The efficacy and safety of ^{225}Ac-PSMA RLT targeted therapy for metastatic castration-resistant prostate cancer: A systematic review and meta-analysis

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Abstract

Objective: Using radiolabeled prostate-specific membrane antigen (PSMA) ligands for the treatment of metastatic prostate cancer is a promising therapeutic approach. This systematic review and meta-analysis aims to assess the efficacy and safety of actinium-225 (^{225}Ac)-PSMA radioligand therapy (RLT) for prostate cancer. **Materials and Methods:** The systematic review and meta-analysis adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Searches were conducted in databases including PubMed, Web of Science, Medline, CNKI, and VIP, for studies related to ^{225}Ac-PSMA RLT for prostate cancer from inception until April 2024. The primary endpoint was the therapeutic effect as measured by post-treatment biochemical response evaluation criteria, while secondary endpoints included evaluating overall survival (OS), progression-free survival (PFS), molecular responses, etc. **Results:** A total of 17 studies involving 1042 patients were included. The pooled proportion of patients with PSA reduction was 85% (95% confidence interval [CI]: 80%-91%), and the pooled rate of PSA reduction >50% was 66% (95% CI: 58%-75%). The combined values for OS and PFS were 13.79 months (95% CI: 11.11-16.48 months) and 9.67 months (95% CI: 6.99-12.35 months), respectively. The molecular response rate was 71% (95% CI: 56-87%). The most common side effect of ^{225}Ac-PSMA RLT was xerostomia, accounting for 63.5%. Anemia, leukopenia, thrombocytopenia, and renal toxicity were observed in 54.3%, 30.4%, 31.8%, 32.0%, respectively. **Conclusions:** Actinium-225 -PSMA RLT is an effective and safe treatment for metastatic castration-resistant prostate cancer (mCRPC) patients, with a low incidence of treatment-related adverse reactions. Additionally, a history of lutetium-177 (^{177}Lu) treatment may have an impact on PSA reduction in mCRPC patients.

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Introduction

Prostate cancer (PCa) is the most common malignancy in men globally. According to the 2023 Annual Cancer Report, prostate cancer has the highest incidence among male cancer cases in the United States, accounting for approximately 29%, making it the second leading cause of cancer-related deaths in men, representing around 11% [1]. The incidence of prostate cancer varies significantly by region, traditionally with lower rates in Asia. However, due to increasing economic levels, aging populations, Westernized lifestyles, and improved prostate cancer detection, the incidence of prostate cancer in Asia is rapidly rising [2-4]. Current treatment methods for prostate cancer primarily include radical surgical removal, chemotherapy, radiotherapy, and androgen deprivation therapy (ADT). However, these treatment approaches are not always curative, and patients may eventually develop metastatic castration-resistant prostate cancer (mCRPC), which is a major cause of patient mortality [4-6]. Although certain treatments such as taxane chemotherapy (docetaxel and cabazitaxel), immunotherapy, next-generation hormone therapies (abiraterone, enzalutamide), and targeted therapies have been approved for mCRPC, resistance mechanisms and adverse reactions may limit the improvement in prognosis and quality of life for some patients [7-10]. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein located on the cell membrane, with increased specific expression in prostate cancer [11-12]. Radioligand therapy (RLT) involves injecting a therapeutic dose of a radiolabeled ligand into the body. When the ligand reaches the target cells, the radiolabel releases alpha particles and/or beta particles, causing DNA single-strand or double-strand breaks, leading to cell death. With a half-life of 9.9 days, actinium-225 (^{225}Ac) produces 4 alpha particles, 2 beta particles, and gamma photons during

its decay. The short range of alpha rays enables the destruction of tumor cells with minimal damage to surrounding normal tissues, making it a favorable choice for patients with bone marrow infiltration. The high energy of alpha rays also makes it suitable for treating beta-resistant prostate cancer cells [13-15]. Clinical trials have evaluated efficacy and safety of ^{225}Ac-PSMA-RLT for the treatment of metastatic prostate cancer. However, only a limited number of systematic reviews or meta-analyses are available on the efficacy and safety of ^{225}Ac-PSMA RLT for metastatic prostate cancer, and the literature included mostly consists of small sample, retrospective studies. The present study aimed to analyze various clinical trials published on ^{225}Ac-PSMA RLT for metastatic prostate cancer, in order to provide further evidence for this treatment.

Materials and Methods

This systematic review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16].

Search strategy

A systematic search was conducted from inception till April 2024 in PubMed, Web of Science, Medline, CNKI, and VIP for studies on ^{225}Ac-PSMA therapy for prostate cancer. The search terms included ("Prostate Cancer" OR "Prostate Tumor") AND "PSMA" AND ("^{225}Ac" OR "^{225}-Actinium"). In case of duplicate records (from the same trial or institution), the most comprehensive one was chosen. However, if two studies included partially different patient populations (overlap rate <50%), they were considered separately.

Inclusion criteria

Study population: Studies including more than 10 patients diagnosed with mCRPC and positive for ^{68}Ga-PSMA-11 imaging; intervention: ^{225}Ac-PSMA RLT for at least one cycle; Outcome: The primary endpoints were any level of prostate-specific antigen (PSA) decline and PSA decline >50%.

Exclusion criteria

Studies with fewer than 10 included patients; duplicate publications, reviews, case reports, communications, abstracts, dosimetry studies, and letters to the editors.

Quality assessment

Two researchers (HJL, JM) independently conducted the systematic search and study selection. Disagreements were resolved through discussion with a third reviewer. Ultimately, 17 studies were selected, and the methodological quality of all included studies was assessed using the Newcastle-Ottawa Scale (NOS). (Studies with NOS scores ≥ 6 were considered to have better quality).

Statistical analysis

All data were analyzed using STATA version 17.0 for meta-analysis. Treatment efficacy was evaluated using PSA decline and PSA decline >50%. Additionally, overall survival (OS), progression-free survival (PFS), molecular responses, and treatment-related toxicities were assessed for all studies. Forest plots were generated for analysis. The I^2 statistic and chi-square test were used for heterogeneity testing. If there was no significant heterogeneity among studies (I^2 ≤50%, P> 0.10), a fixed-effects model was used to pool the data. If significant heterogeneity was present among studies (I^2>50%, P≤0.10), subgroup analysis was conducted, and a random-effects model was used to pool the data.

Results

Literature search results

According to the predetermined search strategy, a total of 228 relevant articles were retrieved. After removing 126 duplicate articles, there were 102 remaining. Upon preliminary review of the titles and abstracts, 80 articles were excluded. Of the remaining articles, 30 were review articles and meta analyses, 14 were preclinical studies, 12 were related to radiopharmaceuticals or drugs, 12 studied dosimetry or imaging, 7 were case reports or brief communications, and 5 were unrelated to PSMA therapy. Further reading of the full texts led to the exclusion of 5 articles. Two articles by Sathekge et al. and Banda et al. focused on metastatic hormone-sensitive prostate cancer, while one by Kremser et al. investigated the prognostic value of neutrophil-to-lymphocyte ratio in prostate cancer patients undergoing radionuclide therapy. Langbein et al. and Feuerecker et al. each contributed 2 articles solely examining salivary gland toxicity of radionuclide therapy. Finally, a total of 17 articles were included [17-33], as shown in Figure 1.

Results

Literature quality assessment and information of studies included

Ultimately, 17 studies were included, comprising 1042 study subjects. All studies included had Newcastle-Ottawa Scale NOS scores greater than 6, indicating good methodological quality (Table 1). The information collected from the studies encompassed the first author and publication date of each article, the number and age of the patients, the presence or absence of prior ^{177}Lu treatment history, the disease stage of the patients, the baseline PSA levels, the Gleason score, and the Eastern Cooperative Oncology Group (ECOG) score (Table 2). Additionally, information pertaining to the radioligand therapy was recorded, such as the ^{225}Ac compound used, the dosage, the duration, and the time intervals between successive administrations (Table 3). Outcome measures for the studies included biochemical and molecular response rates, survival periods, treatment-related deaths, clinical responses, and toxicity reactions. Biochemical response was evaluated according to the criteria defined by the Prostate

Cancer Clinical Trials Working Group 3 (PCWG3) [34], where PSA response was defined as a decrease in PSA levels by more than 50% from baseline, while any level of PSA decrease was recorded. Patients underwent ^{68}Ga-PSMA PET/CT imaging, and molecular response was assessed according to PERCIST 1.0 criteria [35], combining complete response (CR) and partial response (PR) into molecular response rate. Survival periods included PFS and OS, with PFS defined as the time from the first dose of ^{225}Ac-PSMA-RLT to the first evidence of progression or death, or the end of the study period, and OS defined as the time from the first dose of ^{225}Ac-PSMA-RLT to death from any cause. Clinical responses were evaluated using clinical response criteria such as visual analogue score, pain score, Karnofsky Performance Status (KPS), and ECOG criteria. Adverse events and toxicities were recorded and graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE5.0) [36] (Tables 3-5).

