Methodology RL Prostaat PICO 4

# key question

Welke behandeling is geïndiceerd voor pijnlijke botmetastasen bij patiënten met een gemetastaseerd castratie-resistent prostaatcarcinoom?

P Patiënten met gemetastaseerd castratie-resistent prostaatcarcinoom (mCRPC) en pijnlijke botmetastasen

I Behandeling met radionucliden (Samarium-153-EDTMP, Strontium-89, Rhenium-188-HEDP, Radium-223)

C Geen behandeling of een (of meer) van de andere radionuclidenbehandelingen

O Reductie van pijnklachten, Kwaliteit van leven, Toxiciteit, Duur van de respons

# golden hits

**1.** Bodei L, Lam M, Chies C, et al. *EANM procedure guideline for treatment of refractory metastatic bone pain.* Eur J Nucl Med Mol Imaging, 2008 Oct; 35(10): 1934-1940.

**2.** Roqué I Fiquls M, Martinez-Zapata MJ, Scott-Brown, et al. *Radioisotopes for metastatic bone pain.* Cochrane Database Syst Rev, 2011 Jul 6; (7): CD003347.

**3.** Goyal J, Antonarakis ES. *Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases.* Cancer Lett. 2012 Oct 28; 323(2): 135-146.

4.Roqué I Fiquls M, Martinez-Zapata MJ, Scott-Brown, et al. *Radioisotopes for metastatic bone pain.* Cochrane Database Syst Rev, 2011 Jul 6; (7): CD003347.

# Search strategy

The searches were run on 20-07-2015 OVID Medline, OVID Embase, Cochrane (all libraries) were searched. Detailed search strings are given below. The searches were limited to 2008-2015, English and Dutch. Study types: systematic reviews, meta-analysis and RCTs.

# Search results

The Medline search yielded 48 hits, while the search in Embase yielded 58 hits, Cochrane yielded 7 hits.

After merging the search files into one file and removal of the duplicates 108 records were screened on title and abstract. Of these 94 were excluded. The most important reasons for exclusion was that studies were

1. Patient population
2. Intervention

Of the remaining 14 studies, the full text was retrieved. Based on the full text, an additional 10 studies were excluded. Table 4.1 provides an overview of the studies, with the reason for in- or exclusion. In addition the included studies of the Cochrane Review (Roque et al, 2011) were checked on appropriateness in table 4.2

Table 4.1 Full text screening with in-and exclusion criteria

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| 1 | Bilen, M.A., et al., *Randomized phase 2 study of bone-targeted therapy containing strontium-89 in advanced castrate-sensitive prostate cancer.* Cancer, 2015. **121**(1): p. 69-76. | Included | **Design**: RCT**Patient**: castrate-sensitive prostate cancer metastatic to bone**Intervention:** doxorubicin + zoledronic acid + Strontium-89**Control:** doxorubicin + zoledronic acid  |
| 2 | Den, R.B., L.A. Doyle, and K.E. Knudsen, *Practical guide to the use of radium 223 dichloride.* The Canadian journal of urology, 2014. **21**: p. 70-76. | Excluded | Narrative review |
| 3 | Dispenzieri, A., et al., *A Phase II study of (153)Sm-EDTMP and high-dose melphalan as a peripheral blood stem cell conditioning regimen in patients with multiple myeloma.* American Journal of Hematology, 2010. **85**(6): p. 409-13. | Excluded | Solely patients with multiple myeloma are included in this study. |
| 4 | Humm, J.L., et al., *Radium-223 in the treatment of osteoblastic metastases: A critical clinical review.* International Journal of Radiation Oncology Biology Physics, 2015. **91**(5): p. 898-906. | Excluded | Narrative review |
| 5 | James, N.D., et al., *Clinical outcomes in patients with castrate-refractory prostate cancer (CRPC) metastatic to bone randomized in the factorial TRAPEZE trial to docetaxel (D) with strontium-89 (Sr89), zoledronic acid (ZA), neither, or both (ISRCTN 12808747).* Journal of Clinical Oncology, 2013. **1)**. | Excluded | Abstract |
| 6 | Lewis, B. and O. Sartor, *Radiation-based approaches for therapy and palliation of advanced prostate cancer.* Current Opinion in Urology, 2012. **22**(3): p. 183-9. | Excluded | Narrative review |
| 7 | Ma, Y., et al., *Combining Strontium-89 with 99Tc-MDP for treatment of: Painful bone metastases of prostate cancer. [Chinese].* Chinese Journal of Andrology, 2009. **23**(11): p. 23-6. | Excluded | Written in Chinese |
| 8 | Nilsson, S., et al., *Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases.* Clinical Genitourinary Cancer, 2013. **11**(1): p. 20-6. | Included | **Design:** RCT**Patient:** histologically or cytologically confirmed adenocarcinoma of the prostate with multiple bone metastases.**Intervention:** 4 injections of radium-223**Control:** matching placebo injections |
| 9 | Parker, C., et al., *Alpha emitter radium-223 and survival in metastatic prostate cancer.* New England Journal of Medicine, 2013. **369**(3): p. 213-223. | Included | **Design:** RCT**Patient:** histologically confirmed, progressive castration-resistant prostate cancer with two or more bone metastases.**Intervention:** six injections of radium-223**Control:** matching placebo |
| 10 | Parker, C.C., et al., *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**(2): p. 189-97. | Excluded | No control (only different doses) |
| 11 | Porfiri, E., et al., *Initial feasibility and safety results from a phase II/III clinical trial to evaluate docetaxel (D) therapy in combination with zoledronic acid (ZA) +/- strontium-89 (Sr89) in hormone-refractory prostate cancer patients: ISRCTN12808747.* Journal of Clinical Oncology, 2010. **1)**. | Excluded | Abstract |
| 12 | Ren, L.J., B. Li, and X.D. Zhu, *Clinical effect of89SrCl2 combined with zoledronic acid on treatment of multiple osseous metastasis. [Chinese].* Chinese Journal of Cancer Prevention and Treatment, 2010. **17**(19): p. 1584-1585. | Excluded | Written in Chinese |
| 13 | Roque, I.F.M., et al., *Radioisotopes for metastatic bone pain.* Cochrane Database of Systematic Reviews, 2011(7): p. CD003347. | Included | Cochrane review used for this evidence profile. |
| 14 | Seider, M.J., et al., *Randomized phase III trial to evaluate radiopharmaceuticals and zoledronic acid in the palliation of osteoblastic metastases from lung, breast, and prostate cancer: Report of RTOG 0517.* Journal of Clinical Oncology, 2012. **1)**. | Excluded | Abstract |

