**Original Article**

177Lu-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 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 177Lu-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 decrease 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.
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 223Ra.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 177LuPSMA-617,177Lu-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 177Lu-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 I2 was considered to evaluate heterogeneity. When p > 0.1 for χ2 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.

KEYWORDS
endoradiotherapy, PSMA, radioligand therapy
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 had considerable overlap with another study from the same institute 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 \( ^{177} \text{Lu-PSMA I&T} \) (3365 patients), 7 studies evaluated \( ^{177} \text{Lu-PSMA I&T} \) (316 patients), 2 studies included both \( ^{177} \text{Lu-PSMA I&T} \) and without providing separate results (235 patients), one study included \( ^{177} \text{Lu-EB-PSMA-617} \) (5 patients), and 3 studies did not determine the type of PRLT (236 patients). Two studies were randomized controlled trials. 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 \( ^{177} \text{Lu-PSMA 617} \) 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 \( \geq 50\% \) 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 \( \geq 50\% \) 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 \( \geq 50\% \) 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 \( ^{177} \text{Lu-PSMA 617} \) 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 \( \geq 50\% \) 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 \( \geq 50\% \) PSA decline showed survival prolongation after \( ^{177} \text{Lu-PSMA} \) therapy. We noticed significant heterogeneity regarding the proportion of patients showing any PSA decline and \( \geq 50\% \) 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. 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 and VISION clinical trials.

