (Hb), PSA, alkaline phosphatase (ALP), ECOG status, pain score, prior chemotherapy, and external beam radiation therapy (EBRT). Furthermore during/after ^{223}Ra , the PSA doubling time (PSADT), the total number of radium cycles (RaTot), and the use of chemotherapy, EBRT, enzalutamide, and abiraterone were evaluated. A significant reduction of alkaline phosphatase and pain score occurred throughout the ^{223}Ra cycles. The risk of progression was associated with declining ECOG status and decrease in PSADT. RaTot, initial ECOG (Eastern Cooperative Oncology Group) status, ALP, initial pain score, and the use of abiraterone were associated with OS ($P \leq 0.008$), PFS ($P \leq 0.003$), and BeFS ($P \leq 0.020$). RaTot, initial ECOG status, ALP, and initial pain score were significantly associated with bone marrow failure ($P \leq 0.001$), as well as Hb ($P < 0.001$) and EBRT ($P = 0.009$). In the multivariable analysis, only RaTot and abiraterone remained significantly associated with OS ($P < 0.001$ and $P = 0.033$, respectively), PFS ($P < 0.001$ and $P = 0.041$, respectively), and BeFS ($P < 0.001$ and $P = 0.019$, respectively). Additionally, RaTot ($P = 0.027$) and EBRT ($P = 0.013$) remained significantly associated with bone marrow failure. They concluded that the concomitant use of abiraterone and ^{223}Ra seems to have a beneficial effect, while EBRT may increase the risk of bone marrow failure [91].

Recently, Pacilio et al. [90] performed a dosimetry study and showed that the lesion uptake of ^{223}Ra was significantly correlated with that of $^{99\text{m}}\text{Tc}$ -MDP. The D_{RBE} (RBE, relative biological effectiveness; D_{RBE} , RBE-weighted absorbed dose) 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 D_{RBE} was about 19 Gy, and was therefore in a similar range as other radiopharmaceuticals.

Nilsson et al. [92] reported the quality-of-life results of the ALSYMPCA study. It was found that improved survival with ^{223}Ra was accompanied by significant quality-of-life benefits, including a higher percentage of patients with meaningful quality-of-life improvements and a slower decline in quality-of-life over time.

6. Conclusion

A pain response is seen in approximately one-half of patients treated with radionuclides for painful osseous metastases of prostate cancer. The ALSYMPCA study showed an OS benefit with ^{223}Ra treatment. However, it should be mentioned that this study was supported by the company, Bayer. The other radiopharmaceuticals which are mentioned in this chapter were not tested in prospective multicenter trials with a large number of patients. This means that β -emitters could also have an OS benefit, which was shown in only a few studies. A combination of hormone therapy with bone-targeted therapy may be more effective than a single therapy approach. Different combinations of therapies are being studied at the moment. PSMA-targeted therapy has so far shown very promising results. According to the published studies, ^{177}Lu -PSMA therapy after ^{223}Ra is feasible and safe.

Author details

Hojjat Ahmadzadehfar

Address all correspondence to: Hojjat.ahmadzadehfar@ukb.uni-bonn.de;
nuclearmedicine@gmail.com

Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany

References

- [1] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Flechon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS. Increased survival with

enzalutamide in prostate cancer after chemotherapy. *The New England Journal of Medicine* 2012; 367: 1187–97.

