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Review – Prostate Cancer

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A Meta-Analysis and Meta-Regression of the Efficacy, Toxicity, and Quality of Life Outcomes Following Prostate-Specific Membrane Antigen Radioligand Therapy Utilising Lutetium-177 and Actinium-225 in Metastatic Prostate Cancer

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Abstract

Background and objective: Management of metastatic prostate cancer (mPCa) presents significant challenges. In this systematic review, meta-analysis, and meta-regression, the efficacy, safety, and quality of life (QoL) outcomes of prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (PRLT) utilising lutetium-177 ([^{177}Lu]Lu-PSMA) and actinium-225 ([^{225}Ac]Ac-PSMA) were assessed.

Methods: A detailed literature search across PubMed/Medline, EMBASE, Web of Science, Scopus, and Cochrane Library was conducted, culminating in the inclusion of 100 studies involving 8711 patients. Data on prostate-specific antigen (PSA) responses, toxicity profiles, and QoL and survival outcomes were analysed. Proportional meta-analyses and meta-regression analyses were performed.

Key findings and limitations: The estimated proportion of patients with PSA decline ≥50% was 0.49 for [^{177}Lu]Lu-PSMA and 0.60 for [^{225}Ac]Ac-PSMA in mPCa, particularly metastatic castration-resistant prostate cancer. A meta-regression analysis indicated an association between the cumulative amount of administered activity and the proportion of PSA ≥50% decline. Positive PSA responses were observed alongside improved overall survival across both therapies. Our analyses also identified the key factors associated with PSA responses and survival outcomes, including baseline haemoglobin level, and the presence of visceral metastases. Although anaemia was commonly observed, with [^{177}Lu]Lu-PSMA, severe toxicities were infrequent. Improved QoL was observed following [^{177}Lu]Lu-PSMA therapy, whereas it remained stable following the second cycle of [^{225}Ac]Ac-PSMA treatment. Heterogeneity across studies for PSA responses and toxicity profiles is a limitation.

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Conclusions and clinical implications: Our findings suggest an association between PRLT and reductions in PSA levels, as well as associations with enhanced survival outcomes in mPCa. Furthermore, our analysis shows a low incidence of severe toxicity associated with this treatment. These observations highlight the important role of PRLT in the management of mPCa.

ADVANCING PRACTICE

What does this study add?

This paper, which considers all relevant studies published up to February 2024, provides new insights into the relationship between cumulative administered activity of prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (PRLT) utilising lutetium-177 ([^{177}Lu]Lu-PSMA) and prostate-specific antigen (PSA) response rates. Quality of life is improved or maintained after both [^{177}Lu]Lu-PSMA and PRLT utilising actinium-225 ([^{225}Ac]Ac-PSMA) therapy. Furthermore, baseline haemoglobin level and the presence of liver/visceral metastases are confirmed as significant factors associated with PSA response and toxicity, which can aid in better patient selection and personalised treatment planning.

Clinical Relevance

Testosterone-suppressing therapy for prostate cancer was one of the first examples of targeted treatments for malignancy. Only in recent years have other "precision" therapies been explored and proven effective. Among these, therapies targeting the transmembrane protein PSMA with radioligand payloads have gained prominence as potent agents in advanced disease states. In this article, the authors present a comprehensive meta-analysis of the two agents with the strongest evidence—Lutetium-177- and Actinium-225-PSMA. The results consistently show an association between these treatments and PSA decline, improved survival, and stabilization or improvement in quality of life and other patient-reported outcomes. This study underscores the potential of ongoing trials, even in earlier stages of the disease, and highlights the pivotal role PSMA-targeted radioligand therapies are poised to play in shaping future personalised clinical decision-making. Associate Editor: Gianluca Giannarini MD.

Patient Summary

PRLT appears to be a promising treatment option for metastatic prostate cancer. A meta-analysis suggests that this therapy is associated with significant reductions in PSA levels, which may indicate tumour responses. Additionally, it is associated with encouraging survival rates and maintains a manageable safety profile.

1. Introduction

Radical surgery and radiotherapy with neoadjuvant androgen deprivation therapy (ADT) form the cornerstone of treatment for patients with localised high- and intermediate-risk prostate cancer (PCa). As the disease progresses to a recurrent or metastatic stage, standard management shifts towards ADT, androgen receptor targeted agents (ARTA), and chemotherapy [1]. Despite significant improvements in survival through these approaches, a proportion of patients eventually develop castration-resistant disease, which is strongly associated with a poor prognosis [2]. In the context of metastatic castration-resistant prostate cancer (mCRPC), incorporation of systemic therapies, such as taxane-based chemotherapy, abiraterone, enzalutamide, sipuleucel-T, Radium-223 (^{223}Ra), and olaparib, is in line with current clinical guidelines [3]. These treatments have indeed shown survival benefits in various phase 3 trials. However, it is important to note that these therapies can also lead to significant adverse events [4,5].

Prostate-specific membrane antigen (PSMA)-radioligand therapy (PRLT) is a promising molecular radioligand therapy for mCRPC in which a PSMA ligand is radiolabelled with the β-emitting radionuclide lutetium-177 ([^{177}Lu]Lu-PSMA) or the α-emitter actinium-225 ([^{225}Ac]Ac-PSMA). In some studies, [^{177}Lu]Lu-PSMA therapy has been shown to decrease the level of prostate-specific antigen (PSA) by at least 50%, with a favourable toxicity profile in >60% of patients with mCRPC [6,7]. Moreover, in the TheraP trial, a phase 2 study comparing [^{177}Lu]Lu-PSMA therapy with cabazitaxel chemotherapy, the former showed greater reduction in PSA, fewer side effects, and improved quality of life (QoL) [8]. Additionally, the use of [^{225}Ac]Ac-PSMA has also led to effective disease control, even for cases where [^{177}Lu]Lu-PSMA therapy fails [9]. Therefore, these PRLTs are now considered an attractive alternative to other systemic therapies in patients with metastatic PCa (mPCa).

In the past decade, in addition to limited prospective trials, numerous retrospective studies have provided extensive clinical data regarding the prescribed amount of

radioactivity, number of treatment cycles, PSA response, toxicities, and QoL associated with [^{177}Lu]Lu-PSMA. With the growing body of evidence underscoring the clinical advantages of PRLT in mPCa, there is a pressing need to broaden research efforts. This study does not investigate the causal pathways between PRLT and clinical outcomes, but instead focuses on identifying patient characteristics associated with favourable responses to PRLT. In this context, we performed a comprehensive systematic review and meta-analysis, extending the inquiry to encompass [^{225}Ac]Ac-PSMA, and including many studies that have been reported in the past few years [10,11].

