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Effects of ^{225}Ac-labeled prostate-specific membrane antigen radioligand therapy in metastatic castration-resistant prostate cancer: A meta-analysis

Running title: ^{225}Ac-PSMA RLT effects in mCRPC patients

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ABSTRACT

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 alpha 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 50% of prostate-specific antigen (PSA) decline and any PSA decline. Survival outcomes were analyzed by estimating summary survival curves for progression-free survival (PFS) and overall survival (OS). 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 50% of PSA decline and any PSA decline were 60.99% [95% confidence interval (CI) = 54.92–66.83%] and 83.57% (95% CI = 78.62–87.77%), respectively. The estimated mean PFS and mean OS were 9.15 months (95% CI = 6.69–11.03 months) and 11.77 months (95% CI = 9.51–13.49 months), 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 50% of 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: actinium-225; radioligand therapy; prostate-specific membrane antigen; prostate-specific antigen; xerostomia

INTRODUCTION

Increasing worldwide incidence of prostate cancer is inevitable due to 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 a number of 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 de-differentiated 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 beta 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*).

Alpha particle-emitting radionuclides, which have higher energy transfer rates and

shorter path lengths, have attracted great attention as an alternative to beta ray-emitting radionuclides for PSMA-based RLT (*12*). ^{225}Ac has been the first choice as an alpha 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 alpha particle-emitting radioligand therapy (alpha 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, 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 (Ac-225) prostate-specific membrane antigen (PSMA),” and “alpha therapy”. Studies that reported the therapeutic response according to the prostate-specific antigen (PSA) evaluation, survival outcome, and/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 50% of PSA decline or any PSA decline after ^{225}Ac-PSMA RLT. Abstracts, dosimetry/synthesis-related articles, case reports, reviews, editorials, and articles with less than five 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, alpha RLT agent, therapeutic dose, therapy cycle, median PSA, median alkaline phosphatase (ALP), pre-chemotherapy (%), 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 non-randomized studies in meta-analysis (*22*). This quality scale was categorized into three groups (selection, comparability, and outcome) with a perfect score of 8. A maximum of three scores could be awarded for selection and outcome, and a maximum of two scores could be given for comparability. In cases of discrepancy, two 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 50% of PSA decline and any PSA decline with 95% confidence interval (CI). Survival outcomes were analyzed by estimating summary survival curves with random-effects for progression-free survival (PFS) and overall survival (OS) using MetaSurv package in R (*23*). Survival data were read from the Kaplan-Meier curves using the Engauge Digitizer (http://digitizer.sourceforge.net) (*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 ALP, pre-chemotherapy, 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 Egger's tests were 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 test (*27*). The fixed-effects model was used when $I^2 \leq 50\%$ and $P \geq 0.1$ (Cochran's Q test), and the random-effects model was used when $I^2 > 50\%$ or $P < 0.1$ (Cochran's Q test). Statistical analyses were mainly performed using the MedCalc Version 19.1.7 for Windows (Mariakerke, Belgium). Comprehensive Meta-Analysis Software Version 3 (New Jersey, USA) 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), and 112 records remained after removing duplicates. Of these, 42 records were excluded based on the title and abstract due to the use of diagnostic radiotracers for PSMA (n = 4), the use of other therapeutic radiotracers (n = 21), *in vitro/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 due to association with dosimetry/safety/physics (n = 11), association with synthesis/chemistry (n = 3), being published as case report/review/editorial (n = 44), and inadequate data (n = 3). Finally, nine 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.

Seven out of the nine studies were conducted under a retrospective design (*13, 15-19, 21*), and two studies were conducted prospectively (*14, 20*). ^{225}Ac-PSMA-617 was administered in eight studies (*13-15, 17-21*) and ^{225}Ac-PSMA-I&T was used in one study (*16*) as alpha RLT agents. The therapeutic dose range per cycle was reported in three 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 weeks after RLT. Therapeutic responses were reported in all of the nine studies involving 263 patients (*13-21*), and survival outcomes were identified for 200 patients in six of the studies (*13-*

15,17,19-20). Adverse events were documented in eight studies involving 225 patients, which included xerostomia and severe hematotoxicity (*13-20*) (Table 1). Quality assessment of all of the nine 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 50% of 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's 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's Q test) (Fig. 2 and Table 3).

Survival Outcome

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

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's 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's 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's 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's Q test) (Fig. 4 and 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 ALP (xerostomia and leukocytopenia), pre-chemotherapy (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's 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 50% of 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 months and 12 months, 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 beta ray-emitting radionuclides, alpha particle-emitting radionuclides offer several theoretical 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 based on PSA changes, and the commonly defined parameter is more than 50% of PSA decline (*29*). In our study, 61% (95% CI = 55–67%) of patients showed more than 50% of PSA decline, which is higher compared with 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 months) and median OS (12 months) in our study were similar to those (11 months and 14 months, 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 (*30*,*37*,*38*). According to meta-regression analysis, tumor burden and previous damage to bone marrow and 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 are some limitations in this study. The included studies are few in number and

have different patient profiles, and the therapeutic doses and cycles of ^{225}Ac-PSMA RLT were somewhat different. Difference 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 due to a lack of data on individual patients. In the future, prospective, randomized, multi-center clinical trials are needed to confirm the effects of ^{225}Ac-PSMA RLT.

