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ORIGINAL RESEARCH

# Comparative efficacy, tolerability, and survival outcomes of various radiopharmaceuticals in castration-resistant prostate cancer with bone metastasis: a meta-analysis of randomized controlled trials

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Mutahir Tunio[1]
Mushabbab Al Asiri[1]
Abdulrehman Al Hadab[1]
Yasser Bayoumi[2]

[1]Radiation Oncology, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia; [2]Radiation Oncology, National Cancer Institute, Cairo University, Cairo, Egypt

**Background:** A meta-analysis was conducted to assess the impact of radiopharmaceuticals (RPs) in castration-resistant prostate cancer (CRPC) on pain control, symptomatic skeletal events (SSEs), toxicity profile, quality of life (QoL), and overall survival (OS).

**Materials and methods:** The PubMed/MEDLINE, CANCERLIT, EMBASE, Cochrane Library database, and other search engines were searched to identify randomized controlled trials (RCTs) comparing RPs with control (placebo or radiation therapy) in metastatic CRPC. Data were extracted and assessed for the risk of bias (Cochrane's risk of bias tool). Pooled data were expressed as odds ratio (OR), with 95% confidence intervals (CIs; Mantel–Haenszel fixed-effects model).

**Results:** Eight RCTs with a total patient population of 1,877 patients were identified. The use of RP was associated with significant reduction in pain intensity and SSE (OR: 0.63, 95% CI: 0.51–0.78, $I^2$=27%, $P$<0.0001), improved QoL (OR: 0.71, 95% CI: 0.55–0.91, $I^2$=65%, three trials, 1,178 patients, $P$=0.006), and a minimal improved OS (OR: 0.84, 95% CI: 0.64–1.04, $I^2$=47%, seven trials, 1,845 patients, $P$=0.11). A subgroup analysis suggested an improved OS with radium-223 (OR: 0.68, 95% CI: 0.51–0.90, one trial, 921 patients) and strontium-89 (OR: 0.21, 95% CI: 0.05–0.91, one trial, 49 patients). Strontium-89 (five trials) was associated with increased rates of grade 3 and 4 thrombocytopenia (OR: 4.26, 95% CI: 2.22–8.18, $P$=0.01), leucopenia (OR: 7.98, 95% CI: 1.82–34.95, $P$=0.02), pain flare (OR: 6.82, 95% CI: 3.42–13.55, $P$=0.04), and emesis (OR: 3.61, 95% CI: 1.76–7.40, $P$=0.02).

**Conclusion:** The use of RPs was associated with significant reduction in SSEs and improved QoL, while the radium-223-related OS benefit warrants further large, RCTs in docetaxel naive metastatic CRPC patients.

**Keywords:** radiopharmaceuticals, castration-resistant prostate cancer, meta-analysis, pain control, symptomatic skeletal events, quality of life, overall survival

## Introduction

Bone metastasis is a source of significant pain, functional disability, and poor quality of life (QoL) in patients with metastatic castration-resistant prostate cancer (CRPC). Systemic chemotherapy, bisphosphonates, and radiation therapy (RT) are the effective measures of palliating symptoms associated with bone metastasis.[1,2] RT in the form of radiopharmaceuticals (RPs) has also been utilized to allow the targeted delivery of

Correspondence: Mutahir Tunio
Radiation Oncology, Comprehensive Cancer Center, King Fahad Medical City, Khurais Road, Riyadh 5046, Saudi Arabia
Tel +966 11 288 9999
Fax +966 11 461 4006
Email mkhairuddin@kfmc.med.sa

RT to multiple sites of metastatic disease, with evidence of significant palliative relief.[3]

Traditionally, beta (β)-emitting RPs (strontium-89 and samarium-153) have been widely used to control bone pain in CRPC, with pain response rates of 70%–80%; however, most of the published trials were underpowered to detect any overall survival (OS) benefit.[4,5] Recently, alpha (α)-emitting RP agent, radium-223, has demonstrated a significant improvement in pain control, minimal toxicity, and OS benefit in patients with metastatic CRPC.[6,7] However, there are limited data regarding the head-to-head comparisons between various RPs in metastatic CRPC patients to determine their relative efficacy, tolerability in pain palliation, and OS benefit.[8,9] We undertook the present meta-analysis with the aim of determining the comparative efficacy, symptomatic skeletal event (SSE) control rates, functional mobility and QoL, OS, and toxicity profile of various RPs in CRPC patients with bone metastasis.