On December 2020 the US Food and Drug Administration (FDA) approved \( ^{68} \text{Ga-PSMA-11} \) for PET imaging PSMA-positive lesions in prostate cancer. On May 2021 FDA approved \( ^{18} \text{F-DCFPyL} \) (Pylarify) was approved for patients with prostate cancer. Gallium-68 (\( ^{68} \text{Ga} \)) is useful in diagnostic evaluation of the prostate cancer. The positron emission from \( ^{68} \text{Ga} \) can be detected by PET imaging which can be used in diagnostic approaches. On the other
| PMID | First author   | Year | Agent          | Study type     | Number of patients | Randomized controlled trial |
|------|----------------|------|----------------|-----------------|--------------------|----------------------------|
| 1    | Acar          | 2019 | $^{177}$Lu-PSMA I&T | Retrospective | 19                 | No                         |
| 2    | Aghdam        | 2019 | $^{177}$Lu-PSMA 617 | Prospective | 14                 | No                         |
| 3    | Ahmadzadehfar | 2016 | $^{177}$Lu-PSMA 617 | Retrospective | 10                 | No                         |
| 4    | Ahmadzadehfar | 2017 | $^{177}$Lu-PSMA 617 | Retrospective | 100                | No                         |
| 5    | Ahmadzadehfar | 2017 | $^{177}$Lu-PSMA 617 | Retrospective | 49                 | No                         |
| 6    | Ahmadzadehfar | 2017 | $^{177}$Lu-PSMA 617 | Retrospective | 52                 | No                         |
| 7    | Ahmadzadehfar | 2021 | $^{177}$Lu-PSMA 617 | Retrospective | 393                | No                         |
| 8    | Assadi        | 2020 | $^{177}$Lu-PSMA 617 | Prospective | 21                 | No                         |
| 9    | Barber        | 2019 | $^{177}$Lu-PSMA 617 and I&T | Retrospective | 132                | No                         |
| 10   | Barna         | 2020 | $^{177}$Lu-PSMA I&T | Retrospective | 19                 | No                         |
| 11   | Bräuer        | 2017 | $^{177}$Lu-PSMA 617 | Retrospective | 45                 | No                         |
| 12   | Bulbul        | 2020 | $^{177}$Lu-PSMA I&T | Retrospective | 45                 | No                         |
| 13   | Calais        | 2021 | $^{177}$Lu-PSMA 617 | Prospective     | 43                 | Yes                        |
| 14   | Derlin_1      | 2020 | $^{177}$Lu-PSMA 617 | Retrospective | 50                 | No                         |
| 15   | Derlin_2      | 2020 | $^{177}$Lu-PSMA 617 | Retrospective | 39                 | No                         |
| 16   | Emmet         | 2019 | $^{177}$Lu-PSMA 617 | Prospective     | 14                 | No                         |
| 17   | Fendler       | 2016 | $^{177}$Lu-PSMA 617 | Prospective     | 15                 | No                         |
| 18   | Ferdinandus   | 2016 | $^{177}$Lu-PSMA 617 | Retrospective  | 40                 | No                         |
| 19   | Gado          | 2020 | $^{177}$Lu-PSMA 617 | Retrospective | 52                 | No                         |
| 20   | Gafita        | 2020 | $^{177}$Lu-PSMA 617 | Retrospective | 38                 | No                         |
| 21   | Gallyamov     | 2020 | $^{177}$Lu-PSMA 617 and I&T | Retrospective | 103                | No                         |
| 22   | Grubmüller    | 2018 | $^{177}$Lu-PSMA 617 | Retrospective | 38                 | No                         |
| 23   | Gupta         | 2019 | $^{177}$Lu-PSMA 617 | Retrospective | 22                 | No                         |
| 24   | Gupta         | 2020 | $^{177}$Lu-PSMA 617 | Retrospective | 10                 | No                         |
| 25   | Heck          | 2018 | $^{177}$Lu-PSMA I&T | Retrospective | 100                | No                         |
| 26   | Heinzl        | 2019 | $^{177}$Lu-PSMA 617 | Retrospective | 48                 | No                         |
| 27   | Hofmann       | 2018 | $^{177}$Lu-PSMA 617 | Prospective     | 30                 | No                         |
| 28   | Hofmann       | 2021 | $^{177}$Lu-PSMA 617 | Prospective     | 98                 | Yes                        |
| 29   | Huang         | 2021 | Not determined | Retrospective | 46                 | No                         |
| 30   | Kalmthout     | 2019 | $^{177}$Lu-PSMA 617 | Retrospective | 30                 | No                         |
| 31   | Kesavan       | 2018 | $^{177}$Lu-PSMA I&T | Retrospective | 20                 | No                         |
| 32   | Kesavan       | 2021 | $^{177}$Lu-PSMA I&T | Retrospective | 100                | No                         |