2. Methods

2.1. Literature review

This research was executed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework [12]. A comprehensive literature search was conducted in February 2024. The databases included PubMed/Medline, EMBASE, the Cochrane Library, Web of Science, and Scopus. The search strategy employed keywords and phrases such as "Prostate-specific membrane antigen", "Lutetium OR Actinium", "Prostate cancer", and "Quality of life", supplemented with an exhaustive list of all relevant interventions and terms. Where applicable, controlled vocabulary terms, such as Medical Subject Headings (MeSH), were utilised to enhance the precision of the search. No restrictions were applied regarding language or publication date. The study protocol was registered with PROSPERO (registration number: CRD42024538961). The details of the search strategy are documented in Supplementary Table 1.

2.2. Study selection

The study selection criteria encompassed retrospective and prospective human studies of PRLT, including single-arm, double-arm, randomised, and non-randomised studies. Three investigators independently screened full-text articles, focusing on studies involving mPCa patients undergoing therapy with [^{177}Lu]Lu-PSMA or [^{225}Ac]Ac-PSMA, reporting PSA level declines, and documenting toxicity profiles and/or QoL. Abstracts, editorials, commentary, and letters were excluded.

2.3. Data extraction

For data extraction, discrepancies were resolved by consensus. The extracted data included authors, publication year, tumour type, details of PRLT, number of treatment cycles, prescribed and cumulative amounts of administered activity (AA), prior treatments, median follow-up, survival outcomes, PSA responses, and toxicity profiles. The AA values were derived based on the reported activity for each treatment cycle. Special attention was given to the number of patients experiencing a PSA decline following each treatment cycle and the maximum PSA reduction across all cycles. Toxicity data were collected based on the Common Terminology Criteria for Adverse Events (CTCAE), categorising toxicities into minor (grades 1/2) and severe (grades 3/4) grades. Moreover, we excluded generalised descriptions of toxicities, such as haematological toxicity or nausea/vomiting, to focus on specific toxicity grades. For hepatotoxicity, we extracted data for various biochemical markers indicative of liver function and injury. These markers included aspartate transaminase (AST), alanine aminotransferase, total bilirubin, albumin, and gamma-glutamyl transferase. In the evaluation of QoL, data from commonly used questionnaires were collected to capture QoL scores following each treatment cycle.

Quality assessment of randomised controlled studies (RCTs) and observational cohort studies was performed using the Newcastle-Ottawa Scale (NOS) and Cochrane Risk of Bias 2 (RoB 2), respectively [13,14]. All assessments were conducted independently by three authors (Y.H.D., P.H.C., and D.J.L.).

2.4. Meta-analysis

For continuous survival variables such as overall survival (OS) and progression-free survival (PFS) after PRLT, we collected the median OS and median PFS with 95% confidence interval (CI) and used the "metamean" function to obtain the pooled results. For dichotomous outcomes, a proportional meta-analysis was conducted to estimate the proportion of various events of interest, including any decline in PSA levels, a decline in PSA levels of $\geq$50%, and the incidence of grade 1/2 and grade 3/4 toxicities, as well as toxicity of any grade. Subgroup analyses were undertaken to assess PSA responses following cumulative AA across different treatment intervals: after the first, second/third, and fourth/fifth cycles, and across all cycles. For PSA declines reported across all cycles (any period of time from the first cycle until study-defined follow-up), the timing of PSA responses was delineated further into distinct categories such as "after all cycles", "during all cycles", and "during and after all cycles", to elucidate the specific timing of PSA response. Additionally, PSA responses were distinguished based on the specific PSMA ligand used, categorising them into PSMA-617 and PSMA-I&T groups. Patients receiving ligands other than PSMA-617 or PSMA-I&T were removed from this subgroup analysis. This method of distinguishing between ligand types was also applied to assess the toxicity of any grade. A Bayesian meta-analysis was conducted using the "rstanarm" package in R (R Foundation for Statistical Computing, Vienna, Austria) to determine whether there is a significant difference between different radioligands and timings of PSA response assessment [15]. We specified normal priors for treatment effects, assuming a zero mean difference, and conducted the analysis using 2000 iterations across four chains. The posterior distributions obtained were visualised with the "bayesplot" package in R; "meta" package version 7.0.0 in R was used for the meta-analysis and generation of forest plots. We employed logit transformation and inverse variance weighting across all studies to estimate the pooled effect sizes based on a random-effect model. The restricted maximum likelihood method was used to estimate between-study heterogeneity (τ^2) [16].

OS was defined as the time from the start of treatment until death from any cause, while PFS was defined as the time from the start of treatment until disease progression or death, whichever occurred first. These endpoints, along with PSA response and toxicities, were evaluated after the first cycle of PRLT. For QoL, changes of scores from pretreatment baseline after each cycle were estimated using the random-effect model with "metafor" package version 4.4.0 in R.

2.5. Evaluation of publication bias

The potential for a publication bias was evaluated through visual examination of funnel plots and by conducting the regression test of Egger et al [17].

2.6. Evaluation of heterogeneity between studies

To address the sources of study-level heterogeneity in PSA response and toxicity profiles, meta-regression analyses were conducted using the "meta" package. Various covariates that could potentially contribute to heterogeneity were analysed, including publication year, type of radioligand therapy, proportion of patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status Scale score of $\geq$2, baseline PSA level, haemoglobin (Hb) level, alkaline phosphatase level, lactate dehydrogenase (LDH) level, platelet count (PLT), proportion of patients with liver or visceral metastases, bone metastasis, and proportion of patients who had received prior chemotherapy. Moderators with $p < 0.05$ were considered significant. The results were visualised using a heatmap.

