Palliative radionuclide therapy for bone metastases with strontium-89-chloride and samarium-153-EDTMP

K. Chung, MD, PhD; J.M.H. de Klerk, MD, PhD
Department of Nuclear Medicine, Meander Medical Centre, Amersfoort

Abstract
A considerable proportion of patients with cancer will develop bone metastases. Bone metastases frequently cause severe bone pain and seriously affect quality of life. Palliative treatment of patients with bone pain from multiple bone metastases using radiopharmaceuticals such as [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP can be a safe and easily accessible option to effectively relieve bone pain.

Introduction

Cancer incidence is on the rise, with over 124.000 cases alone being diagnosed in 2022 in the Netherlands according to the statistics of the Integral Cancer Center in the Netherlands (IKNL). A considerable proportion of patients with advanced prostate, breast or lung carcinoma will develop bone metastases. Bone metastases are an indicator of progressive disease with bad prognosis, frequently causing severe bone pain and affecting quality of life (1,2).

The aim of treating bone metastases with bone seeking radiopharmaceuticals is purely palliative (except Radium-223). The treatment options are diverse and depend on the disease condition. A common treatment sequence is nonsteroidal analgesics to opioids often combined with radiotherapy, surgery, chemotherapy, hormone treatment, bisphosphonates and radionuclide therapy (3). External beam radiotherapy is preferred for localized pain and limited metastases (4). For patients with multiple or diffuse metastases, or when other treatments do not respond, treatment with bone seeking radiopharmaceuticals is a good alternative, given that metastases are osteoblastic (which can be confirmed with bone scintigraphy). This is mostly the case for prostate cancer metastases, but bone seeking radiopharmaceuticals can also target metastases from many other types of tumors that have a mix of osteoblastic and osteoclastic components (5). On top of allowing systemic treatment, other advantages of treatment with bone seeking radiopharmaceuticals are its repeatability, ease of administration as well as the potential to be combined with other therapies for enhanced effectiveness.

There are different radionuclides that can be used. The most common are the beta-emitting strontium-89-chloride (^{89}Sr-Cl) and samarium-153-EDTMP ([^{153}Sm]Sm-EDMTP) as well as the alpha-emitting radium-223-chloride ([^{223}Ra]$RaCl_2$). In the past, rhenium-188 hydroxyethylidene diphosphonate and rhenium-186-hydroxyethylidene disphosphonate ([^{188}Re]Re-HEDP and [^{186}Re]Re-HEDP) were also used, but these radiopharmaceuticals are now out of production for this indication. After injection, the radionuclides target all osteoblastic bone lesions simultaneously. Pain relief commences in days or weeks, lasting for months (6). Pain reduction is achieved by destruction of malignant and immune cells, leading to a decrease of cytokines and growth factors that lessen periosteal swelling (5). The related treatment toxicity is mainly (reversible) myelosuppression, thrombocytopenia in particular, and depends on the administered dose and type of radionuclide (3).

This review presents insights into the clinical results of using the beta-emitting strontium-89-chloride ([^{89}Sr]$SrCl_2$) and samarium-153-EDTMP ([^{153}Sm]Sm-EDMTP) (approved in Europe and the US) for treatment of bone metastases, including effectiveness for pain relief for different primary tumors and side effects derived from this treatment.

Characteristics and Production

Summary characteristics of both radionuclides are presented in table 1.

Strontium-89-chloride

^{89}Sr was the first radionuclide to receive US Food and Drug Administration approval for the palliation of bone pain. The isotope ^{89}Sr has a half-life of 50.57 days and undergoes decay into stable yttrium-89, emitting mostly high energy beta-particles (Emax = 1.46 MeV). A very small negligible proportion of gamma rays is emitted (910 keV) as well as a small amount

Table 1. Summary characteristics of both radionuclides.

Radionuclide	Half-life (days)	Energy (beta max) (mEv)	Emission	Range in soft tissue (mm)
strontium-89	50.57	1.46	Beta	8.0
samarium-153	1.93	0.71	Beta/Gamma	3.0

of bremsstrahlung. Because of the small proportion of gamma and bremsstrahlung it is safe to administer in an outpatient setting.