| 33   | Kesser        | 2019 | $^{177}$Lu-PSMA 617 | Retrospective | 87                 | No                         |
| 34   | Khreish       | 2021 | $^{177}$Lu-PSMA 617 | Retrospective | 28                 | No                         |
| 35   | Khurshid      | 2018 | $^{177}$Lu-PSMA 617 | Retrospective | 70                 | No                         |
| 36   | Kletting      | 2019 | $^{177}$Lu-PSMA I&T | Retrospective | 13                 | No                         |
| 37   | Kratochwil    | 2016 | $^{177}$Lu-PSMA 617 | Retrospective | 30                 | No                         |
| 38   | Leibowitz     | 2020 | $^{177}$Lu-PSMA 617 | Retrospective | 24                 | No                         |
| 39   | Maffey-Steffan | 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     | 2020 | 177Lu-PSMA 617   | Retrospective  | 30                   | No                          |
| 41    | McBean       | 2019 | 177Lu-PSMA 617   | Retrospective  | 49                   | No                          |
| 42    | Meyrick      | 2021 | Not determined   | Retrospective  | 159                  | No                          |
| 43    | Michalski    | 2021 | 177Lu-PSMA 617   | Retrospective  | 46                   | No                          |
| 44    | Paganelli    | 2020 | 177Lu-PSMA 617   | Prospective    | 41                   | No                          |
| 45    | Prasad       | 2021 | 177Lu-PSMA 617   | Retrospective  | 38                   | No                          |
| 46    | Privé        | 2021 | 177Lu-PSMA 617   | Prospective    | 10                   | No                          |
| 47    | Rahbar_1     | 2016 | 177Lu-PSMA 617   | Retrospective  | 99                   | No                          |
| 48    | Rahbar_2     | 2016 | 177Lu-PSMA 617   | Retrospective  | 74                   | No                          |
| 49    | Rahbar_1     | 2017 | 177Lu-PSMA 617   | Retrospective  | 71                   | No                          |
| 50    | Rahbar_2     | 2017 | 177Lu-PSMA 617   | Retrospective  | 104                  | No                          |
| 51    | Rasul        | 2020 | 177Lu-PSMA 617   | Retrospective  | 54                   | No                          |
| 52    | Rasul_1      | 2021 | 177Lu-PSMA 617   | Retrospective  | 61                   | No                          |
| 53    | Rasul_2      | 2021 | 177Lu-PSMA 617   | Retrospective  | 43                   | No                          |
| 54    | Rathke       | 2017 | 177Lu-PSMA 617   | Retrospective  | 40                   | No                          |
| 55    | Rathke       | 2020 | 177Lu-PSMA 617   | Retrospective  | 100                  | No                          |
| 56    | Rosasr       | 2021 | 177Lu-PSMA 617   | Retrospective  | 22                   | No                          |
| 57    | Sartor       | 2021 | 177Lu-PSMA 617   | Prospective    | 385                  | Yes                         |
| 58    | Scarpa       | 2017 | 177Lu-PSMA 617   | Prospective    | 10                   | No                          |
| 59    | Seifert      | 2020 | 177Lu-PSMA 617   | Retrospective  | 78                   | No                          |
| 60    | Soydal       | 2019 | Not determined   | Retrospective  | 31                   | No                          |
| 61    | Suman        | 2019 | 177Lu-PSMA 617   | Retrospective  | 40                   | No                          |
| 62    | Tatkovic     | 2021 | 177Lu-PSMA 617   | Retrospective  | 66                   | No                          |
| 63    | Violet       | 2020 | 177Lu-PSMA 617   | Prospective    | 50                   | No                          |
| 64    | Völter       | 2021 | 177Lu-PSMA 617   | Retrospective  | 30                   | No                          |
| 65    | Widjaja      | 2021 | 177Lu-PSMA 617   | Retrospective  | 71                   | No                          |
| 66    | Yadav_1      | 2019 | 177Lu-PSMA 617   | Prospective    | 90                   | No                          |
| 67    | Yordanova    | 2019 | 177Lu-PSMA 617   | Retrospective  | 20                   | No                          |
| 68    | Yadav_2      | 2021 | 177Lu-PSMA 617   | Prospective    | 121                  | No                          |
| 69    | Zang         | 2018 | 177Lu-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 177Lu-PSMA 617 versus controlled. 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. The FDA approval of two 68Ga based PSMA targeting agents have paved the road for a future approval of 177Lu PSMA targeting agent.

