# Efficacy and Safety of 177Lu-PSMA-617 in Combination with Radical Prostatectomy and Bilateral Orchiectomy in Men with Castrate-Sensitive Metastatic Prostate Cancer: A Pilot Study

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**Purpose:** To investigate the efficacy and safety of 177Lu-PSMA-617 in combination with radical prostatectomy and bilateral orchiectomy in adult male patients with castrate-sensitive metastatic prostate cancer.

**Methods:** This pilot study included 12 men with metastatic prostate cancer who underwent radical prostatectomy and received 177Lu-PSMA-617 in combination with hormonal therapy. The primary endpoint was the proportion of patients who achieved a PSA response, defined as a $\geq$ 50% reduction in PSA levels at first follow up from baseline. Secondary endpoints were the proportion of patients who achieved a PSA response, defined as a $\geq$ 50% reduction in PSA levels at the second follow up from the first one and progression in pain severity that was defined as an increase in score of 30% or greater from baseline without a decrease in analgesic use based on Brief Pain Inventory-short Form (PBI-SF).

**Results:** The PSA levels of 9(75.0%) patients were reduced after the first course of 177Lu-PSMA-617, additional reduction was observed in 7(58.3%) patients after receiving the 2nd course of treatment. Of the 12 patients, 3(25.0%) achieved a PSA response ($\geq$ 50% reduction in PSA levels) at first follow up visit and 3(25.0%) patients had PSA response at second follow up, 6 patients (50.%) had a pain response. The most common adverse events were Mouth dryness and fatigue, which were manageable with supportive care.

**Conclusion:** This pilot study suggests that radical prostatectomy and hormonal therapy in combination with 177Lu-PSMA-617 is a safe and effective treatment option and may have a role in the management of select patients with castrate-sensitive metastatic prostate cancer. Further studies are needed to confirm these findings and determine the optimal use in this setting.

**Keywords:** 177Lu-PSMA-617; radical prostatectomy; hormonal therapy; metastatic prostate cancer; PSA response; radiographic response; overall survival; safety.

## INTRODUCTION

Prostate cancer is the second most common cancer among men worldwide, with an estimated 1.4 million new cases in 2020 alone[(1)]. Despite the availability of simple and accessible screening methods, a significant number of patients are still diagnosed with advanced and metastatic disease, particularly in developing countries These patients often have poorer outcomes compared to those diagnosed at earlier stages[(2)] While therapeutic options have improved over recent decades, the survival of patients with metastatic prostate cancer has not seen a significant improvement.
According to the 2020 international guidelines on prostate cancer, the standard treatment for patients with metastatic prostate cancer is initially hormone therapy. In cases of castration resistant disease, chemo-radiotherapy is considered, and if there is no response to these treatments, targeted therapy is recommended[(3)]. The treatment options for Castrate-Sensitive Metastatic Prostate Cancer include a range of therapeutic modalities that have significantly evolved in recent years. They include Androgen-Deprivation Therapy (ADT) with and without other modalities including Docetaxel; Androgen Receptor–Signaling Inhibitors (ARSIs)such as abiraterone acetate and apalutamide; novel therapeutic combinations such as PTEN and CDK4/6 inhibitors; Radiation-Directed Therapy and local treatment such as radiotheraphy or radical prostatectomy[(4,5)]. Radical prostatectomy and pelvic lymphadenectomy are not yet considered as standard methods for wide spread metastatic prostate cancer. However, two studies have reported that patients who underwent these procedures may experience an increase in life expectancy and a reduction in the risk of locally recurrent prostate cancer and local complications[(6-8)]. The main prognostic factor

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**Table 1.** Patient characteristics at baseline (pre-Lu177-PMSA) (n=12)

| Characteristics | Mean ± SD | Median (IQR) | Range |
|---|---|---|---|
| Age (Year) | 69.58 ± 5.35 | 70 (65.75,72.75) | 59-80 |
| Pain (Visual Analog Scale score) | 7.58 ± 2.96 | 8.50 (6,10) 0-10 | |
| PSA(ng/ml) | 119.88 ± 341.79 | 7.40 (0.46,59.40) | 0.09-1200 |
| WBC(n/dL) | 6945.83 ± 2330.44 | 6080 (5262.50,8225) | 4800-12100 |
| Hemoglobin (g/dL) | 12.34 ± 1.17 | 12.30 (11.72,13.15) | 10.10-14.30 |
| Platelets ($\times 10^3$/dL) | 258500 ± 64439.54 | 246500 (214000,304250) | 189000-390000 |
| BUN(mg/dL) | 30.16 ± 9.98 | 30 (20.25,36.50) | 18-50 |
| Cr(mg/dL) | 1.01 ± 0.33 | 1.06 (0.91,1.20) | 0.10-1.40 |
| AST(U/L) | 22.33 ± 8.78 | 19.50 (17.25,25.5) | 10-40 |
| ALT(U/L) | 25.25 ± 15.34 | 19.50 (15,31.25) | 11-63 |
| ALK(U/L) | 868.66 ± 985.54 | 338 (208.25,1680.25) | 162-3035 |
| LDH | 313.50 ± 58.66 | 314.50 (266.25,364.50) | 205-391 |

