Review article

# $^{188}$Re-HEDP therapy in the therapy of painful bone metastases


## ABSTRACT

For bone-targeted radionuclide therapy (BTRT), different commercial radiopharmaceuticals are available such as strontium-89, $^{186}$Rhenium-hydroxyethylidene diphosphonate ($^{186}$Re-HEDP), Samarium-153-ethylenediamine tetramethylene phosphonic acid, and radium-223. Unfortunately, the commercial available radiopharmaceuticals are very expensive (from 1,200 to 36,000€ per patient in Europe). The $^{188}$W/$^{188}$Re generator is an ideal source for the long-term (4–6 months) continuous availability of $^{188}$Re suitable for the preparation of radiopharmaceuticals for different radionuclide therapies. Labeling at HEDP, it can use cost-effective for BTRT, if enough patients are available for therapy. And so, $^{188}$Re-HEDP is the ideal candidate in developing countries which high population to replace the other agents. Two German groups documented a response rate of 80% without any severe side effects and similar bone marrow toxicity compared to the other compounds for $^{188}$Re-HEDP. Using $^{188}$Re-HEDP in repeated treatments, a prolonged overall survival of repeated to single application was observed (from 4.5 months for single to 15.7 months using ≥3 applications).


**Keywords:** Bone metastases, bone-targeted radionuclide therapy, breast cancer, pain, prostate cancer

## INTRODUCTION

Skeletal metastases occur in many patients with different kinds of solid malignant tumors, especially in advance stage of prostate, breast, and lung cancer. Resulting bone pain interferes with the patient's quality of life and requires effective treatment. The incidence of bone metastases in patients with cancer is mainly derived from autopsy studies[1] and is most commonly associated with advanced stage of breast cancer (in 47%–85% of patients), prostate cancer (33%–85%), and lung cancer (32%–60%).[2,3] The typical sites of bone metastases are the thoracolumbar spine, pelvis, lower and upper limbs, and the skull.[1] Patients with bone metastasis commonly endure severe bone pain, and this symptom has the most impact on quality of life. The mechanisms involved in bone pain are poorly understood[4] but are likely to be a consequence of osteolysis (bone breakdown).[5] Infiltration of the bone trabeculae and matrix by tumor osteolysis is one of the physical factors. Other factors included microfractures and stretching to the periosteum by tumor growth.[6] Biochemical mechanisms of pain include the stimulation of nerve endings in the endosteum by a variety of chemical mediators which include bradykinin, prostaglandin, histamine, interleukin, and tumor necrosis factor produced by the osteolytic process.[6,7]

Prostate and breast cancer patients are commonly candidates for palliative treatment with bone-seeking radionuclide agents because their use can often result in a relatively long survival time in patients with a high incidence of bone metastases.

Hormone therapy is the first option for prostate and breast cancer because these tumors commonly express hormone receptors. In hormone-sensitive prostate cancer, orchiectomy or castration is effective in relieving pain, but this approach


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has now been mostly replaced with chemical castration. Many hormonal agents work at different points along the hormone axis to inhibit the production or block the action of testosterone. The broad classes of agents are estrogens, progesterone, gonadotropin-releasing hormone analogs, adrenal enzyme synthesis inhibitors, and antiandrogens. A common regimen is a combination of an antiandrogen with a gonadotropin-releasing hormone analog to provide total blockade of androgens.[8] Tamoxifen is the common antihormone drug in hormone-sensitive breast cancer. In case of hormone receptor positive breast and prostate cancer patients reported up to 70% of patients a pain relief after hormonal therapy.[9,10] Unfortunately, this strategy is self-limited, and during the course of the disease, these tumors often become hormone resistant and progress, resulting in recurrence of pain.[11]

