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^{177}Lu-PSMA radioligand therapy effectiveness in metastatic castration-resistant prostate cancer: An updated systematic review and meta-analysis

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Abstract

Background: An updated systematic review and meta-analysis of relevant studies to evaluate the effectiveness of prostate-specific membrane antigen (PSMA)-targeted endoradiotherapy/radioligand therapy (PRLT) in castration resistant prostate cancer (CRPC).

Methods: A systematic search was performed in July 2020 using PubMed/Medline database to update our prior systematic review. The search was limited to papers published from 2019 to June 2020. A total of 472 papers were reviewed. The studied parameters included pooled proportion of patients showing any or ≥50% prostate-specific antigen (PSA) decline after PRLT. Survival effects of PRLT were assessed based on pooled hazard ratios (HRs) of the overall survival (OS) according to any PSA as well as ≥50% PSA decline after PRLT. Response to therapy based on ≥50% PSA decrease after PRLT versus controls was evaluated using Mantel-Haenszel random effect meta-analysis. All p values < 0.05 were considered as statistically significant.

Results: A total of 45 publications were added to the prior 24 studies. 69 papers with total of 4157 patients were included for meta-analysis. Meta-analysis of the two recent randomized controlled trials showed that patients treated with ^{177}Lu-PSMA 617 had a significantly higher response to therapy compared to controls based on ≥50% PSA decrease. Meta-analysis of the HRs of OS according to any PSA decline and ≥50% PSA decline showed survival prolongation after PRLT.

Conclusions: PRLT results in higher proportion of patients responding to therapy based on ≥50% PSA decline compared to controls. Any PSA decline and ≥50% PSA decline showed survival prolongation after PRLT.

Advances in knowledge: This is the first meta-analysis to aggregate the recent randomized controlled trials of PRLT which shows CRPC patients had a higher response to therapy after PRLT compared to controls.

Submission type: Systematic Review and Meta-Analysis

KEYWORDS
endoradiotherapy, PSMA, radioligand therapy

1 | INTRODUCTION

Metastatic castration resistant prostate cancer is the second most common cancer and the fifth cause of death in the world.[1] The current therapeutic approaches include chemotherapy, second generation hormonal therapy, and 223-Ra.[2] Regardless of all these modalities the cancer continues to be incurable and will eventually progress, hence the need for more efficient agents.

Prostate-specific membrane antigen (PSMA) is a transmembrane glutamate carboxypeptidase that is avidly expressed on the cell surface of the vast majority of prostate cancer specimens.[3] Small radiolabeled molecules that target PSMA can provide highly efficient diagnostic and therapeutic agents. Beta-particle-emitting tracers namely ^{177}LuPSMA-617,^{177}Lu-PSMA-I&T (imaging and treatment) are the most widely utilized PSMA-targeted endoradiotherapy/radioligand therapy (PRLT) agents. The emitted beta particles have less than 2 mm tissue penetration which results in damage to the cancer while sparing the surrounding normal tissues.[4]

Previously we reported the results of a meta-analysis of PRLT showing their high effectiveness and low rate of severe toxicity.[5] The majority of the included papers were retrospective studies and none of them were randomized control trials. Since the beginning of 2021 the results of two of the randomized control trials have been published.[6,7] Herein, we will update the results of our prior meta-analysis. The main outcomes that are assessed in this study are the proportion of patients showing any prostate-specific antigen (PSA) decrease, ≥50% PSA decrease, and overall survival (OS) based on ≥50 PSA decrease.

2 | MATERIALS AND METHODS

2.1 | Evidence acquisition

This study was carried out based on the PICo method for systematic reviews.[8] To update our prior systematic review which was done up to Feb 2019, PubMed/Medline databases were searched for the following keywords: (177-Lu OR 177Lu OR Lu-177 OR Lutetium-177 OR theranostic OR theranostics) AND PSMA. The search was limited to only the studies published since 2019 up to the time of the search on July 2020. A total of 472 unique studies were reviewed against our inclusion criteria: all retrospective or prospective studies of ^{177}Lu-labeled, small molecule PRLT ligand in humans with CRPC including randomized and nonrandomized trials published in English that evaluated survival or PSA response. The search output was uploaded to Covidence website (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) to be reviewed. Reviewing the studies and data selection was performed by one of the authors (MS).

