Effects of ^{225}Ac-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy in Metastatic Castration-Resistant Prostate Cancer: A Meta-Analysis

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Prostate-specific membrane antigen (PSMA), overexpressed in prostate cancer, has become a popular target for radionuclide-based theranostic applications in the advanced stages of prostate cancer. We conducted a meta-analysis of the therapeutic effects of PSMA-targeting α-therapy (^{225}Ac-PSMA radioligand therapy [RLT]) in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** A systematic search was performed using the keywords "mCRPC," "^{225}Ac-PSMA," and "alpha therapy." Therapeutic responses were analyzed as the pooled proportions of patients with more than a 50% prostate-specific antigen (PSA) decline and any PSA decline. Survival outcomes were analyzed by estimating summary survival curves for progression-free survival and overall survival. Adverse events were analyzed as the pooled proportions of patients with xerostomia and severe hematotoxicity (anemia, leukocytopenia, and thrombocytopenia). **Results:** Nine studies with 263 patients were included in our meta-analysis. The pooled proportions of patients with more than a 50% PSA decline and any PSA decline were 60.99% (95% CI, 54.92%–66.83%) and 83.57% (95% CI, 78.62%–87.77%), respectively. The estimated mean progression-free survival and mean overall survival were 9.15 mo (95% CI, 6.69–11.03 mo) and 11.77 mo (95% CI, 9.51–13.49 mo), respectively. The pooled proportions of patients with adverse events were 62.81% (95% CI, 39.34%–83.46%) for xerostomia, 14.39% (95% CI, 7.76%–22.63%) for anemia, 4.12% (95% CI, 0.97%–9.31%) for leukocytopenia, and 7.18% (95% CI, 2.70%–13.57%) for thrombocytopenia. **Conclusion:** In our study, around 61% of patients had more than a 50% PSA decline and 84% of patients had any PSA decline after ^{225}Ac-PSMA RLT. The common adverse events in ^{225}Ac-PSMA RLT were xerostomia in 63% of patients and severe hematotoxicity in 4%–14% of patients.

Key Words: ^{225}Ac; radioligand therapy; prostate-specific membrane antigen; prostate-specific antigen; xerostomia

J Nucl Med 2022; 63:840–846
DOI: 10.2967/jnumed.121.262017

The increasing worldwide incidence of prostate cancer is inevitable because of the increasing number of elderly men (*1*). The end-stage form of prostate cancer, known as metastatic castration-resistant prostate cancer (mCRPC), is a progressive disease with limited therapeutic options despite androgen deprivation therapy (*2*). Although several treatment options such as second-generation antiandrogen therapy, taxane-based chemotherapy, and ^{223}Ra are available, a novel treatment approach is necessary given the devastating and lethal course of mCRPC (*3*).

Prostate-specific membrane antigen (PSMA) is a type II membrane glycoprotein overexpressed in prostate carcinoma, and it has been recognized as a reliable biomarker reflecting disease burden in dedifferentiated and castration-resistant prostate cancer (*4,5*). Targeting PSMA with diagnostic and therapeutic radionuclide allows the use of the theranostic approach in patients with recurrent or metastatic prostate cancer (*6*). Recently, the first PSMA-targeting diagnostic radiotracer, ^{68}Ga-PSMA-11, was approved by the U.S. Food and Drug Administration, providing the foundation for PSMA-based theranostics.

PSMA-based radioligand therapy (RLT) with ^{177}Lu, a β-ray–emitting therapeutic radionuclide, has been used in European countries since 2015 for compassionate use in patients with mCRPC (*7,8*). Since then, several studies have reported positive results when using ^{177}Lu-PSMA RLT (*9,10*). However, up to 30%–40% of patients were found to be refractory to ^{177}Lu-PSMA RLT during clinical trials and showed hematotoxicity, which limits dose escalation (*11*).

α-particle–emitting radionuclides, which have higher energy transfer rates and shorter pathlengths, have attracted great attention as an alternative to β-ray–emitting radionuclides for PSMA-based RLT (*12*). ^{225}Ac has been the first choice as an α-particle–emitting radionuclide in recent experimental PSMA-based RLT for managing patients with mCRPC (*13–21*). However, given the limited availability of ^{225}Ac coupled with the unstructured clinical setting in these exploratory studies, there is a lack of strong evidence to guide physicians in managing patients with mCRPC using α-particle–emitting RLT. In this context, we conducted a meta-analysis to estimate the therapeutic response, survival outcome, and adverse event of patients with mCRPC who received ^{225}Ac-PSMA RLT.