Strontium is a calcimimetic agent and thus behaves similar to calcium. After intravenous injection strontium migrates to the bone and is actively taken up by the bone matrix. The high energy beta particles are responsible for the therapeutic effect. The maximum range in soft-tissue is 8 mm (7).

^{89}Sr is produced through neutron activation, irradiating a sample of stable strontium-88 (^{88}Sr) with neutrons in a nuclear reactor. This transforms some of the ^{88}Sr into ^{89}Sr through neutron capture and subsequent beta decay. The resulting ^{89}Sr is separated and purified to the desired level of radioactivity. Finally, it is incorporated with a chloride solution to make it ready for intravenous delivery to the patient (8).

Samarium-153-EDTMP

^{153}Sm was approved in the USA and Europe for the treatment of pain from bone metastases in the late 1990s. ^{153}Sm has desirable characteristics, with a combined radiation of beta and gamma emissions while decaying to stable europium-153. Beta emissions occur at 640, 710 and 810 keV with an average beta particle energy of 233 keV. Its gamma-ray emission of 103 keV allows to assess patient biodistribution and dosimetry after injection via SPECT imaging. The beta particle of [^{153}Sm]Sm-EDMTP has a maximum range of 3.0 mm in soft tissue and 1.7 mm in bone. It has a half-life of 46.3 hours (1.93 days) (9).

[^{153}Sm]Sm-EDMTP has good selective skeletal localization, low blood levels, and low soft tissue retention, including the liver. Accumulation in non-osseous tissue other than the bladder/urine is low. A study by Brenner et al. found a mean bone uptake of 47.7±11.2% at 24 hours, soft-tissue retention at 24 hours was 12.7±4.7%, and urinary excretion 39.5±13.8% at 24h after injection of 37 MBq/kg [^{153}Sm]Sm-EDMTP (10).

^{153}Sm is commonly prepared by neutron irradiation of enriched $^{152}Sm_2O_3$ in a nuclear reactor, which is then chelated with ethylenediaminetetramethylene phosphonic acid (EDTMP) (11).

Clinical Results

Strontium-89-chloride

A standard fixed dose of 150 MBq is recommended by the European Association of Nuclear Medicine (EANM) Guidelines following many investigations (3). [^{89}Sr]$SrCl_2$ is administered intravenously and a slow infusion is recommended to avoid a 'flushing sensation' (3). Good response rates have been reported in clinical trials ranging from 57 to 96% (table 2).

Pain relief in studies is usually reported as either complete or partial pain reduction. Different scales are used to measure pain relief, including numerous numerical weighting systems, ten-point Visual Analogue Scale (VAS), RTOG (Radiation Therapy Oncology Group) pain scoring system or subjectively assessed by the oncologist. In a large meta-analysis from 2012 an overall response rate of 70% (95% CI: 65-75%) was reported (12). Delay in the start of response is usually between 4 days and 28 days, with a response duration of up to 15 months (6).

Additionally, a few studies have shown an improvement of quality of life after radionuclide treatment with [^{89}Sr]$SrCl_2$ (13–15). It has to be noted that naturally, improvement in quality of life generally follows pain relief (16). Although showing acceptable response rates regarding pain relief, another recent meta-analysis (17) showed no benefits in overall survival rates or symptomatic 'skeletal related event (e.g. pathological fractures)' (SRE)-free survival in metastatic castration-resistant prostate cancer (mCRPC).

Retreatment with [^{89}Sr]$SrCl_2$ is possible and safe, though the response to retreatment tends to be significantly worse compared to first treatment (rate of patients with at least good response decreased from 60% to 48%) (18).

Table 2. Summary of efficacy studies on strontium-89-chloride. Pain relief is reported as the response rate of patients with either complete or partial pain reduction.