Table 4.2 Included studies from the Roqué et al. Cochrane review.

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| #1 | Baczyk, M., et al., *89Sr versus 153Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma.* Nucl Med Commun, 2007. **28**(4): p. 245-50. | Included | **Design:** RCT**Patient:** Sixty male patients aged 53–84 years with advanced prostate carcinoma**Intervention:** 89-Sr**Control:** 153Sm-EDTMP |
| #2 | Buchali, K., et al., *Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma.* Eur J Nucl Med, 1988. **14**(7-8): p. 349-51. | Included | **Design:** RCT**Patient:** prostatic carcinoma with multiple skeletal metastasis.**Intervention:** three injections of 89-sr **Control:** placebo |
| #3 | Han, S.H., et al., *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.* J Nucl Med, 2002. **43**(9): p. 1150-6. | Included | **Design:** RCT**Patient:** histologically or cytologically proven prostate cancer with symptomatic bone metastases no longer responding to any medical or surgical endocrine manipulation treatments.**Intervention:** 186Re-etidronate**Control:** placebo |
| #4 | Lewington, V.J., 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**(8): p. 954-8. | Included | **Design:** RCT**Patient:** prostate carcinoma metastatic to bone**Intervention:** strontium-89**Control:** placebo |
| #5 | Maxon, H.R., 3rd, et al., *Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo.* J Nucl Med, 1991. **32**(10): p. 1877-81. | Excluded | Effect of intervention is not stratified among different cancer types. |
| #6 | Nair, N., *Relative efficacy of 32P and 89Sr in palliation in skeletal metastases.* J Nucl Med, 1999. **40**(2): p. 256-61. | Excluded | Effect of intervention is not stratified among different cancer types. |
| #7 | Nilsson, S., et al., *Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study.* Lancet Oncol, 2007. **8**(7): p. 587-94. | Excluded | Effect of intervention is not stratified among different cancer types. |
| #8 | Palmedo, H., 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**(15): p. 2869-75. | Excluded | No control (only different doses) |
| #9 | Porter, A.T. and A.J. McEwan, *Strontium-89 as an adjuvant to external beam radiation improves pain relief and delays disease progression in advanced prostate cancer: results of a randomized controlled trial.* Semin Oncol, 1993. **20**(3 Suppl 2): p. 38-43. | Included | **Design:** RCT**Patient:** prostate cancer with increasing pain requiring radiotherapy and a worsening bone scan.**Intervention:** 89Sr 10,8 mCi monodose iv + Radiotherapy**Control:** Placebo + Radiotherapy |
| #10 | Resche, I., et al., *A dose-controlled study of 153Sm-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases.* Eur J Cancer, 1997. **33**(10): p. 1583-91. | Excluded | No control (only different doses) |
| #11 | Sartor, O., et al., *Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer.* Urology, 2004. **63**(5): p. 940-5. | Included | **Design:** RCT**Patient:** Patients with prostate carcinoma progression**Intervention:** 153Sm-lexidronam**Control:** placebo with nonradioactive samarium-152 |
| #12 | Sciuto, R., et al., *Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients.* Breast Cancer Res Treat, 2001. **66**(2): p. 101-9. | Excluded | Solely patients included that have metastasis from breast cancer. |
| #13 | Serafini, A.N., et al., *Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial.* J Clin Oncol, 1998. **16**(4): p. 1574-81. | Excluded | Effect of intervention is not stratified among different cancer types. |
| #14 | Smeland, S., et al., *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**(5): p. 1397-404. | Excluded | Effect of intervention is not stratified among different cancer types. |
| #15 | Tian, J.H., 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**(1): p. 2-7. | Excluded | No control (only different doses) |

# **Appendix**

# **Search strategies**

**MEDLINE via OVID**

1. exp Bone Neoplasms/sc [Secondary]

2. exp Neoplasm Metastasis/

3. exp “Bone and Bones”/

4. 2 and 3

5. (bone$ adj10 metasta$).mp.