MATERIALS AND METHODS

Data Search and Study Selection

A systematic search of PubMed, Embase, the Cochrane Library, CINAHL, and Web of Science was conducted on June 10, 2021. The searching keywords were as follows: "metastatic castration-resistant prostate cancer (mCRPC)," "actinium-225 (^{225}Ac) prostate-specific membrane antigen (PSMA)," and "alpha therapy." Studies that reported the therapeutic response according to the prostate-specific antigen (PSA) evaluation, survival outcome, or adverse event of patients with mCRPC who received ^{225}Ac-PSMA RLT were selected. The search was restricted to publications between 2000 and 2021 written in English. Therapeutic responses were confined to more than a 50% PSA decline or any PSA decline after ^{225}Ac-

Received Jan. 26, 2021; revision accepted Aug. 20, 2021.
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Published online Sep. 9, 2021.

PSMA RLT. Abstracts, dosimetry/synthesis-related articles, case reports, reviews, editorials, and articles with fewer than 5 patients were not included. When multiple studies were published from the same group, studies with a completely different patient population were included to avoid duplication. Two reviewers independently screened the literature and unanimously selected eligible studies for final inclusion. The protocol of this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration no. CRD42021226139). Institutional review board approval was not required for this meta-analysis because it evaluated published studies.

Data Extraction and Quality Assessment

Publication-related clinical data were extracted from the included articles, and the following information was recorded: first author, year of publication, imaging indication of RLT, number of patients, α-particle–emitting RLT agent, therapeutic dose, therapy cycle, median PSA, median alkaline phosphatase, prechemotherapy (%), prior ^{177}Lu-PSMA (%), prior ^{233}Ra (%), time of PSA evaluation after RLT, therapeutic response, survival outcome, duration of survival follow-up, and adverse events. Two reviewers evaluated each article according to the Newcastle–Ottawa Scale for scoring the quality of nonrandomized studies in meta-analysis (*22*). This quality scale was categorized into 3 groups (selection, comparability, and outcome) with a perfect score of 8. A maximum of 3 scores could be awarded for selection and outcome, and a maximum of 2 scores could be given for comparability. In cases of discrepancy, 2 reviewers made a consensus decision.

Statistical Analysis

Forest plots were generated to evaluate the effects of ^{225}Ac-PSMA RLT. Therapeutic responses were analyzed as the pooled proportions of patients with more than a 50% PSA decline and any PSA decline, with 95% CIs. Survival outcomes were analyzed by estimating summary survival curves with random effects for progression-free survival (PFS) and overall survival (OS) using the MetaSurv package in R (*23*). Survival data were read from the Kaplan–Meier curves using the Engauge Digitizer (http://markummitchell.github.io/engauge-digitizer/) (*24*). Adverse events were analyzed as the pooled proportions of patients with xerostomia and severe hematotoxicity (anemia, leukocytopenia, and thrombocytopenia) with 95% CI. Meta-regression analysis was performed to determine the effect of median PSA, median alkaline phosphatase, prechemotherapy, prior ^{177}Lu-PSMA, and prior ^{223}Ra on the therapeutic response and adverse events. Finally, funnel plots were generated to visually investigate publication bias, and the Egger test was used to evaluate the asymmetry of the funnel plots (*25,26*). Heterogeneity between the studies (for therapeutic responses and adverse events) was assessed by I^2 statistics and χ^2 tests (*27*). The fixed-effects model was used when I^2 was not more than 50% and P was at least 0.1 (Cochran Q test), and the random-effects model was used when I^2 was more than 50% or P was less than 0.1 (Cochran Q test). Statistical analyses were performed mainly using MedCalc, version 19.1.7, for Microsoft Windows. Comprehensive Meta-analysis Software, Version 3, was used for meta-regression.

A P value less than 0.05 was considered statistically significant.

