**RL Prostaat PICO 4**

Uitgangsvraag:

Welke behandeling is geïndiceerd voor pijnlijke bot metastasen 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-186-HEDP, Radium-223)

C Geen behandeling of een (of meer) van de andere radionucliden behandelingen

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

**A 89 Strontium vs placebo**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| * Bilen et al, 2015[[1](#_ENREF_1)]
 | * Design: RCT
* Some authors have conflicts of interest from the pharmaceutical company
* Setting: MD Anderson Cancer Center, Houston, USA
* Sample size: 79
* Median follow-up: 76.9 months
* No existence of protocol reported
 | **Eligibility criteria:**Castrate-sensitive prostate cancer metastatic to bone; **Patient characteristics:**Median age: 63 (range: 46-82), previously surgery only: 63%. | 89 Strontium(4-mCL total dose x1) (N = 39)versusPlacebo (N = 40) | **Relief of pain**Not reported**Quality of Life**Not reported**Toxicity**Total of adverse events (grade 3 / 4)89Sr: 19/39Placebo: 13/40RR= 1.50 95%CI 0.86-2.6 \***Duration of response**Not reported | * Unclear risk (due to no description of randomisation, allocation concealment, blinding, and no protocol).
 |
| * Buchali et al, 1988[[2](#_ENREF_2)] ¥
 | * Design: RCT
* No conflicts of interest reported
* No information about the setting is reported.
* Sample size: 49
* Follow up: 2 years.
* No existence of protocol reported.
 | * **Eligibility criteria:**

prostatic carcinoma with multiple skeletal metastases **Patient characteristics:**Mean age: 67.4 (SD: 10.0) vs 66.5 (SD: 6.9)Extension of metastases: 2.16 vs 2.50, No statistically significant different characteristics between the two groups | 89 Strontium3 injections of 75 MBq (N = 25)versusPlacebo (N = 24) | **Relief of pain at 1-3 years after treatment**89Sr : 7/19Placebo: 11/22P= n.s.**Quality of life**Not reported**Toxicity**Not reported**Duration of response**Not reported | * Unclear risk (due to no description of randomisation, allocation concealment, incomplete outcome data, blinding, and no protocol).
 |
| * Lewington et al, 1991[[3](#_ENREF_3)] ¥
 | * Design: RCT crossover
* No conflicts of interest reported.
* Setting: seven hospitals, UK
* Sample size: 32 patients
* Follow up: 5 weeks.
* No existence of protocol reported.
 | * **Eligibility criteria:** prostate carcinoma with bone metastasis

**Patient characteristcs:** Aged 64-79 years  |  89 Strontium150 MBq (N = 15)versusPlacebo (N = 17)  | **Relief of pain 5 weeks after treatment**89Sr : 4/12Placebo: 1/14Significant (no p-value reported) **Quality of life**Not reported**Toxicity:**Not reported per group.**Duration of response**Not reported | * Low risk
 |
| * Porter et al, 1993 ¥ (Seminar in oncology)[[4](#_ENREF_4)]
* Porter et al, 1993 ¥ (Int J Rad Oncol Biol Phy)[[5](#_ENREF_5)]
 | * Design: RCT
* No conflicts of interest reported
* Setting: eight independent cancer treatment facilities in Canada.
* Sample size: 126
* Follow up: 6 months.
* No existence of protocol reported.
 | * **Eligibitlity criteria:** prostate cancer with multiple bone metastases

**Patient characteristics:**. Median age: 71.5 vs 71.0, mean baseline pain score 11.3 vs 10.0 | 89 Strontium 10.8 mCi in 11 ml(n=68)versus Placebo (n=58)  | **Relief of pain**Overall treatment success (reduced pain score in the absence of increased analgesic use or additional radiotherapy)89Sr : 70%Placebo: 55%**Quality of life**Multivariate analysis of all questionnaires, p= 0.006 n favour of strontium-89.**Toxicity:**White blood cells (grade III or IV)8 (11.9%) vs 0 (RR: 13.2, 95%-CI: 0.8 to 224.1)Platelets (grade III or IV)22(32.8%) vs 2 (3.4%) RR=9.5 (95% CI 2.4-38.8)**Duration of response**Not reported | * High risk of bias because of not giving reasons for patients lost to follow-up.
 |
| ¥ Data was copied and adapted from Roqué et al. 2011. [[6](#_ENREF_6)] |

n.s. not significant, RCT randomized controlled trial, \* self calculated

**B 89 Strontium vs 153 Samarium**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| * Baczyk et al, 2007[[7](#_ENREF_7)] ¥
 | * Design: RCT
* No conflicts of interest reported
* No information regarding the setting reported.
* Sample size: 60
* Duration of follow up: 2 months.
* No existence of protocol reported.
 | * **Eligibility criteria:**

