Clinical outcome of Lu-177 PSMA in metastatic castration-resistant prostate cancer: An initial experience from a tertiary care cancer hospital

Manoj Gupta1,2, Ganesan Karthikeyan3, Partha S. Choudhury1, Anurag Sharma4, Sudhir Rawal5

1) Department of Nuclear Medicine, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India
2) Amity Centre for Radiation Biology, Amity University, Noida, Uttar Pradesh, India
3) Amity Institute of Virology and Immunology, Amity University, Noida, Uttar Pradesh, India
4) Department of Research, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India
5) Department of Uro-Gynaec Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

Abstract
Aim: We analyzed the clinical outcome of Lutetium-177 Prostate-specific membrane antigen (Lu-177 PSMA) in metastatic castration-resistant prostate cancer (mCRPC) patients.

Material and Methods: Twenty-five mCRPC patients were treated with Lu-177 PSMA on a compassionate basis. Pre and 8-10 weeks post-treatment PSA, Eastern cooperative oncology group (ECOG) performance status, Visual analog scale (VAS), and Analgesic quantification scale (AQS) were recorded. Based on PSA response (partial response PR, stable disease SD, progressive disease PD), patients were categorized into responder (PR+SD) and non-responder (PD). Wilcoxon signed-rank, and Kruskal–Wallis test, Kaplan Meier with Log-rank test were computed.

Results: Twenty-five mCRPC patients were treated with a median of 7.4 GBq Lu-177 PSMA. Overall, PR, SD, and PD were 24%, 60%, and 16%, respectively. Sixteen patients who received ≥7.4 GBq Lu-177 PSMA dose, PR, and SD were seen in 31.2% and 68.8%, respectively. We had 84% responders and 16% non-responders. Statistically significant difference (P = < 0.05) was seen in pre and post ECOG, VAS, and AQS parameters while it was in-significant for PSA (P = 0.170). Lu-177 PSMA dose was the only significant pre-therapy variable (P = 0.024) on Kruskal–Wallis test. Overall median PFS was 24 weeks, while two years PFS in PR, SD, and PD response group was 50%, 37.3%, and 0%, respectively. A significant difference was seen in the PFS of responder and non-responder groups.

Conclusions: We concluded that Lu-177 PSMA was a suitable palliative option in heavily pre-treated mCRPC patients with notable PSA response. However, proper randomized studies are warranted.

Keywords: Metastatic castration-resistant prostate cancer, Lu-177 PSMA, Progression-free survival.

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Radio-labelling of Lu-177 PSMA
PSMA-617 made by advanced biochemical compounds (ABx) GmbH, Germany and Non-carrier added Lu-177 manufactured by ITG, Germany was procured through a local vendor. Lu-177 was received on the pre-planned date for therapy in 0.04 M hydrochloric acid aqueous solution with >3000 GBq/mg specific activity and >99% radiochemical purity. In-house radio-labeling of Lu-177 PSMA was done as per company-specific standard method and protocol. Before administration, the final labeled product’s quality control was done with Eckert & Ziegler thin layer chromatography scanner using trisodium citrate buffer.

Administration protocol for Lu-177 PSMA
Before the administration of Lu-177 PSMA, all patients were hydrated with a continuous infusion of one-liter normal saline (NS) at the rate of 250 ml/hour for renal protection. After 30 minutes of NS hydration, Lu-177 PSMA with administered with 50 ml of NS over 15 minutes of infusion.

Clinical and biochemical efficacy parameters
Prostate-specific antigen (PSA) is a recommended biochemical tumor marker for prostate cancer[41]. PSA was assessed before and 8–10 weeks after the Lu-177 PSMA therapy. Based on changes in PSA values, three standard response groups of partial response (PR), stable disease (SD), and progressive disease (PD) were defined. PR was described as a decrease of PSA by ≥50%, while PD was defined as a PSA increase by ≥25% with a minimum of 2 ng/ml increase in absolute value[15]. Stable disease was considered if the change in PSA was in-between PR and PD. Another customized category of >30% decrease in PSA was also analyzed. Patients were further categorized into responder (PR+SD) and non-responder (PD) based on PSA response. Based on the dose of Lu-177 PSMA dose patients were also categorized into two groups (group 1 < 7.4 GBq and group 2 ≥ 7.4 GBq).