If the patients have skeletal metastases than the bisphosphonates, application is indicate, especially in breast cancer patients with more osteolytic activities in bone lesions compared with prostate cancer. Bisphosphonates are analogs of endogenous pyrophosphates.[12] Pamidronate and zoledronic acid are second- and third-generation nitrogen-containing bisphosphonate formulations approved for use in metastatic bone metastases.[11] They have both demonstrated the capability to reduce skeletal complication and morbidity in patients with cancer.[13] Extensive clinical evidence has established bisphosphonates as useful agents for treating bone metastasis associated with breast cancer,[14-18] although not all trials have demonstrated a beneficial effect.[19] There is less evidence demonstrating the therapeutic efficacy of bisphosphonates in metastatic prostate cancer, with some trials suggesting no effects from treatment[20] and other indicating only a reduction in bone pain.[21,22]

Local external beam radiotherapy represents another therapeutic option for local bone pain. Indications for radiotherapy for bone metastases include pain, risk for pathological fracture, and neurological complication arising from spinal cord compression, nerve root pain, or cranial involvement.[23] About 20% of all radiotherapies are performed for painful bone metastases.[24] Meta-analysis data have established that >40% of treated patients can expect at least 50% pain relief and fewer than 30% can expect complete pain relief at 1 month.[25] Numerous external beam radiotherapy regimens may be employed in the management of bone pain included fractionated schedules and single fraction regimens.[11]

Unfortunately, radiotherapy of the whole body is involved with high rate of side effects, and so internal radiotherapy using bone-seeking agents is useful in patients with multifocal pain symptoms. The therapy is effective in delivering high doses of radiation to widespread metastatic bone lesions and can limited dose to healthy tissue.[26] And so for multiple size of bone metastases, a systemic treatment using bone-seeking agents is the recommended option.

## PREPARATION OF $^{188}$RHENIUM-HYDROXYETHYLIDENE DIPHOSPHONATE

$^{188}$Rhenium-hydroxyethylidene diphosphonate $^{188}$Re-HEDP was prepared as previously described by Lin *et al*. and Palmedo *et al*.[23,39] $^{188}$Re-perrhenate was obtained from a 38 GBq alumina-based $^{188}$W/$^{188}$Re generator[17] (Oak Ridge National Laboratory, Oak Ridge, USA). The generator was eluted with 20–25 ml of 0.9% saline. The generator eluates were concentrated to about 1.2 ml using a tandem cation/anion concentration system,[18] which consists of an Ag Plus cartridge (Alltech Associates, Deerfield, IL, USA) attached to a three-way stopcock connected at the outlet to the QMA anion trapping column SepPak® (Waters Corporation, Milford, MA, USA) anion-exchange column. The concentration system was housed in a Lucite shield.

8.3 mg HEDP (Fluka Chemie AG, Buchs, Switzerland), 3.0 mg gentisic acid (Sigma-Aldrich, Steinheim, Germany), and 3.9 mg stannous chloride dihydrate (Merck, Darmstadt, Germany) were weighed in kit vials and mixed with 1.0 ml of carrier-added $^{188}$Re-generator eluate (10 μl HReO4 Aldrich and 100 μmol/ml physiological saline). The solution was heated at 96°C–100°C for 15 min. After cooling to room temperature, 1 ml of a sterile 0.3 M sodium hydroxide solution was added to adjust the pH to a range of 5–6.

Quality control of carrier-added $^{188}$Re-HEDP was performed with thin layer chromatography using Silica Gel (ITLC-SG) strips (Gelman, Ann Arbor, Michigan, USA) to determine free perrhenate. A volume of 1–2 μl of $^{188}$Re-HEDP solution added with acetone was deposited at the start line of the ITCL strip. The $^{188}ReO_2$ remains at the start line of ITLC strip, the $^{188}$Re-perrhenate moved. A solvent 0.9% NaCl solution was used. In addition, anion exchange chromatography was performed based on gradient elution with increasing concentrations of NaCl solutions using a QMA SepPak®. The radiochemical purity determined by both procedures (ITLC and ion exchange) using the following formula: radiochemical purity = 100 − ($\%^{188}ReO_4 + \%^{188}ReO_2$). Sterility and pyrogen tests were performed for each preparation.

