

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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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, CANCELIT, 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

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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, CASCERLIT, 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 $\geq 50\%$ from baseline, increase in analgesics $\geq 25\%$, worsening of daily activities of life $\geq 25\%$, 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

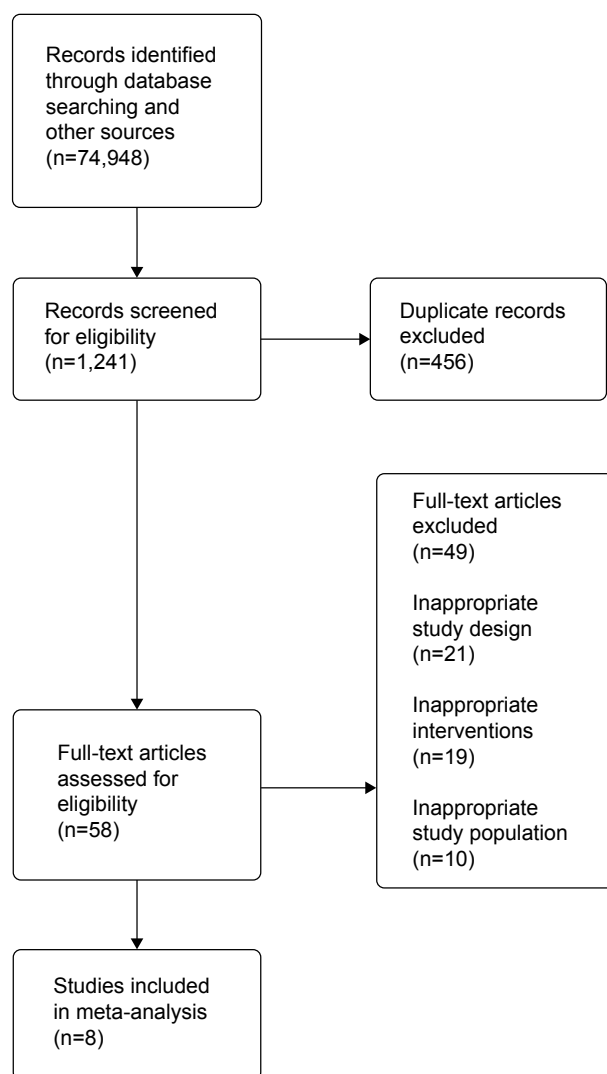


Figure 1 Study flow diagram.

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 30 Gy/10 Fr 20 Gy/5 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)	10 Gy/1 Fr 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 20 Gy/5 Fr 8 Gy/1 Fr 2. Hemibody RT 6 Gy/1 Fr 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 20 Gy/5 Fr 4 Gy/1 Fr 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 $\geq 50\%$ from the baseline, increase in analgesics $\geq 50\%$
Buchali et al ¹⁴	NM	CRPC, symptomatic skeletal metastasis	NM	1. <2 (12) 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) 2. >10 (101)	Medical or surgical endocrine therapy	Increase in bone pain $\geq 50\%$ from the baseline, increase in analgesics $\geq 25\%$, worsening of DAL $\geq 25\%$, 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) 2. 6–10 (22) 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 $\geq 25\%$ from the baseline, increase in analgesics $\geq 25\%$, worsening of ADL $\geq 25\%$, and first request for additional RT
Parker et al ⁶	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) 2. 6–20 (409) 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
Sartor et al ⁷						

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, radiotherapeutic; RT, radiation therapy; SCC, spinal cord compression; VAS, visual analog scale; WHO, World Health Organization.