Each patient’s performance status was recorded as per the Eastern cooperative oncology group (ECOG) before Lu-177 PSMA therapy and 8–10 weeks after the treatment[60]. The intensity of pain was recorded as per the patient’s judgment on the visual analog scale (VAS) of 0 to 10 before and 8–10 weeks after Lu-177 PSMA therapy administration[17]. A two-point improvement in VAS was considered a favorable response. Change in frequency and grade of analgesics is also an important parameter to assess therapeutic response. We customized an analgesic quantification scale (AQS) to 0 to 6 (Supplementary Table 1) and recorded its level pre and 8–10 weeks post Lu-177 PMSA therapy[60]. A one-point improvement in AQS was considered a favorable response.

Progression-free survival (PFS) was defined as the time after starting the Lu-177 PSMA therapy until PSA progression or death due to any cause. Any discontinuation of treatment due to side effects was also considered as an event for PFS calculation. However, lost to follow up was deemed to be censored data due to incomplete information.

Toxicity analysis
Pre and post 8 weeks post Lu-177 PSMA therapy hemoglobin (Hb), total leukocytes counts (TLC), platelets, total bilirubin, and creatinine were recorded. Toxicity grades were defined per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria[39, 40].

Conflict of Interest
All the authors declared that they have no conflict of interest, and there is no source of funding.

Ethical Statement
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis
For quantitative data, the median and range were calculated, while for categorical data, absolute frequencies with percentages were calculated. A non-parametric Wilcoxon signed-rank test was used to compare pre and 8-10 weeks post-treatment changes in clinical efficacy parameters and toxicity parameters. To find out which variable, e.g., age, Gleason score, Lu-177 PSMA dose, ECOG status, VAS, AQS, PSA has a significant impact on response outcome, we performed Kruskal–Wallis test was used. Univariate PFS curves were also computed according to Kaplan Meier and compared with the Log Rank test for responders and non-responders. Log Rank test was used to compare two patients groups based on Lu-177 PSMA dose. P-value < 0.05 was considered statistically significant. Statistical analysis was conducted with
Results

Patients’ characteristics are presented in table 1. The radiochemical purity of the labeled Lu-177 PSMA product was >99%. Twenty-five mCRPC patients with median Gleason score 8.3 (range 7–10) with median 69 years of age (range 45–81) were treated with Lu-177 PSMA. Out of 25 patients, 15 patients received one cycle, three patients received two cycles, two patients received three cycles, and five patients received four cycles (total 47 cycles) of Lu-177 PSMA (Supplementary Table 2). 40% (10/25) of patients had lost to follow-up and incomplete information despite stable disease. Hence to avoid heterogeneity of the data, we have analyzed the clinical outcome of the first cycle of Lu-177 PSMA data in this study. Our 25 patients were administered a median 7.4 GBq (range 3.7–7.7 GBq) of Lu-177 PSMA dose. We administered lower doses in our first four patients due to our initial apprehensions (median 4.5 GBq, range 3.7–4.5 GBq). After that, in the remaining 21 patients, we administered the recommended dose of Lu-177 PSMA (median 7.4 GBq, range 7.0–7.7 GBq). These variations in doses were due to some variations in the pre-calibration of radioactivity. Median Lu-177 PSMA doses in three PSA response groups were presented in table 2. All our patients had multiple sites of PSMA avid metastasis (>10 lesions). All patients had bone metastasis (100%), while visceral metastasis was present in 40% of patients. All patients were previously treated with docetaxel chemotherapy, while cabazitaxel, abiraterone, and enzalutamide were also given in 56%, 28%, and 44% of patients, respectively.

Pre Lu-177 PSMA therapy median PSA was 101.7 ng/ml (range 456–14.1 ng/ml), while after 8–10 weeks of therapy, the median PSA was 48.9 ng/ml (range 494–5.4 ng/ml). In all 25 patients, we had PR, SD, and PD by PSA analysis in 24% (6/25), 60% (15/25), and 16% (4/25), respectively. While in 16 patients with ≥7.4 GBq dose of Lu-177 PSMA (group 2), we had PR and SD in 31.2% (5/16) and 68.8% (11/16), respectively. 9/25 (36%) of our patients showed ≥30% decrease in PSA. In our 25 patients, we had 84% (21/25) responders and 16% (4/25) non-responders. In 9/25 patients who received <7.4 GBq of Lu-177 PSMA (group 1), 55.6% (5/9) were responder while 44.4% (4/9) were non-responders. In group 2, we had all responder patients (Fig. 1).