Reference	Year	Nr. Patients	Diagnosis	Dosage	Pain Relief
Lewington (19)	1991	26	Prostate	150 MBq	75%
Pons (20)	1997	76	Prostate / Breast	148 MBq	89% Prostate 92% Breast
Kasalicky (21)	1998	118	Prostate / Breast / Other	148 MBq	96%
Fuster (22)	2000	40	Breast	148 MBq	92%
Kraeber-Bodere (14)	2000	94	Prostate	150 MBq	78%
Dafermou (18)	2001	527	Prostate	148 MBq	60%
Turner (16)	2001	93	Prostate	150 MBq	63%
Sciuto (23)	2001	25	Breast	148 MBq	84%
Ashayeri (24)	2002	41	Prostate / Breast	150 MBq	81%
Zorga (25)	2003	33	Prostate / Breast / Other	148 MBq	88%
Baczyk (13)	2003	70	Prostate	148 MBq	88%
Oosterhof (26)	2003	203	Prostate	148 MBq	78%
Gunawardana (27)	2004	13	Prostate	148 MBq	57%
Liepe (28)	2007	15	Prostate / Breast	148 MBq	73%
Zenda (29)	2014	54	Prostate / Breast / Other	2 MBq/kg	71%
Furubayashi (30)	2014	18	Prostate	2 MBq/kg to a maximum of 141 MBq per patient.	72%
Ye (31)	2018	246	Prostate / Breast / Lung	2.2 MBq/kg	75% Lung 95% Prostate and Breast

Samarium-153-EDTMP

[^{153}Sm]Sm-EDMTP has been widely used since its approval in the late 1990s. The optimal dosage of 37 MBq/kg has been investigated thoroughly in the past which has been shown to be effective and safe (32,33). Therefore, a dose of 37 MBq/kg is now the recommended dose by the EANM guidelines.

Response rates are comparable to [^{89}Sr]$SrCl_2$ ranging from 57%-90% (table 3). In a large meta-analysis, an overall response rate of 70% (95% CI: 63-96%) was found for [^{153}Sm]Sm-EDMTP, similar to ^{89}Sr-Cl.

Given its much shorter half-life, [^{153}Sm]Sm-EDMTP onset of response after treatment is faster than [^{89}Sr]$SrCl_2$, and pain relief is typically noted rapidly within 5 to 10 days and with a duration up to 4 months (6). Patients who need quick pain relief due to a fast-progressing disease and pain can benefit more from treatment with a short-lived isotope such as [^{153}Sm]Sm-EDMTP. In the case of a good first response, repeated treatment may be desirable and has been shown to improve duration of pain response (6,16,34).

Side Effects

Many of the above mentioned studies reported the observed side effects of [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP. The most common side effects are pain

Table 3. Summary of efficacy studies on samarium-153-EDTMP. Pain relief is reported as the response rate of patients with either complete or partial pain reduction.

Reference	Year	Nr. Patients	Diagnosis	Dosage	Pain Relief
Turner (16)	1991	23	Prostate / Breast / Other	Absorbed dose to bone marrow was fixed at 2 Gy	61%
Collins (35)	1993	52	Prostate	18.5–111 MBq/kg	67%
Resche (33)	1997	114	Prostate / Breast / Other	18.5–37 MBq/kg	70%
Serafini (32)	1998	118	Prostate / Breast / Other	18.5–37 MBq/kg	57-65%
Tian (36)	1999	105	Prostate / Breast / Other	37 MBq/kg	Only complete pain relief reported (25%)
Dolezal (37)	2000	33	Prostate / Breast / Other	37 MBq/kg	71%
Sapienza (38)	2004	73	Prostate / Breast	37 MBq/kg	90% (decrease in pain score by more than 25%)
Etchebehere (39)	2004	58	Prostate / Breast / Other	37–59.2 MBq/kg	78% (decrease in pain score by more than 25%)
Sartor (40)	2004	152	Prostate	37 MBq/kg	65%
Tripathi (41)	2006	84	Prostate / Breast / Other	37 MBq/kg	73%
Ripamonti (42)	2007	13	Prostate	40 MBq/kg	77%
Liepe (28)	2007	15	Prostate / Breast	37 MBq/kg	73%
Gallichio (43)	2014	21	Breast / Lung	37 MBq/kg	86%
Correa-Gonzalez (44)	2014	277	Prostate / Breast / Other	37 MBq/kg	74% Prostate 67% Breast 67-80% Other
Thapa (45)	2015	16	Prostate / Other	37 MBq/kg	75%
Elzahry (46)	2017	110	Prostate / Breast	1.1 GBq	94%

flare and (low grade) hematological side effects such as thrombopenia and leukopenia.