CONCLUSION

In 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 50% of PSA decline and 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 (around 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

The authors declare no conflict of interest regarding this manuscript.

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KEY POINTS

Question: What are the effects of ^{225}Ac-PSMA radioligand therapy (RLT) in patients with metastatic castration-resistant prostate cancer (mCRPC)?

Pertinent Findings: More than 50% of PSA decline and any PSA decline were observed in about 61% (95% CI = 55–67%) and 84% (95% CI = 79–88%) of patients after ^{225}Ac-PSMA RLT, respectively. The estimated mean PFS and mean OS were about 9 months (95% CI = 7-11 months) and 12 months (95% CI = 10–13 months), 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 alpha therapy using ^{225}Ac-PSMA may be a novel therapeutic option for mCRPC patients.

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TABLES

Table 1. Baseline characteristics of the included studies

No.	Author	Year	Imaging indication of RLT	Patient no.	Alpha RLT agent	Median/mean therapeutic dose per cycle (range, MBq)	Median cycle of therapy (range)	Median PSA (range or IQR, ng/ml)	Median ALP (range or IQR, 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 (no. of events)	Duration of survival follow-up (median, month)	Adverse events
1	Feuerecker et al.	2021	Uptake higher than liver in PSMA ligand PET/CT	26	^{225}Ac-PSMA-617	9 (4–13)	2 (1–6)	331 (142–682)	200 (143-517)	25 (96)	26 (100)	6 (23)	After 6 weeks	More than 50% of PSA decline, Any PSA decline	PFS (16), OS (16)	6.4	Xerostomia, Hematotoxicity
2	Rosar et al.	2021	Not mentioned	15	^{225}Ac-PSMA-617	2.7 ± 1.1	2 (1-6)	272 (58–3389)	115 (8-1659)	10 (67)	0 (0)	3 (20)	After 6 ± 2 weeks	More than 50% of PSA decline, Any PSA decline	PFS (14), OS (12)	19.4	Xerostomia, Hematotoxicity
3	Sen et al.	2021	^{68}Ga-PSMA-11 uptake more than or equal to the 68Ga-PSMA-11 uptake in the parotid glands	38	^{225}Ac-PSMA-617	100 kBq/kg	2 (2-5)	147 (4.9–1400)	(-)	38 (100)	9 (24)	2 (5)	After 2 weeks	More than 50% of PSA decline, Any PSA decline	PFS (26), OS (22)	14	Xerostomia, Hematotoxicity
4	Zacherl et al.	2021	Sufficient PSMA expression on ^{18}F-PSMA-1007 PET/CT	14	^{225}Ac-PSMA-I&T	7.8 (6.0–8.5)	(1–5)	112 (20.5–818)	143 (67-695)	12 (86)	11 (79)	2 (14)	After 4 weeks	More than 50% of PSA decline, Any PSA decline	(-)	5.9	Xerostomia, Hematotoxicity
5	Khreish et al.	2020	Uptake higher than normal liver uptake on ^{68}Ga-PSMA-11 PET/CT	20	^{225}Ac-PSMA-617	5.3 (1.5–7.9)	1	215 (6–5547)	160 (53-917)	18 (90)	20 (100)	4 (20)	After 2-4 weeks	More than 50% of PSA decline, Any PSA decline	PFS (16), OS (9)	5.5	Xerostomia, Hematotoxicity
6	Satapathy et al.	2020	Tracer-avid lesion (s) on ^{68}Ga-PSMA-11 PET/CT with SUVmax of lesion being at least 1.5 times greater than that of the normal liver	11	^{225}Ac-PSMA-617	100 kBq/kg	(-)	158 (35–840)	(-)	10 (91)	5 (45)	0 (0)	After 6 weeks	More than 50% of PSA decline, Any PSA decline	(-)	(-)	Xerostomia, Hematotoxicity
7	Sathekge et al.	2020	Uptake greater than twice the normal physiologic liver uptake on ^{68}Ga-PSMA-11 PET/CT	73	^{225}Ac-PSMA-617	(-)	3 (1-8)	57.2	154	27 (37)	14 (19)	0 (0)	After 4 weeks	More than 50% of PSA decline, Any PSA decline	PFS (23), OS (13)	9	Xerostomia, Hematotoxicity
8	Yadav et al.	2020	Intense PSMA expression on ^{68}Ga-PSMA-11 PET/CT greater or equal to liver	28	^{225}Ac-PSMA-617	100 kBq/kg	3 (1-7)	222.2 (47–443.2)	(-)	24 (86)	15 (54)	0 (0)	After 2 weeks	More than 50% of PSA decline, Any PSA decline	PFS (8), OS (6)	10	Xerostomia, Hematotoxicity
9	Kratochwil et al.	2018	^{68}Ga-PSMA-11 PET/CT 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 weeks	More than 50% of PSA decline, Any PSA decline	(-)	(-)	(-)

RLT = radioligand therapy; PSA = prostate-specific antigen; IQR = inter-quartile range; ALP = alkaline phosphatase; PSMA = prostate-specific membrane antigen; PFS = progression-free survival; OS = overall survival; HR = hazard ratio

Table 2. Quality assessment of the included studies using the Newcastle-Ottawa Scale