2.2 | Treatment response

Proportion of patients showing of ≥50% PSA decline and any PSA decline were extracted from the included studies. Regarding the studies that provided PSA alterations after multiple cycles, we considered the overall response whenever possible, and if the overall response was not provided, the best response in any cycle was considered for meta-analysis. Regarding the two randomized controlled trials we applied Mantel Haenszel model with a random effect analysis model using review manager version 5.3 (The Cochrane Collaboration, Copenhagen, Norway). Odds ratios (OR) and their 95% confidence intervals (CI) were computed. For the rest of the studies meta-analysis of single proportion was performed with R version 4.0.3 (2020-10-10)[9] based on "meta"package version 4.15-1.[10] I^2 was considered to evaluate heterogeneity. When $p > 0.1$ for χ^2 test of heterogeneity, we referred to fixed effect models and when $p < 0.1$, we referred to random effect models. The 177Lu-PSMA-617 and 177Lu-PSMA-I&T were compared for PSA response using t test.

2.3 | Overall survival

The OS analysis was based on the pooled hazard ratios (HR) of OS according to any PSA decline and ≥50% PSA decline. HR and 95% CI where extracted from the papers. If these values were not provided, Kaplan–Meier curves were used to have an estimation of HR and 95% CI. For this purpose, GetData Graph Digitizer (http://www.getdata-graph-digitizer.com/) was used to get the graphical representations which were used to calculate estimated HR and 95% CI based on a prior methodology.[11] Survival analysis was done using review manager version 5.3 (The Cochrane Collaboration, Copenhagen, Norway).

2.4 | Publication bias

The funnel plots were created to evaluate publication bias. Subjective evaluation of symmetry was considered to evaluate publication bias.

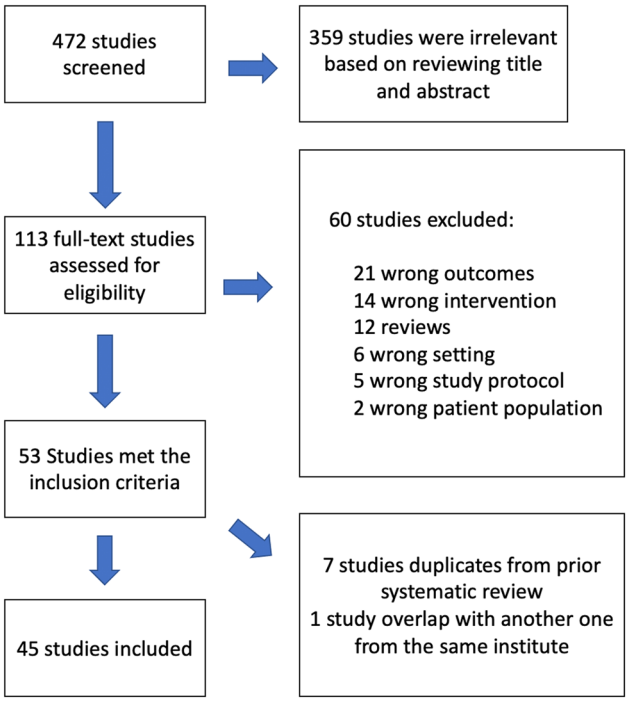

FIGURE 1 Flow chart of the systematic review. PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen

3 | RESULTS

To update our prior meta-analysis a total of 472 papers since 2019 were reviewed individually against the inclusion criteria (Figure 1). Based on the evaluation of the titles and abstracts 359 studies were excluded. The full text of the remaining 113 papers were reviewed and 53 studies met the inclusion criteria. Seven studies were duplicates from the prior systematic review and were omitted. One study[12] had considerable overlap with another study from the same institute[13] and was removed from the meta-analysis. A total of 45 new papers were added to the list of the 24 studies that were included in the prior meta-analysis (Table 1). A total of 69 papers including 4157 patients were included for the meta-analysis. A total of 56 studies evaluated ^{177}Lu-PSMA 617 (3365 patients), 7 studies evaluated ^{177}Lu-PSMA I&T (316 patients), 2 studies included both ^{177}Lu-PSMA 617 and I&T without providing separate results (235 patients), one study included ^{177}Lu-EB-PSMA-617 (5 patients), and 3 studies did not determine the type of PRLT (236 patients). Two studies were randomized controlled trials.[14] A total of 16 studies were prospective studies, and the rest were retrospective.