SD: Standard Deviation; IQR: Interquartile range; ECOG: Eastern Cooperative Oncology Group; PSA: Prostate-specific antigen; WBC: White blood cell; BUN: Blood Urea Nitrogen;

in Castrate-Sensitive Metastatic Prostate Cancer is the Time to Castration Resistance (TTCR), which plays a crucial role in predicting patient outcomes; other prognostic factors including age, prostate-specific antigen level, lactate dehydrogenase (LDH) level, alkaline phosphatase (ALP) level, and Gleason score[9,10].

Prostate-specific membrane antigen (PSMA) is a well-known target for the treatment of prostate cancers[11,12]. Diagnostic PSMA radiopharmaceuticals are currently used for staging and diagnosis of prostate cancers, and imaging can predict response to therapeutic PSMA radiopharmaceuticals[13,14]. While mainly used in the setting of metastatic, castration-resistant disease that has not responded to chemotherapy, clinical trials are investigating the use of PSMA-based therapy at earlier stages, including in hormone-sensitive or hormone-naïve prostate cancers, and in oligometastatic prostate cancers[14,15]. However, the appropriateness of PSMA in hormone-sensitive prostate cancers with widespread metastasis has not been reported yet[16]. In recent years, [177Lu] Lu-PSMA-617 radioligand treatment (177Lu-PSMA) has shown promising results in patients with end-stage metastatic castrate-resistant prostate cancer (mCRPC) with tolerable side effects[17-19]. However, to date, there is only one small study that has been conducted among patients with prostate cancer undergoing 177Lu-PSMA in the hormone-sensitive setting, reporting promising results[20]. There is an ongoing prospective open-label randomized study comparing 177Lu-PSMA-67 in combination with castration versus alone castration in Metastatic Castration-Sensitive Prostate Cancer, which results have not been published yet[21].

Therefore, in this pilot study, we aim to investigate the efficacy and safety of 177Lu-PSMA-617 in combination with radical prostatectomy and bilateral orchiectomy in adult male patients with castrate-sensitive metastatic prostate cancer.

## MATERIALS AND METHODS

The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1401.092) and was registered on the Iranian Registry of Clinical Trials (IRCT20230414057906N1). The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The privacy rights of human subjects have always been observed. All subjects provided written informed consent before study entry. All patients received a consult from a nuclear medicine physician and were informed of the side effects and harms of this new therapy. All local regulations for radiation protection were followed. The trial was done in accordance to the principles of Good Clinical Practice and the Declaration of Helsinki.

### *Participants*

Participants were men with histologically proven adenocarcinoma of prostate cancer, with at least three documented metastatic lesions (bone and/or soft tissue/visceral lesion) that met the inclusion/exclusion criteria as follows:

1- Signed informed consent prior to participation in the study
2- ECOG performance status of 0 to 2
3- Life expectancy >6 months as determined by the principal investigator
4- Confirmed the evidence of PSMA-positive disease based on a 68Ga-PSMA-11 PET/CT scan
5- Platelets 75,000 µL and Hemoglobin $\geq$ 9 g/Dl
6- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq$ 3.0 x upper limit normal (ULN)OR $\leq$ 5.0 x ULN for patients with liver metastases.
7- Renal eGFR $\geq$ 50 mL/min/1.73m2 using the Modification of Diet in Renal Disease (MDRD) equation

### *Exclusion Criteria*

1-Participants with rapidly progressing tumor that requires urgent taxane-based chemotherapy
2- Any prior systemic anti-prostate cancer therapy including chemotherapy, immunotherapy or biological therapy.
3- Previous PSMA-targeted radioligand therapy
4- Known hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
5-Participants with CNS metastases that are neurologically unstable
6-Participants with epidural disease, canal disease and prior cord involvement
7- Patients with unmanageable concurrent bladder outflow obstruction or urinary incontinence
8-Patients diagnosed with other malignancies
9-Concurrent serious medical conditions including NYHA class 3/4 congestive heart failure within 6 months prior to the study, history or current diagnosis