Meta-analysis results

Meta-analysis of any PSA decline rate

A total of 14 relevant studies on single-agent ^{225}Ac-PSMA RLT in mCRPC patients were included, comprising 1005 patients, with 973 patients being evaluated, among whom 781 patients experienced a decline in PSA levels. Significant heterogeneity (I^2=79.4%, P<0.001) was present, thus subgroup analysis (using two groups, 1: representing studies where less than 50% of patients had a history of ^{177}Lu treatment, 2: representing studies where more than 50% of patients had a history of ^{177}Lu treatment) and a random-effects model were used for meta-analysis of the rate of PSA decline. The forest plot suggested that the combined rate of any degree of PSA decline after treatment with ^{225}Ac-PSMA-617/I&T (Figure 2) was 0.85 (95% CI: 0.80-0.91). In studies where fewer than 50% of patients had received prior ^{177}Lu treatment, the pooled response rate was 0.87 (95% CI: 0.80-0.93); in those with more than 50% prior ^{177}Lu treatment, the rate was 0.83 (95% CI: 0.74-0.91).

Meta-analysis of PSA decline rate >50%

A total of 14 relevant studies on single-agent ^{225}Ac-PSMA RLT in mCRPC patients were included, comprising 1005 patients, with 973 patients being evaluated, and 619 (63.6%) achieved a >50% decline in PSA levels. Significant heterogeneity (I^2=85.3%, P<0.001) was present, thus subgroup analysis (using two groups, 1: representing studies where less than 50%

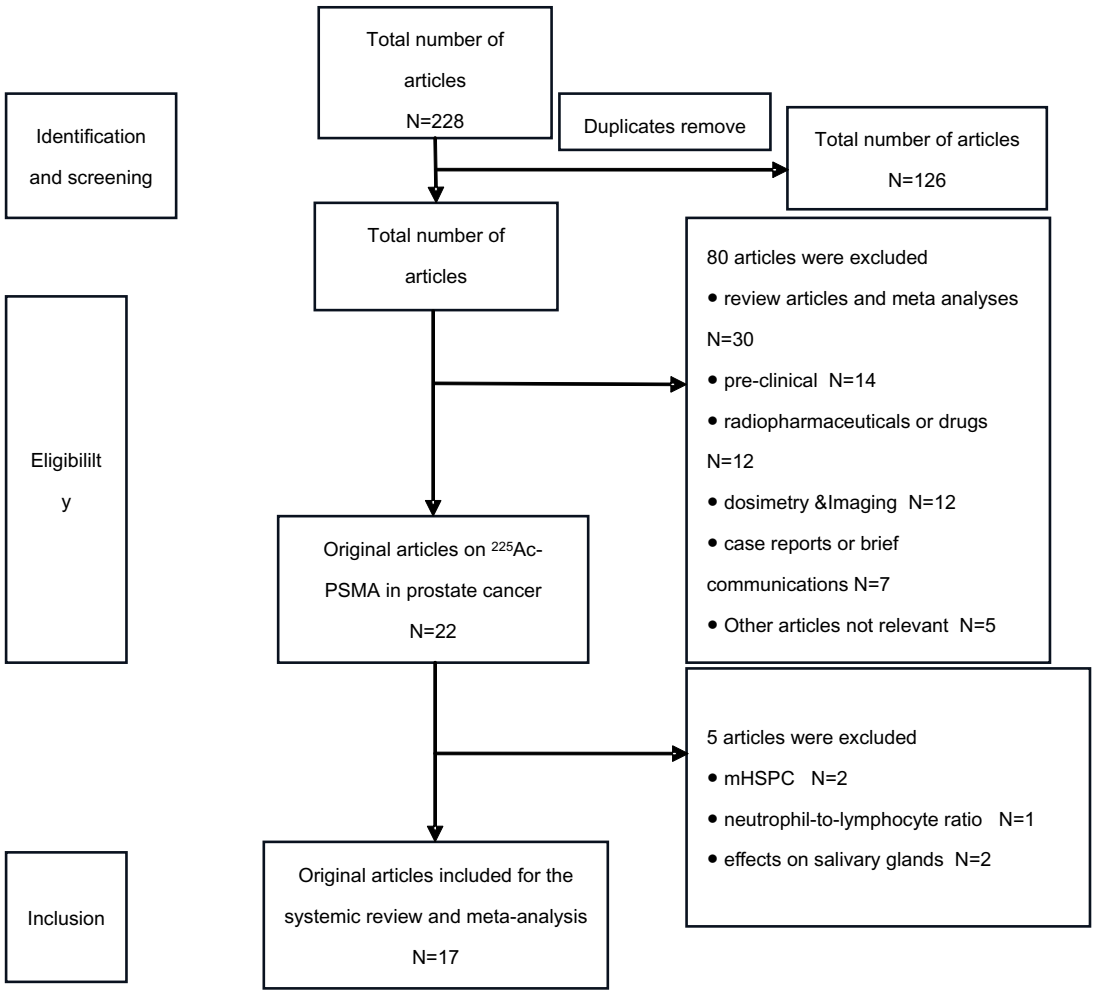

Figure 1. Flowchart of literature screening.

Table 1. Quality assessment of the included studies based on the Newcastle-Ottawa.

NO.	Author and year	Selection	Comparability	Outcome	Score
1	Kratochwil et al., 2018 (17)	3	1	3	7
2	Sathekge et al., 2019 (18)	3	1	3	7
3	Khreish et al., 2020 (19)	3	1	3	7
4	Sathekge et al., 2020 (20)	3	1	3	7
5	Satapathy et al., 2020 (21)	3	1	2	6
6	Yadav et al., 2020 (22)	3	1	3	7
7	van der Doelen et al., 2021 (23)	3	1	3	7
8	Zacherl et al., 2021 (24)	3	1	2	6
9	Feuerecker et al., 2021 (25)	2	1	3	6
10	Sen Ishita et al., 2021 (26)	3	1	3	7
11	Rosar et al., 2021 (27)	3	1	3	7
12	Sanli et al., 2021 (28)	2	1	3	6
13	Lawal et al., 2022 (29)	3	1	3	7
14	Sathekge et al., 2022 (30)	3	1	3	7
15	Ballal et al., 2023 (31)	3	1	3	7
16	Selcuk et al., 2023 (32)	2	1	3	6
17	Sathekge et al., 2024 (33)	3	1	3	7

of patients had a history of ^{177}Lu treatment, 2: representing studies where more than 50% of patients had a history of ^{177}Lu treatment) and a random-effects model were used for the meta-analysis of the rate of PSA decline >50%. The forest plot suggested that the combined rate of PSA decline >50% after treatment with ^{225}Ac-PSMA RLT (Figure 3) was 0.66 (95% CI: 0.58-0.75). In studies with <50% of patients previously treated with ^{177}Lu, the response rate was 0.71 (95% CI: 0.61-0.81), while in studies with >50% prior ^{177}Lu treatment, the rate was 0.51 (95% CI: 0.39–0.64).

Meta-analysis of overall survival (OS)

Overall survival was evaluated in a total of 806 patients in a total of 7 studies on the use of ^{225}Ac-PSMA RLT in the treatment of mCRPC. Since significant heterogeneity was present (I^2=81.3%, P<0.001), a random-effects model was employed for the combined analysis of OS. The forest plot (Figure 4) showed a pooled median OS of 13.79 months (95% CI: 11.11-16.48 months).