## Materials and methods

The search criteria included the studies that were either complete randomized controlled trials (RCTs) or retrospective, if these were well controlled. The abstracts with full details were also included. The PubMed/MEDLINE, CANCERLIT, EMBASE, and Cochrane Library databases were searched using the terms castration-resistant prostate cancer, hormone-refractory prostate cancer, radiopharmaceuticals (strontium-89, samarium-153, rhenium-186, and radium-223), bone metastasis, and bone pain. These terms were then combined to search for randomized controlled reviews and meta-analyses. The relevant articles were retrieved by two reviewers. Any discrepancies between the reviewers were resolved through consensus. Then, only RCTs which met the following criteria were included:

- CRPC patients with confirmed bone metastasis.
- Patients had received RPs as part of bone pain management.
- The studies that included patients with other primary malignancies were excluded.

### Outcome measures

The outcome measures were reductions in pain intensity and SSE, functional mobility and QoL, OS, and toxicity profile of the different RPs used. We hypothesized SSE as "increase in bone pain ≥50% from baseline, increase in analgesics ≥25%, worsening of daily activities of life ≥25%, new sites of bone pain, pathological bone fracture, and first request for additional RT".

### Quality assessment

The internal validity of included RCTs was evaluated using the Cochrane Risk of Bias tool, which consists of the following six domains: 1) selection bias (random sequence generation and allocation concealment), 2) performance bias (blinding of patients/participants), 3) detection bias (blinding of outcome assessment), 4) attrition bias (incomplete outcome data), 5) reporting bias, and 6) other sources of bias. Each separate domain was rated according to a "low", "unclear", or "high" risk of bias.[10] A trial was finally rated as "low risk of bias" (all six domains rated as low risk), "high risk of bias" (one or more domains rated as high risk), and "unclear risk of bias".

### Review analysis

All analyses were carried out on an intention-to-treat analysis basis. For the categorical variables, weighted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using the Review Manager (RevMan) software application, Version 5.3, provided by the Cochrane Collaboration (part of the meta-analytic software program Metaview: Update Software, Oxford, UK). The results were tested for heterogeneity ($I^2$) at the significant level of $P<0.05$. If there was an evidence of heterogeneity ($I^2>50\%$), a random effects model was used for meta-analysis; otherwise, a fixed effects model was used. OR and 95% CI were calculated for each trial and presented in a forest plot. The publication bias was evaluated using the funnel graph, the Begg–Mazumdar-adjusted rank correlation test,[11] and the Egger test.[12] For heterogeneity, we carried out the Cochran's $Q$-test to determine whether the studies are homogenous.

The study was exempt from Institutional ethics Committee approval.

## Results

### Yield of search strategy and characteristics of eligible studies

An electronic search revealed 1,241 relevant citations. After screening, 58 full-text articles were retrieved for further assessment. Finally, eight studies that met the criteria were identified (Figure 1); the total population of patients involved in these studies was 1,877. The details of included studies are shown in Tables 1 and 2.[6,7,13–19] The studies were conducted in several countries. RCTs were published between 1988 and 2013; 75% were multicenter trials. All RCTs included metastatic CRPC patients with bone metastasis. All RCT studies reported on pain control and SSE; while seven RCTs reported OS and toxicity, and the QoL was reported in three