The meta-analysis for the two randomized controlled studies showed that patients treated with ^{177}Lu-PSMA 617 had a significantly higher response to therapy compared to controls based on ≥50% PSA decrease (OR = 5.33, 95% CI: 1.24–22.90, $p < 0.05$) as shown in Figure 2.

OS according to pooled HRs for any PSA decline was 0.26 with significance after ^{177}Lu-PSMA therapy (95% CI: 0.18–0.37, $p < 0.00001$) (Figure 3A) and for ≥50% decrease was 0.52 with significance (95% CI: 0.40–0.67, $p < 0.00001$) (Figure 3B).

The results of the meta-analysis of single proportion for ≥50% PSA decrease, and any PSA decrease showed marked heterogeneity (Figures S1 and S2). There was no statistical different in PSA response between ^{177}Lu-PSMA I&T and ^{177}Lu-PSMA-617. Regarding any PSA decrease the accumulated proportion was 0.68 (95% CI: 0.64; 0.71) with high heterogeneity $I^2 = 63\%$. Aggregated proportion of patients with ≥50% PSA decrease was 0.44 (95% CI: 0.41; 0.48) with high heterogeneity $I^2 = 70\%$.

4 | PUBLICATION BIAS

The funnel plots regarding the survival analysis are overall symmetric (Figure 4). The proportion of patients showing ≥50% PSA decrease the funnel plot showed slight asymmetry, however when the studies were limited to those with more than one cycle of PRLT the funnel plot appears to be subjectively symmetric (Figure S3A). Subjective evaluation of the proportion of patient showing any PSA decline funnel plot shows asymmetry suggestive of presence of publication of bias (Figure S3B).

5 | DISCUSSION

In this systematic review and meta-analysis, we showed that patients treated with ^{177}Lu-PSMA 617 had a significantly higher response to therapy compared to the controls (OR = 5.33, 95% CI: 1.24–22.90, $p < 0.05$) based on the numbers of patients showing ≥50% PSA decrease using the accumulated data from two randomized control studies. We also updated our prior survival analysis and single proportion meta-analysis. Any PSA decline and ≥50% PSA decline showed survival prolongation after ^{177}Lu-PSMA therapy. We noticed significant heterogeneity regarding the proportion of patients showing any PSA decline and ≥50% PSA which will be discussed later under the limitations.

As shown in Table 1, the majority of PRLT studies in prostate cancer patients are retrospective studies based on the "compassionate use" doctrine in Europe.[80] The number of prospective studies is increasing, as the included prospective studies in our prior meta-analysis were only 3 studies, and in the current study we have 16 prospective studies. Most importantly, since the beginning of 2021 the results of two randomized clinical trials have been published with promising findings, namely TheraP[6] and[7] VISION clinical trials.

On December 2020 the US Food and Drug Administration (FDA) approved ^{68}Ga-PSMA-11 for PET imaging PSMA-positive lesions in prostate cancer.[81] On May 2021 FDA approved ^{18}F-DCFPyL (Pylarify)[82] was approved for patients with prostate cancer. Gallium-68 (^{68}Ga) is useful in diagnostic evaluation of the prostate cancer. The positron emission from ^{68}Ga can be detected by PET imaging which can be used in diagnostic approaches. On the other