**Table 2.** The detailed characteristics of the 12 included patients

| N | Known metastases | | | | | Pain (Visual Analog Scale score) | | | PSA(ng/ml) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bone | LN | Lung | Liver | Brain | Pre | 1st follow up | 2nd follow up | Pre | 1st follow up | 2nd follow up |
| 1 | + | + | - | - | - | 8 | 3 | 0 | 8 | 0.13 | 0.04 |
| 2 | + | + | - | - | - | 4 | 4 | 4 | 0.39 | 0.29 | 0.29 |
| 3 | + | - | - | - | - | 6 | 0 | 0 | 1.50 | 0.80 | 0.56 |
| 4 | + | + | + | - | - | 9 | 6 | 0 | 107.4 | 51.26 | 3.10 |
| 5 | + | + | - | - | - | 10 | 7 | 8 | 67.2 | 20.00 | 38.00 |
| 6 | + | - | - | - | - | 5 | 3 | 3 | 0.09 | 0.09 | 0.40 |
| 7 | + | + | - | - | - | 9 | 7 | 3 | 10.3 | 8.36 | 7.00 |
| 8 | + | + | - | - | - | 10 | 8 | 5 | 36.0 | 29.0 | 25.0 |
| 9 | + | + | - | - | - | 10 | 7 | 8 | 6.8 | 2.8 | 6.9 |
| 10 | + | - | - | - | - | 8 | 7 | 7 | 0.30 | 0.30 | 0.30 |
| 11 | + | + | + | + | - | 10 | 7 | 5 | 1200.0 | 736.0 | 304.0 |
| 12 | + | + | - | - | - | 6 | 5 | 4 | 0.68 | 0.68 | 0.40 |

PSA: Prostate-specific antigen; LN: Lymph Node;

of ECG, cardiac or cardiac repolarization abnormality, history of somatic or psychiatric disease.
Moreover, radiotherapy was not considered as an appropriate option among the selected cases due to the large size of the tumor and symptoms of urinary obstruction/ hydronephrosis.

### *Study procedures*

Urinary tract ultrasound was performed to rule out obstructive disease. Patients with urinary obstructions were referred to the urologist before therapy. Blood samples were obtained at baseline and every 4 weeks up to 8 weeks of therapy for the following evaluations: complete blood count (CBC), liver function tests (including aspartate aminotransferase [AST] and alanine transaminase [ALT]), alkaline phosphatase level, renal function tests (urea and creatinine), and PSA level. An ECOG performance status score and a Visual Analog Scale score for pain were used to evaluate the patients' general well-being and daily activities. Pre-therapeutic low-dose [68Ga] Ga-PSMA-11 PET/diagnostic-CT imaging (PSMA-PET) with tumor PSMA uptake was performed on all patients to ensure adequate PSMA expression on the tumoral lesions.