## $^{188}$RHENIUM-HYDROXYETHYLIDENE DIPHOSPHONATE

$^{188}$Re is of special interest in clinical applications because of its excellent availability and cost-effectiveness as product of

an $^{188}$tungsten/$^{188}$Re generator.[27] Radiolabeling of various agents with $^{188}$Re provides a variety of different therapeutic options outside the bone pain palliation, for example, treatment of liver metastases or primary liver cancer with labeling to lipiodol[28] or microsphere[29] and treatment of arthritis with labeling to colloids.[30] Other therapeutic options included $^{188}$Re-labeled antibodies for treatment of leukemia[31,32] or a variety of $^{188}$Re-labeled agents in intracoronary brachytherapy.[33-35]

Diphosphonates such as methylene diphosphonate (MDP) and hydroxymethane diphosphonate (HDP) are well-known bone-seeking agents for imaging with $^{99m}$Tc. However, for unknown reasons, $^{188}$Re-labeled HDP and MDP do not show sufficient uptake in the skeleton, with high soft-tissue uptake.[36] In contrast, HEDP showed significant higher skeletal uptake and similar results in radiolabeling procedures as $^{186}$Re-HEDP.[37,38] The first clinical data, reported by Palmedo *et al*.,[39] showed the results of a dose escalation study using 1.3 GBq (35 mCi), 2.6 GBq (70 mCi), 3.3 GBq (90 mCi), and 4.4 GBq (120 mCi) of $^{188}$Re-HEDP in a small group of prostate cancer patients (22 men). The first hematotoxic results were noted in those patients who have an administered activity of 2.6 GBq $^{188}$Re-HEDP. In the 3.3 GBq group, one patient exhibited reversible Grade 1 and 2 thrombocytopenia. In the 4.4 GBq group, thrombocytopenia of Grades 3 and 4 was observed in one and two patients (baseline platelet counts $<100 \times 10^9$/l), respectively. With respect to bone marrow toxicity, the authors postulated an activity of 3.3 GBq as the standard activity of this agent, with the exception of patients with a baseline platelet count level above $200 \times 10^9$/l, which might also be tolerable at a higher activity of 4.4 GBq. Pain palliation was reported by 64% of patients, with a mean duration of 7.5 weeks. The response rate seemed to increase with higher doses, reaching 75% in the 4.4 GBq group. Liepe *et al*. from Dresden[40] focused on the impact of dosage on the general status of the patient. In 27 patients with prostate cancer who were given 3.3 GBq (90 mCi) of $^{188}$Re-HEDP, an increase in Karnofsky performance scale from 74% ± 7% before therapy to 85% ± 9% at 12 weeks after therapy was obtained ($P = 0.001$). In addition, pain relief was achieved in 76% of patients and 20% of patients were pain free. The pain score showed a maximum decrease from 4.4% ±1.8% to 2.7% ±2.0% in the 3$^{rd}$–8$^{th}$ weeks after therapy ($P = 0.009$) [Figure 1]. Other groups have also described a therapeutic effect from $^{188}$Re-HEDP therapy in other malignancies, such as lung, renal, rhinopharyngeal, and bladder cancer with 70% to 80% pain relief.[41]

Bone marrow toxicity, especially thrombocytopenia, traditionally represents the significant side effect in systemic radionuclide therapy. Liepe *et al*.[40] reported a moderate transient bone marrow toxicity with a decrease in platelet counts 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 [Figure 2]. The authors found no evidence of either local or systemic intolerance to treatment with $^{188}$Re-HEDP, while a flare reaction with an increase in pain within 14 days after therapy was noted in 16% of patients.