The flare phenomenon involves an increase in pain symptoms and typically occurs within 72 hours after the start of the treatment and it is observed in approximately 10% of patients. In the majority of patients the pain symptoms are self-limiting and mild. In general, a flare phenomenon is associated with good response rates of pain relief (6,33,47).

Bone marrow toxicity is the major side-effect in both [^{89}Sr]$SrCl_2$ and [^{153}Sm] Sm-EDMTP. Decreases in thrombocyte and leucocyte counts in the peripheral blood because of myelosuppression is frequently observed, but mainly low-grade and transient. In a study by

Zenda et al. (29) grade 3-4 leucopenia was only found in 1.8% of patients, while in a study by Kraeber-Bodere et al. (14) high grade leuco-thrombopenia was observed in 5% of patients.

When treating patients with [^{89}Sr]$SrCl_2$, the lowest blood cell count (nadir) occurs between 12–16 weeks, showing recovery within six weeks depending on the extent of bone metastases and bone marrow reserve (3,6,48,49). It generally consists of a transient mild thrombocytopenia of around 30%. In theory, because of a longer half-life and maximum beta-radiation energy, [^{89}Sr]$SrCl_2$ yields a longer period of myelosuppression. Therefore, longer follow-up is deemed necessary.

In patients treated with [^{153}Sm]Sm-EDMTP, nadir is usually measured between 3-5 weeks and recovery takes places 6-8 weeks after therapy. Likewise, after repeated doses of [^{153}Sm]Sm-EDMTP the bone marrow toxicity has been shown to be transient and mild (38,40,44).

Discussion

Both [^{89}Sr]$SrCl_2$ and [153Sm]Sm-EDMTP have been widely proven to be effective to reduce pain in patients with bone metastases. Various studies have compared the efficacy of different radiopharmaceuticals in treating metastatic bone pain relief. Most studies reported no significant difference between [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP regarding toxic effects and response rate (23,28,50–52). Therefore, factors such as availability, cost, and clinical experience are often used to decide which radiopharmaceutical to use for palliative pain relief from bone metastases.

Since effectiveness depends on the osteoblastic nature of the metastases, there are some differences in pain relief success among metastases from different cancer types. Ye et al. compared the efficacy of [^{89}Sr]$SrCl_2$ in treating bone metastases in lung versus breast and prostate cancer as a control group. They found that the efficacy was significantly lower in patients with lung cancer than in patients with breast or prostate cancer (75% vs. 90%). Moreover, toxicity was higher for patients with lung cancer, with 67% of patients showing mild-to-moderate reductions of leukocyte and platelet counts 4 weeks after [^{89}Sr]$SrCl_2$ treatment (compared to 47% in the control group) (31). In another study, it was also concluded that treatment non-responders are often patients with primary lung cancer (34 out of 51 non-responders) (36). Although [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP are indicated for all painful metastatic osteoblastic bone lesions (as confirmed by areas of intense uptake on radionuclide bone scans), this could be explained given the fact that lung cancer often develops osteolytic metastases to bone (53).

When it comes to survival benefits, studies with [^{223}Ra]$RaCl_2$, an alpha-emitter radionuclide, have shown to improve overall survival in patients with metastatic castrate resistant prostate cancer and bone metastases (without visceral metastases). Survival benefits after therapy with [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP have not been investigated, and thus there is no evidence that they improve overall survival. However, [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP have been shown to provide palliative pain relief for a wider patient population, as opposed to [^{223}Ra]$RaCl_2$ which is limited to castration resistant prostate cancer patients with bone pain and no visceral metastases.

The efficacy of other anti-cancer treatments combined with boneseeking radionuclide therapy has been investigated. Results are contradictory. Treatment with the combination of [^{89}Sr]$SrCl_2$ and external beam radiation therapy (EBRT) was shown to have similar response rates in some studies (26,54), while in another study pain relief was higher in patients receiving a combination of [^{89}Sr]$SrCl_2$ and EBRT compared to a single treatment of [^{89}Sr]$SrCl_2$ alone (55). However, a combination of a radionuclide and bisphosphonates seems to be promising. Concurrent therapy of [^{89}Sr]$SrCl_2$ and zoledronic acid (bisphosphonate) has been shown to have a higher rate of pain relief (94% of patients) and improvement of quality of life compared to [^{89}Sr]$SrCl_2$ or zoledronic acid use alone, without any increase of toxicity (56). Similar outcomes were found for combination therapy of [^{153}Sm]Sm-EDMTP with bisphosphonates, leading to significantly higher pain responses and better quality of life (57,58).