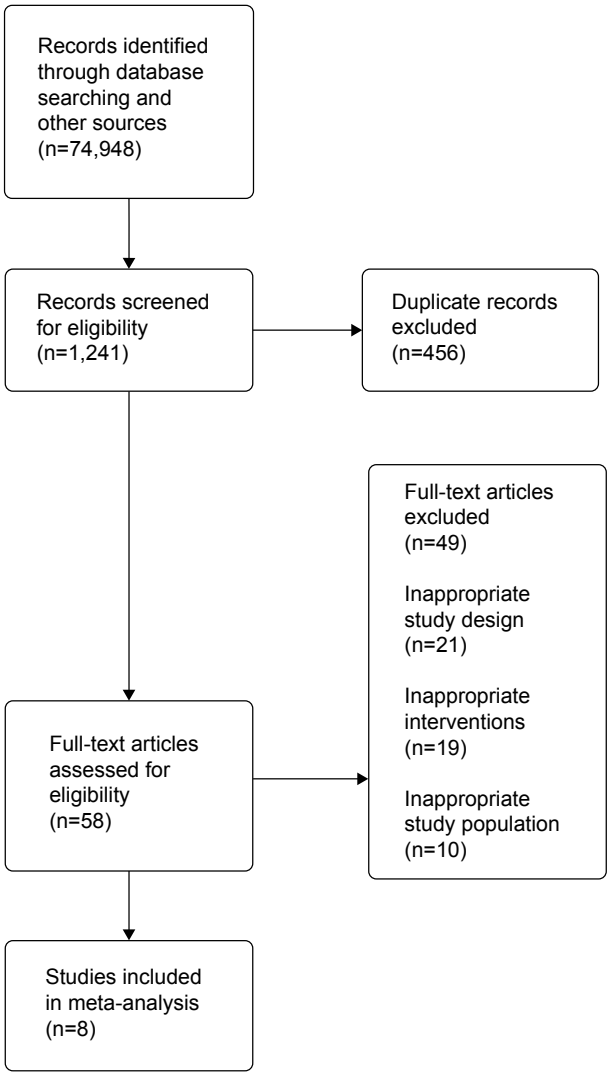


**Figure 1** Study flow diagram.

RCTs. Four RCTs (50%) were rated to be in "high risk" of bias, two trials (25%) were considered to be in "low risk", and two trials (25%) were classified as "unclear" with respect to the risk of bias (Figure 2).

## SSE control rate

All eight RCTs with a population of 1,877 patients analyzed the SSE rate as one of the outcomes. The SSE rate was significantly low in patients treated with RPs ($P<0.0001$). The pooled OR was 0.63 (95% CI: 0.51–0.78, $I^2=27\%$). The result of the test for heterogeneity was not statistically significant ($I^2=27\%$). The overall benefit from RPs and control groups on pain intensity and symptomatic skeletal events is shown in Figure 3.

## Functional mobility and QoL

Three RCTs with 1,178 patients examined the QoL as one of the outcomes. The overall functional mobility and QoL were significantly improved in patients treated with RPs ($P=0.006$). The pooled OR was 0.71 (95% CI: 0.55–0.91, $I^2=65\%$) as shown in Figure 4.

## Overall survival

Seven RCTs, with 1,845 patients, addressed the OS as one of the outcomes. Two RCTs showed a significant improvement in the OS; five RCTs showed no difference and one RCT showed better survival in the control arm. The pooled OR was not statistically different between the RPs and control arms (0.84, 95% CI: 0.64–1.04, $I^2=47\%$, $P=0.11$; Figure 5).

## Toxicity

Strontium-89 was used in five RCTs and samarium-153, rhenium-186, and radium-223 were used in the remaining three RCTs. Grade 3 and 4 hematological adverse events (thrombocytopenia and leucopenia) and nonhematological event (pain flare and emesis) toxicities were significantly high with strontium-89, whereas radium-223 was associated with the least grade ≥3 toxicity as shown in Table 3.

## Publication bias

The funnel plot revealed a narrow funnel (Figure 6) showing no significant publication bias (*P*-values from the Begg–Mazumdar test and Egger test were 0.21 and 0.11, respectively).

# Discussion

Despite an initial response after the androgen deprivation therapy, most prostate patients ultimately suffer disease progression, developing CRPC. Recently, in CRPC patients, the use of second-generation androgen receptor blocking agents, particularly, the cytochrome P450 17 inhibitor abiraterone acetate and the novel antiandrogen enzalutamide have shown an improved OS and QoL in the pre- and postdocetaxel setting.[20] Although several RPs with different physical properties have been used for the treatment of CRPC with bone metastasis; strontium-89 (Metastron; GE Healthcare), samarium-153 (Quadramet; GE Health Care and Dow Chemical Co, USA), and radium-223 (Xofigo; Bayer AG, Leverkusen, Germany) are currently approved in USA and many European countries.[21] In the present meta-analysis, we found that the different RPs (strontium-89, samarium-153, rhenium-186, and radium-223) administered to metastatic CRPC patients were associated with significant pain relief, reduction in SSE, improved functional mobility, and QoL. In RCTs incorporating strontium-89, reductions in pain