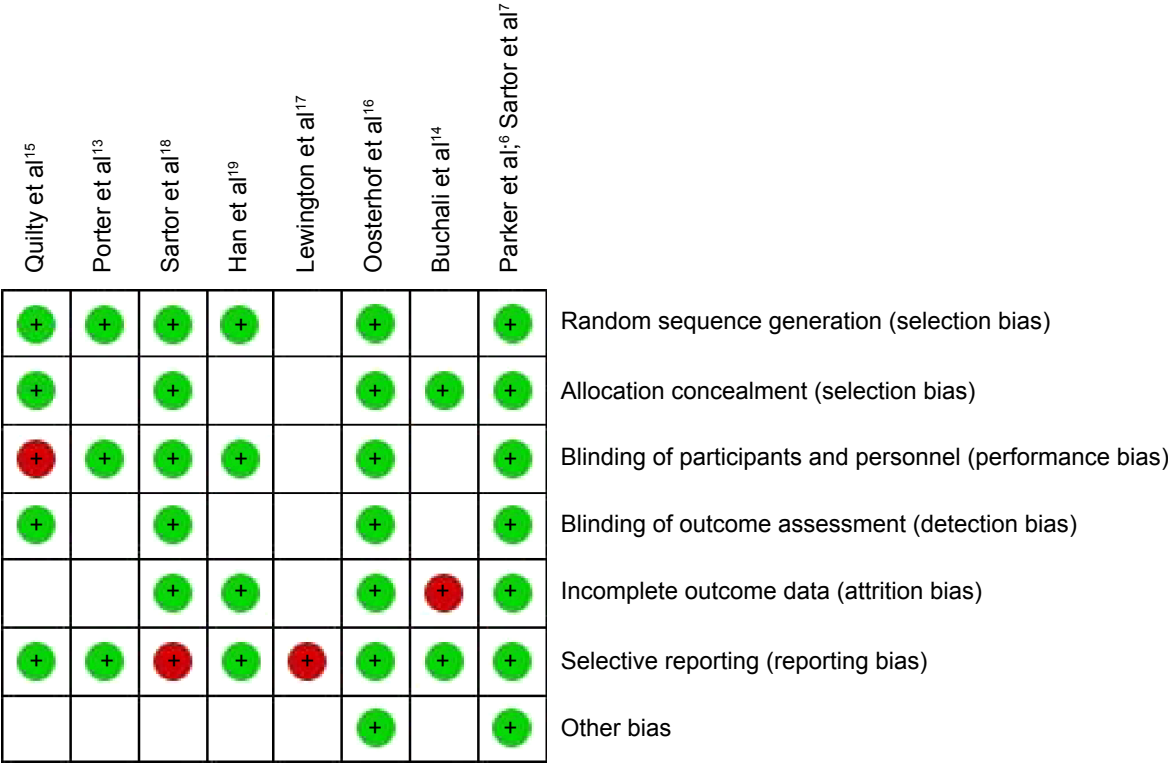


Figure 2 Summary of risk bias assessment.
Notes: red, high risk bias; green, low risk bias; blank, no risk bias.

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

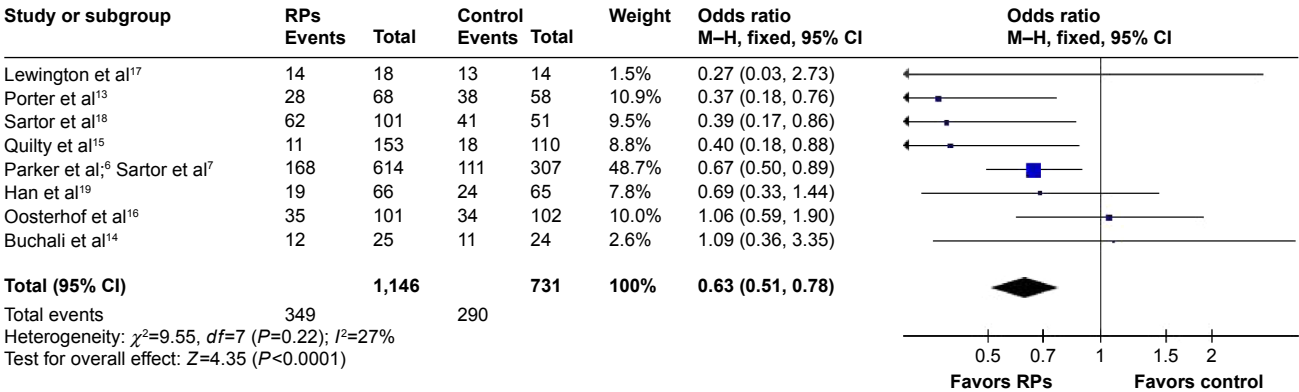


Figure 3 Pain intensity and symptomatic skeletal event (multiple scales).
Note: Horizontal lines represent point estimates varying in size according to the weightage, and 95% confidence intervals.
Abbreviations: CI, confidence interval; df , degrees of freedom; RP, radiopharmaceutical; Z, Z score; M-H,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