Conclusion

Both [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP are beta-emitting radiopharmaceuticals with decades of proven clinical safety and effectiveness to reduce pain in patients with bone metastases.

jmh.de.klerk@meandermc.nl ♦

References

1. Saad F, Clarke N, Colombel M. Natural history and treatment of bone complications in prostate cancer. Eur Urol. 2006;49:429-40
2. Levy MH. Pharmacologic Treatment of Cancer Pain. N Engl J Med. 1996;10;335:1124-32
3. Handkiewicz-Junak D, Poeppel TD, Bodei L, Aktolun C, Ezziddin S, Giammarile F, et al. EANM guidelines for radionuclide therapy of bone metastases with beta-emitting radionuclides. Eur J Nucl Med Mol Imaging. 2018;45:846-59
4. Janjan N. Bone metastases: Approaches to management. Semin Oncol. 2001;28:28-34

5. M.G.E.H. Lam, J.M.H. de Klerk, P.P. van Rijk, B.A. Zonnenberg. Bone Seeking Radiopharmaceuticals for Palliation of Pain in Cancer Patients with Osseous Metastases. Anti-Cancer Agents Med Chem. 2007;7:381-97
6. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol. 2005;6:392-400
7. FDA label 89-strontium-chloride
8. Dickinson CZ, Hendrix NS. Strontium-89 Therapy in Painful Bony Metastases. J Nucl Med Technol. 1993;21:133-7
9. FDA Label samarium-153-EDTMP [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020570s008lbl.pdf
10. Brenner W, Kampen WU, Kampen AM, Henze E. Skeletal uptake and soft-tissue retention of 186Re-HEDP and 153Sm-EDTMP in patients with metastatic bone disease. J Nucl Med Off Publ Soc Nucl Med. 2001;42:230-6
11. Goeckeler WF, Troutner DE, Volkert WA, Edwards B, Simon J, Wilson D. 153Sm radiotherapeutic bone agents. Int J Rad Appl Instrum B. 1986;13:479-82
12. DAngelo G, Sciuto R, Salvatori M, Sperduti I, Mantini G, Maini C, et al. Targeted "bone-seeking" radiopharmaceuticals for palliative treatment of bone metastases: a systematic review and meta-analysis. Q J Nucl Med Mol Imaging. 2012 Dec;56(6):538-43
13. Baczyk M, Milecki P, Baczyk E, Sowiński J. The effectivness of strontium 89 in palliative therapy of painful prostate cancer bone metastases. Ortop Traumatol Rehabil. 2003;5:364-8
14. Kraeber-Bodéré F, Campion L, Rousseau C, Bourdin S, Chatal JF, Resche I. 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
15. Kurosaka S, Satoh T, Chow E, Asano Y, Tabata K ichi, Kimura M, et al. EORTC QLQ-BM22 and QLQ-C30 quality of life scores in patients with painful bone metastases of prostate cancer treated with strontium-89 radionuclide therapy. Ann Nucl Med. 2012;26:485-91
16. Turner SL, Gruenewald S, Spry N, Gebski V, Metastron Users Group. Less pain does equal better quality of life following strontium-89 therapy for metastatic prostate cancer. Br J Cancer. 2001;84:297-302
17. Terrisse S, Karamouza E, Parker CC, Sartor AO, James ND, Pirrie S, et al. Overall Survival in Men With Bone Metastases From Castration-Resistant Prostate Cancer Treated With Bone-Targeting Radioisotopes: A Meta-analysis of Individual Patient Data From Randomized Clinical Trials. JAMA Oncol. 2020;6:206-16
18. Dafermou A, Colamussi P, Giganti M, Cittanti C, Bestagno M, Piffanelli A. A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. Eur J Nucl Med. 2001;28:788-98
19. Lewington VJ, McEwan AJ, Ackery DM, Bayly RJ, Keeling DH, Macleod PM, et al. 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. Eur J Cancer. 1991;27:954-8
20. Pons F, Herranz R, Garcia A, Vidal-Sicart S, Conill C, Grau JJ, et al. Strontium-89 for palliation of pain from bone metastases in patients with prostate and breast cancer. Eur J Nucl Med. 1997;24:1210-4
21. Kasalický J, Krajská V. The effect of repeated strontium-89 chloride therapy on bone pain palliation in patients with skeletal cancer metastases. Eur J Nucl Med. 1998;25:1362-7
22. Fuster D, Herranz D, Vidal-Sicart S, Muñoz M, Conill C, Mateos JJ, et al. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. Nucl Med Commun. 2000;21:623-6
23. Sciuto R, Festa A, Pasqualoni R, Semprebene A, Rea S, Bergomi S, et al. Metastatic bone pain palliation with 89Sr and 186Re HEDP in breast cancer patients. Breast Cancer Res Treat. 2001;66:101-9
24. Ashayeri E, Omogbehin A, Sridhar R, Shankar RA. Strontium 89 in the treatment of pain due to diffuse osseous metastases: a university hospital experience. J Natl Med Assoc. 2002;94:706-11
25. Zorga P, Birkenfeld B, Listewnik MH, Piwowarska-Bilska H. Effectiveness of strontium-89 palliative therapy in patients with painful bone metastases. Ann Acad Med Stetin. 2011;57:49-53; discussion 53.