RESULTS

Study Characteristics

Through electronic database searches, we identified 220 records (Supplemental Tables 1–5; supplemental materials are available at http://jnm.snmjournals.org), and 112 records remained after removing duplicates. Of these, 42 records were excluded on the basis of the title and abstract because of the use of diagnostic radiotracers for PSMA ($n = 4$), the use of other therapeutic radiotracers ($n = 21$), in vitro and in vivo preclinical studies ($n = 7$), and no association with RLT or PSMA ($n = 10$). After a thorough analysis of the full text of the remaining 70 articles, 61 articles were excluded because of an association with dosimetry, safety, or physics ($n = 11$); association with synthesis/chemistry ($n = 3$); being published as case report/review/editorial ($n = 44$); and inadequate data ($n = 3$). Finally, 9 studies with 263 patients were included in our meta-analysis (*13–19*) (Fig. 1). No qualifying study was missed after hand-searching by the reviewers.

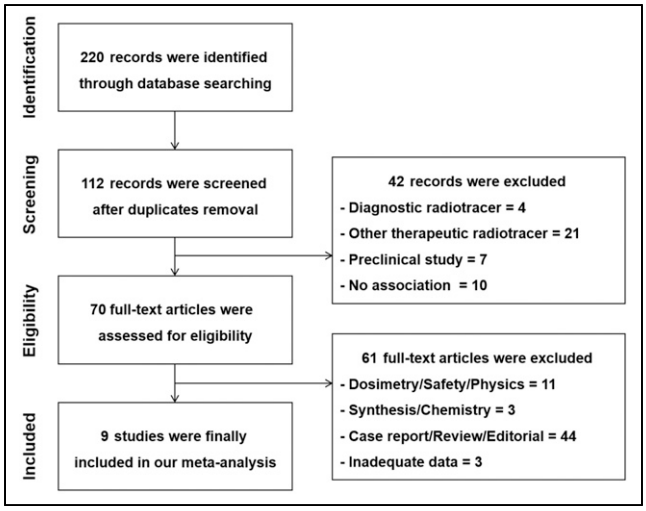

FIGURE 1. Flowchart of study selection process.

Seven of the 9 studies were conducted under a retrospective design (*13,15–19,21*), and 2 studies were conducted prospectively (*14,20*). ^{225}Ac-PSMA-617 was administered in 8 studies (*13–15, 17–21*) and ^{225}Ac-PSMA-I&T was used in 1 study (*16*) as α-particle–emitting RLT agents. The therapeutic dose range per cycle was reported in 3 studies as 1.5–13 MBq (*13,16,17*), and the total number of treatment cycles ranged from 1 to 8. The median level of baseline PSA was 57.2–331 ng/mL, and the follow-up time for PSA evaluation was 2–6 wk after RLT. Therapeutic responses were reported in all 9 studies involving 263 patients (*13–21*), and survival outcomes were identified for 200 patients in 6 of the studies (*13–15,17,19,20*). Adverse events were documented in 8 studies involving 225 patients, which included xerostomia and severe hematotoxicity (*13–20*) (Table 1). Quality assessment of all 9 studies was performed, and the scores of the Newcastle–Ottawa Scale ranged from 6 to 8 (Table 2).

Therapeutic Response

The pooled proportion of patients with more than a 50% PSA decline was 60.99% after ^{225}Ac-PSMA RLT using a random-effects model (95% CI, 54.92%–66.83%), and the I^2 statistic was 25.25% ($P = 0.219$; Cochran Q test). The pooled proportion of patients with any PSA decline was 83.57% after ^{225}Ac-PSMA RLT using a fixed-effects model (95% CI, 78.62%–87.77%), and the I^2 statistic was 0.00% ($P = 0.844$; Cochran Q test) (Fig. 2; Table 3).

Survival Outcome

The estimated mean PFS was 9.15 mo (median PFS, 7.78 mo) after ^{225}Ac-PSMA RLT using a random-effects model (95% CI, 6.69–11.03 mo), and the I^2 statistic was 7.29%. The estimated mean OS was 11.77 mo (median OS, 11.85 mo) after ^{225}Ac-PSMA RLT using a random-effects model (95% CI, 9.51–13.49 mo), and the I^2 statistic was 0.00% (Fig. 3; Table 3).