TABLE 1 Summary of the included studies

PMID	First author	Year	Agent	Study type	Number of patients	Randomized controlled trial
1	Acar[15]	2019	^{177}Lu-PSMA I&T	Retrospective	19	No
2	Aghdam[16]	2019	^{177}Lu-PSMA 617	Prospective	14	No
3	Ahmadzadehfar[17]	2016	^{177}Lu-PSMA 617	Retrospective	10	No
4	Ahmadzadehfar_1[18]	2017	^{177}Lu-PSMA 617	Retrospective	100	No
5	Ahmadzadehfar_2[19]	2017	^{177}Lu-PSMA 617	Retrospective	49	No
6	Ahmadzadehfar_3[20]	2017	^{177}Lu-PSMA 617	Retrospective	52	No
7	Ahmadzadehfar[13]	2021	^{177}Lu-PSMA 617	Retrospective	393	No
8	Assadi[21]	2020	^{177}Lu-PSMA 617	Prospective	21	No
9	Barber[22]	2019	^{177}Lu-PSMA 617 and I&T	Retrospective	132	No
10	Barna[23]	2020	^{177}Lu-PSMA I&T	Retrospective	19	No
11	Bräuer[24]	2017	^{177}Lu-PSMA 617	Retrospective	45	No
12	Bülbül[25]	2020	^{177}Lu-PSMA I&T	Retrospective	45	No
13	Calais[26]	2021	^{177}Lu-PSMA 617	Prospective	43	Yes
14	Derlin_1[27]	2020	^{177}Lu-PSMA 617	Retrospective	50	No
15	Derlin_2[28]	2020	^{177}Lu-PSMA 617	Retrospective	39	No
16	Emmet[29]	2019	^{177}Lu-PSMA 617	Prospective	14	No
17	Fendler[30]	2016	^{177}Lu-PSMA 617	Prospective	15	No
18	Ferdinandus[31]	2016	^{177}Lu-PSMA 617	Retrospective	40	No
19	Gado[32]	2020	^{177}Lu-PSMA 617	Retrospective	52	No
20	Gafita[33]	2020	^{177}Lu-PSMA 617	Retrospective	38	No
21	Gallyamov[34]	2020	^{177}Lu-PSMA 617 and I&T	Retrospective	103	No
22	Grubmüller[35]	2018	^{177}Lu-PSMA 617	Retrospective	38	No
23	Gupta[36]	2019	^{177}Lu-PSMA 617	Retrospective	22	No
24	Gupta[37]	2020	^{177}Lu-PSMA 617	Retrospective	10	No
25	Heck[38]	2018	^{177}Lu-PSMA I&T	Retrospective	100	No
26	Heinzel[39]	2019	^{177}Lu-PSMA 617	Retrospective	48	No
27	Hofman[40]	2018	^{177}Lu-PSMA 617	Prospective	30	No
28	Hofman[6]	2021	^{177}Lu-PSMA 617	Prospective	98	Yes
29	Huang[41]	2021	Not determined	Retrospective	46	No
30	Kalmthout[42]	2019	^{177}Lu-PSMA 617	Retrospective	30	No
31	Kesavan[43]	2018	^{177}Lu-PSMA I&T	Retrospective	20	No
32	Kesavan[44]	2021	^{177}Lu-PSMA I&T	Retrospective	100	No
33	Kessel[45]	2019	^{177}Lu-PSMA 617	Retrospective	87	No
34	Khreish[46]	2021	^{177}Lu-PSMA 617	Retrospective	28	No
35	Khurshid[47]	2018	^{177}Lu-PSMA 617	Retrospective	70	No
36	Kletting[48]	2019	^{177}Lu-PSMA I&T	Retrospective	13	No
37	Kratochwil[49]	2016	^{177}Lu-PSMA 617	Retrospective	30	No
38	Leibowitz[50]	2020	^{177}Lu-PSMA 617	Retrospective	24	No
39	Maffey-Steffan[51]	2019	^{177}Lu-PSMA 617	Prospective	32	No

(Continues)

TABLE 1 (Continued)