Pre Lu-177 PSMA therapy median ECOG score was 3 (range 2–4), while after 8–10 weeks of therapy, the median ECOG score was 3 (range 2–4). 36% (9/25) of patients showed improvement in the ECOG score by the maximum one point. Pre Lu-177 PSMA therapy median VAS was 5 (range 1–9), while after 8–10 weeks of therapy, the median VAS was 4 (range 0–6). 60% (15/25) of patients showed a favorable response in VAS. One patient reported pain ‘flare’ with-in one week of therapy, which improves in the next four weeks with an overall favorable response in VAS. Pre Lu-177 PSMA therapy median AQS was 4 (range 3–4), while after 8–10 weeks of therapy, median AQS was 4 (range 3–4). 64% (16/25) of patients showed improvement in the AQS score by ≥1 point while 12% (3/25) for 2 point improvement in AQS. Statistically significant difference was found following Lu-177 PSMA therapy for ECOG (P = 0.005, Z value -2.5), VAS (P = 0.001, Z value -3.9) and AQS (P = 0.004, Z value -3.5) clinical parameters on Wilcoxon signed-rank test. However, this was statistically not significant.

| Table 1 Patients' characteristics n = 25 |
|----------------------------------------|
| **Age (Years)** | Median | Std. Deviation | Minimum | Maximum |
|----------------|--------|----------------|---------|---------|
| 69.0 | 8.7 | 45.0 | 81.0 |

| **Gleason score** | 8.3 | 0.7 |
|----------------|-----|-----|
| 6.9 | 1.2 | 3.7 | 7.7 |

| **Lu-177 PSMA dose (GBq)** | 3.0 | 0.5 | 2.0 | 4.0 |
|----------------|-----|-----|-----|-----|
| 5.0 | 2.2 | 1.0 | 9.0 |

| **AQS (0–6)** | 4.0 | 0.5 | 3.0 | 4.0 |
|----------------|-------|-----|-----|-----|
| 101.7 | 148.2 | 14.1 | 456.0 |

Lu-177 PSMA: Lutetium-177 Prostate-specific membrane antigen, GBq: Gigabecquerel, ECOG: Eastern cooperative oncology group performance status, VAS: Visual analog scale, AQS: Analgesic quantification scale, PSA: Prostate-specific antigen.

| Table 2 Lu-177 PSMA doses (GBq) in three PSA response groups |
|---------------------------------------------------------------|
| **PSA response group** | Median | Std. Deviation | 95% Confidence Interval |
|-----------------------|--------|----------------|------------------------|
| **PD** | 4.87 | 1.5 | 2.8–7.5 |
| **SD** | 7.40 | 0.8 | 6.8–7.7 |
| **PR** | 7.48 | 0.2 | 7.2–7.7 |
| **Total** | 7.40 | 1.2 | 6.5–7.4 |

Lu-177 PSMA: Lutetium-177 Prostate-specific membrane antigen, GBq: Gigabecquerel, PSA: Prostate-specific antigen, PD: Progressive disease, SD: stable disease, PR: partial response.
for PSA difference ($P = 0.170$, Z value -1.6). A significant difference ($P = 0.024$) was seen in the Lu-177 PSMA dose by Kruskal–Wallis test for PSA response groups. No statistically significant difference was found for age ($P = 0.385$), Gleason score ($P = 0.336$), ECOG ($P = 0.273$), VAS ($P = 0.558$), AQS ($P = 0.568$) and PSA ($P = 0.710$). Mild Xerostomia was seen in 1/25 (4%) of the patients, while no dry eye was reported.

It was that 10/25 patients had no follow-up information while one patient was still on treatment with no event while looking for PFS calculation. These 11 patients were censored during PFS calculation. Overall median PFS was 24 weeks (95% Confidence interval, CI: 9–52) in our study. Median PFS of three PSA response groups PR, SD, and PD were 24, 24, and 8 weeks, respectively. There was a significant difference seen in PFS in three PSA response groups (P = 0.015). Results of the Cox proportional hazards model for three PSA response groups for progression-free survival were summarized in table 3. Two years PFS of PR, SD, and PD response

![Fig. 1 Ga-68 PSMA PET-CT maximum intensity projection (a, c) and fused sagittal (b, d) images. This 79 years old metastatic prostate cancer patient was treated with 7.4 GBq of Lu-177 PSMA. Pre (a, b) and eight weeks post (c, d) therapy, PET-CT images showed a decrease in PSMA avidity in bony lesions as well as partial response in PSA (119 ng/ml to 21.6 ng/ml).](image)