2.7. Correlation between AA and PSA response

A meta-regression analysis was performed to investigate the relationship between AA and PSA response, adjusting for covariates mentioned above. Covariates were included in the analysis only if these were reported in at least ten studies. The meta-regression aimed to assess the relationship between both the prescribed initial amount of AA and the cumulative AA, and the PSA response after the first cycle and after all cycles. A Pearson correlation test was used to evaluate the relationship between the number of treatment cycles and the reported cumulative AA. If the correlation coefficient exceeded 0.8, only cumulative AAs would be used to avoid collinearity. Given that reports on cumulative AA and PSA responses following all cycles were infrequent, the scheduled cumulative AA for each study was estimated by multiplying the prescribed AA per cycle by the reported median or mean number of cycles. If only a range of cycles or AAs were described, the mean was calculated by averaging the endpoints of the range. The mean difference was calculated between the reported and estimated cumulative activities. Moderators of heterogeneity were considered significant when the p value was <0.05.

2.8. Individual patient data analysis for PSA response

To enhance the precision of the time-to-event analyses concerning PSA response after PRLT and to reduce bias in hazard ratio (HR) evaluations, extraction of individual patient data (IPD) utilising the "IPDfromKM" package in R was attempted [18]. Initially, data coordinates were extracted from the Kaplan-Meier (KM) plots published in studies. These data points were then employed to reconstruct IPD using a refined version of the iKM algorithm. Subsequently, the IPD were aggregated based on PSA responses and treatment cycle information. For visualisation, the "survminer" package in R was applied, and the "survival" package was used for HR and 95% CI calculations based on Cox regression models. To accommodate variations in baseline hazards, we included study ID as a stratification factor. The aggregated HRs and 95% CIs were then synthesised using a random-effect model to evaluate the overall prognostic significance of PSA response.

2.9. Association of other clinical factors with survival outcomes

For studies assessing the association of various clinical factors with OS and PFS through a multivariate analysis, the HRs and 95% CIs were extracted. Using a similar approach to the method described in section 2.4, these metrics were pooled to evaluate the survival effects of these factors.

3. Results

3.1. Study characteristics

The results of the literature search are summarised in Figure 1.

Overall, 100 studies encompassing a total of 8711 patients were included in this analysis, consisting of 12 prospective and 88 retrospective studies. These studies predominantly used [^{177}Lu]Lu-PSMA therapy (87 studies, 7826 patients), with the remainder utilising [^{225}Ac]Ac-PSMA therapy (13 studies, 885 patients). Regarding tumour type, all studies evaluated PRLT efficacy in the metastatic setting, particularly mCRPC, except for one study where 39% of the patients (n = 65) were M0 at the time of PRLT [19], and two studies that included metastatic hormone-sensitive prostate cancer (mHSPC; n = 29) [20,21]. The treatments investigated included [^{177}Lu]Lu-PSMA-617 (63 studies), [^{177}Lu]Lu-PSMA-I&T (seven studies), [^{225}Ac]Ac-PSMA-617 (ten studies), and [^{225}Ac]Ac-PSMA-I&T (two studies), along with variations such as Evans blue–modified [^{177}Lu]Lu-PSMA-617 in one study [22]. A few studies did not specify the PSMA radioligand used [23–25].

All included RCTs were evaluated to have either a low risk of bias or some concerns, with no studies identified as being at a high risk. The quality of cohort studies, as assessed by the NOS, ranged from moderate to high. Detailed information on the studies and their quality assessments is provided in Supplementary Tables 2 and 3, and Supplementary Figure 1.

3.2. Meta-analysis of survival outcomes

For [^{177}Lu]Lu-PSMA therapy, the median follow-up periods ranged from 4.0 to 52.3 mo, with the median OS and PFS being 14.0 mo (95% CI: 12.6–15.5) and 7.0 mo (95% CI: 5.9–8.3), respectively. Pooled analyses showed a significant association between the treatment and improved OS compared with best supportive care (HR = 0.61, 95% CI:

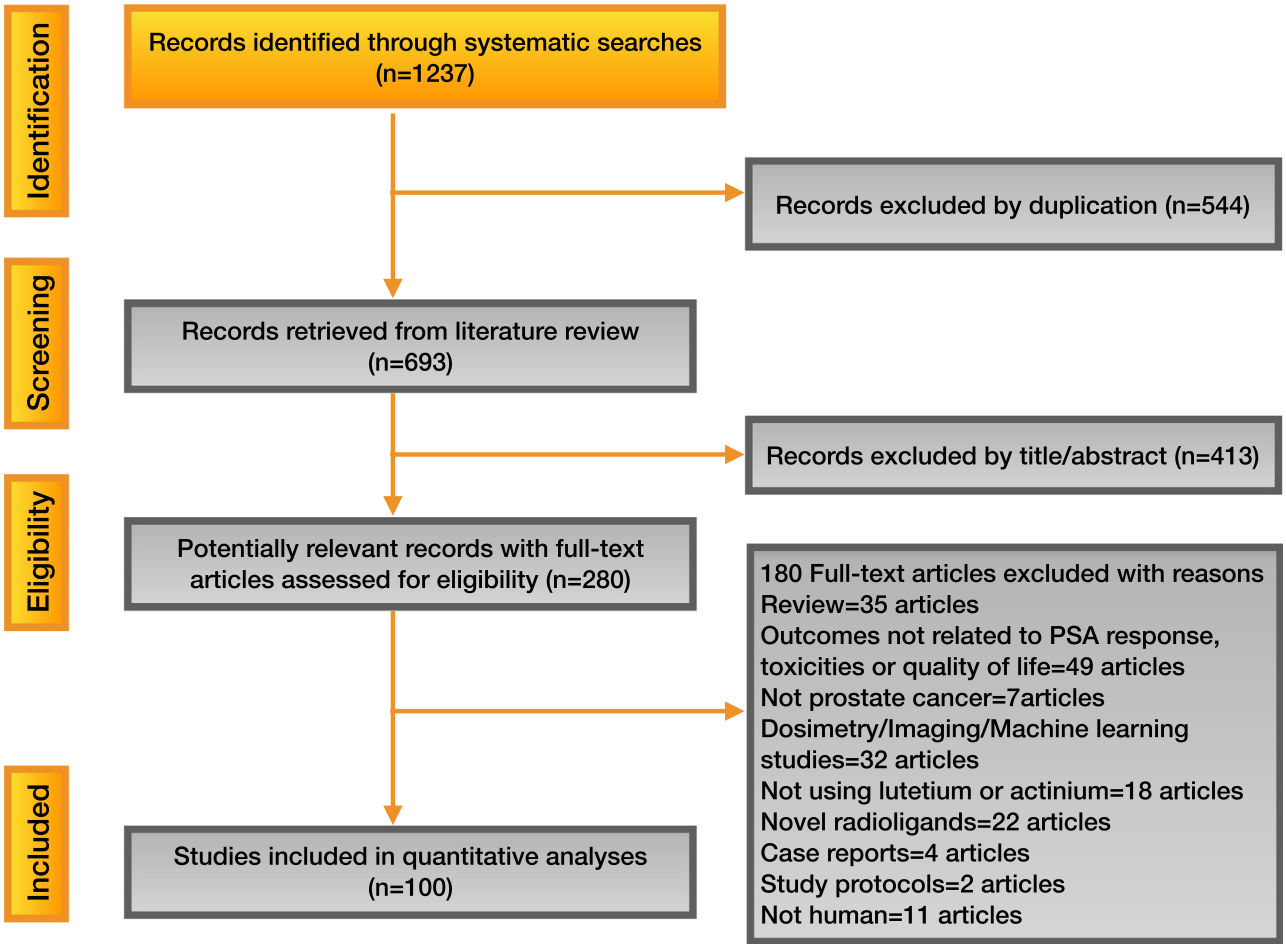

Fig. 1 – The flow chart of the systematic review. PSA = prostate-specific antigen.

0.51–0.72, $p < 0.001$) and better PFS than chemotherapy (HR = 0.67, 95% CI: 0.51–0.89, $p = 0.006$; Supplementary Fig. 2). Patients undergoing [^{225}Ac]Ac-PSMA therapy had median follow-up times of 5.9–10.0 mo, with the pooled median OS of 13.5 mo (95% CI: 10.0–18.2) and median PFS of 10.1 mo (95% CI: 6.3–16.0).

3.3. *Meta-analysis of PSA response*

3.3.1. *PSA response to [^{177}Lu]Lu-PSMA therapy*

Among patients with available PSA response data, the proportion achieving a ≥50% PSA decline across all cycles was estimated at 0.49 (95% CI: 0.46–0.52, I^2 = 63%; Fig. 2A). For patients with recorded maximum PSA response during and after all cycles (n = 1909, 45%), the estimated proportion was 0.49 (95% CI: 0.45–0.53; Supplementary Fig. 3). This estimate was consistent regardless of the periods of assessment—"during" or "during and after" all cycles (Supplementary Fig. 3 and 4). Notably, the estimated proportion of PSA decline ≥50% after the first treatment cycle was 0.37 (95% CI: 0.34–0.41; Supplementary Fig. 5A). Subsequent cycles showed increased PSA declines, with 51% achieving PSA decline ≥50% after the second and third cycles (Supplementary Fig. 5B), and 48% after the fourth and fifth cycles, indicating a cumulative pattern in PSA response (Supplementary Fig. 5C). The estimated proportion of patients with any PSA decline across all cycles (n = 3191) was 0.70 (95% CI: 0.66–0.73; Supplementary Fig. 6). This finding was consistent irrespective of whether the maximum PSA response was evaluated during, during and after, or after all cycles, with around 71% demonstrating a response (Supplementary Fig. 7 and 8). An early treatment response was indicated by a 68% response rate after the first cycle, increasing slightly to 69% after the second and third cycles (Supplementary Fig. 9A and 9B). A subgroup analysis found no significant difference in PSA response rates between mCRPC and mHSPC, or between different types of PRLT across all cycles (Supplementary Table 4 and Supplementary Fig. 10–12). These response rates were comparable to those observed in studies that reported on a combination of [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T treatments (Supplementary Fig. 13). We also observed that prior treatments, including ^{223}Ra, ARTA, and chemotherapy, which were potentially effective in eliciting a PSA response, did not show a correlated decline following [^{177}Lu]Lu-PSMA therapy (Supplementary Fig. 14). Regarding the heterogeneity between studies, baseline Hb level and PLT for PSA ≥50% decline were the primary sources (Fig. 2C).

3.3.2. *PSA response to [^{225}Ac]Ac-PSMA therapy*

For [^{225}Ac]Ac-PSMA therapy, 60% of patients experienced a ≥50% PSA decline across all cycles, closely aligning with