TABLE 1
Baseline Characteristics of Included Studies

Author	Year	Imaging indication of RLT	Patients (*n*)	α-RLT agent	Median/mean therapeutic dose per cycle	Median cycles of therapy	Median PSA* (ng/ml)	Median ALP* (U/L)	No. of pre-chemotherapy	No. of prior ^{177}Lu-PSMA	No. of prior ^{223}Ra	Time of PSA evaluation after RLT	Therapeutic response	Survival outcome†	Median duration of survival follow-up (mo)	Adverse events
Feuerecker	2021	Uptake higher than liver in PSMA ligand PET/CT	26	^{225}Ac-PSMA-617	9 MBq (range, 4–13 MBq)	2 (range, 1–6)	331 (142–682)	200 (143–517)	25 (96%)	26 (100%)	6 (23%)	After 6 wk	>50% of PSA decline, any PSA decline	PFS (16), OS (16)	6.4	Xerostomia, hematotoxicity
Rosar	2021	Not mentioned	15	^{225}Ac-PSMA-617	2.7 ± 1.1 MBq	2 (range, 1–6)	272 (58–3389)	115 (8–1659)	10 (67%)	0 (0%)	3 (20%)	After 6 ± 2 wk	>50% of PSA decline, any PSA decline	PFS (14), OS (12)	19.4	Xerostomia, hematotoxicity
Sen	2021	^{68}Ga-PSMA-11 uptake ≥ ^{68}Ga-PSMA-11 uptake in parotid glands	38	^{225}Ac-PSMA-617	100 kBq/kg	2 (range, 2–5)	147 (4.9–1400)	(−)	38 (100%)	9 (24%)	2 (5%)	After 2 wk	>50% of PSA decline, any PSA decline	PFS (26), OS (22)	14	Xerostomia, hematotoxicity
Zacherl	2021	Sufficient PSMA expression on ^{18}F-PSMA-1007 PET/CT	14	^{225}Ac-PSMA-I&T	7.8 MBq (range, 6.0–8.5 MBq)	Range, 1–5	112 (20.5–818)	143 (67–695)	12 (86%)	11 (79%)	2 (14%)	After 4 wk	>50% of PSA decline, any PSA decline	(−)	5.9	Xerostomia, hematotoxicity
Khreish	2020	Uptake higher than normal liver uptake on ^{68}Ga-PSMA-11 PET/CT	20	^{225}Ac-PSMA-617	5.3 MBq (range, 1.5–7.9 MBq)	1	215 (6–5547)	160 (53-–917)	18 (90%)	20 (100%)	4 (20%)	After 2-4 wk	>50% of PSA decline, any PSA decline	PFS (16), OS (9)	5.5	Xerostomia, hematotoxicity
Satapathy	2020	Tracer-avid lesion on ^{68}Ga-PSMA-11 PET/CT, with SUV_{max} of lesion being ≥1.5 times greater than that of normal liver	11	^{225}Ac-PSMA-617	100 kBq/kg	(−)	158 (35–840)	(−)	10 (91%)	5 (45%)	0 (0%)	After 6 wk	>50% of PSA decline, any PSA decline	(−)	(−)	Xerostomia, hematotoxicity
Sathekge	2020	Uptake greater than twice normal physiologic liver uptake on ^{68}Ga-PSMA-11 PET/CT	73	^{225}Ac-PSMA-617	(−)	3 (range, 1–8)	57.2	154	27 (37%)	14 (19%)	0 (0%)	After 4 wk	>50% of PSA decline, any PSA decline	PFS (23), OS (13)	9	Xerostomia, hematotoxicity
Yadav	2020	Intense PSMA expression on ^{68}Ga-PSMA-11 PET/CT ≥ liver	28	^{225}Ac-PSMA-617	100 kBq/kg	3 (range, 1–7)	222.2 (47–443.2)	(−)	24 (86%)	15 (54%)	0 (0%)	After 2 wk	>50% of PSA decline, any PSA decline	PFS (8), OS (6)	10	Xerostomia, hematotoxicity
Kratochwil	2018	^{68}Ga-PSMA-11 PET/CT–positive or ^{99m}Tc-MIP-1427 scan–positive lesion with higher uptake than liver	40	^{225}Ac-PSMA-617	100 kBq/kg	3–5	169	181	35 (88%)	0 (0%)	9 (23%)	After 4 wk	>50% of PSA decline, any PSA decline	(−)	(−)	(−)

*Data in parentheses are range or interquartile range.
†Data in parentheses are number of events.
α-RLT = α-particle-emitting RLT; ALP = alkaline phosphatase.