- [2] Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin ME, Higano CS, de Souza P, de Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A, Rathkopf DE. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *The Lancet Oncology* 2015; 16: 152–60.
- [3] Wei Q, Li M, Fu X, Tang R, Na Y, Jiang M, Li Y. Global analysis of differentially expressed genes in androgen-independent prostate cancer. *Prostate Cancer and Prostatic Diseases* 2007; 10: 167–74.
- [4] Kraeber-Bodere F, Bodet-Milin C, Rousseau C, Eugene T, Pallardy A, Frampas E, Carlier T, Ferrer L, Gaschet J, Davodeau F, Gustin JF, Faivre-Chauvet A, Barbet J, Chérel M. Radioimmunoconjugates for the treatment of cancer. *Seminars in Oncology* 2014; 41: 613–22.
- [5] Mier W, Kratochwil C, Hassel JC, Giesel FL, Beijer B, Babich JW, Friebe M, Eisenhut M, Enk A, Haberkorn U. Radiopharmaceutical therapy of patients with metastasized melanoma with the melanin-binding benzamide 131I-BA52. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 2014; 55: 9–14.
- [6] van der Zwan WA, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. GEPNETs update: radionuclide therapy in neuroendocrine tumors. *European Journal of Endocrinology/European Federation of Endocrine Societies* 2015; 172: R1–8.
- [7] Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, Lepensky C, Kwekkeboom DJ, Baum RP, Krenning EP, Modlin IM. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *European Journal of Nuclear Medicine and Molecular Imaging* 2015; 42: 5–19.
- [8] Ahmadzadehfar H, Eppard E, Kurpig S, Fimmers R, Yordanova A, Schlenkhoff CD, Gartner F, Rogenhofer S, Essler M. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget*. 2016 Mar 15;7(11):12477-88. doi: 10.18632/oncotarget.7245.
- [9] Ahmadzadehfar H, Biersack HJ, Ezziddin S. Radioembolization of liver tumors with yttrium-90 microspheres. *Seminars in Nuclear Medicine* 2010; 40: 105–21.
- [10] Parker C, Sartor O. Radium-223 in prostate cancer. *The New England Journal of Medicine* 2013; 369: 1659–60.
- [11] Ahmadzadehfar H, Sabet A, Biersack H, Risse J. Therapy of hepatocellular carcinoma with iodine-131-lipiodol. In: Lau J, ed. *Hepatocellular Carcinoma - Clinical Research* 2012.
- [12] Haberkorn U, Eder M, Kopka K, Babich JW, Eisenhut M. New strategies in prostate cancer: prostate-specific membrane antigen (PSMA) ligands for diagnosis and therapy.

Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 2016; 22: 9–15.

- [13] Santoni M, Scarpelli M, Mazzucchelli R, Lopez-Beltran A, Cheng L, Cascinu S, Montironi R. Targeting prostate-specific membrane antigen for personalized therapies in prostate cancer: morphologic and molecular backgrounds and future promises. *Journal of Biological Regulators and Homeostatic Agents* 2014; 28: 555–63.
- [14] Banerjee SR, Pullambhatla M, Byun Y, Nimmagadda S, Green G, Fox JJ, Horti A, Mease RC, Pomper MG. ⁶⁸Ga-labeled inhibitors of prostate-specific membrane antigen (PSMA) for imaging prostate cancer. *Journal of Medicinal Chemistry* 2010; 53: 5333–41.
- [15] Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid ⁶⁸Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *Journal of Nuclear Medicine* 2015; 56: 668–74.
- [16] Giesel FL, Fiedler H, Stefanova M, et al. PSMA PET/CT with Glu-urea-Lys-(Ahx)-[⁶⁸Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 2015; 42: 1794–800.
- [17] Morigi JJ, Stricker PD, van Leeuwen PJ, et al. Prospective comparison of ¹⁸F-fluoromethylcholine versus ⁶⁸Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. *Journal of Nuclear Medicine* 2015; 56: 1185–90.
- [18] Hijazi S, Meller B, Leitsmann C, et al. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by ⁶⁸Ga-PSMA-positron emission tomography/computerized tomography. *Prostate* 2015; 75: 1934–40.
- [19] Deb N, Goris M, Trisler K, Fowler S, Saal J, Ning S, Becker M, Marquez C, Knox S. Treatment of hormone-refractory prostate cancer with 90Y-CYT-356 monoclonal antibody. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 1996; 2: 1289–97.
- [20] Tagawa ST, Milowsky MI, Morris M, Vallabhajosula S, Christos P, Akhtar NH, Osborne J, Goldsmith SJ, Larson S, Taskar NP, Scher HI, Bander NH, Nanus DM. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 2013; 19: 5182–91.
- [21] Bander NH, Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ. Phase I trial of ¹⁷⁷lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 2005; 23: 4591–601.
- [22] Vallabhajosula S, Goldsmith SJ, Hamacher KA, Kostakoglu L, Konishi S, Milowski MI, Nanus DM, Bander NH. Prediction of myelotoxicity based on bone marrow radiation-

absorbed dose: radioimmunotherapy studies using ^{90}Y - and ^{177}Lu -labeled J591 antibodies specific for prostate-specific membrane antigen. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 2005; 46: 850-8.