PMID	First author	Year	Agent	Study type	Number of patients	Randomized controlled trial
40	Marinova[52]	2020	^{177}Lu-PSMA 617	Retrospective	30	No
41	McBean[53]	2019	^{177}Lu-PSMA 617	Retrospective	49	No
42	Meyrick[54]	2021	Not determined	Retrospective	159	No
43	Michalski[55]	2021	^{177}Lu-PSMA 617	Retrospective	46	No
44	Paganelli[56]	2020	^{177}Lu-PSMA 617	Prospective	41	No
45	Prasad [57]	2021	^{177}Lu-PSMA 617	Retrospective	38	No
46	Privé[58]	2021	^{177}Lu-PSMA 617	Prospective	10	No
47	Rahbar_1[59]	2016	^{177}Lu-PSMA 617	Retrospective	99	No
48	Rahbar_2[60]	2016	^{177}Lu-PSMA 617	Retrospective	74	No
49	Rahbar_1[61]	2017	^{177}Lu-PSMA 617	Retrospective	71	No
50	Rahbar_2[62]	2017	^{177}Lu-PSMA 617	Retrospective	104	No
51	Rasul[63]	2020	^{177}Lu-PSMA 617	Retrospective	54	No
52	Rasul_1[64]	2021	^{177}Lu-PSMA 617	Retrospective	61	No
53	Rasul_2[65]	2021	^{177}Lu-PSMA 617	Retrospective	43	No
54	Rathke [66]	2017	^{177}Lu-PSMA 617	Retrospective	40	No
55	Rathke[67]	2020	^{177}Lu-PSMA 617	Retrospective	100	No
56	Rosasr[68]	2021	^{177}Lu-PSMA 617	Retrospective	22	No
57	Sartor[7]	2021	^{177}Lu-PSMA 617	Prospective	385	Yes
58	Scarpa[69]	2017	^{177}Lu-PSMA 617	Prospective	10	No
59	Seifert[70]	2020	^{177}Lu-PSMA 617	Retrospective	78	No
60	Soydal[71]	2019	Not determined	Retrospective	31	No
61	Suman[72]	2019	^{177}Lu-PSMA 617	Retrospective	40	No
62	Tatkovic[73]	2021	^{177}Lu-PSMA 617	Retrospective	66	No
63	Violet[74]	2020	^{177}Lu-PSMA 617	Prospective	50	No
64	Völter[75]	2021	^{177}Lu-PSMA 617	Retrospective	30	No
65	Widjaja[76]	2021	^{177}Lu-PSMA 617	Retrospective	71	No
66	Yadav[14]	2019	^{177}Lu-PSMA 617	Prospective	90	No
67	Yordanova[77]	2019	^{177}Lu-PSMA 617	Retrospective	20	No
68	Yadav[78]	2021	^{177}Lu-PSMA 617	Prospective	121	No
69	Zang[79]	2018	^{177}Lu-EB-PSMA 617	Prospective	5	No

Abbreviation: PSMA, prostate-specific membrane antigen.

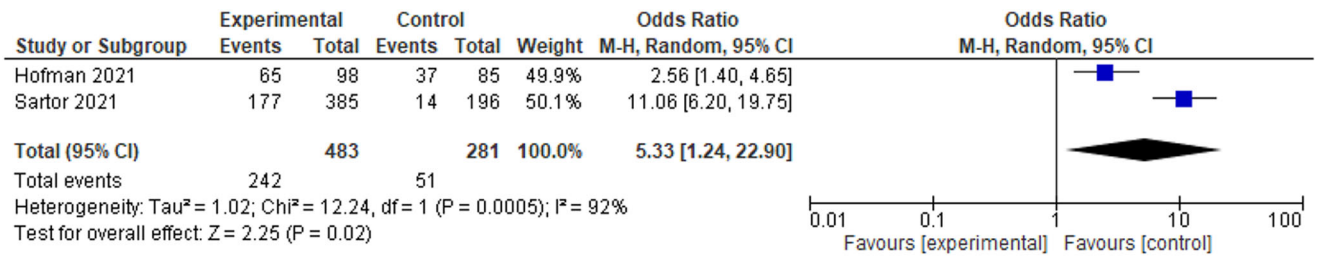

FIGURE 2 Forest plot based on the meta-analysis of the comparison of patients showing ≥50% PSA decrease after ^{177}Lu-PSMA 617 versus controlled. PSA, prostate-specific antigen