Advanced prostate carcinoma, metastatic bone lesions* **Patient characteristics**:

Age range 53-84.. | 89 Strontium150 MBq(N = 30)versus153Sm- EDTMP37 MBq/kg of body mass. (N = 30) | **Reduction of pain**2 months after therapy: pain-relief complete effect (VAS < 2):89-SR: 10/30 (33%)153-SM: 12/30 (40%)RR: 0.93 (95%-CI: 0.43 – 1.63).Median change (range) of pain intensity (baseline to 2 months after therapy) VAS scale (0-10) 89-SR: -4 (-8 to +2)153-SM: -4 (-7 to +1)**Quality of life**Not reported**Toxicity**Results not stratified between prostate and breast cancer.**Duration of response**Not reported | * Unclear risk (due to no description of randomisation, allocation concealment, blinding, and no protocol).
 |
| ¥ Data was copied and adapted from Roqué et al. 2011. [[6](#_ENREF_6)] |

VAS visual analogue scale

**C 186 Rhenium vs placebo**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| * Han et al, 2002[[8](#_ENREF_8)] ¥ [Pacorhen study]
 | * Design: RCT
* No conflicts of interest reported
* Setting: University Medical Center Utrecht, the Netherlands
* Sample size: 131
* Aug 1993- Sept 199
* Follow up: 12 weeks.
* No existence of protocol reported.
 | * **Eligibility criteria:** prostate cancer with symptomatic bone metastases
* **Patient characteristics**

Mean age: 70.0 (SD: 8.3) vs 69.2 (SD: 7.4). | 186Rhenium  (N = 66)versusPlacebo(N = 65) | **Relief of Pain (response days ≥ 5)** Rhenium 28/43 (65%)Placebo 13/36 (36%)RR=1.80 (95% CI 1.1-2.9) p=0.01**Quality of life**not reported**Toxicity**not reported**Duration of response:** Not reported | * Unclear risk of bias due to no identification of a protocol. High percentage of patients with incomplete data
 |

|  |
| --- |
| ¥ Data was copied and adapted from Roqué et al. 2011. [[6](#_ENREF_6)] |

SD standard deviation, RCT randomised controlled trial

**D 223 Radium vs placebo**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| * Nilsson et al, 2007[[9](#_ENREF_9)] ¥
* Nilsson et al, 2013[[10](#_ENREF_10)]
 | * Design: RCT
* Several conflicts of interest by pharmaceutical companies reported.
* Setting: 11 centres in Sweden, Norway, and the UK.
* Sample size: 64 patients
* Follow up: 4 months
* No existence of protocol reported.
 | * **Eligibility criteria:** Adenocarcinoma of the prostate; multiple bone metastases or one painful lesion.
* **Patient characteristics:**

Mean age: 73 (57-88) vs 72 (60-84), ECOG performance status: 0: 15/64; 38/64; 11/64. | 223RadiumFour repeated monthly injections of 50 kBq/kg (n=33)versusPlacebo (n=31) | **Relief of pain**not reported**Quality of life**not reported**Toxicity****Haematological AEs: grade 3-4[**[**10**](#_ENREF_10)**]**Radium-group: 3/33Placebo: 2/31RR= 1.29 (95% CI 0.23-7.24)\* **Serious AEs[**[**10**](#_ENREF_10)**]** Radium-group: 8/33Placebo: 14/31RR= 0.52 (95%CI 0.25-1.06)\* **Duration of response:**Not reported | * Unclear risk since blinding of outcome assessment was not described
 |
| * Parker et al, 2013[[11](#_ENREF_11)]

**ALSYMPCA** | * Design: RCT
* Some conflicts of interests are reported and some have some pharmaceutical conflicts.
* Setting: 136 study centers in 19 countries
* Sample size: 921 patients
* Follow-up: 3 years
* ClinicalTrials.gov number: NCT00699751
 | * **Eligibility criteria:** castration-resistant prostate cancer with two or more bone
* **Patient characteristics:** .