Meta-analysis of progression-free survival (PFS)

PFS was evaluated in 834 patients across 8 studies investigating ^{225}Ac-PSMA RLT for the treatment of mCRPC. Since significant heterogeneity was present (I^2=86.8%, P<0.001), a random-effects model was used for the combined analysis of PFS. The forest plot (Figure 5) showed a pooled median PFS of 9.67 months (95% CI: 6.99-12.35 months).

Molecular response

Molecular responses were evaluated by gallium-68 (^{68}Ga)-PSMA PET/CT in 111 of 123 patients across 5 studies evaluating ^{225}Ac-PSMA RLT in the treatment of mCRPC. Molecular responses were observed in 72 patients. Since significant heterogeneity was present (I^2=69.3%, P=0.011), a random-effects model was used to combine the molecular response rates. Meta-analysis showed a pooled molecular response rate of 0.71 (95% CI: 0.56 to 0.87), as shown in Figure 6.

Adverse reactions

Among the 17 studies analyzed, 15 studies examined the adverse events of single-agent ^{225}Ac-PSMA-RLT according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0). The most common adverse event was xerostomia (dry mouth), occurring in 63.5% (638/1005) of

Table 2. *Basic characteristics of the studies included.*

Author and year	Patients (N)	Age (yr) (median and/or range)	Prior ^{177}Lu treatment (%)	Study population	Baseline PSA (ng/mL) (median and/or range)	GS	ECOG
Kratochwil et al., 2018 (17)	40	70	0%	mCRPC	169	NR	0-1 (80%) ≥2 (20%)
Sathekge et al., 2019 (18)	17	64.5 (45-82)	18%	mCRPC	33.84 (1.2-1300.69)	9 (6-10)	0-1 (88%) ≥2 (12%)
Khreish et al., 2020 (19)	20	72 (57-88)	20%	mCRPC	215 (6-5547)	NR	0-1 (60%) ≥2 (40%)
Sathekge et al., 2020 (20)	73	69 (45-85)	14%	mCRPC	57.2	8 (6-10)	0-1 (82%) 2-3 (18%)
Satapathy et al., 2020 (21)	11	68 (57–81)	46%	mCRPC	158 (35-840)	8 (7-9)	0-1 (64%) 2 (36%)
Yadav et al., 2020 (22)	28	69.7 (46-87)	54%	mCRPC	222.2 (47-443.2)	≤7 (21%) ≥8 (79%)	≤2 (28%) ≥3 (72%)
van der Doelen et al., 2021 (23)	13	71 (64-77)	15%	mCRPC	878 (203-1611)	≤7 (54%) ≥8 (46%)	0 (23%) 1-2 (77%)
Zacherl et al., 2021 (24)	14	75 (64-88)	79%	mCRPC	112 (20.5-818)	NR	0-1 (79%） 2 (21%)
Feuerecker et al., 2021 (25)	26	72.5 (63–75.8)	100%	mCRPC	331 (142–682)	8 (7-9)	≤2 (100%)
Sen Ishita et al., 2021 (26)	38	68 (53-84)	24%	mCRPC	NR	≤7 (10%) ≥8 (90%)	0-2 (100%)
Rosar et al., 2021 (27)	17	69.4(57-89)	100%	mCRPC	152(5.9-2570)	NR	0-1 (94%) ≥2 (6%)
Sanli et al., 2021 (28)	12	70 (45-89)	58%	mCRPC	129 (10.7-765)	9 (6-10)	0-1 (50%) ≥2 (50%)
Lawal et al., 2022 (29)	106	NR (44-86)	7%	mCRPC	250.2 (2.8-4494.0)	8 (6-10)	NR
Sathekge et al., 2022 (30)	53	63.4 (45-83)	0%	mCRPC	466 (102-4405)	NR	0-1 (79%) ≥2 (21%)
Ballal et al., 2023 (31)	63	67 (39-87)	43%	mCRPC	NR	≤7 (11%) ≥8 (89%)	3 (1-4)
Selcuk et al., 2023 (32)	23	70.3 (61.5-79.1)	100%	mCRPC	103.79 (0.349–727.8)	NR	NR
Sathekge et al., 2024 (33)	488	68·1 (59.3-76.9)	32%	mCRPC	169·5 (34·6–519·8)	NR	0-1 (65%) ≥2 (28%)

NR, not reported; mCRPC, metastatic castration-resistant prostate cancer; PSA,prostate-specific antigen; ECOG, Eastern Cooperative Oncology Group; GS, Gleason score.

Table 3. *Treatment characteristics of the studies included.*

Author and year	Patients analyzed for PSA decline (N)	RLT agent	Dose	Number of cycles (median and/or range)	Follow-up (wk)	Any PSA decline (n/N (%))	PSA decline >50% (n/N (%))
Kratochwil et al., 2018 (17)	38	^{225}Ac-PSMA-617	100KBq/kg BW	1-3	8	33/38 (87%)	24/38 (63%)
Sathekge et al., 2019 (18)	17	^{225}Ac-PSMA-617	7.4±1.5MBq/cycle	2-6	8	16/17 (94%)	15/17 (88%)
Khreish et al., 2020 (19)	20	^{225}Ac-PSMA-617/^{177}Lu-PSMA-617 tandem therapy	^{225}Ac-PSMA-617: 5.3 (1.5-7.9) MBq/cycle, 177Lu-PSMA-617: 6.9 (5.0-11.6) GBq/cycle	1 (0-5)	NR	18/20 (90%)	13/20 (65%)
Sathekge et al., 2020 (20)	73	^{225}Ac-PSMA-617	4-8MBq/cycle	3 (1-8)	8	60/73 (83%)	51/73 (70%)
Satapathy et al., 2020 (21)	11	^{225}Ac-PSMA-617	100KBq/kg BW	2 (1-4)	8-12	8/11 (73%)	5/11 (46%)
Yadav et al., 2020 (22)	28	^{225}Ac-PSMA-617	100KBq/kg BW	3 (1-7)	8	22/28 (79%)	11/28 (39%)
van der Doelen et al., 2021 (23)	13	^{225}Ac-PSMA-617	6-8MBq/cycle	3 (1-4)	8	11/13 (85%)	9/13 (69%)
Zacherl et al., 2021 (24)	14	^{225}Ac-PSMA-I&T	7.8 (6.0-8.5) MBq/cycle	1-5	8	11/14 (79%)	7/14 (50%)
Feuerecker et al., 2021 (25)	26	^{225}Ac-PSMA-617	9MBq/cycle	2 (1-6)	8	23/26 (88%)	17/26 (65%)

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Sen Ishita et al., 2021 (26)	38	^{225}Ac-PSMA-617	100KBq/kg BW	2 (2-5)	8	33/38 (87%)	25/38 (66%)
Rosar et al., 2021 (27)	17	^{225}Ac-PSMA-617/^{177}Lu-PSMA-617 tandem therapy	^{225}Ac-PSMA-617: 1.8-6.9 MBq/cycle, ^{177}Lu-PSMA-617: 3.8-8.2GBq/cycle	1	NR	10/17 (59%)	5/17 (29%)
Sanli et al., 2021 (28)	12	^{225}Ac-PSMA-617	7.4 (5.9-9.9) MBq/cycle	2 (1-3)	8	9/12 (75%)	6/12 (50%)
Lawal et al., 2022 (29)	106	^{225}Ac-PSMA-617	100KBq/kg BW	4 (1-9)	NR	95/106 (90%)	85/106 (80%)
Sathekge et al., 2022 (30)	53	^{225}Ac-PSMA-617	4-8MBq/cycle	3 (1-7)	8	51/53 (96%)	48/53 (91%)
Ballal et al., 2023 (31)	63	^{225}Ac-PSMA-617	100-150KBq/kg	3-9	8	51/56 (91%)	38/56 (68%)
Selcuk et al., 2023 (32)	23	^{225}Ac-PSMA-RLT	7.6 (6.2-10)/cycle	13 (8-28)	4.5 (2-9)	NR	NR
Sathekge et al., 2024 (33)	488	^{225}Ac-PSMA-RLT	8MBq/cycle	2 (2-4)	8	358/488 (73%)	278/488 (57%)

NR, not reported; BW, body weight; PSA, prostate specific antigen.