The European Association of Nuclear Medicine (EANM) has published guidelines regarding the use of PRLT in 2019. This guideline considered PRLT as an “unproven intervention in clinical practice”. 177Lu-PSMA-617 and 177Lu-PSMA-I&T are the two most commonly used small-molecule radioligands in PRLT and they have shown similar biodistribution and efficacy, 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

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
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 and TheraP. 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 $^{177}$Lu-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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REFERENCES
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi:10.3332/caac.21492
2. Nuhn P, De Bono JS, Fizazi K, et al. Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. Eur Urol. 2019;75(1):88-99. doi:10.1016/j.eururo.2018.03.028
3. Kinoshita Y, Kuratsukuri K, Landas S, et al. Expression of prostate-specific membrane antigen in normal and malignant human tissues. World J Surg. 2006;30(4):628-636. doi:10.1007/s00268-005-0544-5
4. Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci. 2017;64(1):52-60. doi:10.1002/jmrs.227
5. Sadaghian MS, Sheikhbahaei S, Werner RA, et al. A systematic review and meta-analysis of the effectiveness and toxicities of lutetium-177-labeled prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. Eur Urol. 2021;80(1):82-94. doi:10.1016/j.eururo.2021.03.004
6. Hofman MS, Emmett L, Sandhu S, et al. ([177]Lu-Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet (London, England). 2021;397(10276):797-804. doi:10.1016/S0140-6736(21)00237-3
7. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Medicine. Published online June 2021. doi:10.1056/NEJMoa2107322
8. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007;7:16. doi:10.1186/1472-6947-7-16
9. Computing RF for S. Team RC: R: a Language and Environment for Statistical Computing. Published online 2017.
10. Guido S. meta: an R package for meta-analysis. R News. 2007;(7):40-45.
11. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16. doi:10.1186/1745-6215-8-16
12. Ahmadzadehfar H, Matern R, Baum RP, et al. The impact of the extent of the bone involvement on overall survival and toxicity in mCRPC patients receiving ([177]Lu)-PSMA-617: a WARMTH multicentre study. Eur J Nucl Med Mol Imaging. Published online May 2021. doi:10.1007/s00259-021-05383-3
13. Ahmadzadehfar H, Rahbar K, Baum RP, et al. Prior therapies as prognostic factors of overall survival in metastatic castration-resistant prostate cancer patients treated with ([177]Lu)-PSMA-617. A WARMTH multicenter study (the 617 trial). Eur J Nucl Med Mol Imaging. 2021;48(1):113-122. doi:10.1007/s00259-020-04797-9
14. Yadav MP, Ballal S, Bal C, et al. Efficacy and safety of [177]Lu-PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer patients. Clin Nucl Med. 2020;45(1):19-31. doi:10.1097/RLU.0000000000002833
15. Acar E, Özdöguna O, Aksu A, Derebek E, Bekiş R, Çapa Kaya G. The use of molecular volumetric parameters for the evaluation of Lu-177 PSMA I&T therapy response and survival. Ann Nucl Med. 2019;33(9):681-688. doi:10.1007/s12249-019-01376-3
16. Aghdam RA, Amoui M, Ghodsirad M, et al. Efficacy and safety of [177]LuLutetium-prostate-specific membrane antigen therapy in metastatic castration-resistant prostate cancer patients: first experience in west asia—a prospective study. World J Nucl Med. 2019;18(3):258-265. doi:10.4103/wjnm.WJNM_66_18
17. Ahmadzadehfar H, Rahbar K, Küpping S, et al. Early side effects and first results of radioligand therapy with ([177]Lu)-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. EJNMMI Res. 2015;5(1):114. doi:10.1186/s13550-015-0114-2
18. Ahmadzadehfar H, Schlolaut S, Fimmers R, et al. Predictors of overall survival in metastatic castration-resistant prostate cancer patients receiving [177]Lu-PSMA-617 radioligand therapy. Oncotarget. 2017;8(61):103108-103116. doi:10.18632/oncotarget.21600
19. Ahmadzadehfar H, Zimbelman S, Yordanova A, et al. Radioligand therapy of metastatic prostate cancer using [177]Lu-PSMA-617 after radiation exposure to 223Ra-dichloride. Oncotarget. 2017;8(33):55567-55574. doi:10.18632/oncotarget.15698
20. Ahmadzadehfar H, Wegen S, Yordanova A, et al. Overall survival and response pattern of castration-resistant metastatic prostate cancer to multiple cycles of radioligand therapy using [177]Lu-PSMA-
21. Assad M, Rezaei S, Jafari E, et al. Potential application of lutetium-177-labeled prostate-specific membrane antigen-617 radioligand therapy for metastatic castration-resistant prostate cancer in a limited resource environment: initial clinical experience after 2 years. World J Nucl Med. 2020;19(1):15-20. doi:10.4103/wjnm.WJNM_20_19

22. Barber TW, Singh A, Kulkarni HR, Niepsch K, Billah B, Baum RP. Clinical outcomes of 177Lu-PSMA radioligand therapy in earlier and later phases of metastatic castration-resistant prostate cancer grouped by previous taxane chemotherapy. J Nucl Med. 2019;60(7):955-962. doi:10.2967/jnumed.118.216820

23. Barna S, Haug AR, Hartenbach M, et al. Dose calculations and dose-effect relationships in 177Lu-PSMA I&T radionuclide therapy for metastatic castration-resistant prostate cancer. Clin Nucl Med. 2020;45(9):661-667. doi:10.1097/RLU.0000000000003157

24. Bräuer A, Grubert LS, Roll W, et al. 177Lu lutetium ligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. Eur J Nucl Med Imaging. 2017;44(10):1663-1670. doi:10.1007/s00259-017-3751-z

25. Bülbül O, Ünek Ü, Kefi A, Tuna EB, Bekiş R. Factors affecting overall survival and progression-free survival in patients with metastatic castration resistant prostate cancer received (177)Lu PSMA I&T therapy. J Nucl Med. 2020;23(3):229-239. doi:10.1967/s002449912021