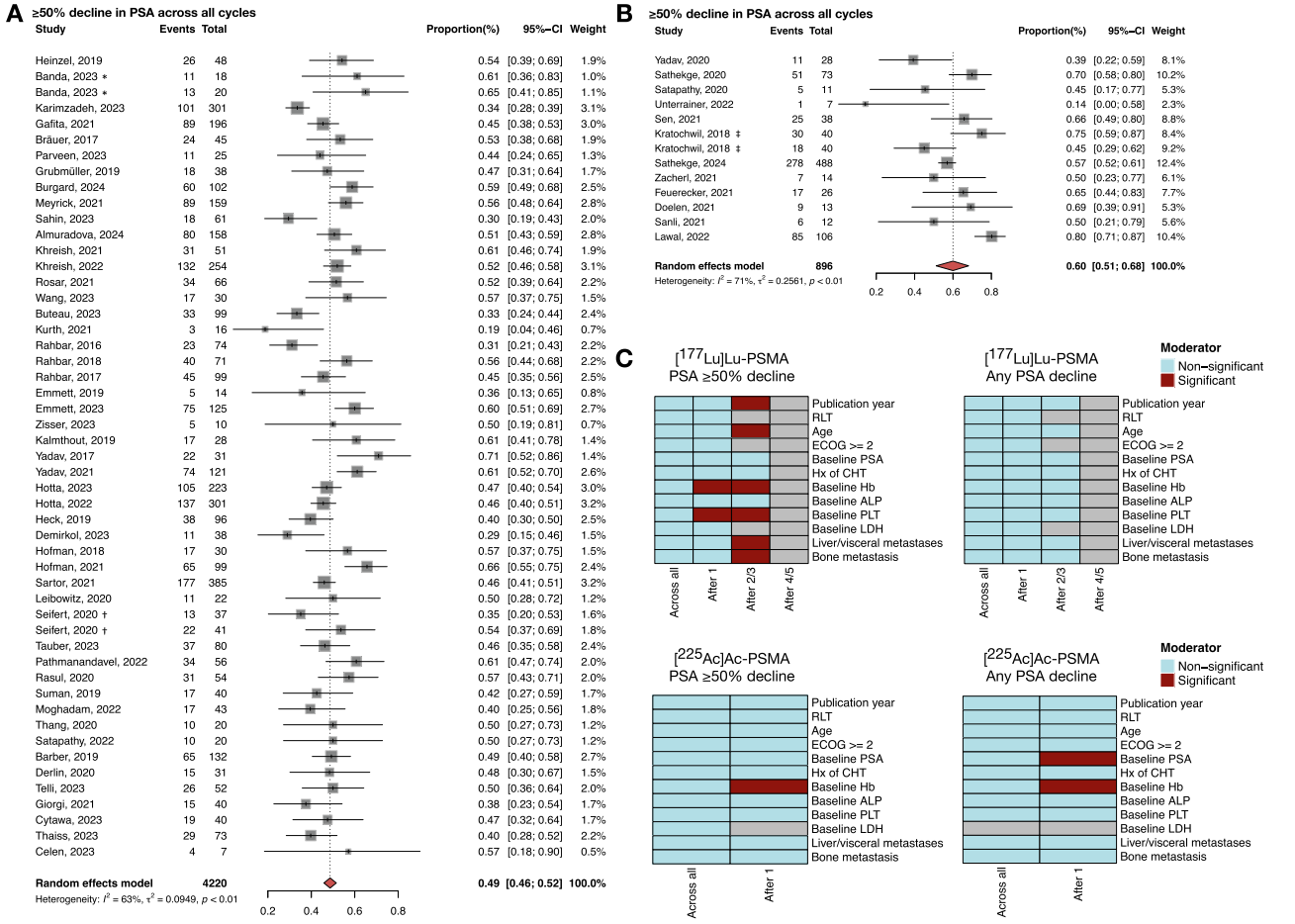

Fig. 2 – Forest plots revealing the estimated proportions of patients with PSA response: (A) PSA decline ≥50% across all cycles in patients receiving [^{177}Lu]Lu-PSMA therapy, (B) PSA decline ≥50% across all cycles in patients undergoing [^{225}Ac]Ac-PSMA therapy, and (C) heatmaps showing moderators of heterogeneity for PSA ≥50% decline and any PSA decline. *indicates two response rates: PSA responses evaluated for [^{177}Lu]Lu-PSMA therapy alone and in combination with two cases of tandem [^{225}Ac]Ac-PSMA therapy. † denotes that two groups of administered activities were used for each cycle in the study: 6 GBq and 7.5 GBq. ‡ indicates two timings of PSA response evaluated: 'during and after' and 'after'. Grey squares indicate "not applicable" due to inadequate data for estimation. [^{225}Ac]Ac-PSMA = PSMA-targeted radioligand therapy utilising actinium-225; ALP = alkaline phosphatase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group Performance Status Scale; Hb = haemoglobin; Hx of CHT = history of chemotherapy; LDH = lactate dehydrogenase; [^{177}Lu]Lu-PSMA = PSMA-targeted radioligand therapy utilising lutetium-177; PLT = platelet count; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RLT = radioligand therapy.

the 61% response rate for maximum PSA responses documented during and after all cycles (Fig. 2B, and Supplementary Fig. 15 and 16). The response rate after all cycles was slightly lower at 52%, but no significant differences were observed in the Bayesian meta-analysis (Supplementary Fig. 17). Comparable to [^{177}Lu]Lu-PSMA therapy, the initial cycle showed a 37% response rate for a ≥50% PSA decline (I^2 = 68%; Supplementary Fig. 15). The overall incidence of any PSA decline was high at 80%, with a notable early treatment response of 74% after the first cycle (I^2 = 69% and 56%, respectively; Supplementary Fig. 15). Interestingly, the proportion of patients with a PSA decline after completing all cycles was 0.76 (95% CI: 0.63–0.86), slightly lower than the proportion of 0.81 (95% CI: 0.70–0.89) observed when evaluating responses during and after all treatment cycles (Supplementary Fig. 18), yet without significant differences between these assessment times (Supplementary Fig. 19). The majority of studies used [^{225}Ac]Ac-PSMA-617 (ten of 13), and the estimated proportions for various conditions were similar to the overall estimates (Supplementary Fig. 20). The primary moderator for heterogeneity among studies was baseline Hb level for both PSA ≥50% decline and any PSA decline, suggesting its association with treatment response (Fig. 2C).

3.4. *Meta-analysis of toxicity*

Toxicity profiles for [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA therapies revealed distinct patterns in a meta-analysis (Table 1 and Supplementary Fig. 21–23). Grade 1/2 anaemia emerged as the most prevalent toxicity associated with [^{177}Lu]Lu-PSMA therapy, affecting about half of the patients (estimated proportion = 0.50, 95% CI: 0.40–0.59), with grade 3/4 toxicities being rare across the remaining toxicity categories, under 10%. Notably, no significant differences were found between the different radioligands (PSMA-617 vs

Table 1 – Meta-analysis of the toxicity profiles after [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA therapies

Toxicity	CTCAE grade 1/2					CTCAE grade 3/4				
	N	Estimated proportion (%)	95% CI	I^2 (%)	*p* value	*N*	Estimated proportion (%)	95% CI	I^2 (%)	*p* value
[^{177}Lu]Lu-PSMA										
Anaemia	2588	43	31–55	93	<0.001	3183	9.0	7.0–11	66	<0.001
Leukopenia	2255	19	15–24	81	<0.001	2600	2.4	1.6–3.7	49	0.002
Neutropenia	414	18	11–28	74	<0.001	589	4.3	2.8–6.7	0	0.5
Thrombocytopenia	2563	22	19–26	72	<0.001	3158	5.1	4.1–6.4	26	0.08
Fatigue	1515	36	27–46	88	<0.001	1600	2.5	1.5–4.1	23	0.2
Nausea	1580	17	10–29	90	<0.001	1600	1.2	0.72–1.9	0	1
Vomiting	1069	12	6.0–24	86	<0.001	1164	1.0	0.54–1.8	0	0.9
Diarrhoea	1200	10.	7.0–15	67	<0.001	1275	0.90	0.52–1.6	0	1
AST	421	23	16–32	71	<0.001	421	2.6	1.3–5.2	0	0.9
ALT	351	13	5.0–30	91	<0.001	351	2.5	1.1–5.5	0	0.5
Bilirubin	191	4.2	2.0–8.0	0	0.9	191	0.89	0.18–4.3	0	0.8
Albumin	44	4.6	1.0–16	0	0.9	44	2.2	0.31–14	0	0.9
GGT	222	21	16–28	41	0.16	222	5.2	2.0–14	53	0.09
Nephropathy	1587	9.1	6.0–13	72	<0.001	1487	1.2	0.72–2.0	0	1
Xerostomia	1975	30.	22–40	87	<0.001	2050	1.5	0.93–2.3	0	1
[^{225}Ac]Ac-PSMA										
Anaemia	202	61	32–84	84	<0.001	202	15	7.2–28	67	0.006
Leukopenia	138	26	12–47	78	0.004	138	6.4	1.4–25	76	0.005
Neutropenia	50	11	4.0–23	0	0.4	50	2.2	0.31–14	0	0.6
Thrombocytopenia	202	18	10–32	69	0.004	202	8.0	3.6–17	40	0.13
Fatigue	124	52	32–72	61	0.051	124	2.0	0.51–7.8	0	0.8
Nausea	136	23	17–31	0	0.7	136	1.9	0.46–7.1	0	0.8
Vomiting	84	6.0	3.0–14	0	0.7	84	1.6	0.23–11	0	0.4
Xerostomia	202	82	58–94	84	<0.001	202	4.8	1.8–12	20	0.3