- [23] Vallabhajosula S, Goldsmith SJ, Kostakoglu L, Milowsky MI, Nanus DM, Bander NH. Radioimmunotherapy of prostate cancer using ^{90}Y - and ^{177}Lu -labeled J591 monoclonal antibodies: effect of multiple treatments on myelotoxicity. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 2005; 11: 7195s–200s.
- [24] Liu H, Moy P, Kim S, Xia Y, Rajasekaran A, Navarro V, Knudsen B, Bander NH. Monoclonal antibodies to the extracellular domain of prostate-specific membrane antigen also react with tumor vascular endothelium. *Cancer Research* 1997; 57: 3629–34.
- [25] Smith-Jones PM, Vallabhajosula S, Goldsmith SJ, Navarro V, Hunter CJ, Bastidas D, Bander NH. In vitro characterization of radiolabeled monoclonal antibodies specific for the extracellular domain of prostate-specific membrane antigen. *Cancer Research* 2000; 60: 5237–43.
- [26] Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ, Bander NH. Phase I trial of yttrium-90-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for androgen-independent prostate cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 2004; 22: 2522–31.
- [27] Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, Joyal J, Kopka K, Debus J, Babich JW, Haberkorn U. Radiation dosimetry and first therapy results with a $(^{124}\text{I})/(^{131}\text{I})$ -labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. *European Journal of Nuclear Medicine and Molecular Imaging* 2014; 41: 1280–92.
- [28] Maresca KP, Hillier SM, Femia FJ, Keith D, Barone C, Joyal JL, Zimmerman CN, Kozikowski AP, Barrett JA, Eckelman WC, Babich JW. A series of halogenated heterodimeric inhibitors of prostate specific membrane antigen (PSMA) as radiolabeled probes for targeting prostate cancer. *Journal of Medicinal Chemistry* 2009; 52: 347–57.
- [29] Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, Zimmerman CN, Barrett JA, Eckelman WC, Pomper MG, Joyal JL, Babich JW. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. *Cancer Research* 2009; 69: 6932–40.
- [30] Yeong CH, Cheng MH, Ng KH. Therapeutic radionuclides in nuclear medicine: current and future prospects. *Journal of Zhejiang University Science B* 2014; 15: 845–63.
- [31] Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benesova M, Mier W, Kopka K, Haberkorn U. [^{177}Lu]Lutetium-labeled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 2015; 42: 987–8.

- [32] Ahmadzadehfar H, Rahbar K, Kurpig S, Bogemann M, Claesener M, Eppard E, Gartner F, Rogenhofer S, Schafers M, Essler M. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research* 2015; 5: 114.
- [33] Schlenkhoff CD, Gaertner F, Essler M, Schmidt M, Ahmadzadehfar H. Positive influence of 177Lu PSMA-617 therapy on bone marrow depression caused by metastatic prostate cancer. *Clin Nucl Med*. 2016 Jun;41(6):478-80. doi: 10.1097/RLU.0000000000001195.
- [34] Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, Bögemann M. Radioligand therapy with 177Lu-PSMA-617 as a novel therapeutic option in patients with metastatic castration resistant prostate cancer. *Clin Nucl Med*. 2016 Apr 15. [Epub ahead of print].
- [35] Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nature Reviews Cancer* 2002; 2: 584–93.
- [36] Crawford ED, Kozlowski JM, Debruyne FM, Fair WR, Logothetis CJ, Balmer C, Robinson RG, Porter AT, Kirk D. The use of strontium 89 for palliation of pain from bone metastases associated with hormone-refractory prostate cancer. *Urology* 1994; 44: 481–5.
- [37] Koslowski J, Ellis W, Grayhack J. Advanced prostatic carcinoma early versus late endocrine therapy. *Urologic Clinics of North America* 1991; 18: 15–24.
- [38] Nair N. Relative efficacy of 32P and 89Sr in palliation in skeletal metastases. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 1999; 40: 256–61.
- [39] Liepe K, Kotzerke J. A comparative study of 188Re-HEDP, 186Re-HEDP, 153Sm-EDTMP and 89Sr in the treatment of painful skeletal metastases. *Nuclear Medicine Communications* 2007; 28: 623–30.
- [40] Yuan J, Liu C, Liu X, Wang Y, Kuai D, Zhang G, Zaknun JJ. Efficacy and safety of 177Lu-EDTMP in bone metastatic pain palliation in breast cancer and hormone refractory prostate cancer: a phase II study. *Clinical Nuclear Medicine* 2013; 38: 88–92.
- [41] Meckel M, Nauth A, Timpe J, Zhernosekov K, Puranik AD, Baum RP, Rosch F. Development of a [177Lu]BPAMD labeling kit and an automated synthesis module for routine bone targeted endoradiotherapy. *Cancer Biotherapy & Radiopharmaceuticals* 2015; 30: 94–9.
- [42] Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa 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, Franzen L, Coleman R, Vogelzang NJ, O'Bryan-Tear CG, Staudacher K, Garcia-Vargas J, Shan M, Bruland OS, Sartor O. Alpha emitter radium-223 and survival in metastatic prostate cancer. *The New England Journal of Medicine* 2013; 369: 213–23.