One clinical trial using $^{188}$Re-HEDP, $^{186}$Re-HEDP, Samarium-159-ethylenediamine tetramethylene phosphonic acid ($^{153}$Sm-EDTMP), and strontium-89 ($^{89}$Sr) in 79 patients with breast and prostate cancer[42] found no significant differences in thrombocytopenia and leukopenia ($P = 0.059$–$0.470$). Anemia plays a minor role in the toxicity of bone pain palliation. After $^{188}$Re-HEDP administration, patients showed a 30% decrease in the platelet counts from the baseline level to nadir. Typically, the nadir is early for thrombocytopenia and leukopenia using radionuclides with short physical half-lives such as $^{188}$Re-HEDP (nadir between the 2$^{nd}$ and 4$^{th}$ weeks after therapy) in contrast to the radionuclides with a longer physical half-life such as $^{89}$Sr (nadir between the 4$^{th}$ and the 6$^{th}$ weeks after therapy).

New important therapeutic advances for bone pain palliation include the option of repeated radiotracer administration rather than a single administration. The group from Bonn[43] compared a standard single dose with two administrations of 3.3 GBq (90 mCi) of $^{188}$Re-HEDP in 64 patients with prostate cancer. An important finding was the significant extension of the median times to progression and time of survival, from 2.3 and 7.0 months for a single administration to 7.0 and 12.7 months for two administrations, with an interval of 8 weeks, respectively ($P < 0.01$). There was also a 60% response in pain relief following a single administration to 90% after twice administration ($P < 0.01$). Moreover, a significant reduction in the levels of the prostate-specific antigen was documented following repeated administration, whereas this effect was not observed after just a single injection.[43] The same group also used three or more administrations and found a significant extension of the overall survival, from 4.5 months to 15.7 months in patients with multiple injections ($P < 0.01$) (Biersack, 2011 #502). In another study,[44] 12 patients with hormone-refractory prostate cancer were treated with 37 MBq/kg (1 mCi/kg) $^{188}$Re-HEDP in combination with two applications of capecitabine (Xeloda®). A dose of 2500 mg/m$^2$ capecitabine per day in combination with $^{188}$Re-HEDP was reported as safe, but data on pain relief or Karnofsky performance scale were not documented. Clinical data using $^{188}$Re-HEDP in primary bone tumors or a

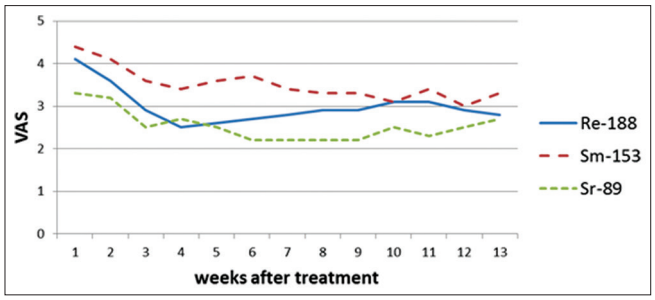


**Figure 1: Time curve of pain documented with a 10-step visual analog scale for $^{188}$rhenium-hydroxyethylidene diphosphonate (Re-188), samarium-159-ethylenediamine tetramethylene phosphonic acid (Sm-153), and strontium-89 (Sr-89). The standard deviation is 1.7–2.4 for $^{188}$rhenium-hydroxyethylidene diphosphonate, 1.8–2.4 for samarium-159-ethylenediamine tetramethylene phosphonic acid, and 1.8–2.2 for strontium-89, respectively**