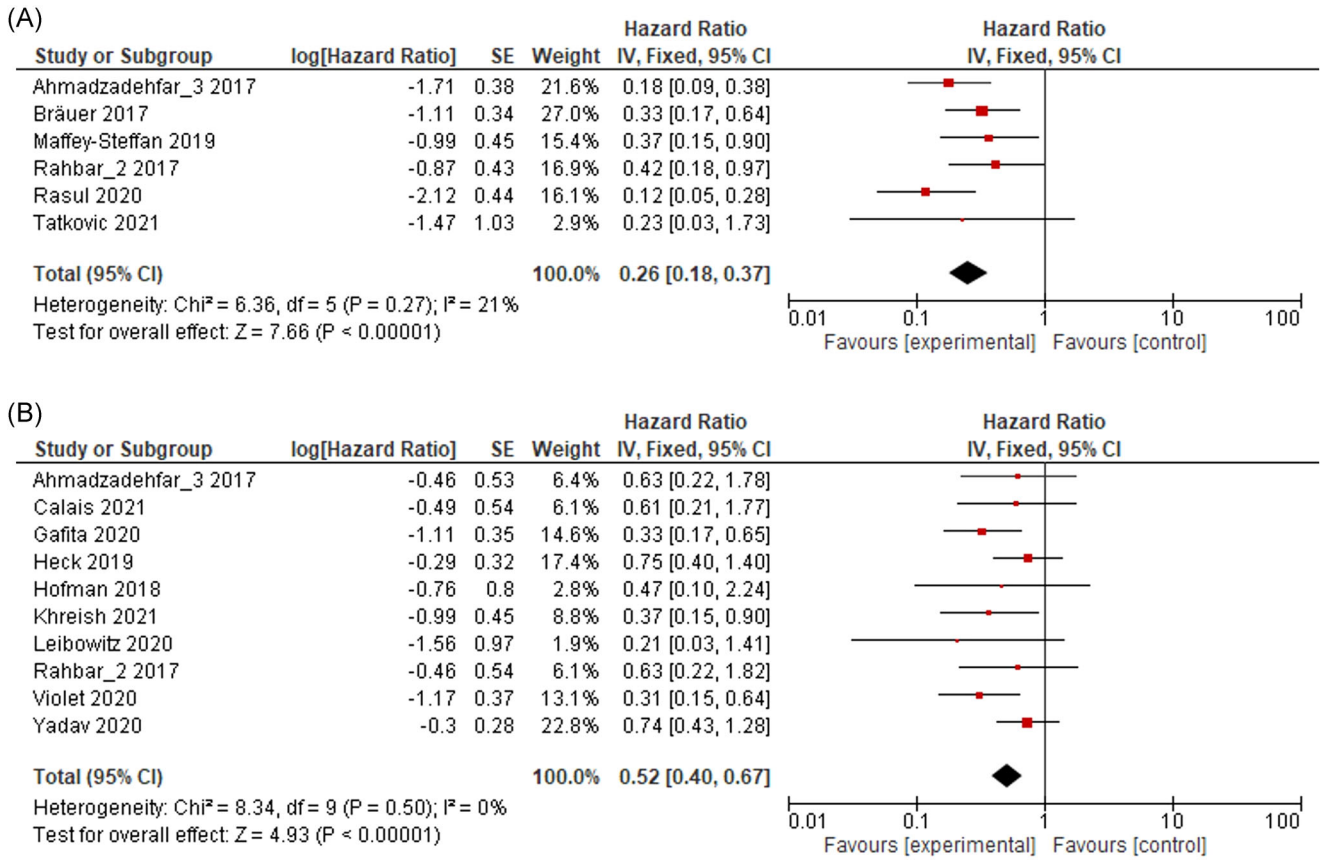

FIGURE 3 Forest plot of the overall survival analysis according to pooled hazard ratios (HRs) for any PSA decline (A) and for ≥50% PSA decline (B). PSA, prostate-specific antigen