**Table 3** Cox proportional hazards model for three PSA response groups (PD, SD, and PR) progression-free survival

|         | PD          | SD          | PR          |
|---------|-------------|-------------|-------------|
| PD      | -           | 0.1571 (0.01595 to 1.5468) | 0.1567 (0.01592 to 1.5424) |
| SD      | 6.3661 (0.6465 to 62.6867) | -           | 0.9975 (0.3387 to 2.9374) |
| PR      | 6.3822 (0.6484 to 62.8248) | 1.0025 (0.3404 to 2.9522) | -           |

PSA: Prostate-specific antigen, PD: Progressive disease, SD: stable disease, PR: Partial response.
Fig. 2 Kaplan Meier curve for progression-free survival (PFS) for responder (PR+SD) and non-responder (PD) group based on PSA response. There was a significant difference that was seen in the PFS outcome of the responder and non-responder group on the Log-rank test ($P = 0.003$, Hazard ratio 0.1569, 95% CI: 0.0170–1.4478). PSA: Prostate-specific antigen, PD: Progressive disease, PR: Partial response, SD: Stable disease, CI: Confidence interval.

Table 4: Comparison of safety parameters for toxicity evaluation pre and eight weeks post Lu-177 PSMA therapy by Wilcoxon signed-rank test (n-25)

| Parameters       | Pre therapy | Post therapy | P-value |
|------------------|-------------|--------------|---------|
|                  | Absolute value (Mean ± SD) | CTCEA grade (0–5) (Mean ± SD) | Absolute value (Mean ± SD) | CTCEA grade (0–5) (Mean ± SD) | For absolute value | For CTCEA grade |
| Hb (g/dl)        | 10.43 ± 1.4 | 1.68 ± 0.85 | 10.02 ± 1.78 | 1.68 ± 0.85 | 0.443 | 0.328 |
| TLC (per mm$^3$) | 8172.36 ± 2297.65 | 0 ± 0 | 6965.64 ± 2398.73 | 0.04 ± 0.2 | 0.099 | 0.337 |
| Platelets (lac/mm$^3$) | 3.43 ± 1.21 | 0 ± 0 | 2.67 ± 0.88 | 0 ± 0 | **0.019** | 1.000 |
| Creatinine (mg/dl) | 0.97 ± 0.28 | 0.08 ± 0.28 | 0.98 ± 0.30 | 0.12 ± 0.43 | 0.883 | 0.984 |
| Total Bilirubin (mg/dl) | 0.86 ± 0.15 | 0 ± 0 | 0.84 ± 0.14 | 0 ± 0 | 0.692 | 1.000 |

Lu-177 PSMA: Lutetium 177-prostate specific membrane antigen, Hb: Haemoglobin, TLC: Total leukocytes counts, CTCAE: Common terminology criteria for adverse events version 4.03.

group was 50%, 37.3%, and 0%, respectively. PFS curves for responder and non-responder groups were computed by Kaplan Meier and compared with the Log-rank test (Fig. 2). There was a significant difference seen in the PFS of responders and non-responders groups ($P = 0.003$, Hazard ratio 0.1569, 95% CI: 0.0170–1.4478). Two years PFS of responder and non-responder groups was 43.3% and 0%, respectively. There was a significant difference seen in PFS of group 1 and group 2 based on Lu-177 PSMA dose on the Log-rank test ($P = 0.018$, Hazard ratio 0.2914, 95% CI: 0.06422 to 1.3227).

Pre and 8–10 weeks post Lu-177 PSMA therapy, various safety parameters were tabulated (Table 4). Five patients (20%) developed grade-3 anemia post Lu-177 PSMA therapy, and all these five patients already had grade-2 anemia before starting Lu-177 treatment. No patients with normal or grade 1 anemia at baseline showed no level 3 or 4 toxicity. A total of eight patients showed a one-point decrease in anemia grade following Lu-177 PSMA therapy. Wilcoxon signed-rank test showed no significant difference ($P > 0.05$) in CTCAE grade of Hb, TLC, total bilirubin, and creatinine post-therapy. However, significant change was seen in the post-therapy absolute value of platelet counts, but it was insignificant in CTCAE grade.
Targeted therapy is a unique way of manipulating cancer cells by affecting their specific part or process. Similarly, radionuclide therapy delivers therapeutic radiation to the cancer cells after binding to a particular receptor and internalization. Many novel radionuclides labeled biological agents have been in the process of development. A unique concept of ‘Theranostics’ has been evolved in this process of development of radionuclide therapy. This indeed has made the strategy and implementation of radionuclide therapy easier than other anticancerous agents. Radionuclide therapies for thyroid carcinoma and neuroendocrine tumor are the promising prototypes of that\(^{20}\). Prostate cancer has also been one of the significant areas of endo-radi nuclide therapy research working on the same principle, and the unique properties of PSMA made it suitable\(^{21, 22}\). PSMA is a non-secretory type II transmembrane glycoprotein with a major extracellular component. It gets internalized after binding to its ligand and ensures high radiation delivery to its cell. Many PSMA specific whole antibodies, fragmented antibodies, small peptides have been developed over the years\(^{20}\). One such novel, Lu-177 labeled PSMA targeting small peptide PSMA-617, has been found suitable for endo-radi nuclide therapy in mCRPC patients. Phase 1 studies on Lu-177 PSMA have established favorable dosimetry with simple kidney protection\(^{24, 25}\).