[^{225}Ac]Ac-PSMA = PSMA-targeted radioligand therapy utilising actinium-225; ALT = alanine transaminase; AST = aspartate transaminase; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; GGT = gamma-glutamyl transferase; [^{177}Lu]Lu-PSMA = PSMA-targeted radioligand therapy utilising lutetium-177; PSMA = prostate-specific membrane antigen.

PSMA-I&T) with respect to toxicities, including anaemia, neutropenia, thrombocytopenia, and xerostomia (Supplementary Fig. 22). For [^{225}Ac]Ac-PSMA therapy, xerostomia was the most common toxicity (estimated proportion = 0.87, 95% CI: 0.63–0.96), with anaemia also being reported frequently (estimated proportion = 0.75, 95% CI: 0.50–0.90). Grade 3/4 anaemia (0.15, 95% CI: 0.07–0.28) was more prevalent than severe xerostomia (0.05, 95% CI: 0.02–0.12). Across both therapies, severe toxicities were infrequent. The heterogeneity for toxicity profiles appeared to be influenced by the varying proportions of liver/visceral and bone metastases across studies, which were associated with different rates of haematological toxicity, especially for [^{177}Lu]Lu-PSMA (Supplementary Fig. 24).

3.5. Meta-analysis of QoL

Multiple studies evaluating QoL following [^{177}Lu]Lu-PSMA therapy were pooled. The primary questionnaires utilised were the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30) and the Brief Pain Inventory-Short Form (BPI-SF). Significant improvements in global health status were noted across multiple cycles, with an estimated change of scores from baseline showing improvements in cycle 2 (6.24, 95% CI: 2.67–9.82), cycle 3 (6.22, 95% CI: 1.58–10.9), and cycle 4 (5.62, 95% CI: 1.03–10.2; Supplementary Table 5 and Supplementary Fig. 25). Emotional functioning also improved significantly starting from cycle 1 (8.84, 95% CI: 0.00–14.5) and was sustained through to the 3-mo follow-up time point (4.82, 95% CI: 0.99–8.66). Role functioning showed a notable increase in cycle 1 (12.2, 95% CI: 4.89–19.4). Pain (EORTC QLQ-C30 items), pain intensity, and pain interference (BPI-SF items) all demonstrated consistent significant reductions from cycle 2 onwards, especially notable in cycle 4 for pain (−12.1, 95% CI: −18.7 to −5.60). Other symptoms, including nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea, showed no consistent patterns of improvement or worsening. For [^{225}Ac]Ac-PSMA therapy, most QoL metrics remained stable, with the notable exception of constipation, which showed significant improvement after the second treatment cycle (Supplementary Table 6).

3.6. Publication bias

A funnel plot analysis revealed minimal publication bias across most outcomes for [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA (Supplementary Fig. 26). For [^{177}Lu]Lu-PSMA, exceptions included a potential bias in reports of any-grade anaemia, diarrhoea, nausea, nephropathy, AST elevation, and any PSA decline across all cycles. For [^{225}Ac]Ac-PSMA, evidence of a possible bias was found for any-grade anaemia and nephropathy. Other assessed outcomes showed no apparent bias.

3.7. Relationship between AA and PSA response

An analysis of 24 studies with reported AAs showed no significant association between the prescribed amount of AA for the initial cycle of [^{177}Lu]Lu-PSMA and PSA response for decline of $\geq$50% or any decline (Fig. 3A and Supplementary Table 7). In evaluating the cumulative AA for PSA response following all cycles of [^{177}Lu]Lu-PSMA, only three studies reported median or mean cumulative AA [26–28]. Among 33 studies available for the evaluation of cumulative AA, we found that the mean difference between the

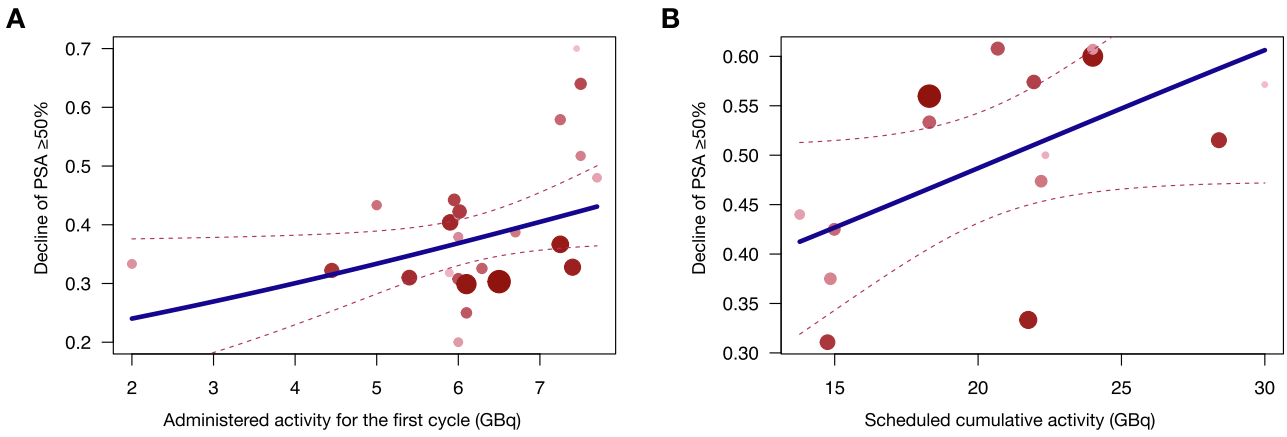

Fig. 3 – Meta-regression analysis demonstrating the proportions of patients with ≥50% PSA decline after the first cycle and all cycles of [^{177}Lu]Lu-PSMA therapy. Regression was conducted against the (A) activity given at the first cycle and (B) scheduled cumulative activity. [^{177}Lu]Lu-PSMA = PSMA-targeted radioligand therapy utilising lutetium-177; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen. The size each symbol is scaled based on the weight of the corresponding study, which is inversely proportional to its variance.