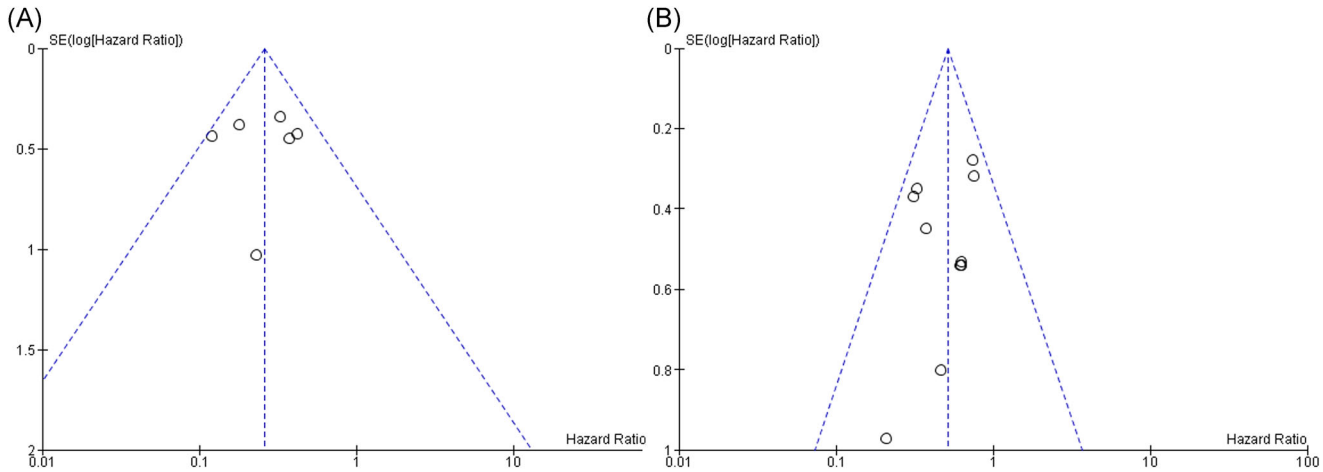

FIGURE 4 Funnel plots for pooled hazard ratios (HR) for any PSA decline (A) and for ≥50% PSA decline (B). PSA, prostate-specific antigen

hand, 177Lu emits moderate energy beta particles which can be used in therapeutic approaches and low energy gamma photons which can be used in diagnostic approaches.[83] The FDA approval of two ^{68}Ga based PSMA targeting agents have paved the road for a future approval of ^{177}Lu PSMA targeting agent.

The European Association of Nuclear Medicine (EANM) has published guidelines regarding the use of PRLT in 2019.[84] This guideline considered PRLT as an "unproven intervention in clinical practice". ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T are the two most commonly used small-molecule radioligands in PRLT and they have shown similar biodistribution and efficacy,[84] hence the guideline considered these tracers to be exchangeable in practice. According to EANM, PRLT should be considered among men with mCRPC who have failed or are not eligible to standard of care managements and

those with adequate uptake of a PSMA-targeted radiotracer on a prior PET scan.

The are some limitations in this study. Only two randomized controlled trials were available for analysis. In addition, the majority of studies were retrospective with small number of patients. There is significant heterogeneity in the meta-analysis regarding comparison of ^{177}Lu-PSMA with control studies in the randomized clinical trials. This could at least partially be explained by some differences in the between the VISION[7] and TheraP.[6] Both studies were multicenter trials, however TheraP was done at 11 centers in Australia while VISION was done at 84 sites (52 in North America and 32 in Europe). In addition, ^{18}F-FDG PET positive and PSMA negative patients were excluded from TheraP while this was not considered in VISION. Moreover, regarding the aggregate proportion of patients showing ≥50% or any PSA decline there was considerable heterogeneity. The reason might be related to different doses of therapy, different number of cycles, different prior therapies, and extent of the disease. The emergence of the results of more randomized controlled trials updating this meta-analysis provides a better estimation of the effectiveness of 177Lu-PSMA therapy in patients CRPC.

CONFLICTS OF INTEREST

Under a license agreement between Progenics (a wholly-owned subsidiary of Lantheus) and the Johns Hopkins University, MGP and the University are entitled to royalties on an invention described in this article. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. MAG has served as a consultant to Progenics. SPR is a consultant to Progenics.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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