- [43] Silberstein EB. The treatment of painful osseous metastases with phosphorus-32-labeled phosphates. *Seminars in Oncology* 1993; 20: 10–21.
- [44] Burnet NG, Williams G, Howard N. Phosphorus-32 for intractable bony pain from carcinoma of the prostate. *Clinical Oncology (The Royal College of Radiologists)* 1990; 2: 220–3.
- [45] Lewington VJ. Bone-seeking radionuclides for therapy. *Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine* 2005; 46 Suppl 1: 38S–47S.
- [46] Silberstein EB, Elgazzar AH, Kapilivsky A. Phosphorus-32 radiopharmaceuticals for the treatment of painful osseous metastases. *Seminars in Nuclear Medicine* 1992; 22: 17–27.
- [47] Blake GM, Zivanovic MA, Blaquiére RM, Fine DR, McEwan AJ, Ackery DM. Strontium-89 therapy: measurement of absorbed dose to skeletal metastases. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 1988; 29: 549–57.
- [48] Blake GM, Zivanovic MA, McEwan AJ, Ackery DM. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. *European Journal of Nuclear Medicine* 1986; 12: 447–54.
- [49] Lewington VJ, McEwan AJ, Ackery DM, Bayly RJ, Keeling DH, Macleod PM, Porter AT, Zivanovic MA. A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *European Journal of Cancer* 1991; 27: 954–8.
- [50] Laing AH, Ackery DM, Bayly RJ, Buchanan RB, Lewington VJ, McEwan AJ, Macleod PM, Zivanovic MA. Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *British Journal of Radiology* 1991; 64: 816–22.
- [51] Mertens WC, Stitt L, Porter AT. Strontium 89 therapy and relief of pain in patients with prostatic carcinoma metastatic to bone: a dose response relationship? *American Journal of Clinical Oncology* 1993; 16: 238–42.
- [52] Mertens WC, Porter AT, Reid RH, Powe JE. Strontium-89 and low-dose infusion cisplatin for patients with hormone refractory prostate carcinoma metastatic to bone: a preliminary report. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 1992; 33: 1437–43.
- [53] Buchali K, Correns HJ, Schuerer M, Schnorr D, Lips H, Sydow K. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *European Journal of Nuclear Medicine* 1988; 14: 349–51.
- [54] van der Poel HG, Antonini N, Hoefnagel CA, Horenblas S, Valdes Olmos RA. Serum hemoglobin levels predict response to strontium-89 and rhenium-186-HEDP radionuclide treatment for painful osseous metastases in prostate cancer. *Urologia Internationalis* 2006; 77: 50–6.