No.	Author	Selection	Comparability	Outcome	Score
1	Feuerecker et al.	☆☆☆	☆☆	☆☆	7
2	Rosar et al.	☆☆☆	☆	☆☆☆	7
3	Sen et al.	☆☆☆	☆	☆☆☆	7
4	Zacherl et al.	☆☆☆	☆	☆☆	6
5	Khreish et al.	☆☆☆	☆	☆☆☆	7
6	Satapathy et al.	☆☆☆	☆	☆☆	6
7	Sathekge et al.	☆☆☆	☆☆	☆☆☆	8
8	Yadav et al.	☆☆☆	☆	☆☆☆	7
9	Kratochwil et al.	☆☆☆	☆	☆☆☆	7

Table 3. Summary of the therapeutic responses and survival outcomes following ^{225}Ac-PSMA RLT

Therapeutic response and survival outcome	No. of studies	Model	Pooled estimate	95% CI of pooled estimate	I^2 (%)
More than 50% of 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

CI = confidence interval

Table 4. Summary of the adverse events following ^{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 the adverse event

Adverse event	Variable	No. of studies	Regression coefficient	*P*-value
Xerostomia grade 1 or 2	Median PSA	8	-0.0028	0.6448
	Median ALP	5	0.0700	0.0012*
	Pre-chemotherapy (%)	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
	Pre-chemotherapy (%)	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*
	Pre-chemotherapy (%)	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
	Pre-chemotherapy (%)	8	0.0392	0.0208*
	Prior ^{177}Lu-PSMA (%)	8	0.0153	0.0937
	Prior ^{223}Ra (%)	8	0.0415	0.2755

* $P < 0.05$

FIGURE LEGENDS

FIGURE 1. Flowchart of the study selection process.

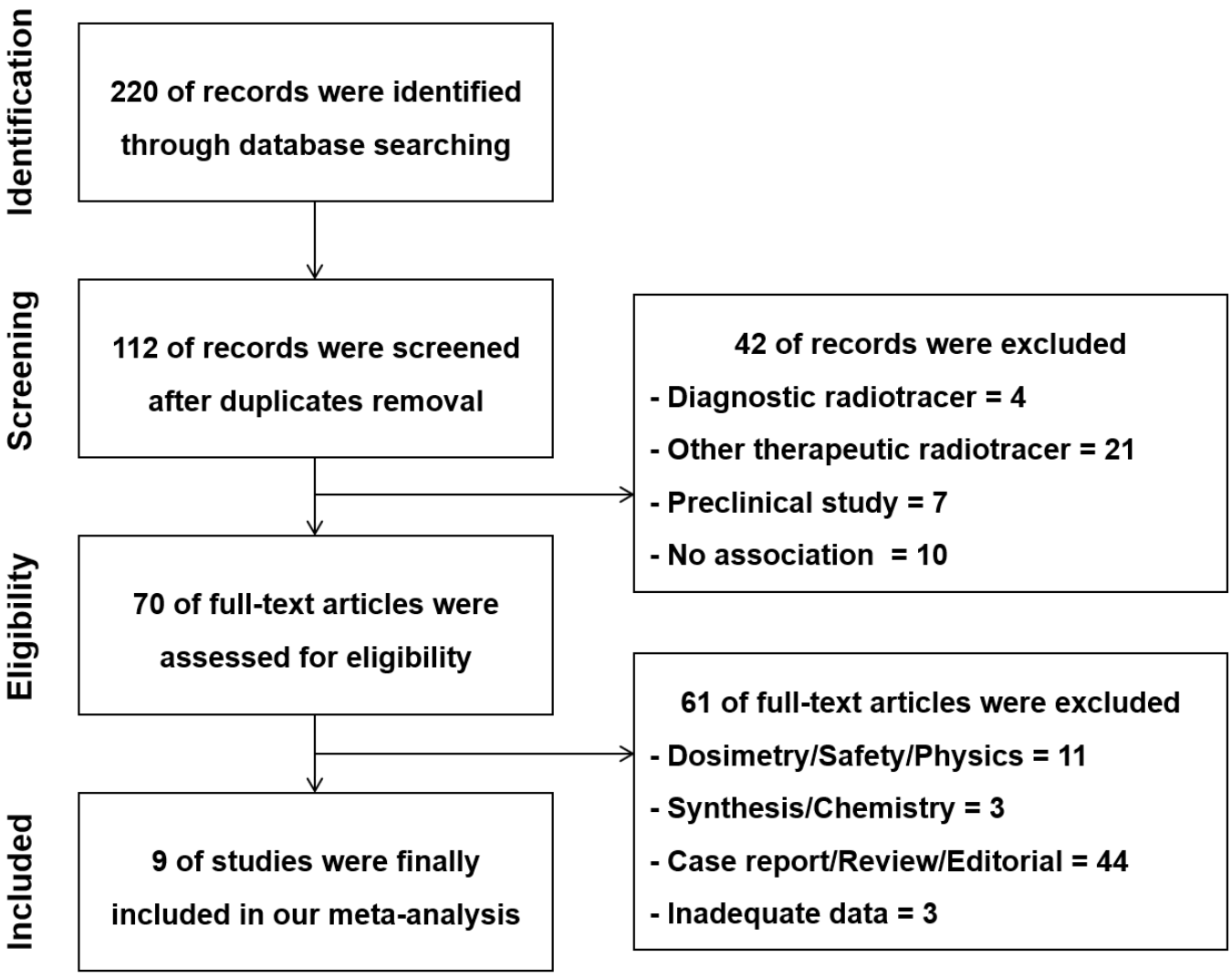


FIGURE 2. Forest plot for therapeutic responses after ^{225}Ac-PSMA RLT. (A) More than 50% of PSA decline. (B) Any PSA decline.