Table 4. *Outcome measurements in the studies included.*

Author and year	Patients (N)	Molecular response (n/N (%))	OS (months) (median and/or range)	PFS (months) (median and/or range)	Treatment related deaths, (n/N (%))	Post-therapy clinical response parameters
Kratochwil et al., 2018 (17)	40	NR	>12.0 (NR)	7.0 (NR)	NR	NR
Sathekge et al., 2019 (18)	17	15/17 (88%)	NR	NR	NR	NR
Khreish et al., 2020 (19)	20	10/20 (50%)	48 (4-92)	19 (12-26)	NR	NR
Sathekge et al., 2020 (20)	73	NR	18 (16.2-19.9)	15.2 (13.1-17.4)	NR	NR
Satapathy et al., 2020 (21)	11	NR	NR	NR	3/11 (27%)	NR
Yadav et al., 2020 (22)	28	12/22 (55%)	17 (16-NR)	12 (9-13)	NR	VAS max: 4.7 (0 - 9) Analgesic score： 2 (0-3) KPS: 75.5 (40-90) ECOG: 2 (0-4)
van der Doelen et al., 2021 (23)	13	6/7 (86%)	8.5 (NR)	5.5(NR)	NR	NR
Zacherl et al., 2021 (24)	14	NR	NR	NR	NR	NR
Feuerecker et al., 2021 (25)	26	NR	7 (4.5–12.1)	3.5 (1.8–11.2)	NR	VAS: 25 (0-90)

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Sen Ishita et al., 2021 (26)	38	17/38 (45%)	12 (9.1-14.9)	8 (5.3-10.6)	NR	NR
Rosar et al., 2021 (27)	17	5/17 (29%)	NR	3.7 (3.0-4.4)	NR	NR
Sanli et al., 2021 (28)	12	9/12 (75%)	10 (1-24)	4 (1-20)	NR	NR
Lawal et al., 2022 (29)	106	NR	15 (12.8-17.2)	14 (8.15-19.86)	NR	NR
Sathekge et al., 2022 (30)	53	30/53 (57%)	＞55 (NR)	22 (NR)	NR	NR
Ballal et al., 2023 (31)	63	NR	15 (10-19)	9 (7-15)	NR	VAS: 5 (0-10) Analgesic score: 2 (0-3) KPS: 70 (40-90) ECOG: 2 (0-4)
Selcuk et al., 2023 (32)	23	NR	7.7 (NR)	3.1 (NR)	NR	NR
Sathekge et al., 2024 (33)	488	NR	15.5 (13.4-18.3)	7.9 (6.8-8.9)	0/488 (0%)	NR

NR, not reported; OS, overall survival; PFS, progression-free survival; VAS: Visual analgesic score; KPS: Karnofsky Performance Status.

Table 5. *Treatment-related toxicity of the studies included.*

Author and year	Patients (N)	Hematological toxicity (n/N)		Nephrotoxicity (n/N)		Xerostomia (n/N)		Other side effects (n/N)
		Any grade	Grade≥3	Any grade	Grade≥3	Any grade	Grade≥3	
Kratochwil et al., 2018 (17)	40	NR	NR	NR	NR	19/40	NR	NR
Sathekge et al., 2019 (18)	17	NR	NR	1/17	1/17	17/17	0/17	NR
Khreish et al., 2020 (19)	20	① NR ② NR ③ NR	3/20 2/20 2/20	NR	0/20	13/20	0/20	nausea 1/20, fatigue 5/20, anorexia 4/20
Sathekge et al., 2020 (20)	73	① 27/73 ② 9/73 ③ 7/73	5/73 2/73 1/73	23/73	5/73	62/73	0/73	nausea 15/73, anorexia 23/73, constipation 19/73 fatigue 37/73, weight loss 28/73, hypoalbuminemia 14/73, dysuria 13/73, xerophthalmia 4/73
Satapathy et al., 2020 (21)	11	① 8/11 ② 5/11 ③ 5/11	1/11 0/11 2/11	1/11	1/11	8/11	1/11	nausea 2/11, constipation 2/11, fatigue 3/11, weight loss 2/11, anorexia 3/11

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Yadav et al., 2020 (22)	28	① 28/28 ② 11/28 ③ 4/28	1/28 0/28 0/28	4/28	0/28	8/28	0/28	fatigue 15/28
van der Doelen et al., 2021 (23)	13	① 0/13 ② 0/13 ③ 0/13	0/13 0/13 0/13	0/13	0/13	13/13	0/13	NR
Zacherl et al., 2021 (24)	14	① 14/14 ② 5/14 ③ 6/14	3/14 1/14 0/14	2/14	0/14	5/14	0/14	dysgeusia 6/14, anorexia 9/14, nausea 5/14, fatigue 12/14, weightloss 4/14
Feuerecker et al., 2021 (25)	26	① 15/26 ② 13/26 ③ 14/26	9/26 7/26 5/26	5/26	0/26	26/26	0/26	fatigue 12/26, Weight loss 3/26, anorexia 8/26
Sen Ishita et al., 2021 (26)	38	① 11/38 ② 6/38 ③ 4/38	0/38 0/38 3/38	NR	NR	37/38	5/38	weight loss 21/38, hearing loss 2/38 nausea 9/38
Rosar et al., 2021 (27)	17	① 17/17 ② 5/17 ③ 3/17	0/17 0/17 1/17	7/17	0/17	5/17	0/17	NR
Sanli et al., 2021 (28)	12	① 11/12 ② 2/12 ③ 3/12	0/12 0/12 1/12	2/12	0/12	12/12	0/12	NR

(continued)

Lawal et al., 2022 (29)	106	① 43/106 ② 40/106 ③ 33/106	1/106 3/106 3/106	NR	NR	NR	NR	NR
Sathekge et al., 2022 (30)	53	① 8/53 ② 5/53 ③ 5/53	1/53 1/53 0/53	10/53	3/53	43/53	0/53	NR
Ballal et al., 2023 (31)	63	① 52/56 ② 12/56 ③ 9/56	2/56 3/56 0/56	2/56	1/56	18/56	0/56	fatigue 41/56, nausea 7/56, vomiting 7/56, gstritis 15/56, anorexia 24/56, myalgia 21/56, constipation 13/56, ascites with pleural effusion 1/56
Selcuk et al., 2023 (32)	23	NR	NR	NR	NR	23/23	NR	NR
Sathekge et al., 2024 (33)	488	① 329/488 ② 198/488 ③ 230/488	64/488 19/488 32/488	272/488	22/488	347/488	NR	NR

① anemia; ② leucopenia; ③ thrombocytopenia; NR, not reported.

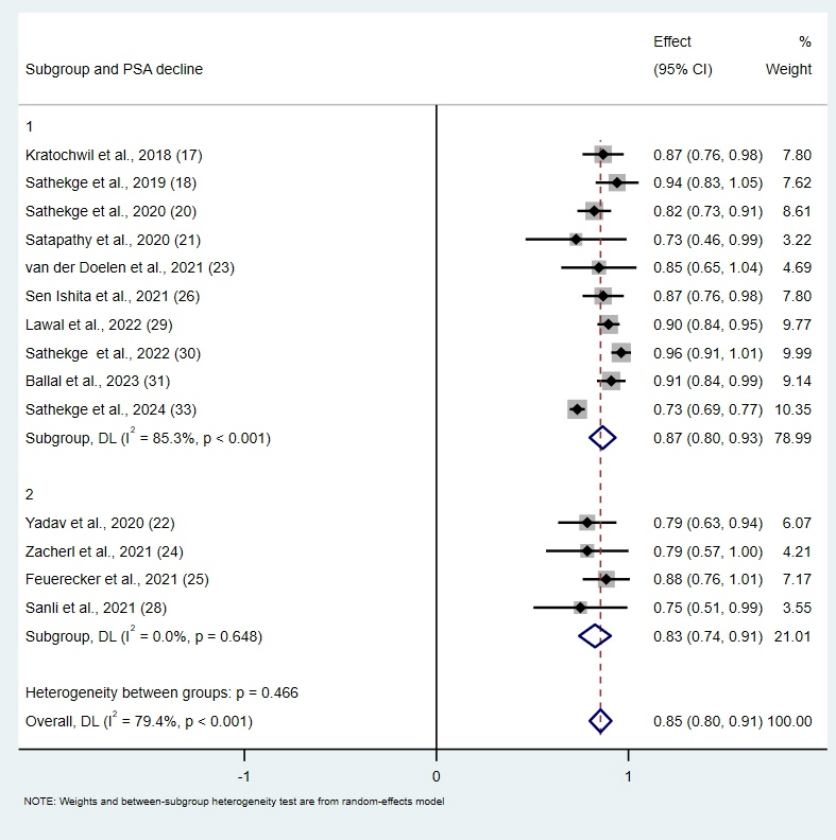

Figure 2. Forest plot for PSA decline after treatment.