reported cumulative AA and the scheduled estimates was small (1.06 ± 3.13 GBq). Additionally, the correlation analysis showed a strong correlation between the number of treatment cycles and the reported cumulative AA (Pearson's coefficient = 0.89, $p < 0.001$; Supplementary Fig. 27). Therefore, the scheduled cumulative AA was used for subsequent analyses. A significant association was observed between scheduled cumulative AA and a ≥50% PSA decline across 15 studies (coefficient = 0.159, 95% CI: 0.0362–0.281, $p < 0.001$), but not for any PSA decline (Fig. 3B). The sole outlier at 21.75 GBq originated from a prospective trial that applied an intention-to-treat analysis [29]. Had a per-protocol approach been adopted, the PSA response rate would have been 0.52, resulting in a slightly higher coefficient (coefficient = 0.165; Supplementary Fig. 28). For [^{225}Ac]Ac-PSMA, the number of studies with detailed cycle and/or covariate information was less than ten, precluding their inclusion in the meta-regression analysis. Nevertheless, Pearson's test showed a borderline correlation between the scheduled cumulative AA and any PSA response (Pearson's coefficient = 0.67, $p = 0.09$).

3.8. *IPD for survival analysis*

Survival outcomes associated with PSA decline in this study were evaluated using KM plots and IPD, focusing on declines ≥50% and any decline after the initial cycle and across all cycles. Specifically, for [^{225}Ac]Ac-PSMA, survival data came from three studies, two of which provided data on ≥50% PSA decline after the first cycle. By aggregating data from 31 studies, six reconstructed KM plots were generated (Fig. 4). Patients who exhibited PSA responses had significantly improved OS and PFS with both therapies (all $p < 0.05$). The meta-analysis for [^{177}Lu]Lu-PSMA showed a pooled HR of 0.43 (95% CI: 0.33–0.55, $p < 0.001$) for OS, indicating that a PSA response is positively associated with survival outcomes. These findings, including HRs and 95% CIs for OS and PFS across different scenarios, are detailed in Supplementary Table 8 and illustrated in Supplementary Figure 29.

3.9. *Factors associated with survival after PRLT*

The meta-analysis of [^{177}Lu]Lu-PSMA therapy in mCRPC patients identified key prognostic factors associated with survival. Elevated Hb level was associated with improved OS. Conversely, high levels of LDH, C-reactive protein, poor performance status (ECOG ≥2), and the presence of visceral and liver metastases were associated with an increased mortality risk, highlighting their negative prognostic value (Supplementary Fig. 30). Specifically, visceral metastasis was associated with an increased mortality risk (HR = 1.70, 95% CI: 1.42–2.04, $p < 0.001$), and liver metastases in particular had a pronounced association (HR = 2.31, 95% CI: 1.91–2.79, $p < 0.001$). Prior chemotherapy history was also associated with increased mortality (HR = 1.54, 95% CI: 1.22–1.95, $p < 0.001$). For PFS, visceral metastasis was a critical predictor of poor survival (HR = 1.48, 95% CI: 1.09–2.01, $p = 0.012$). Similarly, liver metastasis was associated with reduced OS (HR = 2.23, 95% CI: 1.04–4.78, $p = 0.039$) and PFS (HR = 2.12, 95% CI: 1.17–3.82, $p = 0.013$) after [^{225}Ac]Ac-PSMA therapy (Supplementary Fig. 31).

4. Discussion

This comprehensive study evaluated [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA therapies for mPCa, primarily mCRPC, observing significant associations with efficacy and safety. In patients treated with [^{177}Lu]Lu-PSMA therapy, approximately 49% experienced a ≥50% reduction in PSA, with 37% showing this response after the first cycle and 70% exhibiting a PSA decline of any magnitude. The response rates for [^{225}Ac]Ac-PSMA were higher, with a ≥50% PSA reduction in 60% and any PSA decline in 80% of patients. Both treatments were associated with anaemia but generally exhibited manageable safety profiles with few severe toxicities reported. Additionally, while [^{225}Ac]Ac-PSMA therapy preserved most aspects of QoL after the second cycle, [^{177}Lu]Lu-PSMA therapy significantly improved QoL, particularly in global health, emotional and role