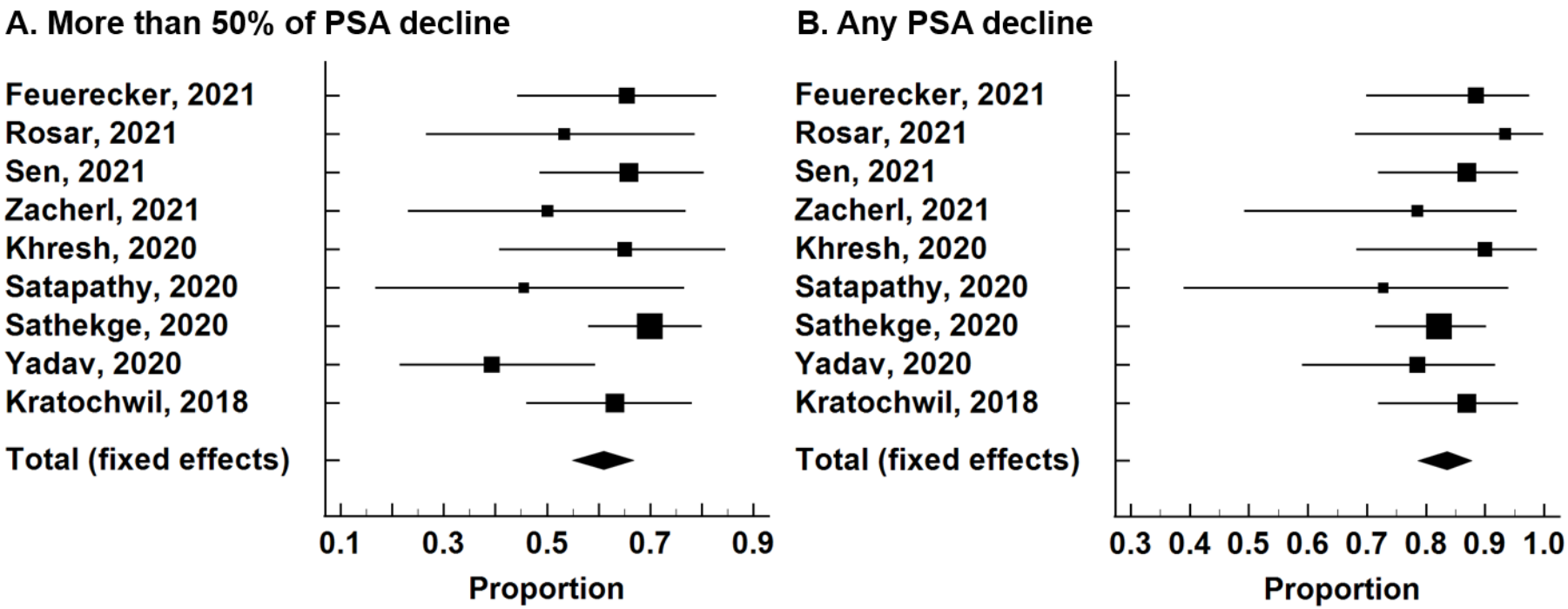


FIGURE 3. Survival outcomes estimation after ^{225}Ac-PSMA RLT. (A) PFS. (B) OS.