**Table 1** Characteristics of included studies

| Study/publication date | RCT type/country | Number of patients (RP/control) | RP type/dose | Control group | Primary outcome | Secondary outcomes | Follow-up |
|---|---|---|---|---|---|---|---|
| Porter et al[13] (1993) | Multicenter/UK, Canada | 126 (68/58) | Strontium-89 400 MBq (10.8 mCi) single injection | Local RT<br>30 Gy/10 Fr<br>20 Gy/5 Fr<br>10 Gy/1 Fr | Symptomatic skeletal event | OS, efficacy, toxicity, QoL | 15 months |
| Buchali et al[14] (1988) | Single center/Germany | 49 (25/24) | Strontium-89 75 MBq q 4 weeks (three injections) | Placebo (isotonic sterile saline) | Symptomatic skeletal event | OS, toxicity | 36 months |
| Quilty et al[15] (1994) | Multicenter/UK | 305 (153/152) | Strontium-89 200 MBq (5.4 mCi) single injection | 1. Local RT<br>20 Gy/5 Fr<br>8 Gy/1 Fr<br>2. Hemibody RT<br>6 Gy/1 Fr<br>8 Gy/1 Fr | Symptomatic skeletal event | OS, toxicity, new pain sites | 27.5 months |
| Oosterhof et al[16] (2003) | Multicenter/the Netherlands, UK, Denmark, Belgium | 203 (101/102) | Strontium-89 150 MBq (4 mCi) single injection | Local RT<br>20 Gy/5 Fr<br>4 Gy/1 Fr<br>43/24 Fr | Symptomatic skeletal event | OS, economic costs | 66 months |
| Lewington et al[17] (1991) | Multicenter/UK, Canada | 32 (18/14) | Strontium-89 150 MBq (4 mCi) q 6 weeks × two injections | Placebo (nonradioactive strontium-88) | Symptomatic skeletal event | Safety | 3 months |
| Sartor et al[18] (2004) | Multicenter/UK, USA, France | 152 (101/51) | Samarium-153 1 mCi/kg single injection | Placebo (nonradioactive samarium-152) | Symptomatic skeletal event | OS, change in opioid use, safety | 3 months |
| Han et al[19] (2002) | Single center/the Netherlands | 131 (66/65) | Rhenium-186 1,295–2,960 MBq (35–80 mCi) single injection | Placebo (isotonic sterile saline) | Symptomatic skeletal event | OS, efficacy, QoL | 3.3 months |
| Parker et al;[6] Sartor et al[7] (2013) | Multicenter/UK, Norway, Sweden, Germany, USA, Poland, Czech Republic, Brazil, Slovakia | 921 (614/307) | Radium-223 50 kBq/kg q 4 weeks × six injections | Best standard care (local RT, corticosteroids, antiandrogens, ketoconazole, or estrogens) | OS | Symptomatic skeletal event, alkaline phosphatase response, efficacy, safety, QoL | 36 months |

**Abbreviations:** RCT, randomized controlled trial; RP, radiopharmaceutical; RT, radiation therapy; Fr, fraction; OS, overall survival; QoL, quality of life; q, every.

**Table 2** Inclusion and exclusion criteria of included studies

| Study | Mean age, years (range) | Inclusion criteria | Exclusion criteria | Number of skeletal metastasis (n) | Previous treatment (n) | Definition of symptomatic skeletal event |
|---|---|---|---|---|---|---|
| Porter et al[13] | 71.3 (48–86) | CRPC, symptomatic skeletal metastasis, life expectancy >3 months, intense pain requiring local RT to ≥2 treatment volumes | Soft tissue and visceral metastasis, patients refused informed consent | NM | Medical or surgical endocrine therapy | First use of RT to the painful index (initial) site and the subsequent (other) site, progression of bone pain ≥50% from the baseline, increase in analgesics ≥50% |