TABLE 2
Quality Assessment of Included Studies Using Newcastle-Ottawa Scale

Author	Selection	Comparability	Outcome	Score
Feuerecker	⋆⋆⋆	⋆⋆	⋆⋆	7
Rosar	⋆⋆⋆	⋆	⋆⋆⋆	7
Sen	⋆⋆⋆	⋆	⋆⋆⋆	7
Zacherl	⋆⋆⋆	⋆	⋆⋆	6
Khreish	⋆⋆⋆	⋆	⋆⋆⋆	7
Satapathy	⋆⋆⋆	⋆	⋆⋆	6
Sathekge	⋆⋆⋆	⋆⋆	⋆⋆⋆	8
Yadav	⋆⋆⋆	⋆	⋆⋆⋆	7
Kratochwil	⋆⋆⋆	⋆	⋆⋆⋆	7

3 or 4 stars in Selection column AND 1 or 2 stars in Comparability column AND 2 or 3 stars in Outcome column = good quality; 2 stars in Selection column AND 1 or 2 stars in Comparability column AND 2 or 3 stars in Outcome column = fair quality; and 0 or 1 star in Selection column OR 0 star in Comparability column OR 0 or 1 star in Outcome column = poor quality.

Adverse Event

The pooled proportion of patients with xerostomia grade 1 or 2 was 62.81% after ^{225}Ac-PSMA RLT using a random-effects model (95% CI, 39.34%–83.46%), and the I^2 statistic was 92.04% ($P < 0.0001$; Cochran Q test). The pooled proportion of patients with anemia grade 3 or 4 was 14.39% after ^{225}Ac-PSMA RLT using a random-effects model (95% CI, 7.76%–22.63%), and the I^2 statistic was 59.32% ($P = 0.016$; Cochran Q test). The pooled proportion of patients with leukocytopenia grade 3 or 4 was 4.12% after ^{225}Ac-PSMA RLT using a random-effects model (95% CI, 0.97%–9.31%), and the I^2 statistic was 58.47% ($P = 0.018$; Cochran Q test). The pooled proportion of patients with thrombocytopenia grade 3 or 4 was 7.18% after ^{225}Ac-PSMA RLT using a random-effects model (95% CI, 2.70%–13.57%), and the I^2 statistic was 58.83% ($P = 0.017$; Cochran Q test) (Fig. 4; Table 4).

Meta-Regression

Meta-regression analysis for the therapeutic response showed no significant results (Supplemental Table 6). However, the results were significant for adverse events in terms of median PSA (leukocytopenia), median alkaline phosphatase (xerostomia and leukocytopenia), prechemotherapy (anemia and thrombocytopenia), prior ^{177}Lu-PSMA (leukocytopenia), and prior ^{223}Ra (leukocytopenia) (Table 5).

Publication Bias

Visual investigation of the funnel plots showed no evidence of publication bias for the therapeutic responses and adverse events of ^{225}Ac-PSMA RLT. Egger tests also demonstrated no evidence of funnel plot asymmetry (Fig. 5; Supplemental Fig. 1).

DISCUSSION

We investigated the effects of ^{225}Ac-PSMA RLT in patients with mCRPC through a meta-analysis. Around 61% of patients achieved more than a 50% PSA decline, and 84% of patients demonstrated any PSA decline after ^{225}Ac-PSMA RLT. The estimated mean PFS and mean OS were approximately 9 and 12 mo, respectively. Xerostomia grade 1 or 2 was observed in 63% of patients, and severe hematotoxicity was noted in approximately 4%–14% of patients.

In comparison with β-ray–emitting radionuclides, α-particle– emitting radionuclides offer several theoretic advantages (*12,28*). First, the relatively short range of penetration allows the selective killing of targeted tumor tissues while minimizing unwanted damage in the surrounding normal tissues. Second, higher-linear-energy transfer delivers intensive radiation to cancer cells, resulting in more effective DNA strand breakage and reducing the development of treatment resistance.

According to the Prostate Cancer Clinical Trials Working Group 3, the response to therapy of mCRPC patients should be assessed on the basis of PSA changes, and the commonly defined parameter is more than a 50% PSA

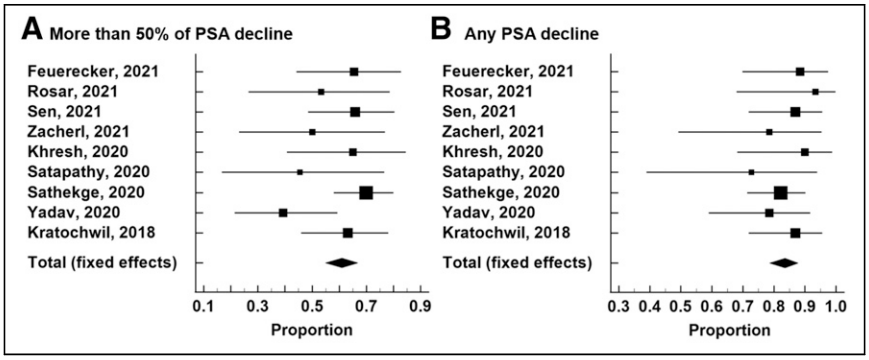

FIGURE 2. Forest plot for therapeutic responses after ^{225}Ac-PSMA RLT: more than 50% PSA decline (A) and any PSA decline (B).

