**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**

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| **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)  versus  Placebo (N = 40) | **Relief of pain**  Not reported  **Quality of Life**  Not reported  **Toxicity**  Total of adverse events (grade 3 / 4)  89Sr: 19/39  Placebo: 13/40  RR= 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 Strontium  3 injections of 75 MBq (N = 25)  versus  Placebo (N = 24) | **Relief of pain at 1-3 years after treatment**  89Sr : 7/19  Placebo: 11/22  P= 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 Strontium  150 MBq  (N = 15)  versus  Placebo (N = 17) | **Relief of pain 5 weeks after treatment**  89Sr : 4/12  Placebo: 1/14  Significant (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**

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| **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 Strontium  150 MBq  (N = 30)  versus  153Sm- EDTMP  37 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**

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| **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)  versus  Placebo  (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 |

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| ¥ 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**

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| **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. | 223Radium  Four repeated monthly injections of 50 kBq/kg  (n=33)  versus  Placebo (n=31) | **Relief of pain**  not reported  **Quality of life**  not reported  **Toxicity**  **Haematological AEs: grade 3-4[**[**10**](#_ENREF_10)**]**  Radium-group: 3/33  Placebo: 2/31  RR= 1.29 (95% CI 0.23-7.24)\*  **Serious AEs[**[**10**](#_ENREF_10)**]**  Radium-group: 8/33  Placebo: 14/31  RR= 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)  versus  Placebo (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: -2.7  Placebo: -6.8  p=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**

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| **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)  versus  Placebo (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

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