- [55] Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD, Reed NS, Russell JM, Yardley J. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology* 1994; 31: 33–40.
- [56] Robinson RG, Blake GM, Preston DF, McEwan AJ, Spicer JA, Martin NL, Wegst AV, Ackery DM. Strontium-89: treatment results and kinetics in patients with painful metastatic prostate and breast cancer in bone. *Radiographics: A Review Publication of the Radiological Society of North America, Inc* 1989; 9: 271–81.
- [57] Robinson RG, Preston DF, Schiefelbein M, Baxter KG. Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995; 274: 420–4.
- [58] Liepe K, Kotzerke J. Internal radiotherapy of painful bone metastases. *Methods* 2011; 55: 258–70.
- [59] Tu SM, Millikan RE, Mengistu B, Delpassand ES, Amato RJ, Pagliaro LC, Daliani D, Papandreou CN, Smith TL, Kim J, Podoloff DA, Logothetis CJ. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001; 357: 336–41.
- [60] Bilen MA, Johnson MM, Mathew P, Pagliaro LC, Araujo JC, Aparicio A, Corn PG, Tannir NM, Wong FC, Fisch MJ, Logothetis CJ, Tu SM. Randomized phase 2 study of bone-targeted therapy containing strontium-89 in advanced castrate-sensitive prostate cancer. *Cancer* 2015; 121: 69–76.
- [61] Akerley W, Butera J, Wehbe T, Noto R, Stein B, Safran H, Cummings F, Sambandam S, Maynard J, Di Rienzo G, Leone L. A multiinstitutional, concurrent chemoradiation trial of strontium-89, estramustine, and vinblastine for hormone refractory prostate carcinoma involving bone. *Cancer* 2002; 94: 1654–60.
- [62] Windsor PM. Predictors of response to strontium-89 (Metastron) in skeletal metastases from prostate cancer: report of a single centre's 10-year experience. *Clinical Oncology (Royal College of Radiologists)* 2001; 13: 219–27.
- [63] Oosterhof GO, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der Maase H, Neymark N, Debois M, Collette L. Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. *European Urology* 2003; 44: 519–26.
- [64] Dafermou A, Colamussi P, Giganti M, Cittanti C, Bestagno M, Piffanelli A. A multi-centre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. *European Journal of Nuclear Medicine* 2001; 28: 788–98.
- [65] Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, Sathyanarayana JR, Yakemchuk VN, Thomas GM, Erlich LE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation

in the management of endocrine resistant metastatic prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 1993; 25: 805–13.

- [66] Zyskowski A, Lamb D, Morum P, Hamilton D, Johnson C. Strontium-89 treatment for prostate cancer bone metastases: does a prostate-specific antigen response predict for improved survival? *Australasian Radiology* 2001; 45: 39–42.
- [67] de Klerk JM, Zonnenberg BA, van het Schip AD, van Dijk A, Han SH, Quirijnen JM, Blijham GH, van Rijk PP. Dose escalation study of rhenium-186 hydroxyethylidene diphosphonate in patients with metastatic prostate cancer. *European Journal of Nuclear Medicine* 1994; 21: 1114–20.
- [68] de Klerk JM, van het Schip AD, Zonnenberg BA, van Dijk A, Quirijnen JM, Blijham GH, van Rijk PP. Phase 1 study of rhenium-186-HEDP in patients with bone metastases originating from breast cancer. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 1996; 37: 244–9.
- [69] Maxon HR, Deutsch EA, Thomas SR, Libson K, Lukes SJ, Williams CC, Ali S. Re-186(Sn) HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. *Radiology* 1988; 166: 501–7.
- [70] Maxon HR, 3rd, Schroder LE, Thomas SR, Hertzberg VS, Deutsch EA, Scher HI, Samarasingha RC, Libson KF, Williams CC, Moulton JS, et al. Re-186(Sn) HEDP for treatment of painful osseous metastases: initial clinical experience in 20 patients with hormone-resistant prostate cancer. *Radiology* 1990; 176: 155–9.
- [71] Han SH, de Klerk JM, Tan S, van het Schip AD, Derksen BH, van Dijk A, Kruitwagen CL, Blijham GH, van Rijk PP, Zonnenberg BA. The PLACORHEN study: a double-blind, placebo-controlled, randomized radionuclide study with (186)Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. Placebo Controlled Rhenium Study. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 2002; 43: 1150–6.
- [72] O'Sullivan JM, McCready VR, Flux G, Norman AR, Buffa FM, Chittenden S, Guy M, Pomeroy K, Cook G, Gadd J, Treleaven J, Al-Deen A, Horwich A, Huddart RA, Dearnaley DP. High activity Rhenium-186 HEDP with autologous peripheral blood stem cell rescue: a phase I study in progressive hormone refractory prostate cancer metastatic to bone. *British Journal of Cancer* 2002; 86: 1715–20.
- [73] Palmedo H, Gohlke S, Bender H, Sartor J, Schoeneich G, Risse J, Grunwald F, Knapp FF, Jr., Biersack HJ. Dose escalation study with rhenium-188 hydroxyethylidene diphosphonate in prostate cancer patients with osseous metastases. *European Journal of Nuclear Medicine* 2000; 27: 123–30.
- [74] Palmedo H, Manka-Waluch A, Albers P, Schmidt-Wolf IG, Reinhardt M, Ezziddin S, Joe A, Roedel R, Fimmers R, Knapp FF, Jr., Gohlke S, Biersack HJ. Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: randomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenedi-

phosphonate. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 2003; 21: 2869–75.