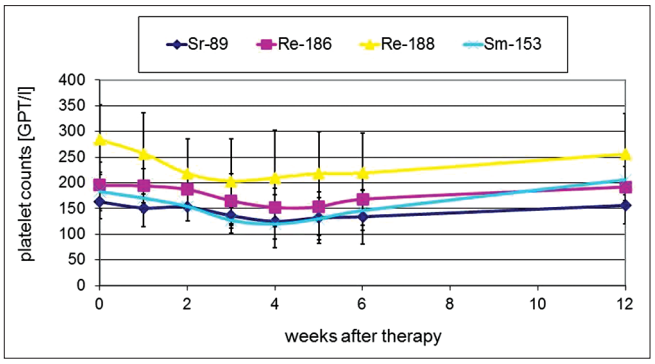


**Figure 2: Time curve of platelet counts for strontium-89 (Sr-89), $^{186}$rhenium-hydroxyethylidene diphosphonate (Re-186), $^{188}$rhenium-hydroxyethylidene diphosphonate (Re-188), and samarium-159-ethylenediamine tetramethylene phosphonic acid (Sm-153)**

combination with bisphosphonates in patients with bone metastases have not been published.

The kinetics of $^{188}$Re-HEDP are favorable for bone pain palliation. Approximately 51% of the injected dose is absorbed by the skeleton 3 h after administration. The decay-corrected whole-body retention as the percentage of the administered activity decreases rapidly, in contrast to a slow decrease from the bone metastases. The biological half-life values ($T^1/_2{}_{biol}$) also differ significantly between the whole body ($T^1/_2{}_{biol}$ = 51 ± 43 h) and the bone metastases ($T^1/_2{}_{biol}$ = 269 ± 166 h). These values correspond with rapid urinary excretion of $^{188}$Re-HEDP; 8 and 48 h after administration, 40% ID and 60 ID% of the dose, respectively, were excreted.[45] Savio *et al*.[46] reported a urinary clearance of 70% within the first 6 h, bone uptake values of 10%–70%, and a remaining blood dose of 9% at 2 h. The bone uptake 24 h postadministration was 43%. The dosimetric data for $^{188}$Re-HEDP are comparable with the data from the commercially available radiopharmaceuticals used for bone pain palliation, with values of 3.83 ± 2.01 mGy/MBq for bone metastases, 0.61 ± 0.21 mGy/MBq for the bone marrow, 0.07 ± 0.02 mGy/MBq for the whole body, 0.71 ± 0.22 mGy/MBq for the kidneys, and 0.99 ± 0.18 mGy/MBq for the bladder.

A single report described the effectiveness of bone-targeted radionuclide therapy in bone metastases of neuroendocrine tumors which show no effect to peptide receptor radionuclide therapy. A small cohort of six patients with progressive bone metastases with falling effect to $^{177}$Lu-octreotate therapy were treated with a total of 11 cycles using 2.6–3.3 GBq $^{188}$Re-HEDP per cycle. Using a 10-step visual analog scale (VAS), the mean pain level decreased from 6.6 (range: 5–8) to 3.7 (range: 2–7). Five patients reported pain response defined as a decrease of pain level ≥2 steps documented on the VAS for at least of 2 weeks.[47]

## SUMMARY

Internal Radiotherapy using $^{188}$Re-HEDP is effective in the treatment of metastatic bone pain and can improve quality of life. Using $^{188}$Re-HEDP in larger group of patients, the cost for therapy is significant lower compare the approved radiopharmaceuticals such as $^{89}$Sr, $^{186}$Re-HEDP, $^{153}$SM-EDTMP, or radium-223. The problem of the widespread use of $^{188}$Re-HEDP is the lack of approved HEDP for therapy. In fact, the company Shanghai YITAI Pharmaceutical Technology Co., Ltd., initiated a Phase IIB clinical trial for castration-resistant prostate cancer patients to have enough clinical data for an approval procedure.