TABLE 3
Summary of Therapeutic Responses and Survival Outcomes After ^{225}Ac-PSMA RLT

Therapeutic response and survival outcome	No. of studies	Model	Pooled estimate	95% CI of pooled estimate	I^2 (%)
>50% PSA decline	9	Fixed effects	60.99%	54.92%–66.83%	25.25
Any PSA decline	9	Fixed effects	83.57%	78.62%–87.77%	0.00
Mean PFS	6	Random effects	9.15 mo	6.69–11.03 mo	7.29
Mean OS	6	Random effects	11.77 mo	9.51–13.49 mo	0.00

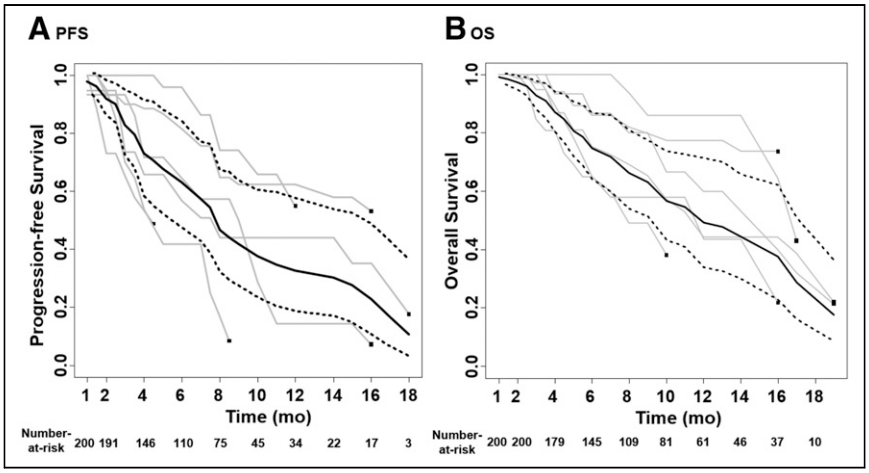

FIGURE 3. Survival outcome estimation after ^{225}Ac-PSMA RLT: PFS (A) and OS (B).

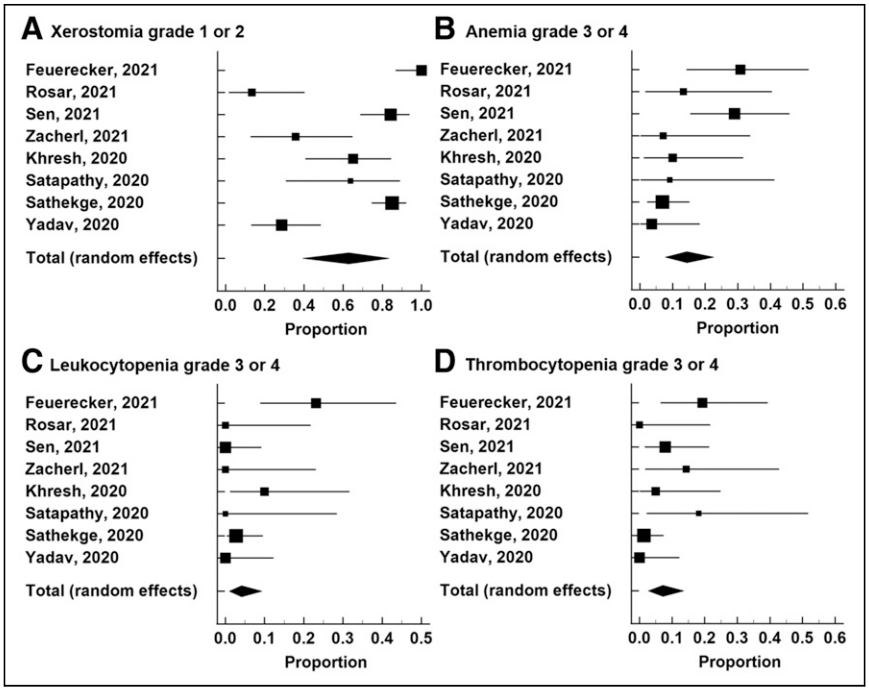

FIGURE 4. Forest plot for adverse events after ^{225}Ac-PSMA RLT: xerostomia grade 1 or 2 (A), anemia grade 3 or 4 (B), leukocytopenia grade 3 or 4 (C), and thrombocytopenia grade 3 or 4 (D).