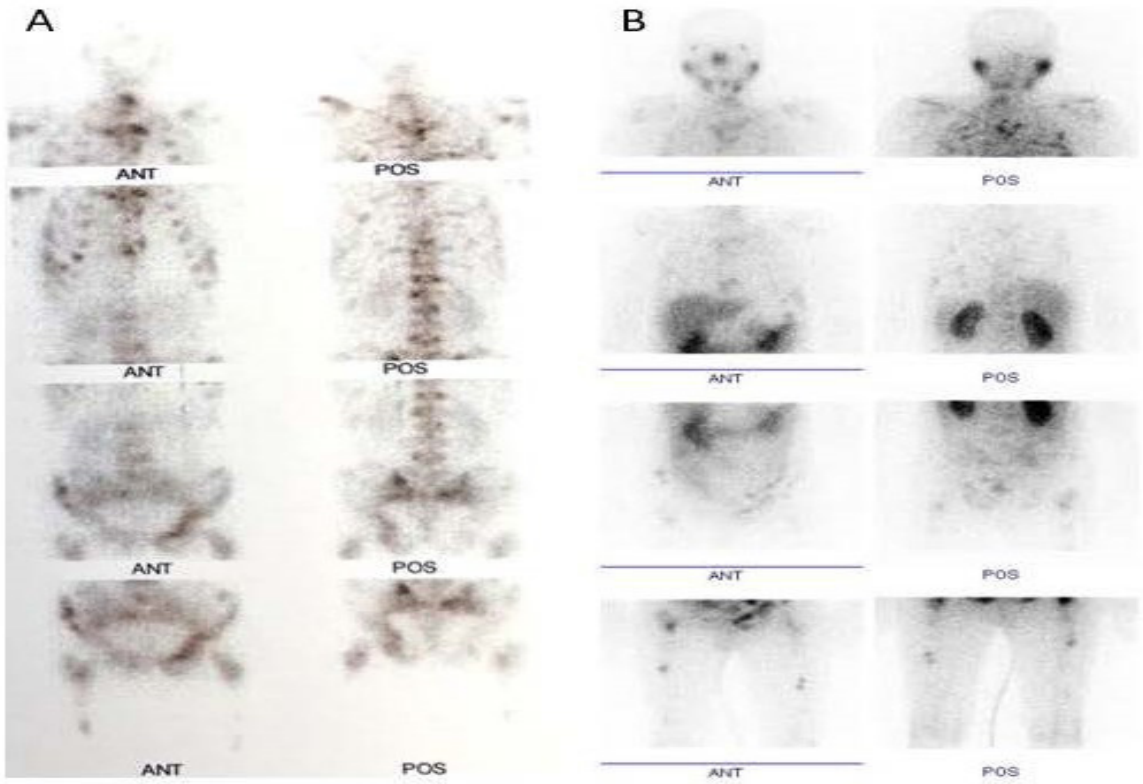


**Figure 1.** Case no.4; a 64-year-old male patient with metastatic prostate cancer underwent four cycles of treatment. The initial scan (A) shows bone, lung and lymph node avid metastases, these metastasis were significantly decreased after the second cycle (B). The patient's baseline prostate specific antigen (107.4 ng/ml) dropped to 3.1 ng/ml, after two cycles of 177Lu-PSMA.

**Tabl 3.** Proportion of patients with ≥ 50% decrease in Prostate-specific antigen (PSA) and/or reduction in pain severity ≥ 30% from baseline according to the Brief Pain Inventory-short Form (PBI-SF) at 1st and 2nd follow up compare to pre-treatment status and 1st follow up

| | | Number of patients (%) | | |
|---|---|---|---|---|
| | | 1st follow up in compare to pre-treatment n (%) | 2nd follow up in compare to pre-treatment n (%) | 2nd follow up in compare to 1st follow up n (%) |
| PSA reduction | < 50% | 8 (66.8) | 7 (58.3) | 3 (25.0) |
| | ≥ 50% | 4 (33.3) | 5 (41.7) | 9 (75.0) |
| Pain score | < 0.30% | 2 (16.7) | 4 (33.3) | 4 (33.3) |
| | ≥ 0.30% | 10 (83.3) | 8 (66.7) | 8 (66.7) |

177 Lutetium -prostate-specific membrane antigen

### *preparation*

The 177Lu-PSMA-617 (will be called 177Lu-PSMA afterward) was prepared based on the Iranian society of nuclear medicine standards and the manufacturer's instructions (Pars Isotope Co, Iran). Quality control was performed by an expert radiochemist before the administration of each dose and double-checked by the attending physician during clinical workup, patients underwent PSMA-PET imaging to evaluate PSMA-positive tumor lesions.

### *177 Lutetium -prostate-specific membrane antigen administration*

After 8 weeks from radical prostatectomy and ADT, participants were refereed for 177LU-PSMA which was administrated by slow intravenous injection (5.5–6.5 GBq) within 30–-60 s followed by injection of 1000 ml isotonic saline solution. All patients were instructed to drink enough liquid before and after 177Lu-PSMA administration to stay hydrated. Cold compression of salivary glands with ice packs was started 30 min before to 4 h after injection of the radiopharmaceutical. According to the Iranian radiation exposure rules, the therapies were done in the outpatient setting of the department of nuclear medicine. The patients were observed until 4 h after injection of the Lu-PSMA and discharged after the third urination and radiation at a one-meter distance of less than 25 μSiv/h.

Post therapeutic 177 Lutetium -prostate-specific membrane antigen imaging

The imaging of each patient was interpreted by two independent readers blinded to the results of the previous or following cycle(s).

### *Toxicity*

The Common Terminology Criteria for Adverse Events, version 4.03, was used to evaluate hematological toxicity and other adverse effects.

### *Outcome Measures*

1- Prostate-specific antigen response; it is defined as the proportion of patients who have a more/equal 50% decrease in PSA from baseline, it will be calculated at 2 and 4 months.

2- Pain severity progression; it is defined as an increase in score of 30% or greater from baseline without decrease in analgesic use based on Brief Pain Inventory-short Form (PBI-SF).

3- Number of participants with Treatment Emergent Adverse Events from initiation of the study assessed up to 6 months.

4- Progressive disease was defined as >25% increase in PSA level after receiving the 2nd course of 177Lu-PSMA in comparison to the 1st course of treatment

### *Statistical analysis*

The baseline characteristics of participants were described. For the continuous variables, the Kolmogorov–Smirnov test demonstrated that the variable distribution was skewed, so the Wilcoxon's signed rank test was used to compare the different groups; median and interquartile range were reported. The categorical variables were described as frequencies (%) and compared by the Chi-squared or Fisher exact test (for tables with sparse cells). Statistical analysis was performed using the software package STATA (version 12; STATA Inc., College Station, TX, USA). The P-values less than 0.05 were considered statistically significant.

## RESULTS

Between May 2023 and August 2023, among the 15 patients with mCSPC who had previously undergone radical prostatectomy and bilateral orchiectomy and were referred to the Nuclear Medicine department, 12 patients were eligible for enrollment in this study according to the inclusion and exclusion criteria. All the 12 patients received two cycles of 177Lu-PSMA with an average dose of 5.7 GBq (range, 4.4–6.6 GBq). None of the patients died during the study.