Some investigators prefer radionuclides which emit low beta particles for the treatment of bone pain because the assumption of lower bone marrow toxicity of this agents. However, neither dosimetric data for radiation absorbed dose to the bone marrow[45,48,49] nor clinical blood count depression[50,51] have shown any significant differences between these agents. Other researchers suggest enhanced antitumoral effects using high-energy beta emitters and propose aggressive first-line treatment in the early disease stage instead of using these radiopharmaceuticals only in end-stage patients suffering intractable bone pain.[52,53] Another approach consists of including other treatment modalities such as autologous stem cell rescue or in combination with chemo or bisphosphonate therapy to a radionuclide treatment scheme.[44,52,54] Future research should focus more on the curative effects of combination with radiosensitizer, for example, chemotherapy[55] or repeated treatments with bone-seeking agents.[43]

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### Conflicts of interest
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## REFERENCES


1. Body JJ. Metastatic bone disease: Clinical and therapeutic aspects. Bone 1992;13 Suppl 1:S57-62.
2. Galasko CS. Skeletal metastases. Clin Orthop Relat Res 1986;210:18-30.
3. Bhardwaj S, Holland JF. Chemotherapy of metastatic cancer in bone. Clin Orthop Relat Res 1982;169:28-37.
4. Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain. Nat Rev Cancer 2002;2:201-9.
5. Mundy GR. Metastasis to bone: Causes, consequences and therapeutic opportunities. Nat Rev Cancer 2002;2:584-93.
6. Serafini AN. Current status of systemic intravenous radiopharmaceuticals for the treatment of painful metastatic bone disease. Int J Radiat Oncol Biol Phys 1994;30:1187-94.
7. Nielsen OS, Munro AJ, Tannock IF. Bone metastases: Pathophysiology and management policy. J Clin Oncol 1991;9:509-24.
8. Zlotta AR, Schulman CC. Neoadjuvant and adjuvant hormone therapy for prostate cancer. World J Urol 2000;18:179-82.
9. Auclerc G, Antoine EC, Cajfinger F, Brunet-Pommeyrol A, Agazia C, Khayat D, *et al.* Management of advanced prostate cancer. Oncologist 2000;5:36-44.
10. Kudachadkar R, O'Regan RM. Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer. CA Cancer J Clin 2005;55:145-63.
11. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. Semin Nucl Med 2010;40:89-104.
12. Lipton A. Bisphosphonates and breast carcinoma. Cancer 1997;80:1668-73.
13. Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, *et al.* Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer 2001;91:1191-200.
14. van Holten-Verzantvoort AT, Kroon HM, Bijvoet OL, Cleton FJ, Beex LV, Blijham G, *et al.* Palliative pamidronate treatment in patients with bone metastases from breast cancer. J Clin Oncol 1993;11:491-8.
15. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, *et al.* Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: Results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. J Clin Oncol 1996;14:2552-9.
16. Rizzoli R, Forni M, Schaad MA, Slosman DO, Sappino AP, Garcia J, *et al.* Effects of oral clodronate on bone mineral density in patients with relapsing breast cancer. Bone 1996;18:531-7.
17. Diel IJ, Solomayer EF, Costa SD, Gollan C, Goerner R, Wallwiener D, *et al.* Reduction in new metastases in breast cancer with adjuvant clodronate treatment. N Engl J Med 1998;339:357-63.
18. Powles T, Paterson S, Kanis JA, McCloskey E, Ashley S, Tidy A, *et al.* Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol 2002;20:3219-24.
19. Saarto T, Blomqvist C, Virkkunen P, Elomaa I. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. J Clin Oncol 2001;19:10-7.
20. Mason MD, Sydes MR, Glaholm J, Langley RE, Huddart RA, Sokal M, *et al.* Oral sodium clodronate for nonmetastatic prostate cancer – Results of a randomized double-blind placebo-controlled trial: Medical research council PR04 (ISRCTN61384873). J Natl Cancer Inst 2007;99:765-76.