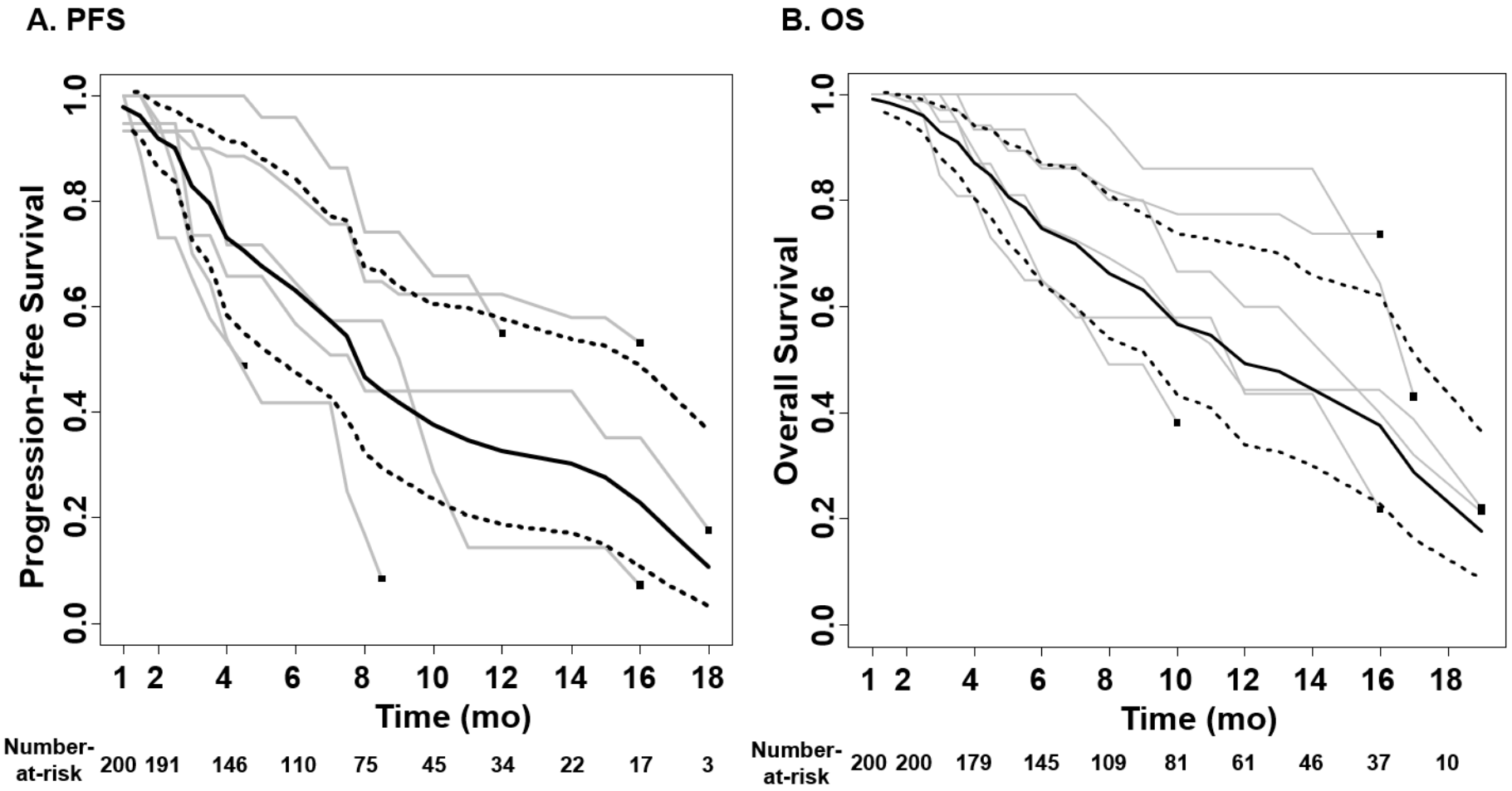


FIGURE 4. Forest plot for adverse events after ^{225}Ac-PSMA RLT. (A) Xerostomia grade 1 or 2. (B) Anemia grade 3 or 4. (C) Leukocytopenia grade 3 or 4. (D) Thrombocytopenia grade 3 or 4.