26. Oosterhof GON, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der Maase H, et al. 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. Eur Urol. 2003;44:519-26
27. Gunawardana DH, Lichtenstein M, Better N, Rosenthal M. Results of strontium-89 therapy in patients with prostate cancer resistant to chemotherapy. Clin Nucl Med. 2004;29:81-5
28. 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
29. Zenda S, Nakagami Y, Toshima M, Arahira S, Kawashima M, Matsumoto Y, et al. Strontium-89 (Sr-89) chloride in the treatment of various cancer patients with multiple bone metastases. Int J Clin Oncol. 2014;19:739-43
30. Furubayashi N, Negishi T, Ura S, Hirai Y, Nakamura M. Palliative effects and adverse events of strontium-89 for prostate cancer patients with bone metastasis. Mol Clin Oncol. 2015;3:257-63
31. Ye X, Sun D, Lou C. Comparison of the efficacy of strontium-89 chloride in treating bone metastasis of lung, breast, and prostate cancers. J Cancer Res Ther. 2018;14(Supplement):S36-40
32. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. J Clin Oncol Off J Am Soc Clin Oncol. 1998;16:1574-81
33. Resche I, Chatal JF, Pecking A, Ell P, Duchesne G, Rubens R, et al. A dose-controlled study of 153Sm-ethylenediaminetetramethylen ephosphonate (EDTMP) in the treatment of patients with painful bone metastases. Eur J Cancer. 1997;33:1583-91
34. Menda Y, Bushnell DL, Williams RD, Miller S, Thomas MO. Efficacy and safety of repeated samarium-153 lexidronam treatment in a patient with prostate cancer and metastatic bone pain. Clin Nucl Med. 2000;25:698-700
35. Collins C, Eary JF, Donaldson G, Vernon C, Bush NE, Petersdorf S, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. J Nucl Med Off Publ Soc Nucl Med. 1993;34:1839-44
36. Tian JH, Zhang JM, Hou QT, Oyang QH, Wang JM, Luan ZS, et al. Multicentre 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. Eur J Nucl Med. 1999;26:2-7
37. Dolezal J. Systemic radionuclide therapy with Samarium-153-EDTMP for painful bone metastases. Nucl Med Rev Cent East Eur. 2000;3:161-3
38. Sapienza MT, Ono CR, Guimarães MIC, Watanabe T, Costa PA, Buchpiguel CA. Retrospective evaluation of bone pain palliation after samarium-153-EDTMP therapy. Rev Hosp Clin. 2004;59:321-8
39. Etchebehere ECS de C, Pereira Neto CAC, Lima MCL de, Santos A de O, Ramos CD, Silva CM, et al. Treatment of bone pain secondary to metastases using samarium-153-EDTMP. Sao Paulo Med J. 2004;122:208-12
40. Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, et al. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. Urology. 2004;63:940-5
41. Tripathi M, Singhal T, Chandrasekhar N, Kumar P, Bal C, Jhulka PK, et al. Samarium-153 ethylenediamine tetramethylene phosphonate therapy for bone pain palliation in skeletal metastases. Indian J Cancer. 2006;43:86-92
42. Ripamonti C, Fagnoni E, Campa T, Seregni E, Maccauro M, Bombardieri E. Incident pain and analgesic consumption decrease after samarium infusion: a pilot study. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2007;15:339-42
43. Gallicchio R, Giacomobono S, Nardelli A, Pellegrino T, Simeon V, Gattozzi D, et al. Palliative treatment of bone metastases with samarium-153 EDTMP at onset of pain. J Bone Miner Metab. 2014;32:434-40
44. 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
45. Thapa P, Nikam D, Das T, Sonawane G, Agarwal JP, Basu S. Clinical Efficacy and Safety Comparison of 177Lu-EDTMP with 153Sm-EDTMP on an Equidose Basis in Patients with Painful Skeletal Metastases. J Nucl Med. 2015;56:1513-9
46. Elzahry M, Diab W, Sinzinger H. Assessment of Bone Pain Response in Cancer Patients Receiving Single Dose of Sm-153 EDTMP Therapy. J Nucl Med Radiat Ther. 2017;8:4
47. Taylor AJ. Strontium-89 for the palliation of bone pain due to metastatic disease. J Nucl Med. 1994;35:2054
48. Lewington VJ. Bone-seeking radionuclides for therapy. J Nucl Med Off Publ Soc Nucl Med. 2005;46 Suppl 1:38S-47S
49. Ahmadzadehfar H, Essler M, Rahbar K, Afshar-Oromieh A. Radionuclide Therapy for Bone Metastases: Utility of Scintigraphy and PET Imaging for Treatment Planning. PET Clin. 2018;13:491-503
50. Dickie GJ, Macfarlane D. Strontium and samarium therapy for bone metastases from prostate carcinoma. Australas Radiol. 1999;43:476-9
51. Nair N. Relative efficacy of 32P and 89Sr in palliation in skeletal metastases. J Nucl Med.