21. Heidenreich A, Elert A, Hofmann R. Ibandronate in the treatment of prostate cancer associated painful osseous metastases. Prostate Cancer Prostatic Dis 2002;5:231-5.
22. Weinfurt KP, Anstrom KJ, Castel LD, Schulman KA, Saad F. Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. Ann Oncol 2006;17:986-9.
23. Lin A, Ray ME. Targeted and systemic radiotherapy in the treatment of bone metastasis. Cancer Metastasis Rev 2006;25:669-75.
24. Janjan N. Palliation and supportive care in radiation medicine. Hematol Oncol Clin North Am 2006;20:187-211.
25. Agarawal JP, Swangsilpa T, van der Linden Y, Rades D, Jeremic B, Hoskin PJ, *et al.* The role of external beam radiotherapy in the management of bone metastases. Clin Oncol (R Coll Radiol) 2006;18:747-60.
26. Breen SL, Battista JJ. Cavity theory applied to the dosimetry of systemic radiotherapy of bone metastases. Phys Med Biol 2000;45:879-96.
27. Liepe K, Kotzerke J. Internal radiotherapy of painful bone metastases. Methods 2011;55:258-70.
28. Lambert B, Bacher K, Defreyne L, Gemmel F, Van Vlierberghe H, Jeong JM, *et al.* 188Re-HDD/lipiodol therapy for hepatocellular carcinoma: A phase I clinical trial. J Nucl Med 2005;46:60-6.
29. Liepe K, Brogsitter C, Leonhard J, Wunderlich G, Hliscs R, Pinkert J, *et al.* Feasibility of high activity rhenium-188-microsphere in hepatic radioembolization. Jpn J Clin Oncol 2007;37:942-50.
30. Liepe K, Zaknun JJ, Soroa VE, Barrenechea E, Shrikant S, Jeong JM. Radiosynovectomy using yttrium-90, phosphorus-32 and rhenium-188 colloids in rheumatoid arthritis. Eur J Nucl Med 2007;34 Suppl 2:476.
31. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, *et al.* Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-28.
32. Bunjes D, Buchmann I, Duncker C, Seitz U, Kotzerke J, Wiesneth M, *et al.* Rhenium 188-labeled anti-CD66 (a, b, c, e) monoclonal antibody to intensify the conditioning regimen prior to stem cell transplantation for patients with high-risk acute myeloid leukemia or myelodysplastic syndrome: Results of a phase I-II study. Blood 2001;98:565-72.
33. Wöhrle J, Nusser T, Krause BJ, Kochs M, Habig T, Mottaghy FM, *et al.* Patients with in-stent restenoses: Comparison of intracoronary beta-brachytherapy using a rhenium-188 filled balloon catheter with the polymer-based paclitaxel-eluting taxus-express stent. Nuklearmedizin 2007;46:185-91.
34. Cho YS, Kim MA, Hwang KK, Koo BK, Oh S, Chae IH, *et al.* Two-year clinical follow-up results of intracoronary radiation therapy with rhenium-188-diethylene triamine penta-acetic acid-filled balloon. Catheter Cardiovasc Interv 2004;63:274-81.
35. Reynen K, Köckeritz U, Kropp J, Wunderlich G, Knapp FF, Schmeisser A, *et al.* Intracoronary radiotherapy with a (188) rhenium liquid-filled PTCA balloon system in in-stent restenosis: Acute and long-term angiographic results, as well as 1-year clinical follow-up. Int J Cardiol 2004;95:29-34.
36. Hsieh BT, Hsieh JF, Tsai SC, Lin WY, Wang SJ, Ting G, *et al.* Comparison of various rhenium-188-labeled diphosphonates for the treatment of bone metastases. Nucl Med Biol 1999;26:973-6.
37. Maxon HR 3rd, Schroder LE, Washburn LC, Thomas SR, Samaratunga RC, Biniakiewicz D, *et al.* Rhenium-188(Sn)HEDP for treatment of osseous metastases. J Nucl Med 1998;39:659-63.
38. Lin WY, Hsieh JF, Lin CP, Hsieh BT, Ting G, Wang SJ, *et al.* Effect of reaction conditions on preparations of rhenium-188 hydroxyethylidene diphosphonate complexes. Nucl Med Biol 1999;26:455-9.
39. Palmedo H, Guhlke S, Bender H, Sartor J, Schoeneich G, Risse J, *et al.* Dose escalation study with rhenium-188 hydroxyethylidene diphosphonate in prostate cancer patients with osseous metastases. Eur J Nucl Med 2000;27:123-30.
40. Liepe K, Kropp J, Runge R, Kotzerke J. Therapeutic efficiency of rhenium-188-HEDP in human prostate cancer skeletal metastases. Br J Cancer 2003;89:625-9.
41. Li S, Liu J, Zhang H, Tian M, Wang J, Zheng X, *et al.* Rhenium-188 HEDP to treat painful bone metastases. Clin Nucl Med 2001;26:919-22.
42. 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.