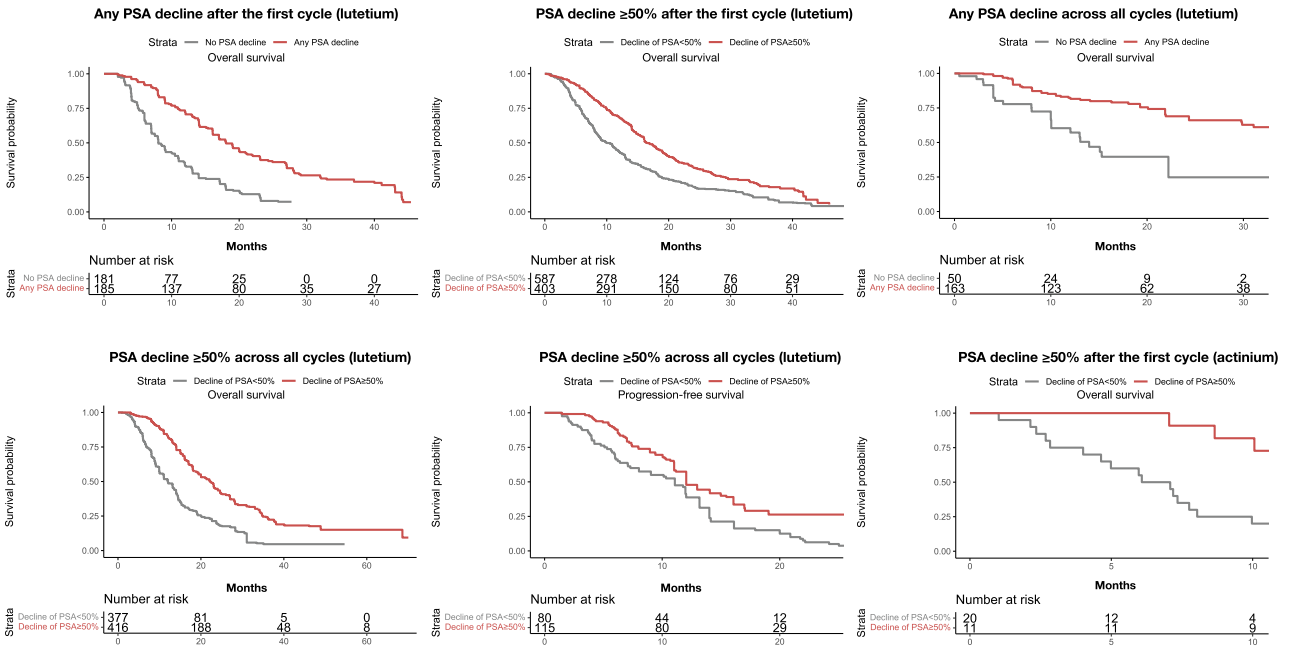

Fig. 4 – Reconstructed KM plots from IPD for OS and PFS based on PSA responses (decline ≥50% and any decline) after the first cycle and across all cycles in patients receiving [^{177}Lu]Lu-PSMA therapy and [^{225}Ac]Ac-PSMA therapy. [^{225}Ac]Ac-PSMA = PSMA-targeted radioligand therapy utilising actinium-225; IPD = individual patient data; KM = Kaplan-Meier; [^{177}Lu]Lu-PSMA = PSMA-targeted radioligand therapy utilising lutetium-177; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

functioning, and pain relief. These observations are consistent with recent reports, supporting the potential efficacy and safety of these therapies for managing mPCa [10,11,30,31]. It is important to highlight, however, that the clinical significance of these findings may not fully extend to patients with mHSPC. Only two independent studies in our analysis focused on mHSPC, neither of which demonstrated a strong link between clinical factors and PSA response or survival outcomes in this group. This indicates a clear need for further research specifically targeting mHSPC to better understand the efficacy of these treatments.

Research on AA (up to 9.3 GBq per cycle) in safety and toxicity trials has yielded mixed results on how the number of cycles and cumulative AA affect treatment response and survival following [^{177}Lu]Lu-PSMA therapy [32–34]. Recent analyses, including a multivariate study by Rahbar et al [32], which employed a cumulative AA cut-off of 11.8 GBq, did not identify it as strongly prognostic compared with the number of cycles. However, independent studies have shown that cumulative AA exceeding 12.95 and 16 GBq correlate with prolonged OS [19,35–37]. Given that initial AA and treatment cycles have increased in recent trials (eg, 8.5 GBq, five cycles), re-evaluation of these cut-off values for cumulative AA may be warranted. The current meta-regression analysis, adjusting for various factors, confirmed a positive relationship between cumulative AA and a response of significant PSA decline (≥50%), but not for any PSA decline. This highlights the importance of sufficient cumulative activity across multiple cycles to achieve a substantial PSA response; and more research is necessary to further explore this trend in [^{225}Ac]Ac-PSMA therapy.

For mCRPC, [^{225}Ac]Ac-PSMA delivers potent antitumour effects through α particle emission, achieving higher PSA response rates than [^{177}Lu]Lu-PSMA, as demonstrated in meta-analyses and clinical studies [31,38]. Despite its shorter particle range aimed at minimising damage to healthy tissues, notable side effects include grade 1/2 xerostomia and anaemia due to unintended radiation exposure of salivary glands and bone marrow [39,40]. Factors such as age, number of treatment cycles, and renal function are predictors of haematological toxicity [41]. Prior chemotherapy and its impact on bone marrow reserve raise further concerns about haematological risks, compounded by previous treatments such as ^{223}Ra [42]. In addition to the complexities introduced by intratumoural variability in treatment response, the VISION dosimetry substudy emphasised the importance of precise radiation dose assessment to vital organs [43,44]. These findings highlight the need for meticulous patient selection and management to optimise therapeutic benefits while mitigating risks.

Recent advancements, particularly in positron emission tomography (PET) imaging, have resulted in the approval of agents such as ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, which enhance the precision of detecting metastatic lesions [45,46]. Studies demonstrate that PSMA PET/computed tomography (CT) scans not only surpass traditional imaging modalities in sensitivity and specificity, but also align closely with PSA responses, indicating a strong predictive value for treatment efficacy in mCRPC patients [47]. However, the varied methodologies used across studies to associate PSMA PET findings with clinical endpoints have complicated efforts to accurately estimate its overall value through pooled analyses [29,35,48]. As PSMA imaging continues to show great potential in shaping clinical practice, the use of standardised reporting guidelines may be necessary to measure its impact [49].

It is important to note that the heterogeneous nature of the included studies, in terms of treatment protocols, patient populations, and reporting standards, introduces variability that could obscure more nuanced insights into treatment effectiveness and toxicity. Secondly, the absence of long-term follow-up data restricts our understanding of the durability of treatment responses and late-emerging toxicities. Finally, while the meta-regression attempted to identify predictors of PSA response rates, the limited number of studies meeting the specific criteria for inclusion in this analysis restricted the robustness and generalisability of these findings. The estimated cycle numbers and activities per cycle, derived from mean or median values, may not depict the real-world conditions of individual patients accurately. This approach, while necessary for an analysis, might not fully capture the patient-specific treatment scenarios. These limitations underscore the need for more comprehensive, multicentre trials with standardised reporting and longer follow-up to better assess the efficacy and safety of PRLT in mPCa.

5. Conclusions

This meta-analysis highlights the association between [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA therapies and their significant correlations with PSA reduction, survival outcomes, and QoL in treating mPCa. It also underscores the potential of these therapies, emphasising the importance of patient selection and pointing to the need for further research to refine treatment protocols and enhance patient care.

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Study concept and design: Dai, Vallis
Acquisition of data: Dai.
Analysis and interpretation of data: Dai, Vallis.
Drafting of the manuscript: Dai, Vallis.
Critical revision of the manuscript for important intellectual content: Dai, Vallis.
Statistical analysis: Dai.
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Supplementary material

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