1999;40:256-61
52. Jong JM van D de, Oprea-Lager DE, Hooft L, de Klerk JMH, Bloemendal HJ, Verheul HMW, et al. Radiopharmaceuticals for Palliation of Bone Pain in Patients with Castration-resistant Prostate Cancer Metastatic to Bone: A Systematic Review. Eur Urol. 2016;70:416-26
53. Otsuka S, Hanibuchi M, Ikuta K, Yano S, Goto H, Ogino H, et al. A bone metastasis model with osteolytic and osteoblastic properties of human lung cancer ACC-LC-319/bone2 in natural killer cell-depleted severe combined immunodeficient mice. Oncol Res. 2009;17:581-91
54. Smeland S, Erikstein B, Aas M, Skovlund E, Hess SL, Fosså SD. Role of strontium-89 as adjuvant to palliative external beam radiotherapy is questionable: results of a double-blind randomized study. Int J Radiat Oncol Biol Phys. 2003;56:1397-404
55. Heianna J, Toita T, Endo W, Kasuya G, Ariga T, Hashimoto S, et al. Concurrent use of strontium-89 with external beam radiotherapy for multiple bone metastases: early experience. Ann Nucl Med. 2015;29:848-53
56. Storto G, Klain M, Paone G, Liuzzi R, Molino L, Marinelli A, et al. Combined therapy of Sr-89 and zoledronic acid in patients with painful bone metastases. Bone. 2006;39:35-41
57. Rasulova N, Lyubshin V, Arybzhanov D, Sagdullaev Sh, Krylov V, Khodjibekov M. Optimal Timing of Bisphosphonate Administration in Combination with Samarium-153 Oxabifore in the Treatment of Painful Metastatic Bone Disease. World J Nucl Med. 2013;12:14-8
58. Baczyk M, Baczyk E, Sowiński J. Preliminary results of combined application of radioisotopes and biphosphonates in the management of pain associated with osteoblastic-osteolytic bone metastases of breast cancer. Ortop Traumatol Rehabil. 2003;5:234-7