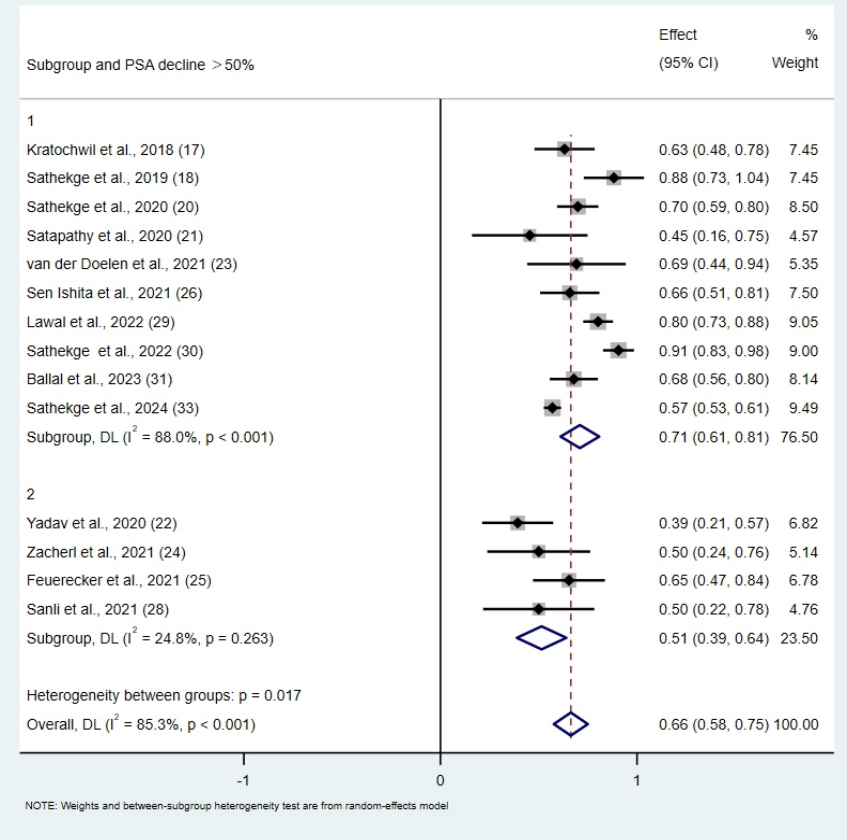

Figure 3. Forest plot for > 50% PSA decline after treatment.

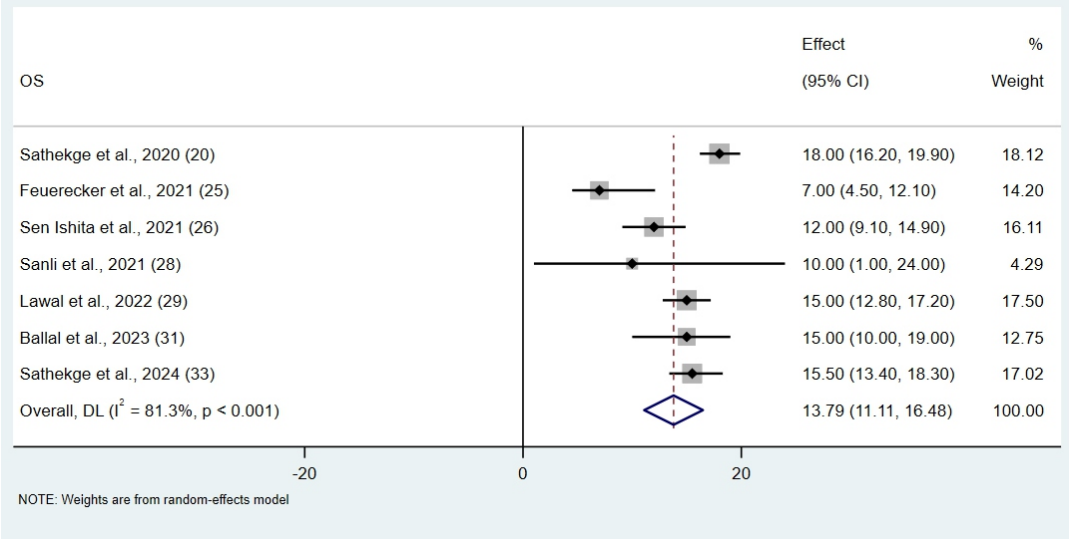

Figure 4. Forest plot for overall survival.

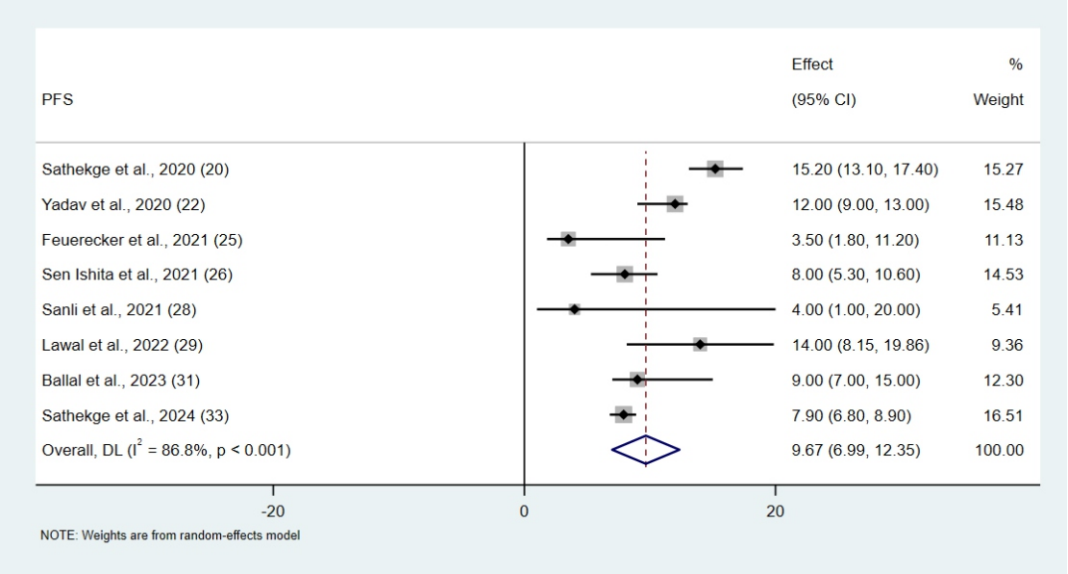

Figure 5. Forest plot for progression-free survival.

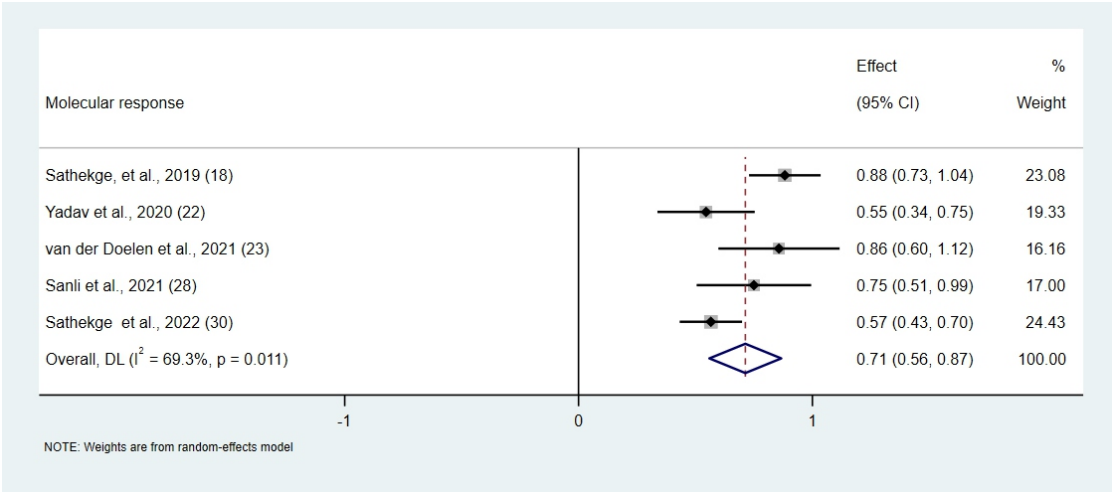

Figure 6. Forest plot for molecular response.