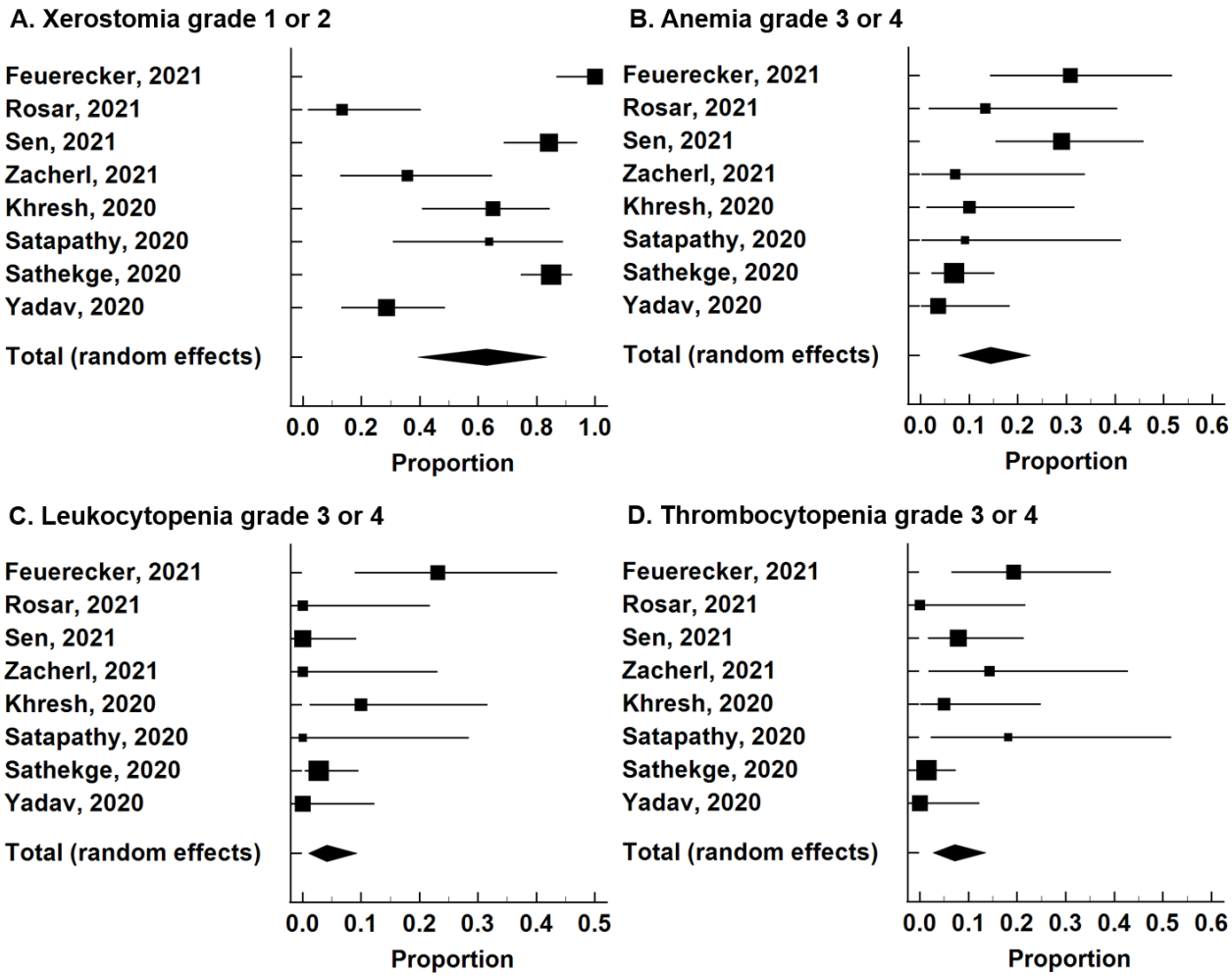
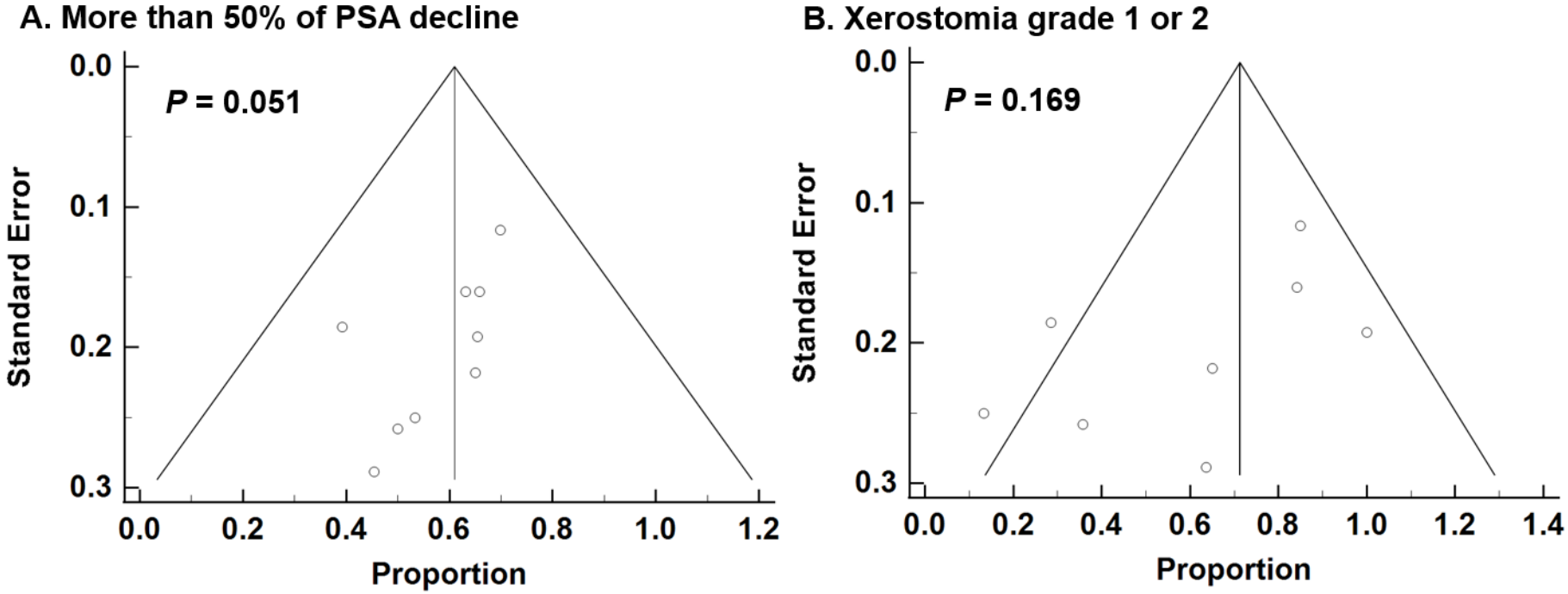
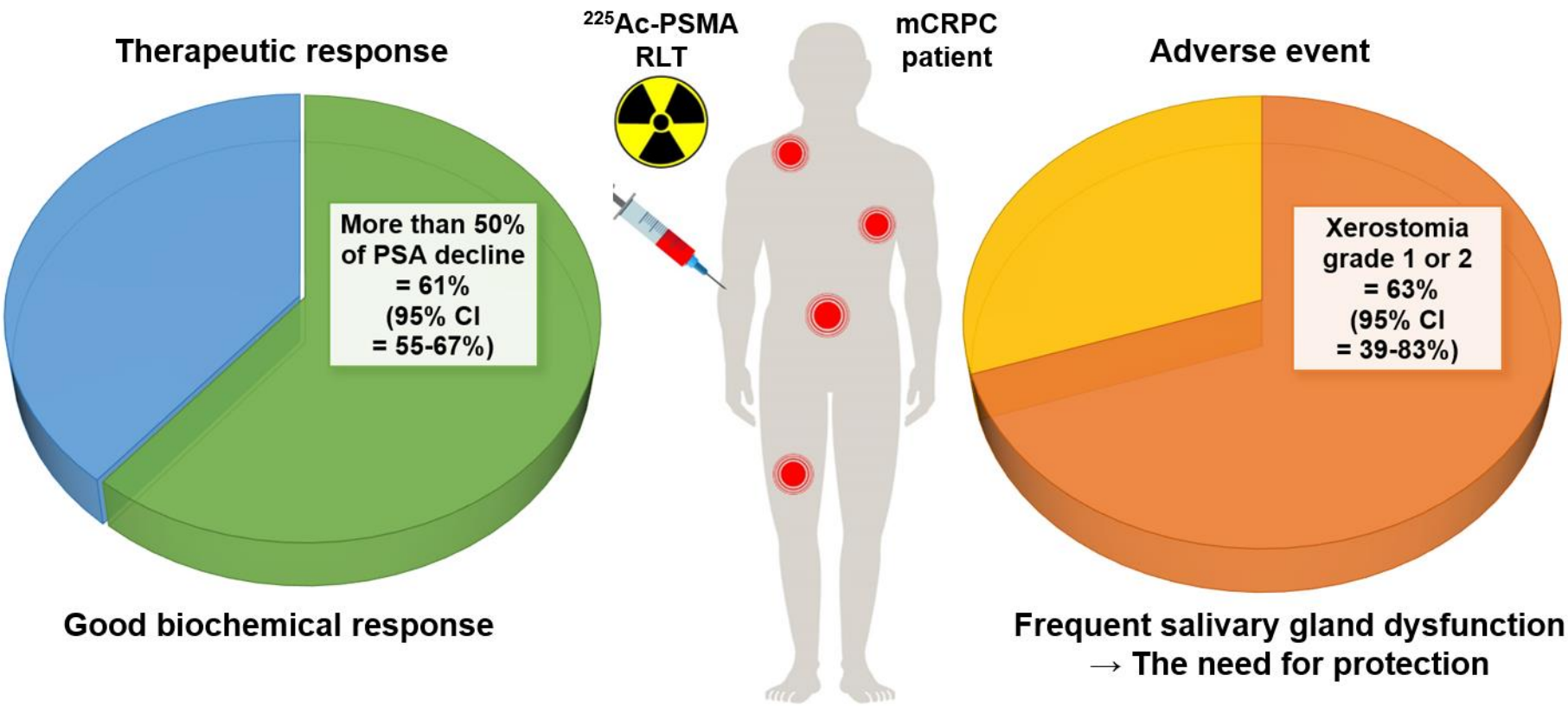