26. Calais J, Gaffita A, Eiber MR, et al. Prospective phase 2 trial of PSMA-targeted molecular Radioligand with (177)Lu-PSMA-617 for metastatic Castration‐ResISTant Prostate Cancer (RESIST-PC). Efficacy results of the UCLA cohort. J Nucl Med: official publication, Society Nucl Med. Published online May 2021. doi:10.2967/jnumed.121.261982

27. Derlin T, Werner RA, Lapos M, et al. Neuroendocrine differentiation and response to PSMA-targeted radioligand therapy in advanced metastatic castration-resistant prostate cancer: a single-center retrospective study. J Nucl Med. 2020;61(11):1602-1606. doi:10.2967/jnumed.120.241588

28. Derlin T, Sommerlah Sohns JM, Schmuck S, et al. Influence of short-term dexamethasone on the efficacy of (177) Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. Prostate. 2020;80(8):619-631. doi:10.1002/pros.23974

29. Emmett L, Crumbaker M, Ho B, et al. Results of a prospective phase 2 pilot trial of (177)Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer including imaging predictors of treatment response and patterns of progression. Clin Genitourin Cancer. 2019;17(1):15-22.

30. Fendler WP, Reinhardt S, Ilhan H, et al. Preliminary experience with dosimetry, response and patient reported outcome after 177Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. Oncotarget. 2017;8(2):3581-3590. doi:10.18632/oncotarget.12240

31. Ferdinandus J, Eppard E, Gaertner FC, et al. Predictors of response to radioligand therapy of metastatic castration-resistant prostate cancer with 177Lu-PSMA-617. J Nucl Med. 2017;58(2):312-319. doi:10.2967/jnumed.116.178228

32. Gadot M, Davidson T, Aharon M, et al. Clinical variables associated with PSA response to lutetium-177-PSMA ([177]Lu-PSMA-617) radionuclide treatment in men with metastatic castration-resistant prostate cancer. Cancers. 2020;12(5):1078. doi:10.3390/cancers12051078

33. Gaffita A, Fendler WP, Hui W, et al. Efficacy and Safety of (177)Lu-labeled prostate-specific membrane antigen radionuclide treatment in patients with diffuse bone marrow involvement: a multicenter retrospective study. Eur Urol. 2020;78(2):148-154. doi:10.1016/j.eururo.2020.05.004
48. Kletting P, Thieme A, Eberhardt N, et al. Modeling and Predicting Tumor Response in Radioligand Therapy. J Nucl Med. 2019;60(1):65-70. doi:10.2967/jnumed.118.210377

49. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-targeted radio- nuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176. doi:10.2967/jnumed.115.171397

50. Leibowitz R, Davidson T, Gadot M, et al. A retrospective analysis of the safety and activity of lutetium-177–prostate-specific membrane antigen radionuclide treatment in older patients with metastatic castration-resistant prostate cancer. Oncology. 2020;25(9):787-792. doi:10.1634/theoncologist.2020-0100

51. Maffey-Steffan J, Scarpai L, Sviridenka A, et al. The (68)Ga/(177)Lu-theragnostic concept in PSMA-targeting of metastatic castration-resistant prostate cancer: impact of post-therapeutic whole-body scintigraphy in the follow-up. Eur J Nucl Med Mol Imaging. 2020;47(3):695-712. doi:10.1007/s00259-019-04583-2

52. Marinova M, Alamdar R, Ahmadzadehfar H, et al. Improving the quality of life in patients with metastatic prostate cancer following one cycle of 177Lu-PSMA-617 radioligand therapy: a pilot study. Nuklearmedizin. 2020;59(6):409-414. doi:10.1342/58491

53. McBean R, O’Kane B, Parsons R, Wong D. Lu177-PSMA therapy for men with advanced prostate cancer: initial 18 months experience at a single Australian tertiary institution. J Med Imaging Radiat Oncol. 2019;63(4):538-545. doi:10.1111/1754-9485.12891