43. Palmedo H, Manka-Waluch A, Albers P, Schmidt-Wolf IG, Reinhardt M, Ezziddin S, *et al.* Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: Tandomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenediphosphonate. J Clin Oncol 2003;21:2869-75.
44. Lam MG, Bosma TB, van Rijk PP, Zonnenberg BA. (188)Re-HEDP combined with capecitabine in hormone-refractory prostate cancer patients with bone metastases: A phase I safety and toxicity study. Eur J Nucl Med Mol Imaging 2009;36:1425-33.
45. Liepe K, Hliscs R, Kropp J, Runge R, Knapp FF Jr., Franke WG, *et al.* Dosimetry of 188Re-hydroxyethylidene diphosphonate in human prostate cancer skeletal metastases. J Nucl Med 2003;44:953-60.
46. Savio E, Gaudiano J, Robles AM, Balter H, Paolino A, López A, *et al*. Re-HEDP: Pharmacokinetic characterization, clinical and dosimetric evaluation in osseous metastatic patients with two levels of radiopharmaceutical dose. BMC Nucl Med 2001;1:2.
47. Sabet A, Khalaf F, Mahjoob S, Al-Zreiqat A, Biersack HJ, Ezziddin S, *et al.* May bone-targeted radionuclide therapy overcome PRRT-refractory osseous disease in NET? A pilot report on (188)Re-HEDP treatment in progressive bone metastases after (177)Lu-octreotate. Am J Nucl Med Mol Imaging 2013;4:80-8.
48. Maxon HR 3rd, Schroder LE, Thomas SR, Hertzberg VS, Deutsch EA, Scher HI, *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.
49. Eary JF, Collins C, Stabin M, Vernon C, Petersdorf S, Baker M, *et al.* Samarium-153-EDTMP biodistribution and dosimetry estimation. J Nucl Med 1993;34:1031-6.
50. Liepe K, Runge R, Kotzerke J. The benefit of bone-seeking radiopharmaceuticals in the treatment of metastatic bone pain. J Cancer Res Clin Oncol 2005;131:60-6.
51. Liepe K, Runge R, Kotzerke J. Systemic radionuclide therapy in pain palliation. Am J Hosp Palliat Care 2005;22:457-64.
52. O'Sullivan JM, Norman AR, McCready VR, Flux G, Buffa FM, Johnson B, *et al.* A phase 2 study of high-activity 186Re-HEDP with autologous peripheral blood stem cell transplant in progressive hormone-refractory prostate cancer metastatic to bone. Eur J Nucl Med Mol Imaging 2006;33:1055-61.
53. Enrique O, Zhonyun P, Prma EP, Pusuwan P, Ricobona G, Tian JH, *et al*. Efficacy and toxicity of Sm-153 EDTMP in the palliative treatment of painful bone metastases. World J Nucl Med 2002;1:21-7.
54. Lam MG, de Klerk JM, Zonnenberg BA. Treatment of painful bone metastases in hormone-refractory prostate cancer with zoledronic acid and samarium-153-ethylenediaminetetramethylphosphonic acid combined. J Palliat Med 2009;12:649-51.
55. Tu SM, Millikan RE, Mengistu B, Delpassand ES, Amato RJ, Pagliaro LC, *et al.* Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: A randomised phase II trial. Lancet 2001;357:336-41.