FIGURE 5. Funnel plot and Egger's test for publication bias assessment. (A) More than 50% of PSA decline. (B) Xerostomia grade 1 or 2.


A. More than 50% of PSA decline
P = 0.051
Standard Error
0.0
0.1
0.2
0.3
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Proportion
B. Xerostomia grade 1 or 2
P = 0.169
Standard Error
0.0
0.1
0.2
0.3
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
Proportion

GRAPHICAL ABSTRACT



SUPPLEMENTAL DATA

Supplemental Table 1. Results of electronic search on PubMed (Date: 2021.06.10)

NO.	Search Query	Results
#1	Neoplasm Metastasis[Mesh]	210,313
#2	Metasta*[TW]	611,877
#3	#1 OR #2	620,398
#4	Prostatic Neoplasms, Castration-Resistant[Mesh]	4,468
#5	Prostat*[TW] AND (Cancer[TW] OR Cancers[TW] OR Neoplasm*[TW]) AND (Castration-Resistant*[TW] OR Hormone-Refractor*[TW] OR Androgen-Independent*[TW])	14,338
#6	#4 OR #5	-
#7	#3 AND #6	7,489
#8	"mCRPC"[TW]	1,967
#9	**#7 OR #8**	**7,652**
#10	"Actinium-225" [Supplementary Concept] OR "225"[TW] OR "(225)AC"[TW] OR "225AC"[TW] OR "225 AC"[TW] OR "AC225"[TW] OR "Ac 225"[TW] OR "actinium 225"[TW] OR "actinium225"[TW]	33,364
#11	"Alpha Particles"[Mesh] OR "α"[TW] OR Alpha[TW]	1,192,842
#12	**#10 OR #11**	**1,224,403**
#13	"Antigens, Surface"[Mesh]	502,238
#14	(Prostat*[TW] AND Specific*[TW] AND membrane*[TW] AND Antigen*[TW]) OR "PSMA"[TW] OR radioligand*[TW]	34,703
#15	**#13 OR #14**	**535,229**
#16	**#9 AND #12 AND #15**	**85**
#17	**#16 AND ("2000/01/01"[pdat]:"3000/01/01"[pdat])**	**84**

Supplemental Table 2. Results of electronic search on Embase (Date: 2021.06.10)

NO.	Search Query	Results
#1	'metastasis'/exp	698,595
#2	Metasta*:ab,ti,kw	796,441
#3	#1 OR #2	969,574
#4	'castration resistant prostate cancer'/exp	15,449
#5	(Prostat* NEAR/6 (Cancer OR Cancers OR Neoplasm*) NEAR/6 (Castration-Resistant* OR Hormone-Refractor* OR Androgen-Independent*)):ab,ti,kw	18,077
#6	#4 OR #5	22,115
#7	#3 AND #6	13,552
#8	'mCRPC':ab,ti,kw	5,504
#9	**#7 OR #8**	**14,581**
#10	'actinium 225'/exp OR ('actinium 225' OR 'actinium225' OR '225' OR '225ac' OR '225 ac' OR '(225)ac' OR 'ac225' OR 'ac 225'):ab,ti,kw	44,496
#11	'alpha radiation'/exp OR ('α' OR Alpha):ab,ti,kw	1,174,814
#12	**#10 OR #11**	**1,217,040**
#13	'prostate specific membrane antigen'/exp OR 'radioligand'/exp	17,779
#14	(Prostat* NEAR/6 Specific* NEAR/6 Membrane NEAR/6 Antigen*):ab,ti,kw OR ('PSMA' OR radioligand*):ab,ti,kw	28,232
#15	**#13 OR #14**	**33,289**
#16	**#9 AND #12 AND #15**	**169**
#17	**#16 AND [2000-2021]/py**	**168**
#18	**#17 AND ([article]/lim OR [article in press]/lim OR [review]/lim)**	**67**