| Buchali et al[14] | NM | CRPC, symptomatic skeletal metastasis | NM | 1. <2 (12)<br>2. >2 (37) | Medical or surgical endocrine therapy | Increase in pain (not specified), increase in analgesics, and progression on bone |
| Quilty et al[15] | 69 (40–87) | CRPC, symptomatic skeletal metastasis, life expectancy >3 months | Risk of pathological bone fracture, SCC, taking calcium supplements, urinary incontinence | NM | Medical or surgical endocrine therapy | Increase in pain at one site (−1) or at multiple sites (−2) on a (−2, −1, 0, +1, and +2) scoring system |
| Oosterhof et al[16] | 70.8 (42.9–89.3) | CRPC, symptomatic skeletal metastasis, WHO performance status 0–2 | Second primary tumor, previous HT within 3 months, urinary incontinence, calcium supplements, severe renal dysfunction, SCC | 1. <10 (102)<br>2. >10 (101) | Medical or surgical endocrine therapy | Increase in bone pain ≥50% from the baseline, increase in analgesics ≥25%, worsening of DAL ≥25%, and first request for an additional RT |
| Lewington et al[17] | 71.5 (64–79) | CRPC, symptomatic skeletal metastasis, increase in daily narcotic analgesics | Currently on RT, age >80 years, unable to complete consent form, KPS <50 | NM | Medical or surgical endocrine therapy | Increase in pain at one site (−1) or at multiple sites (−2) on a (−2, −1, 0, +1, and +2) scoring system |
| Sartor et al[18] | 70 (46–87) | CRPC, symptomatic skeletal metastasis, pain score >30 mm on 100 mm pain intensity VAS, use of daily morphine ≈60 mg, KPS >50, life expectancy >4 months | Local RT within 6 weeks, change in HT within 8 weeks, pathological bone fracture, SCC, hemibody RT, prior RP, or bisphosphonates within 6 months | 1. <6 (26)<br>2. 6–10 (22)<br>3. >10 (113) | Medical or surgical endocrine therapy, chemotherapy (39), bisphosphonates | Increase in pain >30 mm on 100 pain intensity VAS, strong pain on PDS, daily morphine need ≈60 mg, and first use of RT |
| Han et al[19] | 69.6 (61.8–78.3) | CRPC, symptomatic skeletal metastasis, KPS ≥60, life expectancy >3 months | Brain metastasis, SCC, impending bone fracture, heart failure (AHA III/IV), severe arrhythmia, complete BBB, active infection, bisphosphonates within 3 weeks, and change/stop HT within 2 weeks | 4 and above (131) | Medical or surgical endocrine therapy | Increase in bone pain ≥25% from the baseline, increase in analgesics ≥25%, worsening of ADL ≥25%, and first request for additional RT |
| Parker et al;[6] Sartor et al[7] | 71 (44–94) | CRPC, symptomatic skeletal metastasis, PSA >5 ng/mL, ECOG 0–2 | Previous hemibody RT, previous RP within 12 weeks, chemotherapy within 4 weeks, blood transfusion or EPO within 4 weeks, lymph node >3 cm, visceral metastasis, and SCC | 1. <6 (138)<br>2. 6–20 (409)<br>3. >20 (84) | Medical or surgical endocrine therapy, docetaxel (526), bisphosphonates (374), and RT (147) | First use of RT to relieve skeletal symptoms, new symptomatic pathological bone fractures, SCC, or tumor-related orthopedic surgery |