The baseline characteristics of participants (pre-Lu177-PMSA), including blood, renal, and liver parameters before treatment are presented in Table 1. The mean (SD) of age, pain score and PSA levels prior to the therapy commencement were 69.58 (5.35) years, 7.58 (2.96) and 119.88 (341.79) ng/ml. Bone metastasis was observed in all of 12 patients (7wide and 5oligo) based on previous conventional imaging. Lymph node metastases existed in nine patients, lung metastases in two patients, and liver in one patient. None of the participants had brain metastasis. The Visual Analog Scale score for pain severity was 5 or more in 11 patients (3 of them had 10 score). The detailed characteristics of the 12 included patients are presented in Table 2. Case no 11 was a 71-year-old patient who had bone, liver, lung and lymph node metastasis whose PSA before treatment was 1200 ng/ml; it was decreased to 304 ng/ml after two courses of treatment (**Table 2**). Figure 1 shows the initial scan of case no. 4 with bone, lung and lymph node avid metastases (A) who underwent four cycles of treatment and his metastasis significantly decreased after the second cycle (B); patient no.4 was 64 years old men whose PSA before treatment was 107.4 ng/ml; it was decreased to 3.1 ng/ml after two cycles of 177Lu-PSMA.

Biochemical and blood parameters after two cycles of 177Lu-PSMA of each individual cases are presented in Figure 2. None of the patients had liver, kidney and blood parameters exceed than those considered as exclusion cut off points after two cycles of 177Lu-PSMA and the changes of these parameters were not significant. The median of the serum alkaline phosphatase