individuals at any grade, with only 0.6% (6/1005) experiencing grade III or higher xerostomia. The second most common event was anemia, affecting 54.3% (546/1005), with grade III or higher anemia observed in 8.7% (87/1005). Leukopenia occurred in 30.4% (306/1005), with grade III or higher leukopenia seen in 3.6% (36/1005), while thrombocytopenia affected 31.8% (320/1005), with grade III or higher thrombocytopenia observed in 4.7% (47/1005). Renal toxicity was reported in 32.0% (322/1005), with grade III or higher renal toxicity observed in 3.3% (33/1005). Other adverse events included fatigue (11.9% [120/1005]), anorexia (6.7% [67/1005]), weight loss (5.8% [58/1005]), constipation (3.4% [34/1005]), and nausea (3.8% [38/1005]). Furthermore, some studies have reported rare adverse reactions, such as urinary difficulty, dry eyes, vomiting, muscle pain, etc. Treatment-related deaths were reported in only one study, with three out of eleven patients experiencing treatment-related deaths.

A total of 9 studies reported anemia. After excluding data that could not be analyzed, we applied a random-effects model and subgroup analysis based on previous standards. The final forest plot indicated an incidence of anemia of 0.59 (95% CI: 0.41-0.76). A total of 11 studies reported leucopenia and thrombocytopenia, with the final forest plot showing incidences of 0.28 (95% CI: 0.18-0.38) for leukopenia and 0.26 (95% CI: 0.14-0.38) for thrombocytopenia. Furthermore, in studies where over 50% of patients received ^{177}Lu treatment, the incidences of leukopenia and thrombocytopenia were higher, at 0.36 (95% CI: 0.22-0.50) and 0.33 (95% CI: 0.13-0.54), respectively. A total of 10 studies reported renal toxicity, with an incidence of 0.19 (95% CI: 0.02-0.36). Finally, 9 studies reported xerostomia, with an incidence of 0.62 (95% CI: 0.48-0.77). The forest plots about adverse events are shown in Figures 7-11.

Discussion

This systematic review and meta-analysis of 17 studies comprehensively evaluated the efficacy and safety of ^{225}Ac-PSMA RLT in mCRPC. Our analysis indicates that ^{225}Ac-PSMA RLT is effective with limited adverse reactions in mCRPC patients. Approximately 85% of patients experienced a decrease in PSA levels following treatment, with around 66% of patients experiencing a decrease of over 50%. The average PFS and OS were 9.67 and 13.79 months, respectively. This conclusion is undoubtedly promising for patients with advanced prostate cancer who have failed other treatment modalities. Xerostomia was the most prominent side effect in ^{177}Lu/^{225}Ac-PSMA RLT for prostate cancer [37], with 63.5% of patients in our study experiencing xerostomia, mostly at grade II or below and

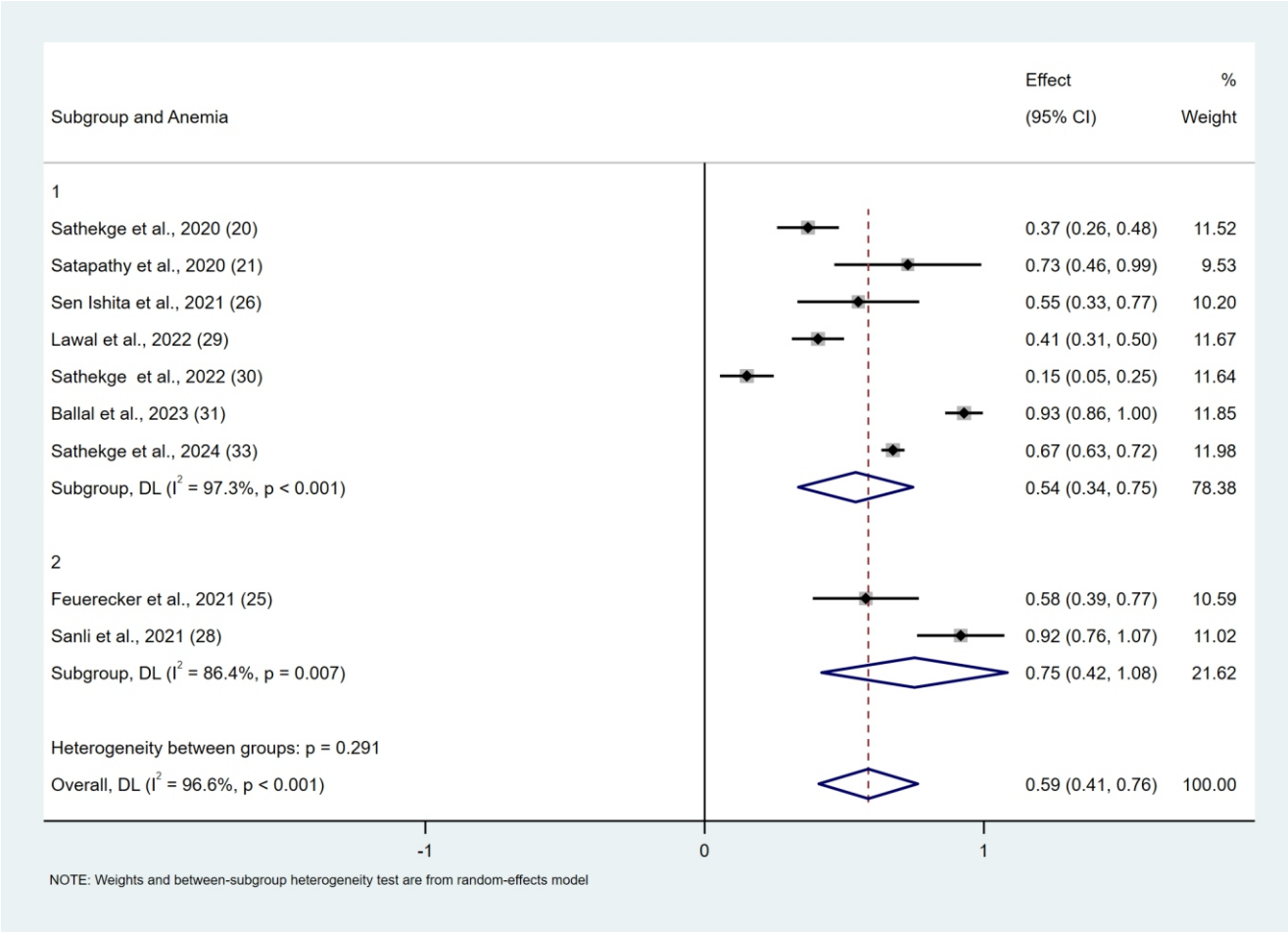

Figure 7. Forest plot for anemia .