6. 1 or 4 or 5

7. PAIN, INTRACTABLE/ or PAIN/

8. Palliative Care/

9. complicat$.ti,ab.

10. complications.hw.

11. hypercalcemia/

12. hypercalc$.ti,ab.

13. BONE FRACTURES/

14. fractur$.ti,ab.

15. SPINAL CORD COMPRESSION/

16. spin$ compression.ti,ab.

17. NERVE COMPRESSION SYNDROMES/

18. radicular compres$.ti,ab.

19. or/7-18

20. exp RADIOISOTOPES/

21. (radionucleotide$ or radionuclide$ or radioisotope$).ti,ab.

22. (strontium or samarium or rhenium).ti,ab.

23. or/20-22

24. 6 and 19 and 23

25. randomized controlled trial.pt.

26. controlled clinical trial.pt.

27. randomized.ab.

28. placebo.ab.

29. drug therapy.fs.

30. randomly.ab.

31. trial.ab.

32. groups.ab.

33. or/25-32

34. humans.sh.

35. 33 and 34

36. 24 and 35

**EMBASE via OVID**

1. Bone Metastasis/

2. osseous metasta$.mp.

3. (bone$ adj6 metasta$).ti,ab.

4. or/1-3

5. exp Palliative Therapy/

6. complication.hw.

7. complicat$.ti,ab.

8. hypercalcaemia/

9. (hypercalcaemia or hypercalcaemia).mp.

10. exp FRACTURE/

11. fractur$.ti,ab.

12. Spinal Cord Compression/

13. spin$ cord compress$.ti,ab.

14. Nerve Root Compression/

15. radicular compress$.mp. or nerve compress$.ti,ab. or nerve-root-compress$.mp.

16. exp PAIN/

17. pain$.ti,ab.

18. or/5-17

19. exp Radioisotope/

20. radioisotope$.mp. or radionucleotide$.ti,ab. or radionuclide$.ti,ab.

21. (samarium or strontium).ti,ab.

22. rhenium.ti,ab.

23. or/19-22

24. 4 and 18 and 23

25. random$.ti,ab.

26. factorial$.ti,ab.

27. (crossover$ or cross over$ or cross-over$).ti,ab.

28. placebo$.ti,ab.

29. (doubl$ adj blind$).ti,ab.

30. (singl$ adj blind$).ti,ab.

31. assign$.ti,ab.

32. allocat$.ti,ab.

33. volunteer$.ti,ab.

34. CROSSOVER PROCEDURE.sh.

35. DOUBLE-BLIND PROCEDURE.sh.

36. RANDOMIZED CONTROLLED TRIAL.sh.

37. SINGLE BLIND PROCEDURE.sh.

38. or/25-37

39. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/

40. HUMAN/

41. 40 and 39

42. 39 not 41

43. 38 not 42

44. 24 and 43

**Cochrane**

1. Exp BONE NEOPLASMS sc

2. Exp NEOPLASM METASTASIS

3. Exp BONE AND BONES

4. #2 AND #3

5. (osseous metasta\* or (bone\* near metasta\*))

6. #1 OR #4 OR #5

7. PALLIATIVE CARE (Single term MeSH)

8. Exp PAIN

9. (complicat\*:ti or complicat\*:ab)

10. hypercalcaemia (Single term MeSH)

11. (hypercalcaemia or hypercalcaemia)

12. Exp BONE FRACTURES (Changed from FRACTURES)

13. (fractur\*:ti or fractur:ab)

14. SPINAL CORD COMPRESSION (Single term MeSH)

15. ((spin\*:ti next cord:ti next compress\*:ti) or (spin\*:ab next cord:ab next compress\*:ab))

16. Exp NERVE COMPRESSION SYNDROMES

17. ((nerve near compress\*:ti) or (nerve near compress\*:ab) or (radicular:ti next compress\*:ti) or (radicular:ab next compress\*:ab))

18. (pain\*:ti or pain\*:ab)

19. (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)

20. Exp RADIOISOTOPES

21. (radionucleotide\*:ti or radionucleotide\*:ab or radionuclide\*:ti or radionuclide\*:ab)

22. (samarium:ti or samarium:ab or strontium:ti or strontium:ab or rhenium:ti or rhenium:ab)

23. (#20 or #21 or #22)

24. (#6 and #19 and #23)