decline (*29*). In our study, 61% (95% CI, 55%–67%) of patients showed more than a 50% PSA decline, which is higher than the response in a previous meta-analysis for ^{177}Lu-PSMA RLT (46%; 95% CI, 40%–53%) (*30*) and a previous phase 2 clinical trial of ^{177}Lu-PSMA-617 (57%) (*31*). As survival is an important marker in mCRPC patients, the secondary outcomes of our study were PFS and OS after ^{225}Ac-PSMA RLT. The median PFS (8 mo) and median OS (12 mo) in our study were similar to those (11 mo and 14 mo, respectively) in a previous meta-analysis of ^{177}Lu-PSMA RLT (*30*).

Despite the encouraging therapeutic response and survival of patients who received ^{225}Ac-PSMA RLT, dose reduction or discontinuation of the therapy is often required (*32*). Xerostomia is a major adverse event in ^{225}Ac-PSMA RLT (*33*), and our results revealed an incidence rate of 63% (95% CI, 39%–83%). A study highlighted the beneficial effects of sialendoscopy with steroid injection on salivary gland function after ^{225}Ac-PSMA RLT (*34*); however, it is an invasive procedure. Another study suggested that ^{225}Ac-PSMA/^{177}Lu-PSMA tandem therapy could improve salivary gland function (*17*). Therefore, more techniques are needed in addition to ^{225}Ac-PSMA RLT to protect salivary gland function (*35*). In a previous phase 2 clinical trial of ^{177}Lu-PSMA-617, the incidence rate of xerostomia grade 1 or 2 was 87%, which is similar to the incidence rate (63%; 95% CI, 39%–83%) in our study (*31*). Severe hematotoxicity is another common adverse event of ^{225}Ac-PSMA RLT in previous studies (*36*), and our study showed anemia grade 3 or 4 in 14% of cases (95% CI, 8%–23%), leukocytopenia grade 3 or 4 in 4% of cases (95% CI, 1%–9%), and thrombocytopenia grade 3 or 4 in 7% of cases (95% CI, 3%–14%). The incidence rates are similar to those in previous studies of ^{177}Lu-PSMA RLT (*10,30,37*). According to meta-regression analysis, tumor burden and previous damage to bone marrow and

TABLE 4
Summary of Adverse Events After ^{225}Ac-PSMA RLT

Adverse event	No. of studies	Model	Pooled proportion	95% CI of pooled proportion	I^2 (%)
Xerostomia grade 1 or 2	8	Random-effects	62.81%	39.34%–83.46%	92.04
Anemia grade 3 or 4	8	Random-effects	14.39%	7.76%–22.63%	59.32
Leukocytopenia grade 3 or 4	8	Random-effects	4.12%	0.97%–9.31%	58.47
Thrombocytopenia grade 3 or 4	8	Random-effects	7.18%	2.70%–13.57%	58.83

TABLE 5
Results of Meta-Regression Analysis for Adverse Event

Adverse event	Variable	No. of studies	Regression coefficient	*P*
Xerostomia grade 1 or 2	Median PSA	8	−0.0028	0.6448
	Median ALP	5	0.0700	0.0012*
	Prechemotherapy (%)	8	0.0049	0.8613
	Prior ^{177}Lu-PSMA (%)	8	0.0112	0.4814
	Prior ^{223}Ra (%)	8	−0.0061	0.9181
Anemia grade 3 or 4	Median PSA	8	0.0043	0.2482
	Median ALP	5	0.0194	0.0747
	Prechemotherapy (%)	8	0.0244	0.0235*
	Prior ^{177}Lu-PSMA (%)	8	0.0031	0.7643
	Prior ^{223}Ra (%)	8	0.0404	0.2761
Leukocytopenia grade 3 or 4	Median PSA	8	0.0092	0.0016*
	Median ALP	5	0.0352	0.0050*
	Prechemotherapy (%)	8	0.0237	0.2148
	Prior ^{177}Lu-PSMA (%)	8	0.0265	0.0013*
	Prior ^{223}Ra (%)	8	0.0990	0.0013*
Thrombocytopenia grade 3 or 4	Median PSA	8	0.0045	0.2505
	Median ALP	5	0.0216	0.2520
	Prechemotherapy (%)	8	0.0392	0.0208*
	Prior ^{177}Lu-PSMA (%)	8	0.0153	0.0937
	Prior ^{223}Ra (%)	8	0.0415	0.2755