The first clinical outcome study on Lu-177 PSMA reported encouraging 50% PSA partial response\(^{26}\). Heck et al. claimed 33% PSA PR with Lu-177 PSMA in mCRPC patients\(^{27}\). The first multicenter retrospective study from Germany reported 45% PSA PR after completion of therapy cycles\(^{20}\). Our research had 24% overall PSA PR while it was 31.2% in patients with \(\geq7.4\) GBq Lu-177 PSMA dose. We found lower response rates in our patients’ population, even with the recommended doses. This may be due to poor performance (ECOG 3–4) status in our study population, while it was fair in other reported studies (ECOG < 3). Calopedos et al. published a meta-analysis and reported PSA PR in 51% of patients under Lu-177 PSMA/\text{I&T} therapy\(^{20}\). Fair performance status (ECOG < 3) and multiple Lu-177 PSMA cycles were the main difference compared to our study group.

Madhav et al. reported PSA response as 64.5% PR, 9.6% SD, and 19.3% PD in 31 mCRPC patients with mean 5069 ± 1845 MBq Lu-177 PSMA. 26/31 of their patients received two cycles of Lu-177 PSMA\(^{20}\). However, the exact criteria to define the PSA response groups were not documented. Further mean ECOG was 2.54 in their study while it was 3 in our study group. Median PFS of 12 months was reported from their group as compared to 24 weeks in our patients. Inadequate biochemical response in our study may be attributed to low-performance status and one treatment cycle. However, we have seen similar, statistically significant clinical parameter response outcomes.

LuPSMA, a phase 2 trial of Lu-177 PSMA in mCRPC patients, reported PSA PR in 57%, while 70% of patients showed >30% decrease in PSA\(^{31}\). These results were much better than ours. We found that significant attributes for these discrepancies were better performance status and more than one cycle of Lu-177 PSMA therapy. A high mean dose of Lu-177 PSMA (>7.4 GBq) in all patients could be another factor for a better overall response rate in this study. We have also established that Lu-177 PSMA dose is the only significant factor in determining PSA response outcomes in our study. Indeed, patients who received high Lu-177 PSMA doses (\(\geq7.4\) GBq) had higher PSA PR (31.3% Vs. 11.1%) and statistically significant higher PFS (19.3 Vs. 8.1 weeks) in our study. High dose may have led to better radiation dose depositions to tumor cells; hence, better response. However, to prove this hypothesis, a proper randomized study is warranted.

We encountered some limitations in our study during the analysis. One of the significant factor was the small number of patients. Due to the experimental status of this drug, patients were referred after consuming all the approved options and quite late in their disease course. These patients have a higher disease burden and toxicities due to previous therapies and have limited financial resources. Financial constraint was found to be an essential cause of non-confirmatory in follow-up patients besides no-response. We also realized that patient who gets pain relief, and PSA response generally continues this treatment. Our study had 40% (10/25) of patients who were lost on follow-up following the first cycle only. Hence, these patients were censored during PFS calculation. Poor performance of our patients also contributed to poor outcomes in our study as compared to published literature. In this study, we have reported the results of one cycle of Lu-177 PSMA to avoid heterogeneity of the data. Future studies with multiple cycles of therapy in low performance (ECOG 3–4) and good performance (ECOG 0–2) status patients with adequate Lu-177 PSMA dose (7.4 GBq) would be likely to yield better results. Survival information of most of these patients was not available. Therefore, overall survival (OS) was not evaluated during this analysis, which was another limitation of our study. A drug combination trial of lower doses of Lu-177 PSMA with anti-androgen therapy may also deliver better results due to its synergism and may be worth trying in patients with low-performance status\(^{32, 33}\).

**Conclusions:** We concluded that Lu-177 PSMA was a suitable palliative option in end-stage mCRPC patients with notable PSA response despite low-performance status. It has the potential to become a valid treatment option for these patients if applied early in disease management. Formal randomized studies in this direction are warranted.
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