**Abbreviations:** ADL, activities of daily life; AHA, American Heart Association; BBB, bundle branch block; CRPC, castration-resistant prostate carcinoma; DAL, daily activities of life; ECOG, Eastern cooperative Oncology group; EPO, erythropoietin; HT, hormonal therapy; KPS, Karnofsky performance scale; NM, not mentioned; PSA, prostate specific antigen; PDS, pain descriptor scale; RP, radiopharmaceutical; RT, radiation therapy; SCC, spinal cord compression; VAS, visual analog scale; WHO, World Health Organization.

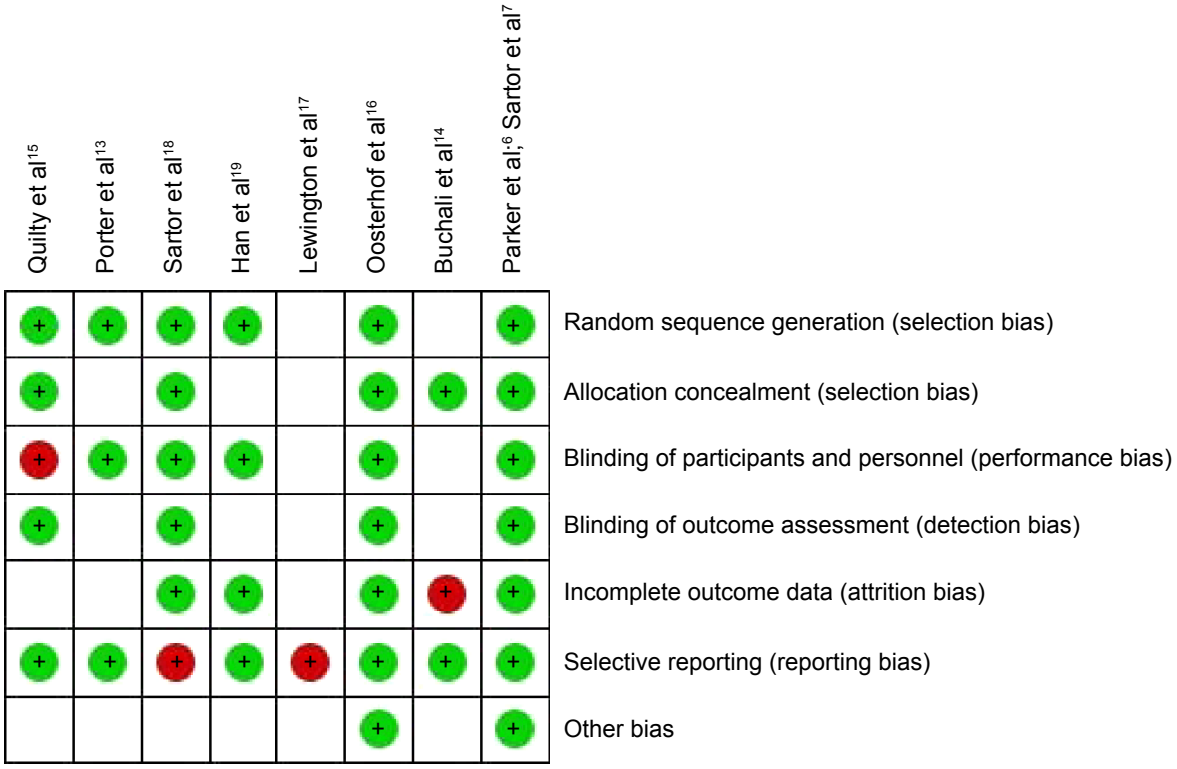


**Figure 2** Summary of risk bias assessment.
**Notes:** red, high risk bias; green, low risk bias; blank, no risk bias.

intensity and SSEs were greater when used above 150 MBq (4 mCi), and in the form of single-dose administration.[13,15,22] There was no significant difference in pain relief with six monthly injections of radium-223 and a single injection of β-emitting RPs (strontium-89, samarium-153, and rhenium-183).

The pooled adjusted estimates from included RCTs showed that radium-223 and strontium-89 (one trial) were associated with significant improvement in OS.[6,7,14] Interestingly, in three RCTs of strontium-89, the OS rates were better in control groups.[13,15,16] Similarly, samarium-153 and rhenium-186 failed to show any OS benefit. However, it was clear in the meta-analysis that the trials using strontium-89 and samarium-153 were underpowered and mainly consisted of docetaxel naive patients. The OS benefit of strontium-89 and samarium-153 in docetaxel-treated metastatic CRPC patients deserves further exploration, as prolonged OS rates have been reported in the recent Phase II

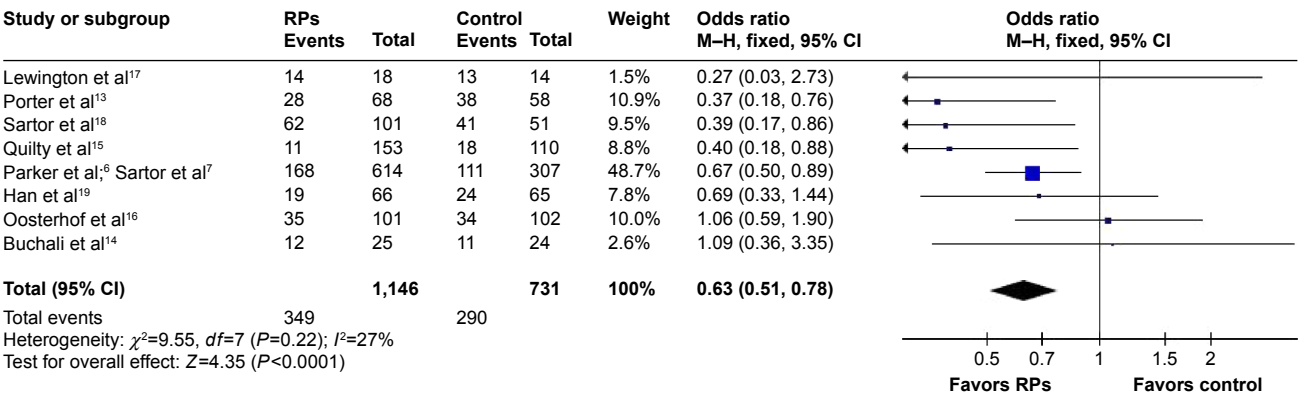


**Figure 3** Pain intensity and symptomatic skeletal event (multiple scales).
**Note:** Horizontal lines represent point estimates varying in size according to the weightage, and 95% confidence intervals.
**Abbreviations:** CI, confidence interval; *df*, degrees of freedom; RP, radiopharmaceutical; Z, Z score; M–H, Mantel–Haenszel.