*$P < 0.05$.
ALP = alkaline phosphatase.

salivary glands might adversely affect the toxicity of ^{225}Ac-PSMA RLT. Future studies should consider tumor burden and previous therapy history. Moreover, patient-based dosimetry is required to reduce adverse events and increase the antitumor activity of ^{225}Ac-PSMA RLT.

There were some limitations in this study. The included studies were few in number and had different patient profiles, and the therapeutic doses and cycles of ^{225}Ac-PSMA RLT were somewhat different. Differences in patient profiles likely contributed to the observed heterogeneity, which limits the generalizability of the pooled outcome estimates beyond the reported studies and requires careful interpretation, especially in the aspect of adverse events. Moreover, patient-based analyses could not be performed because of a lack of data on individual patients. In the future, prospective, randomized, multicenter clinical trials are needed to confirm the effects of ^{225}Ac-PSMA RLT.

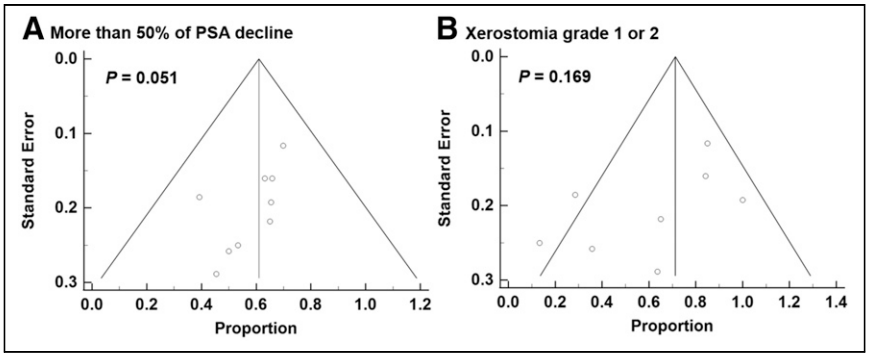

FIGURE 5. Funnel plot and Egger test for publication bias assessment: more than 50% PSA decline (A) and xerostomia grade 1 or 2 (B).

CONCLUSION

^{225}Ac-PSMA RLT may be an effective treatment option for patients with mCRPC. Our meta-analysis revealed that approximately 61% of patients (95% CI, 55%–67%) showed more than a 50% PSA decline and that 84% of patients (95% CI, 79%–88%) showed any PSA decline after ^{225}Ac-PSMA RLT. Among mCRPC patients who received ^{225}Ac-PSMA RLT, xerostomia (63% of patients; 95% CI, 39%–83%) was the most common adverse event, followed by severe hematotoxicity (4%–14% of patients; 95% CI, 1%–23%).

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank Seonok Kim, Msc (Department of Clinical Epidemiology and Biostatistics, Asan Medical Center) for statistical analysis of survival outcomes.

KEY POINTS

QUESTION: What are the effects of ^{225}Ac-PSMA RLT in patients with mCRPC?

PERTINENT FINDINGS: More than a 50% PSA decline and any PSA decline were observed in about 61% (95% CI, 55%–67%) and 84% (95% CI, 79%–88%), respectively of patients after ^{225}Ac-PSMA RLT. The estimated mean PFS and mean OS were about 9 mo (95% CI, 7–11 mo) and 12 mo (95% CI, 10–13 mo), respectively. Xerostomia was the most common adverse event (63%; 95% CI = 39-83%), followed by severe anemia (14%; 95% CI, 6%–23%), severe leukocytopenia (4%; 95% CI, 1-9%), and severe thrombocytopenia (7%; 95% CI, 3%–14%).

IMPLICATIONS FOR PATIENT CARE: PSMA-targeted α-therapy using ^{225}Ac-PSMA may be a novel therapeutic option for mCRPC patients.

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