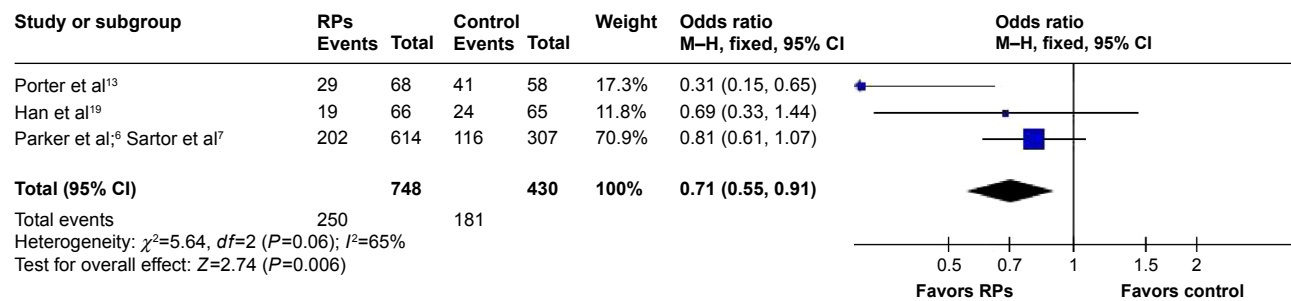


Figure 4 Quality of life (multiple scales).

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; χ^2 , 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

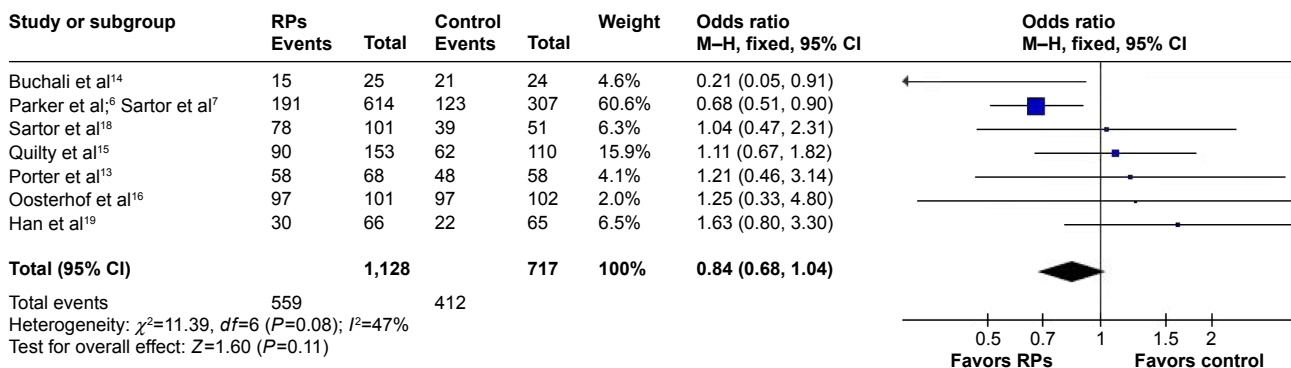


Figure 5 Overall survival.

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.

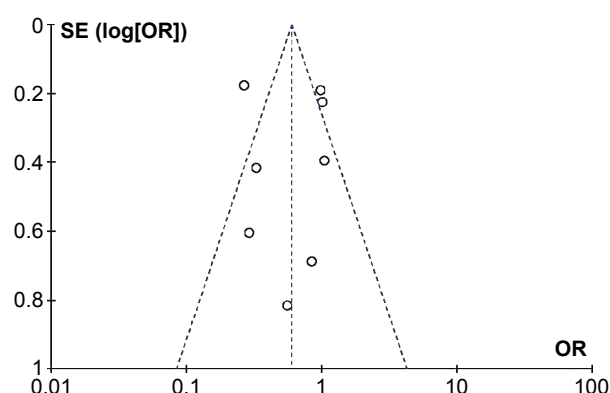


Figure 6 Graph showing the publication bias.

Abbreviations: OR, odds ratio; SE, standard error.

Disclosure

All authors report no conflict of interest in this work.

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