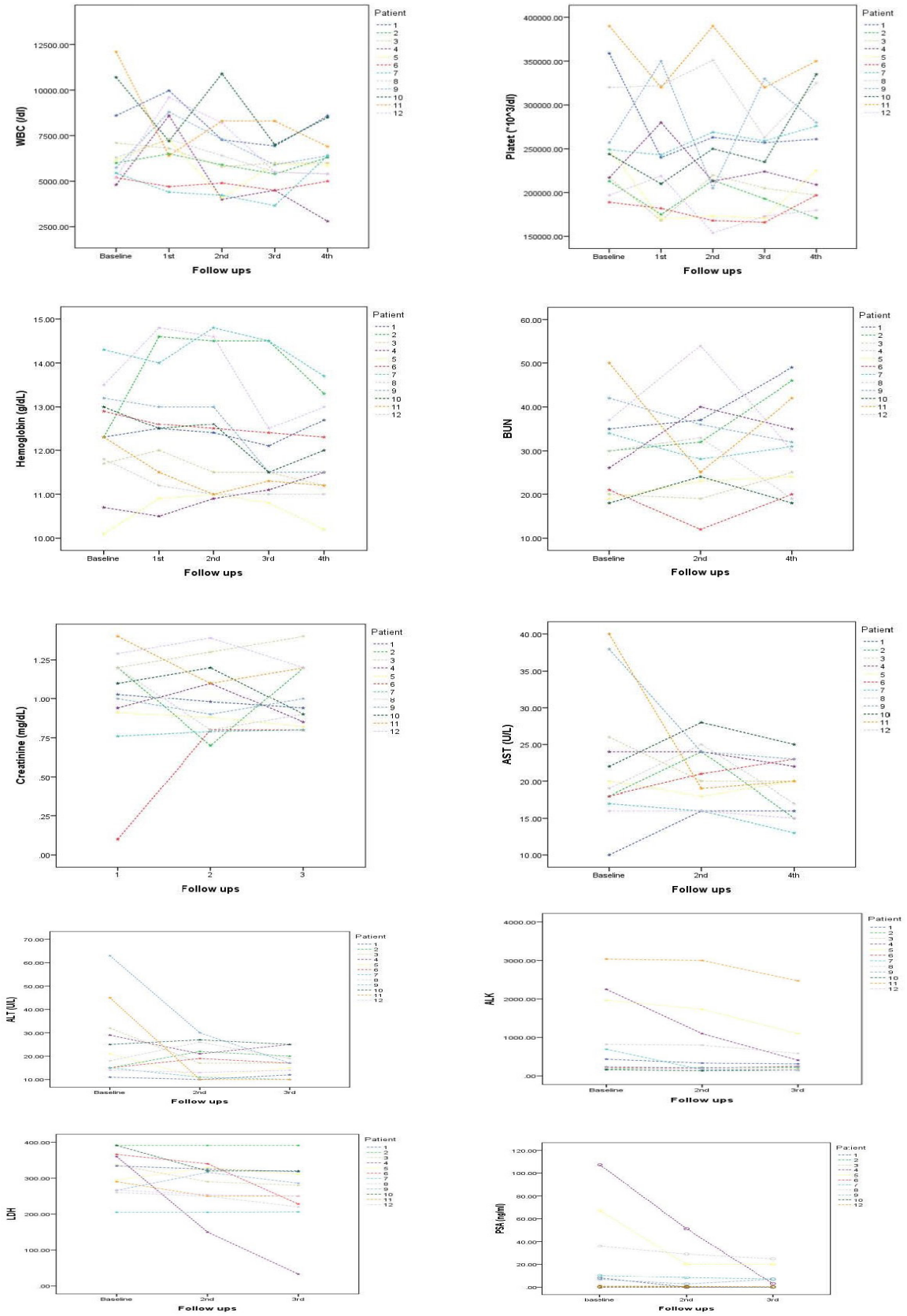


**Figure 2.** Trend of blood parameters of the 12 patients during the study (raw scores).
WBC: White Blood Cell; BUN: Blood Urea Nitrogen; AST: Aspartate aminotransferase; ALT: Alanine transaminases; ALK: Alkaline Phosphatase; LDH: Lactate dehydrogenase
*The case no.11 was removed from figure for better presenting the results for PSA

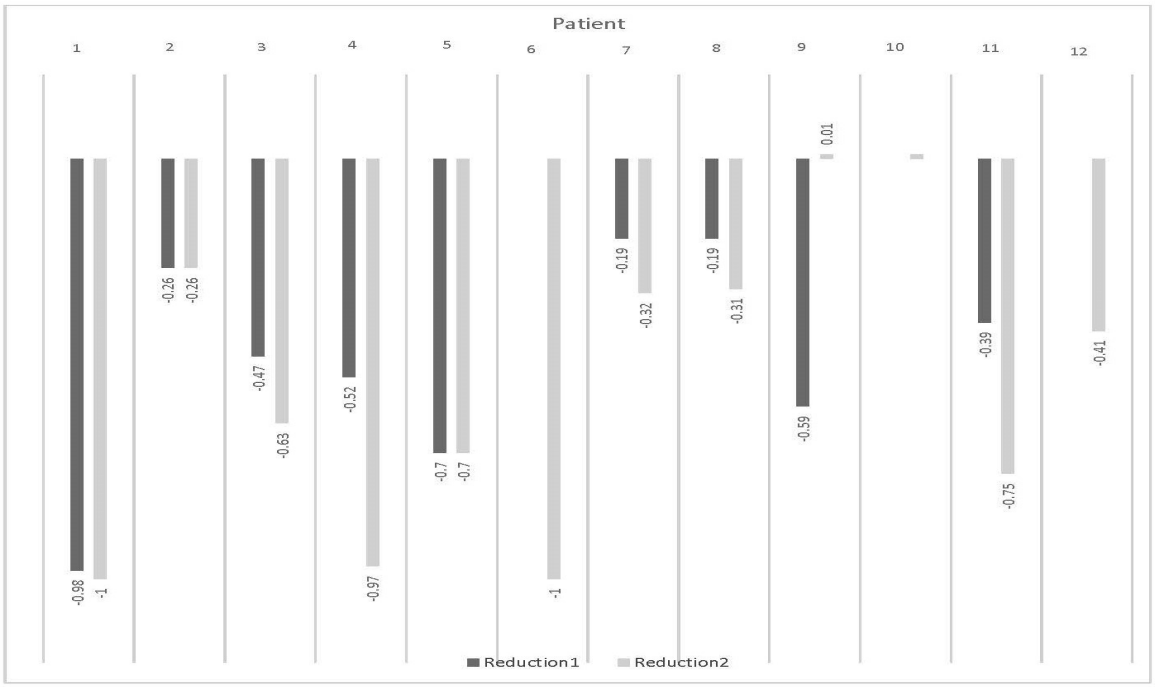


**Figure 3.** Bar chart showing percentage of reduction in Prostate-specific antigen (PSA) values in 1st and 2nd follow up

level declined from 338.0 U/L (range162-3035 U/L) to 216.5 U/L (range, 135–3000 U/L), but the difference was not statistically significant ($P$ =0.6).

### *Outcomes evaluation after first and second cycles of 177Lu-PSMA*

PSA levels declined in 9 out of 12 patients after first cycle; additional decrease after 2nd cycle was observed in 7 patients, in comparison to the 1st course of 177Lu-PSMA.The first cycle of therapy was associated without any changes in PSA among 3 cases (Table 2). Of the 12 patients, 3(25.0%) achieved a PSA complete response ($\geq$ 50% reduction in PSA levels) at the first follow up visit and 3(25.0%) patients had PSA com-