- [75] Liepe K, Kropp J, Runge R, Kotzerke J. Therapeutic efficiency of rhenium-188-HEDP in human prostate cancer skeletal metastases. *British Journal of Cancer* 2003; 89: 625–9.
- [76] Biersack HJ, Palmedo H, Andris A, Rogenhofer S, Knapp FF, Guhlke S, Ezziddin S, Bucerius J, von Mallek D. Palliation and survival after repeated (188)Re-HEDP therapy of hormone-refractory bone metastases of prostate cancer: a retrospective analysis. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 2011; 52: 1721–6.
- [77] Singh A, Holmes RA, Farhangi M, Volkert WA, Williams A, Stringham LM, Ketrting AR. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 1989; 30: 1814–8.
- [78] Turner JH, Claringbold PG. A phase II study of treatment of painful multifocal skeletal metastases with single and repeated dose samarium-153 ethylenediaminetetramethylene phosphonate. *European Journal of Cancer* 1991; 27: 1084–6.
- [79] Collins C, Eary JF, Donaldson G, Vernon C, Bush NE, Petersdorf S, Livingston RB, Gordon EE, Chapman CR, Appelbaum FR. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 1993; 34: 1839–44.
- [80] Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, Kotler JA, Freeman LM, Olivier P. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* 2004; 63: 940–5.
- [81] Tian JH, Zhang JM, Hou QT, Oyang QH, Wang JM, Luan ZS, Chuan L, He YJ. Multi-centre trial on the efficacy and toxicity of single-dose samarium-153-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. *European Journal of Nuclear Medicine* 1999; 26: 2–7.
- [82] Enrique O, Zhongyun P, Parma EP, Pusuwan P, Riccabona G, Tian J-H, Obaldo J, Padhy AK. Efficacy and toxicity of Sm-153 EDTMP in the palliative treatment of painful bone metastases. *World Journal of Nuclear Medicine* 2002; 1: 21–7.
- [83] Dickie GJ, Macfarlane D. Strontium and samarium therapy for bone metastases from prostate carcinoma. *Australasian Radiology* 1999; 43: 476–9.
- [84] Liepe K, Runge R, Kotzerke J. The benefit of bone-seeking radiopharmaceuticals in the treatment of metastatic bone pain. *Journal of Cancer Research and Clinical Oncology* 2005; 131: 60–6.
- [85] Anderson RM, Stevens DL, Sumption ND, Townsend KM, Goodhead DT, Hill MA. Effect of linear energy transfer (LET) on the complexity of alpha-particle-induced chromosome aberrations in human CD34+ cells. *Radiation Research* 2007; 167: 541–50.

- [86] Hafeez S, Parker C. Radium-223 for the treatment of prostate cancer. *Expert Opinion on Investigational Drugs* 2013; 22: 379–87.
- [87] Nilsson S, Larsen RH, Fossa 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. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 2005; 11: 4451–9.
- [88] Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, Lennernas 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. *The Lancet Oncology* 2007; 8: 587–94.
- [89] Parker CC, Pascoe S, Chodacki A, O'Sullivan JM, Germa JR, O'Bryan-Tear CG, Haider T, Hoskin P. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. *European Urology* 2013; 63: 189–97.
- [90] 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. *European Journal of Nuclear Medicine and Molecular Imaging* 2016; 43: 21–33.
- [91] Etchebehere EC, Milton DR, Araujo JC, Swanston NM, Macapinlac HA, Rohren EM. Factors affecting (223)Ra therapy: clinical experience after 532 cycles from a single institution. *European Journal of Nuclear Medicine and Molecular Imaging* 2016; 43: 8–20.
- [92] Nilsson S, Cislo P, Sartor O, Vogelzang NJ, Coleman RE, O'Sullivan JM, Reuning-Scherer J, Shan M, Zhan L, Parker C. Patient-reported quality of life analysis of radium-223 dichloride from the phase 3 ALSYMPCA study. *Ann Oncol.* 2016 May; 27(5):868-74. doi: 10.1093/annonc/mdw065.
- [93] Falkmer U, et al. A systematic overview of radiation therapy effects in skeletal metastases. *Acta Oncology* 2003; 42(5-6): 620–33.
- [94] Lewington. Bone-seeking radionuclides for therapy. *Journal of Nuclear Medicine* 2005; 46: 38S–47S.
- [95] Bauman G et al. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. *Radiother Oncol* 2005;75(3):258-70.