Age median: 71 (49-90) vs 71 ( 44-94), ECOG performance status %: 0: 27% vs 25%, 1: 60% vs 61%, ≥ 2: 13% vs 13%. | 223Radium(N=614)versusPlacebo (n=307) | **Relief of pain**not reported**Quality of life (mean change in score FACT-P from baseline to week 16)**Increase in the score of ≥10 points on a scale of 0 to 156 with higher scores indicating a better overall quality of life) 223Radium: -2.7Placebo: -6.8p=0.006**Quality of life (FACT-P during the period of study-drug administration)**Increase in the score of ≥10 points on a scale of 0 to 156 with higher scores indicating a better overall quality of life) 223Radium: 25% Placebo: 16%p=0.02**Toxicity**:Adverse events (grade III or IV)223Radium: 339/600 (56%)placebo: 188/301 (62%)p>0.05**Duration of response:**Not reported | * Low risk
 |
| ¥ Data was copied and adapted from Roqué et al. 2011. [[6](#_ENREF_6)] |

AE adverse event, FACT-P Functional Assessment of Cancer Therapy-Prostate, RCT randomised controlled trial, \* Self calculated

**E 153 Samarium vs placebo**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| * Sartor et al, 2004[[12](#_ENREF_12)] ¥
 | * Design: RCT
* No conflicts of interest reported
* No information regarding the setting reported
* Sample size: 152
* Follow-up: 16 weeks.
* No existence of protocol reported.
 | * **Eligibility criteria:** Hormone-refractory prostate carcinoma with positive bone scan
* **Patient characteristics**

Median age: 70(50-87) vs 70 (46-86). | 153 Samarium (n= 101)versusPlacebo (n=51) | **Relief of pain (complete responders):****153**Samarium 38/101 (38%)Placebo 9/51 (18%)RR= 2.13 (95% CI 1.12-4.06) p=0.008**Quality of life****n**ot reported**Toxicity****Hemoglobin toxicity (grade III and IV)**153Samarium: 11/93 (12%)Placebo: 6/47 (13%)RR=0.93 (95% CI 0.37-2.35)**Platelets toxicity (grade III and IV)**153Samarium: 3/93 (3%)Placebo: 0/47 (0%)RR=3.5 (95%-CI: 0.2 - 65.7)**White blood cells toxicity (grade III and IV)**153Sararium: 5/93 (5%)Placebo: 0/47 (0%)RR=5.3 (95%-CI: 0.3 to 94.5)**Duration of response:**Not reported | * High risk of bias because of a non-blinded outcome assessor.
 |
| ¥ Data was copied and adapted from Roqué et al. 2011. [[6](#_ENREF_6)] |

AE adverse event, RCT randomised controlled trial

References

[1] Bilen MA, Johnson MM, Mathew P, Pagliaro LC, Araujo JC, Aparicio A, et al. Randomized phase 2 study of bone-targeted therapy containing strontium-89 in advanced castrate-sensitive prostate cancer. Cancer. 2015; 121: 69-76. <http://dx.doi.org/10.1002/cncr.28971>.

[2] 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. Eur J Nucl Med. 1988; 14: 349-51.

[3] 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.

[4] Porter AT, McEwan AJ. 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: 38-43.

[5] Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, 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. Int J Radiat Oncol Biol Phys. 1993; 25: 805-13.

[6] Roque IFM, Martinez-Zapata MJ, Scott-Brown M, Alonso-Coello P. Radioisotopes for metastatic bone pain. Cochrane Database Syst Rev. 2011; CD003347. <http://dx.doi.org/10.1002/14651858.CD003347.pub2>.

[7] Baczyk M, Czepczynski R, Milecki P, Pisarek M, Oleksa R, Sowinski J. 89Sr versus 153Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. Nucl Med Commun. 2007; 28: 245-50. 10.1097/MNM.0b013e32805b72a0.

[8] Han SH, de Klerk JM, Tan S, van het Schip AD, Derksen BH, van Dijk A, 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. Journal of nuclear medicine. 2002; 43: 1150-6.

[9] Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol. 2007; 8: 587-94. 10.1016/s1470-2045(07)70147-x.

[10] Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, 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. Clin Genitourin Cancer. 2013; 11: 20-6. <http://dx.doi.org/10.1016/j.clgc.2012.07.002>.

[11] Parker C, Nilsson DHS, Helle SI, O'Sullivan JM, Fossa SD, Chodacki A, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. New England Journal of Medicine. 2013; 369: 213-23. <http://dx.doi.org/10.1056/NEJMoa1213755>.

[12] 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. 10.1016/j.urology.2004.01.034.