54. Meyrick D, Gallyamov M, Sabarirumugan S, Falzone N, Lenzo N. Real-world data analysis of efficacy and survival after lutetium-177 labelled PSMA ligand therapy in metastatic castration-resistant prostate cancer. Target Oncol. 2021;16(3):369-380. doi:10.1007/s11523-021-00801-w

55. Michalski K, Klein C, Brueggemann T, Meyer PT, Jilg CA, Ruf J. Assessing Response to ([177]Lu)PSMA Radioligand Therapy using modified PSMA PET Progression Criteria. J Nucl Med: official publication, Society Nucl Med. Published online March 2021. doi:10.2967/jnumed.120.260836

56. Paganelli G, Samelli A, Severi S, et al. Dosimetry and safety of (177) Lu PSMA-617 along with polyglutamate parotid gland protector: preliminary results in metastatic castration-resistant prostate cancer patients. J Nucl Med Mol Imaging. 2020;47(13):3008-3017. doi:10.1007/s00259-020-04956-0

57. Prasad V, Huang K, Prasad S, Makowski MR, Czech N, Brenner W. In comparison to PSA, interim Ga-68 PSMA PET/CT response evaluation based on modified RECIST 1.1 after 2nd cycle is better predictor of overall survival of prostate cancer patients treated with [177]Lu-PSMA. Front Oncol. 2021;11:578093. doi:10.3389/fonc.2021.578093

58. Privé BM, Peters SMB, Muselaers CHJ, et al. Lutetium-177-PSMA- 617 in low-volume hormone-sensitive metastatic prostate cancer: a prospective pilot study. Clin Cancer Res. 2021;27(13):3595-3601. doi:10.1158/1078-0432.CCR-20-4298

59. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med. 2017;58(1):85-90. doi:10.2967/jnumed.116.183194

60. Rahbar K, Schmidt M, Heinzel A, et al. Response and tolerability of a single dose of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis. J Nucl Med. 2016;57(9):1334-1338. doi:10.2967/jnumed.116.173757

61. Rahbar K, Bögemann M, Yordanova A, et al. Delayed response after repeated 177Lu-PSMA-617 radioligand therapy in patients with metastatic castration resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2018;45(2):243-246. doi:10.1007/s00259-017-3877-z

62. Rahbar K, Boegemann M, Yordanova A, et al. PSMA targeted radiodi- gangandtherapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging. 2018;45(1):12-19. doi:10.1007/s00259-017-3848-4

63. Rasul S, Hacker M, Kretschmer-Chott E, et al. Clinical outcome of standardized (177)Lu-PSMA-617 therapy in metastatic prostate cancer patients receiving 7400 MBq every 4 weeks. Eur J Nucl Med Mol Imaging. 2020;47(3):713-720. doi:10.1007/s00259-019-04584-1

64. Rasul S, Hartenbach M, Wollenweber T, et al. Prediction of response and survival after standardized treatment with 7400 MBq (177)Lu- PSMA-617 every 4 weeks in patients with metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2021;48(5):1650-1657. doi:10.1007/s00259-020-05082-5

65. Rasul S, Wollenweber T, Zisser L, et al. Response and toxicity to the second course of 3 Cycles of (177)Lu-PSMA therapy every 4 weeks in patients with metastatic castration-resistant prostate cancer. Cancers. 2021;13(10):2489. doi:10.3390/cancers13102489

66. Rathke H, Holland-Leutz T, Mier W, et al. Response prediction of (177)Lu-PSMA-617 radioligand therapy using prostate-specific antigen, chromogranin A, and lactate dehydrogenase. J Nucl Med. 2020;61(5):689-695. doi:10.2967/jnumed.119.231431

67. Rosar F, Kochems N, Bartholomá F, et al. Renal safety of (177)Lu- PSMA-617 radioligand therapy in patients with compromised baseline kidney function. Cancers. 2021;13(12):3095. doi:10.3390/ cancers13123095

68. Scarpa L, Buxbaum S, Kendler D, et al. The (68)Ga/(177)Lu ther- agonistic concept in PSMA targeting of castration-resistant prostate cancer: correlation of SUVmax values and absorbed dose estimates. Eur J Nucl Med Mol Imaging. 2017;44(5):788-800. doi:10.1007/s00259-016-3609-9