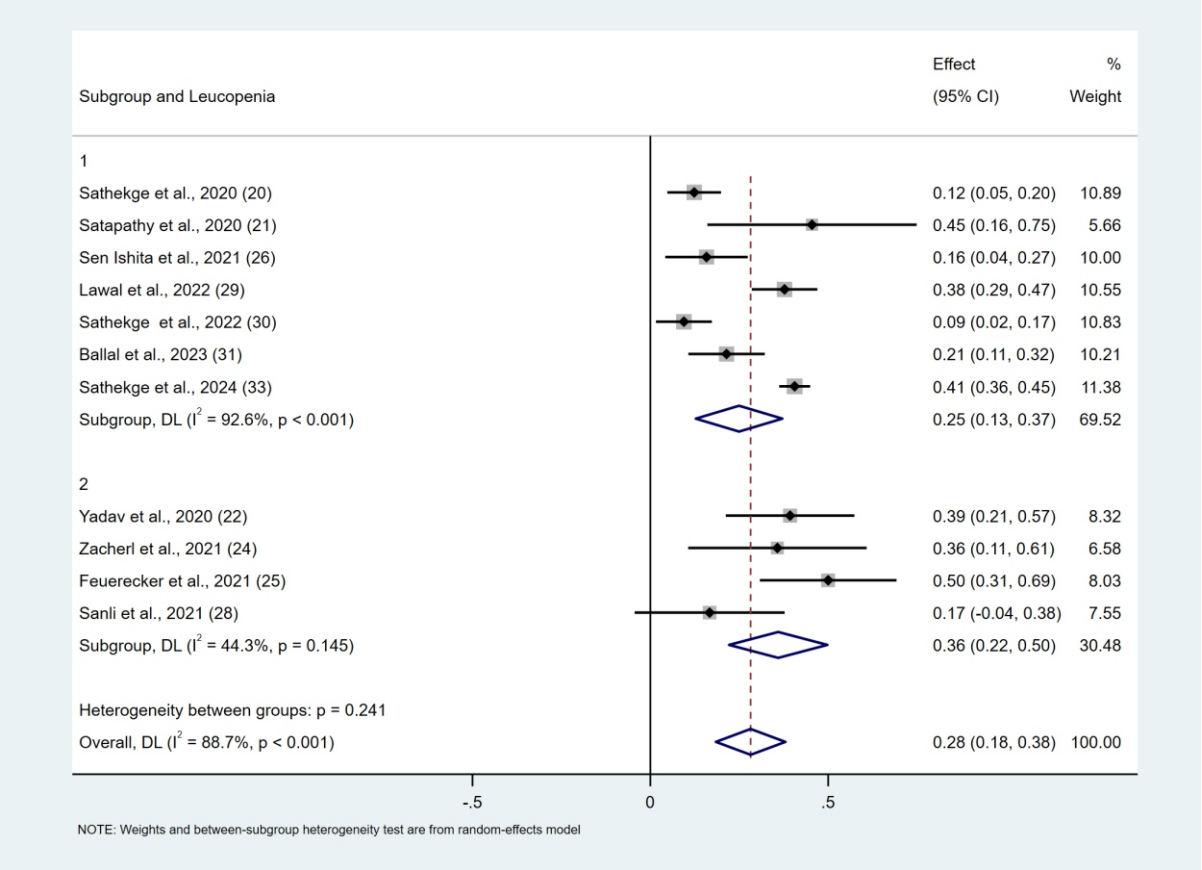

Figure 8. Forest plot for leucopenia.

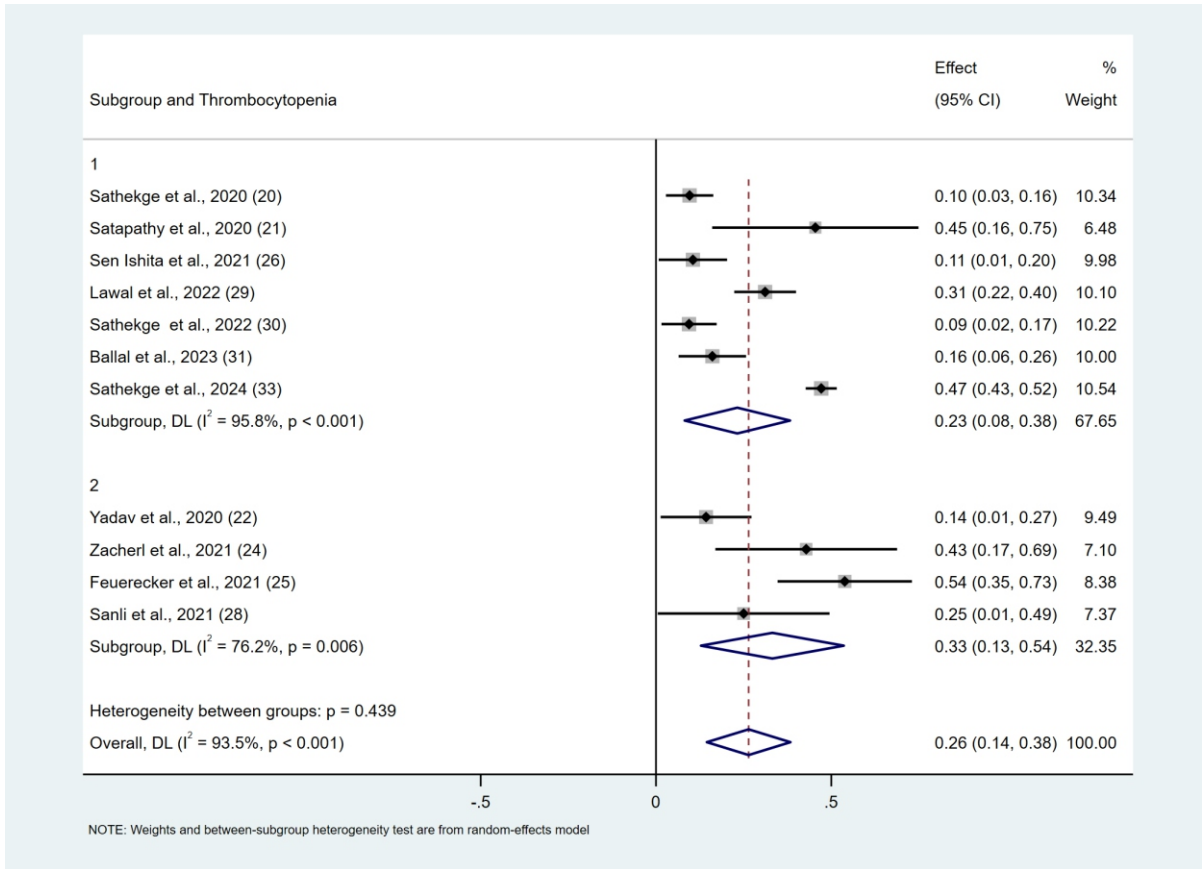

Figure 9. Forest plot for thrombocytopenia.

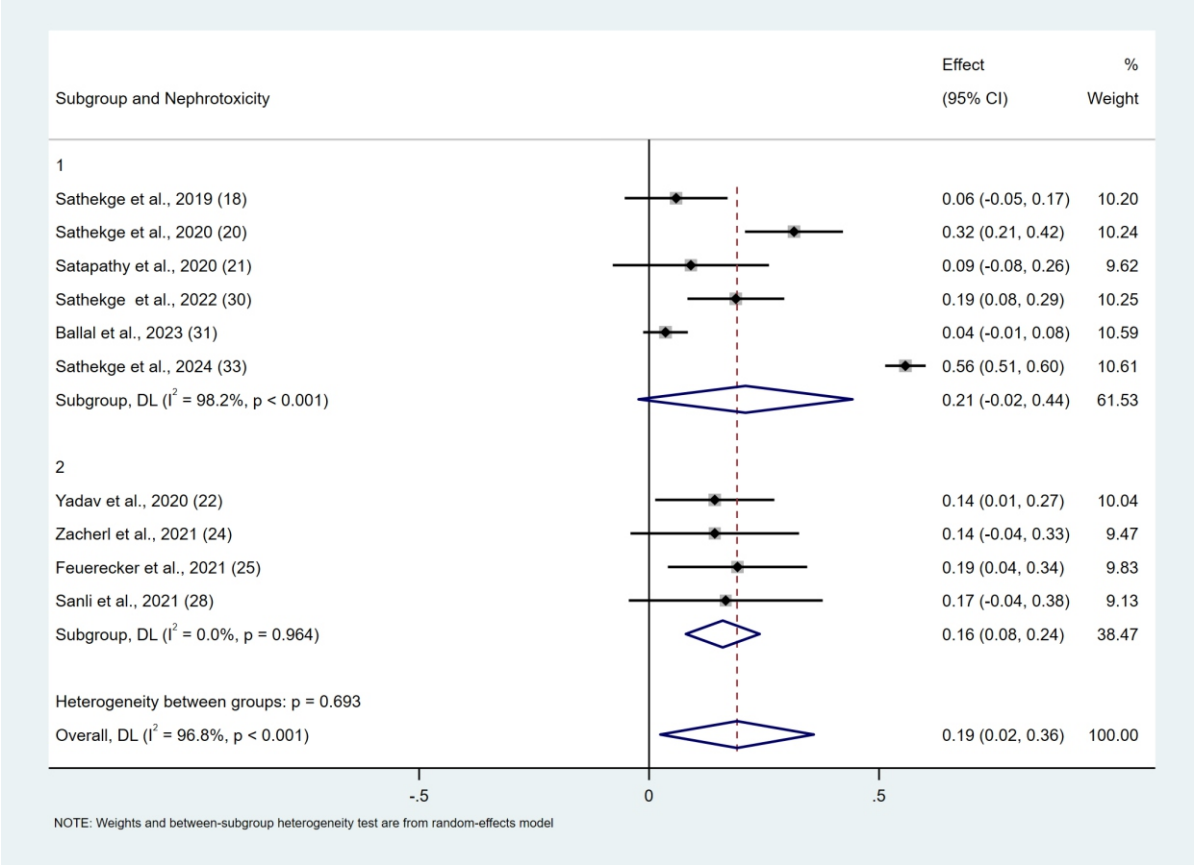

Figure 10. Forest plot for nephrotoxicity.