Supplemental Table 3. Results of electronic search on Cochrane Library (Date: 2021.06.10)

NO.	Search Query	Results
#1	[mh "Neoplasm Metastasis"]	5,263
#2	Metasta*:ab,ti,kw	44,023
#3	#1 or #2	44,155
#4	[mh "Prostatic Neoplasms, Castration-Resistant"]	268
#5	(Prostat* near/6 (Cancer or Cancers or Neoplasm*) near/6 (Castration-Resistant* or Hormone-Refractor* or Androgen-Independent*)):ab,ti,kw	2,294
#6	#4 or #5	2,294
#7	#3 and #6	1,845
#8	mCRPC:ab,ti,kw	963
#9	**#7 or #8**	**2,044**
#10	(225 or "actinium 225" or "actinium225" or "225ac" or "(225)ac" or "ac225" or "ac 225"):ab,ti,kw	9,633
#11	[mh "Alpha Particles"] or "α":ab,ti,kw or Alpha:ab,ti,kw	50,448
#12	**#10 or #11**	**59,672**
#13	[mh "Antigens, Surface"]	5,710
#14	(Prostat* near/6 Specific* near/6 membrane near/6 Antigen*):ab,ti,kw or "PSMA":ab,ti,kw or radioligand*:ab,ti,kw	582
#15	**#13 or #14**	**6,283**
#16	**#9 and #12 and #15**	**6**

Supplemental Table 4. Results of electronic search on CINAHL (Date: 2021.06.10)

NO.	Search Query	Results
S1	(MH "Neoplasm Metastasis+")	40,559
S2	Metasta*	91,553
S3	S1 OR S2	92,242
S4	(MH "Prostatic Neoplasms, Castration-Resistant")	1,271
S5	Prostat* AND (Cancer OR Cancers OR Neoplasm*) AND (Castration-Resistant* OR Hormone-Refractor* OR Androgen-Independent*)	2,941
S6	S4 OR S5	2,941
S7	S3 AND S6	1,944
S8	"mCRPC"	585
S9	**S7 OR S8**	**1,992**
S10	"225" OR "actinium225" OR "actinium 225" OR "ac225" OR "ac 225" OR "225AC" OR "225 AC"	3,964
S11	"α" OR Alpha	126,048
S12	**S10 OR S11**	**129,797**
S13	(MH "Antigens, Surface")	12,776
S14	(Prostat* N6 Specific* N6 Membrane N6 Antigen*) OR "PSMA" OR radioligand*	1,262
S15	**S13 OR S14**	**13,921**
S16	**S9 AND S12 AND S15**	**15**
S17	**S16 AND (2000-2021); Academic Journal article**	**13**

Supplemental Table 5. Results of electronic search on Web of Science (Date: 2021.06.10)

NO.	Search Query	Results
#1	(TS=(Metasta* AND Prostat* AND (Cancer OR Cancers OR Neoplasm*) AND (Castration-Resistant* OR Hormone-Refractor* OR Androgen-Independent*))) OR (TS=mCRPC)	9,539
#2	TS=("225" OR "actinium225" OR "actinium 225" OR "ac225" OR "ac 225" OR "225AC" OR "225 AC" OR "α" OR Alpha)	1,828,709
#3	TS=(Prostat* NEAR/6 Specific* NEAR/6 Membrane NEAR/6 Antigen*) OR TS=("PSMA" OR radioligand*)	23,119
#4	**#1 AND #2 AND #3**	**81**
#5	**#4 AND PY=(2000-2021)**	**80**
#6	**#5 Refined by: DOCUMENT TYPES: (ARTICLE OR EARLY ACCESS OR REVIEW)**	**50**

Supplemental Table 6. Results of meta-regression analysis for the therapeutic response

Therapeutic response	Variable	No. of studies	Regression coefficient	*P*-value
More than 50% of PSA decline	Median PSA	9	-0.0016	0.3689
	Median ALP	6	0.0041	0.5461
	Pre-chemotherapy (%)	9	-0.0064	0.3477
	Prior ^{177}Lu-PSMA (%)	9	-0.0017	0.6979
	Prior ^{223}Ra (%)	9	0.0082	0.6250
Any PSA decline	Median PSA	9	0.0017	0.4052
	Median ALP	6	0.0043	0.6828
	Pre-chemotherapy (%)	9	0.0030	0.6536
	Prior ^{177}Lu-PSMA (%)	9	-0.0003	0.9565
	Prior ^{223}Ra (%)	9	0.0255	0.1523

* $P < 0.05$

Supplemental Figure 1. Funnel plot and Egger's test for publication bias assessment. (A) Any PSA decline. (B) Anemia grade 3 or 4. (C) Leukocytopenia grade 3 or 4. (D) Thrombocytopenia grade 3 or 4.