69. Seifert R, Kessel K, Schlack K, Weckesser M, Bögemann M, Rahbar K. Radioligand therapy using ([177]Lu)-PSMA-617 in mCRPC: a pre-VISION single-center analysis. Eur J Nucl Med Mol Imaging. 2020;47(9):2106-2112. doi:10.1007/s00259-020-04703-3

70. Söydal C, Araz M, Urun Y, Nak D, Ozkan E, Kucuk NO. Prognostic importance of PSA response in patients who received Lutetium-177 PSMA treatment for castration resistant prostate cancer. Q J Nucl Med Mol Imaging: official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Asso- ciation of Radiopharmacology (IAR), [and] Section of the Society of. Published online October 2019. doi:10.23736/ S1824-4785.19.03165-0

71. Suman S, Parghane RV, Joshi A, et al. Therapeutic efficacy, prognostic variables and clinical outcome of (177)Lu-PSMA-617 PRLT in progressive mCRPC following multiple lines of treatment: prognostic implications of high FDG uptake on dual tracer PET-CT vis-à-vis Gleason score in such cohort. Br J Radiol. 2019;92(1104):20190380. doi:10.1259/bjr.20190380

72. Tatkovic A, McBean R, Wong D Lu177-PSMA therapy for men with advanced prostate cancer: 18 months survival analysis in a single Australian tertiary institution. J Med Imaging Radiat Oncol. Published online April 2021. doi:10.1111/1754-9485.13182

73. Violet J, Sandhu S, Iravani A, et al. Long-term follow-up and out- comes of retreatment in an expanded 50-patient single-center phase II prospective trial of (177)Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. J Nucl Med. 2020;61(6):857-865. doi:10.2967/jnumed.119.236414
75. Völter F, Mittlmeier L, Gosewisch A, et al. Correlation of an index-lesion-based SPECT dosimetry method with mean tumor dose and clinical outcome after (177)Lu-PSMA-617 radioligand therapy. Diagnostics (Basel, Switzerland). 2021;11(3):428. doi:10.3390/diagnostics11030428

76. Widjaja L, Werner RA, Ross TL, Bengel FM, Derlin T. PSMA expression predicts early biochemical response in patients with metastatic castration-resistant prostate cancer under (177)Lu-PSMA-617 radioligand therapy. Cancers. 2021;13(12):2938. doi:10.3390/cancers13122938

77. Yordanova A, Linden P, Hauser S, et al. Outcome and safety of rechallenge ((177)Lu)-PSMA-617 in patients with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2019;46(5):1073-1080. doi:10.1007/s00259-018-4222-x

78. Yadav MP, Ballal S, Sahoo RK, et al. Long-term outcome of 177Lu-PSMA-617 radioligand therapy in heavily pre-treated metastatic castration-resistant prostate cancer patients. PLoS One. 2021;16(5), e0251375. doi:10.1371/journal.pone.0251375

79. Zang J, Fan X, Wang H, et al. First-in-human study of 177Lu-EB-PSMA-617 in patients with metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2019;46(1):148-158. doi:10.1007/s00259-018-4096-y

80. Rahbari M, Rahbari NN. Compassionate use of medicinal products in Europe: current status and perspectives. Bull World Health Organ. 2011;89(3):163. doi:10.2471/BLT.10.085712

81. Carlucci G, Ippisch R, Slavik R, Mishoe A, Blecha J, Zhu S. (68)Ga-PSMA-11 NDA Approval: a Novel and Successful Academic Partnership. J Nucl Med. 2021;62(2):149-155. doi:10.2967/jnumed.120.260455

82. Food and Drug Administration.

83. Solnes LB, Werner RA, Jones KM, et al. Theranostics: leveraging Molecular Imaging and Therapy to Impact Patient Management and Secure the Future of Nuclear Medicine. J Nucl Med. Published online March 2020.

84. Kratochwil C, Fendler WP, Eiber M, et al. EANM procedure guidelines for radionuclide therapy with 177Lu-labelled PSMA-ligands (177Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging. 2019;46(12):2536-2544. doi:10.1007/s00259-019-04485-3

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