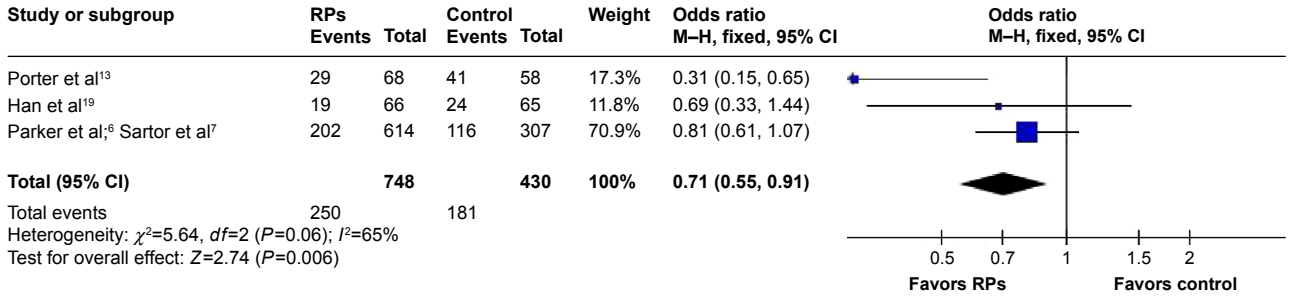


**Figure 4** Quality of life (multiple scales).
**Note:** Horizontal lines represent point estimates varying in size according to the weightage, and 95% confidence intervals.
**Abbreviations:** CI, confidence interval; *df*, degrees of freedom; RP, radiopharmaceutical; $\chi^2$, ; Z, Z score; M–H, Mantel–Haenszel.

and retrospective studies incorporating strontium-89 or samarium-153 in previously treated patients with systemic chemotherapy.[23–25]

Further pooled adjusted estimates of acute toxicities showed that strontium-89 was associated with more acute grade ≥3 thrombocytopenia, leucopenia, pain flare, and emesis; while an isolated grade ≥3 leucopenia was observed with samarium-153. The acute toxicity of rhenium-186 was not reported in included trials; however, rhenium-186 is known to cause myelotoxicity as other β-emitting RPs.[26] Radium-223 was found to be the safest RP without any statistically significant hematological and nonhematological toxicity. However, late adverse events, especially the potential risk of second malignancies, which are of great concern, were not addressed in all included studies. Few case reports have suggested the leukemogenic potential of strontium-89 in CRPC patients.[27,28] The leukemogenic potential of other RPs is yet to be established. Recently, an Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial at a 1.5-year follow-up (radium-223, n=406; placebo, n=168) reported no case of acute myelogenous leukemia, myelodysplastic syndrome, or primary bone cancer.[6,7,29]

The strengths of our meta-analysis were 1) completeness of the search strategy, including searching multiple databases, trial registries, and conference proceedings for RCTs comparing RPs to the control group (placebo, RT, or best supportive care) in metastatic CRPC patients, 2) patient-centered outcomes (pain intensity, SSE, and QoL), and 3) evaluation of the OS benefit and acute toxicity profile of RPs.

The limitations of our meta-analysis were 1) inherent methodological issues in the included trials (50% trials were rated to be in high risk of bias and 25% were classified as unclear with respect to the risk of bias) and 2) attrition and reporting bias in most of the included trials, which might have resulted in underestimated estimates.

## Conclusion

The use of RPs was associated with significant reductions in pain intensity, SSEs, improved functional mobility, and

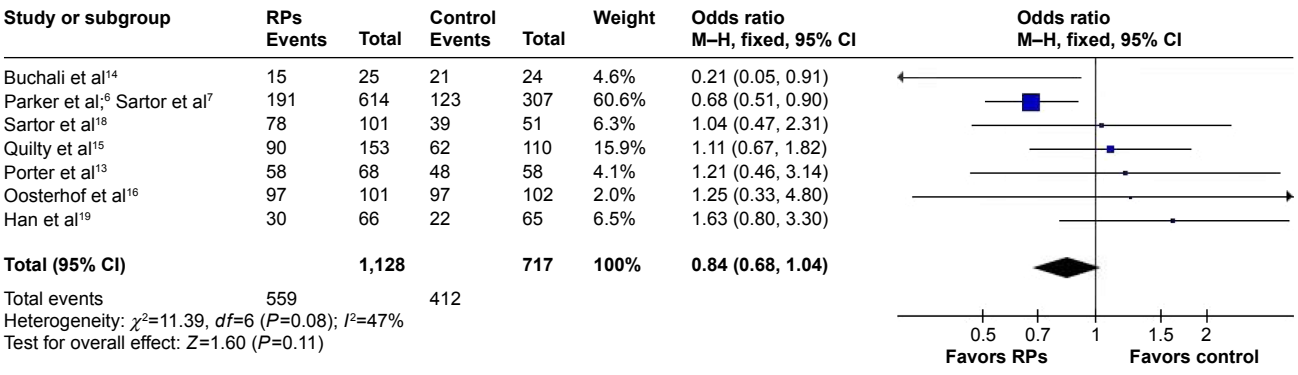


**Figure 5** Overall survival.
**Note:** Horizontal lines represent point estimates varying in size according to the weightage, and 95% confidence intervals.
**Abbreviations:** CI, confidence interval; *df*, degrees of freedom; RP, radiopharmaceutical; Z, Z score; M–H, Mantel–Haenszel.