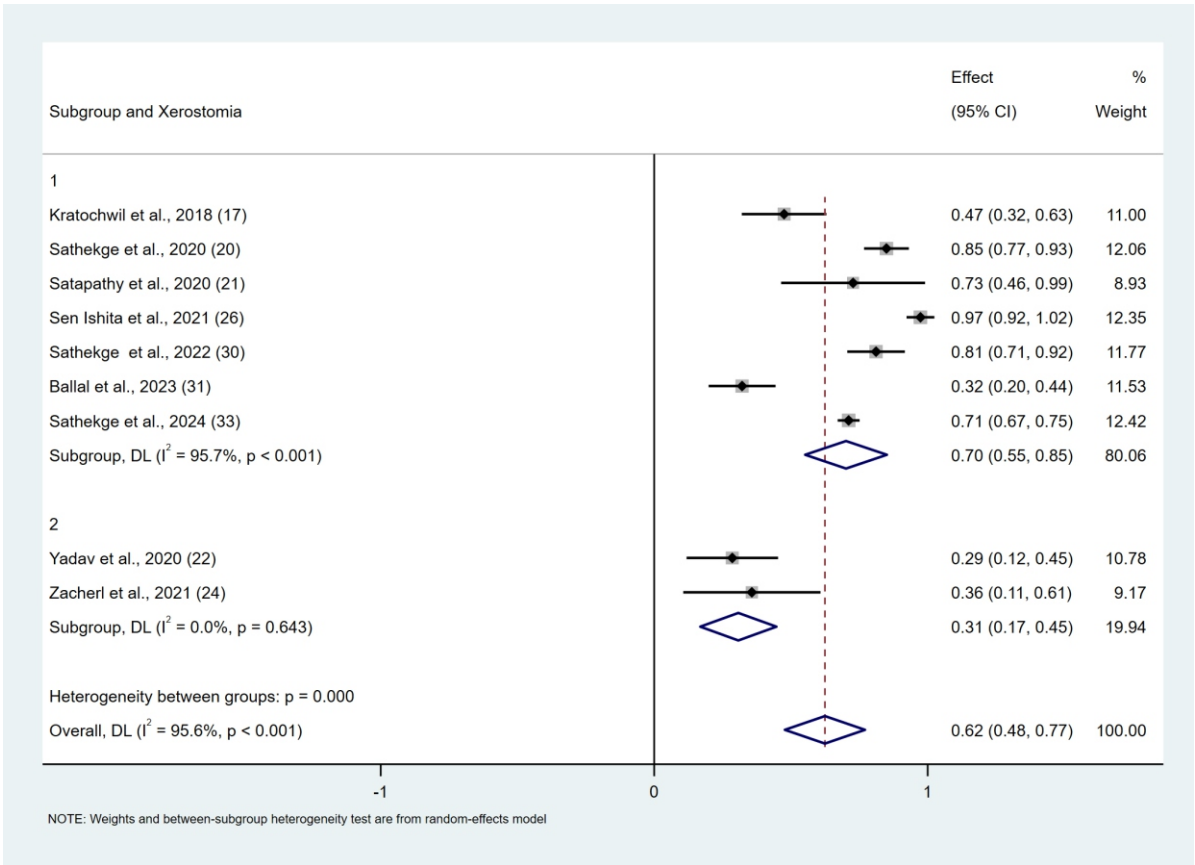

Figure 11. Forest plot for xerostomia.

and transient. The presence of severe xerostomia, hematologic toxicity, and renal toxicity in only a minority of patients suggests that this treatment modality is a viable option for mCRPC patients. Severe xerostomia may contribute to treatment discontinuation in some patients. Hence, some studies have explored methods to reduce salivary gland uptake, such as adding cold PSMA-11 [38] or substituting Glu in alternative pharmacophores [39].

Due to the potential influence of prior ^{177}Lu treatment on treatment outcomes [40], we conducted subgroup analyses to determine whether more than 50% of patients in the included studies had received ^{177}Lu treatment. Our analysis revealed a lower proportion of patients experiencing >50% PSA decrease in studies where more than 50% of patients had received ^{177}Lu treatment. Therefore, we speculate that prior ^{177}Lu treatment may impact the efficacy of targeted alpha therapy with ^{225}Ac. However, due to the limited number of studies included, we cannot confirm the validity of this hypothesis nor its potential impact on OS and PFS. Thus, more clinical research is needed to explore this issue further.

Furthermore, in our systematic review, we included two studies [19, 27] in which mCRPC patients were given ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617 in the same cycle. One study [19] indicated that 90% of patients experienced a reduction in PSA to some extent, with a PFS of 19 months and an OS of 48 months. Sixty-five percent of patients experienced xerostomia. However, another study [27] showed only 59% of patients experiencing any level of PSA reduction, and a PFS of only 3.7 months. Anemia, leukopenia, thrombocytopenia, nephrotoxicity, and xerostomia appeared in 100%, 29%, 17%, 41%, and 29% of patients, respectively. As mentioned earlier, in single-agent ^{225}Ac treatment, the overall incidence of PSA reduction at any level is 85%, with PFS and OS values of 9.7 months and 13.8 months, respectively. The overall incidence of adverse reactions is as follows: anemia 59%, leukopenia 28%, thrombocytopenia 26%, nephrotoxicity 19%, and xerostomia 62%. Therefore, the results of these two studies taken together are not yet conclusive about efficacy and safety of concurrent ^{177}Lu/^{225}Ac therapy compared with single-agent ^{225}Ac therapy. Hence, further research is needed to explore the potential value of concurrent ^{177}Lu/^{255}Ac therapy in the treatment of mCRPC.

However, several limitations of the present study should be acknowledged. While we included one recent large-sample study, the majority of studies were small-sample and predominantly single-arm retrospective observational studies, which are associated with a higher risk of bias. Additionally, these studies had short follow-up periods, limiting the analysis of patient survival, and there were few studies assessing OS, PFS, and comprehensive molecular response. Consequently, the data available for synthesis were limited. Furthermore, not all studies reported all adverse reactions; some only reported one or a few specific adverse reactions. When analyzing the results, we assumed that if a study did not report a certain adverse reaction, it meant that the reaction did not occur in that study. However, this assumption may lead to an underestimation of the incidence of adverse reactions associated with ^{225}Ac-PSMA RLT, as it cannot be ruled out that some adverse reactions occurred in certain studies but were not reported. Lastly, there was heterogeneity across trials in terms of study design, inclusion of other diseases, prostate cancer progression, previous treatment modalities, and PSMA expression levels. Therefore, evaluating the efficacy and safety of ^{225}Ac-PSMA RLT still requires high-quality, multicenter, prospective, randomized controlled trials.

In conclusion, the treatment of mCRPC patients with ^{225}Ac-PSMA RLT appears to be a safe and effective option, demonstrating a relatively low incidence of treatment-related toxicities. Given these findings, it may serve as a promising therapeutic strategy for mCRPC patients who have progressed after other late-stage treatments. Furthermore, prior exposure to ^{177}Lu-PSMA therapy may influence PSA response rates in subsequent ^{225}Ac-PSMA treatment; however, additional high-quality clinical trials are needed to clarify its impact and underlying mechanisms.

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