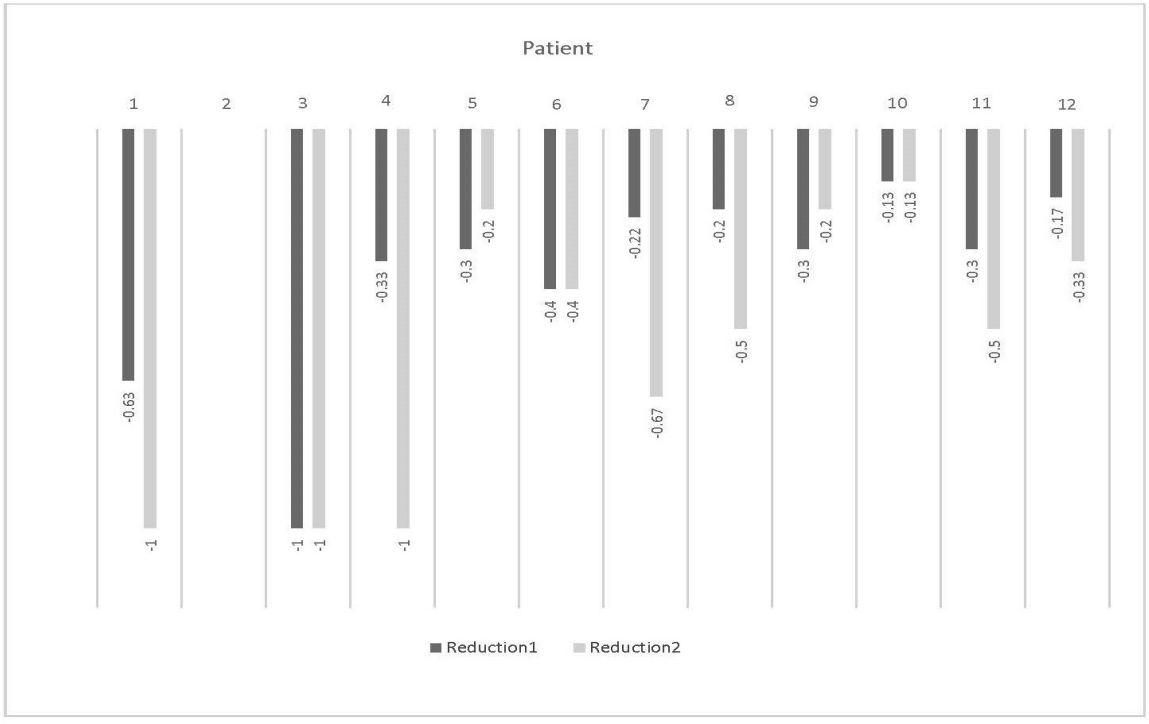


**Figure 4.** Bar chart showing percentage of reduction in pain Visual Analog Scale score in 1st and 2nd follow up

plete response at the second follow up (**Table 3**). On overall after two courses of 177Lu-PSMA, 6 patients (50.7%) showed 50% or more decline in PSA level compared to pre-treatment level. (**Table 3**); in two cases PSA was increased (progressive disease) after 2nd cycles of 177Lu-PSMA compared to 1st cycle (case no.9 and case no.5); in case no.9 , following the second course of treatment, the PSA levels were found to have risen to a level higher than the pre-treatment baseline (6.9 versus 6.8 ng/ml). The bar chart depicted in **Figure 4** illustrates the percentage of reduction in Prostate-specific antigen (PSA) values during the first and second cycles of treatment.

### *Clinical symptoms*

At baseline, all of the patients had bone metastases and reported skeletal bone pain. Among these, pain improved in 11 patients after treatment. One patient showed no significant change in pain severity and required the continued use of analgesics (patient no.9). Bar chart in Figure 4 shows the percentage of reduction in pain Visual Analog Scale score in 1st and 2nd follow up visit after cycles of 177Lu-PSMA.

### *Toxicity and side effects*

There were no adverse effects immediately after the 177Lu-PSMA injections. No concerning changes in body temperature or blood pressure were recorded. During the two-cycle treatment, four patients had nausea, five patients had fatigue, three patients had myalgia, and eight patients had dryness

## DISCUSSION

This study prospectively evaluated 177Lu-PSMA for the first time in combination with radical prostatectomy and bilateral orchiectomy in adult male patients with castrate-sensitive metastatic prostate cancer and observed safety and tolerability in 12 patients. Following the two cycles of 177Lu-PSMA, none of the patients had severe treatment-related toxicities. No liver, kidney, or bone marrow toxicity was seen during the two-weekly blood evaluations. A clinically relevant improvement in pain severity according to the PBI-SF after treatment of 177Lu- PSMA was observed. Additionally, during long-term follow-up, none of the patients developed a dry mouth. About half of our patients showed a PSA decline $\geq$50%; the PSA responses observed in this study are similar to those reported after androgen deprivation therapy (ADT) and chemo-radiotherapy in castration resistant disease[22,23].