**Table 3** Comparison of grade 3 and 4 acute toxic events for different radiopharmaceuticals in included studies

| Toxicity | Events (%) | OR (95% CI) | $I^2$ | *P*-value |
|---|---|---|---|---|
| Hematological: thrombocytopenia | | | | |
| $Sr^{89}$ | 48 (13.2) | 4.26 (2.22–8.18) | 63.5 | 0.01 |
| $Sm^{153}$ | 0 (0) | 0.25 (0.01–6.34) | 0 | 0.09 |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 39 (6.4) | 2.91 (1.28–6.58) | 36.0 | 0.65 |
| Anemia | | | | |
| $Sr^{89}$ | 30 (8.2) | 1.22 (0.70–2.13) | 70.0 | 0.98 |
| $Sm^{153}$ | 11 (10.9) | 0.92 (0.32–2.64) | 0 | 0.16 |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 76 (12.4) | 0.94 (0.63–1.42) | 50.0 | 0.08 |
| Leucopenia | | | | |
| $Sr^{89}$ | 13 (3.6) | 7.98 (1.82–34.95) | 50.7 | **0.02** |
| $Sm^{153}$ | 5 (4.9) | 2.60 (0.30–22.90) | 65.8 | **0.03** |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 13 (2.2) | 1.31 (0.46–3.70) | 67.3 | 0.09 |
| Infection | | | | |
| $Sr^{89}$ | 24 (6.6) | 1.10 (0.6–2.02) | 0 | 0.09 |
| $Sm^{153}$ | NM | – | – | – |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 7 (1.2) | 0.70 (0.22–2.21) | 81.3 | 0.06 |
| Nonhematological: pain flare | | | | |
| $Sr^{89}$ | 61 (16.7) | 6.82 (3.42–13.55) | 95 | **0.04** |
| $Sm^{153}$ | 6 (5.9) | 1.01 (0.24–4.22) | 63.9 | 0.54 |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 125 (20.4) | 0.76 (0.55–1.06) | 79 | 0.15 |
| Spinal cord compression | | | | |
| $Sr^{89}$ | 21 (5.7) | 0.83 (0.42–1.52) | 80.1 | 0.62 |
| $Sm^{153}$ | 7 (6.9) | 0.69 (0.21–2.28) | 0 | 0.05 |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 21 (3.4) | 0.24 (0.14–0.41) | 50.5 | 0.05 |
| Nausea/vomiting | | | | |
| $Sr^{89}$ | 35 (9.6) | 3.61 (1.76–7.40) | 65 | **0.02** |
| $Sm^{153}$ | NM | – | – | – |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 20 (3.3) | 0.76 (0.37–1.55) | 65.2 | 0.61 |
| Diarrhea | | | | |
| $Sr^{89}$ | 8 (2.2) | 1.94 (0.58–6.50) | 82 | 0.54 |
| $Sm^{153}$ | NM | – | – | – |
| $Re^{186}$ | NM | – | – | – |
| $Ra^{223}$ | 9 (1.5) | 0.90 (0.30–2.7) | 73.3 | 0.33 |

**Note:** Bold text indicates a significant *P*-value.
**Abbreviations:** CI, confidence interval; NM, not mentioned; OR, odds ratio.

improved QoL in metastatic CRPC patients. Radium-223 was found to be the least toxic RP and with clear survival benefit. However, the radium-223-related survival benefit warrants further large RCTs to evaluate the efficacy of radium-223 in docetaxel naive CRPC patients and to determine whether the therapeutic index of radium-223 could be improved by coupling it with other antibodies and/or nanoparticles.

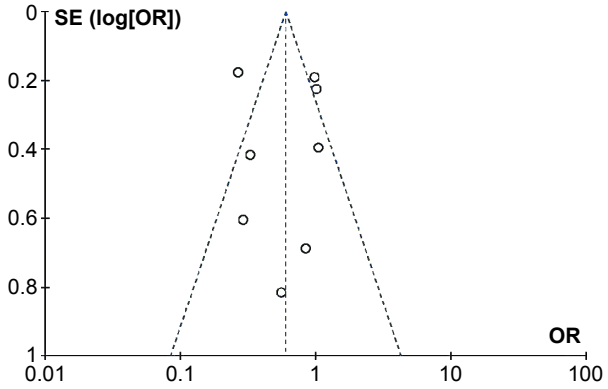


**Figure 6** Graph showing the publication bias.
**Abbreviations:** OR, odds ratio; SE, standard error.

## Disclosure

All authors report no conflict of interest in this work.

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