Metastatic prostate cancer is a challenging disease to treat, and new therapeutic options are needed to improve patient outcomes. [177Lu]Lu-PSMA-617 radioligand treatment (177Lu-PSMA) is a promising approach for the treatment of metastatic prostate cancer, as it targets prostate-specific membrane antigen (PSMA), a protein that is overexpressed in prostate cancer cells[24,25].177Lu-PSMA works by delivering a radioactive isotope, lutetium-177, to PSMA-expressing cancer cells. The radiation emitted by lutetium-177 damages the DNA of cancer cells, leading to cell death. Moreover, the radiation emitted by lutetium-177 has a short range, which minimizes damage to surrounding healthy tissues[26].

Several clinical trials have evaluated the safety and efficacy of 177Lu-PSMA in patients with metastatic prostate cancer[14,27-33]. In a phase II trial, 50 patients with metastatic castration-resistant prostate cancer (mCRPC) received up to six cycles of 177Lu-PSMA. The study found that 66% of patients had a PSA response, and 45% had a radiographic response, indicating a reduction in tumor burden. Moreover, the median overall survival was 13.5 months, which is promising for patients with advanced disease[34].

There was a randomized, parallel-group, open-label, phase 2, and non-inferiority trial that aimed to prospectively compare the efficacy and safety of 177Lu-PSMA-617 and docetaxel in chemotherapy-naïve mCRPC patients[30]. They found that 177Lu-PSMA-617 is safe and non-inferior to docetaxel and could be considered earlier in these patients rather than being solely reserved for end-stage disease. Another phase II trial evaluated the safety and efficacy of 177Lu-PSMA in patients with mCRPC who had previously received chemotherapy and androgen receptor-targeted therapy[34]. The study found that 66% of patients had a PSA response, and 37% had a radiographic response. Moreover, the median overall survival was 13.3 months, which is comparable to other treatments for mCRPC.

Hormone-sensitive metastatic prostate cancer (HSMPC) is a subtype of metastatic prostate cancer that is initially responsive to ADT. However, most patients eventually develop resistance to ADT, leading to the development of castration-resistant prostate cancer (CRPC). Several trials have evaluated the use of 177Lu-PSMA in patients with HSMPC. In a prospective study aimed to determine the kinetics of 177Lu-PSMA in HSMPC patients, they reported a statistically significant association between treatment response and absorbed index lesion dose[20]. In a pilot study among 10 patients with metastatic hormone-sensitive prostate cancer with PSMA expression, they assessed the treatment effect of 177Lu-PSMA and reported that all patients presented altered PSA kinetics and suspended androgen deprivation medication. Five of these patients revealed a PSA response of > 50%[35]. Satapathy et al reported the benefit of treatment with a short course 177Lu-PSMA-617 therapy in a man with a high volume HSMPC[36].

In the context of metastatic prostate cancer, radical prostatectomy may be considered in select patients with low-volume disease and good performance status. Several studies have evaluated the use of radical prostatectomy in patients with metastatic prostate cancer. A retrospective study of 1,643 patients with metastatic prostate cancer found that radical prostatectomy was associated with improved overall survival compared to non-surgical management (median survival 30 vs. 13 months, $p < 0.001$)[1]. Another retrospective study of 1,590 patients with metastatic prostate cancer found that radical prostatectomy was associated with improved overall survival compared to radiation therapy (median survival 30 vs. 21 months, $p < 0.001$)[2].

However, these studies have several limitations, including selection bias and lack of randomization. Moreover, radical prostatectomy is a major surgical procedure that carries significant risks, including urinary incontinence, erectile dysfunction, and bowel dysfunction. There is currently no universally accepted standard method for Lu177-PMSA, and various approaches in terms of interval and frequency have been employed in previous studies. In the context of the present pilot study, we considered a two-cycle treatment regimen with a four-week interval between cycles. Subsequent courses of treat-

ment were administered as required; however, the data pertaining to these additional treatments were not collected for the purpose of the present investigation. The values of PSA observed in the present study were highly variable, which may be attributable to factors such as the type and extent of metastasis, as well as the patients' previous responses to bilateral orchiectomy. However, all participants in our study were diagnosed with adenocarcinoma and underwent 177LU-PSMA treatment eight weeks following radical prostatectomy and androgen deprivation therapy (ADT). This variability in PSA values may be considered as a potential limitation of the present study, which should be taken into account when interpreting the findings. By our knowledge, there is not any other trial to assess the efficacy and safety of 177Lu-PSMA-617 in combination with radical prostatectomy and bilateral orchiectomy in patients with metastatic prostate cancer. Neither Radical Prostatectomy nor Bilateral Orchiectomy nor 177Lu-PSMA-617 are universally recognized as standard treatments for Metastatic Prostate Cancer. Our pilot study was designed based on the following premises: Radical Prostatectomy, when performed by a skilled surgeon, is not associated with an increase in surgical complications[37]. Additionally, research indicates that over one-third of patients with metastatic prostate cancer experience tumor progression over time, leading to complications such as urinary retention, bilateral hydronephrosis, and elevated serum creatinine levels. By undergoing radical prostatectomy, there is a potential reduction in these complications, which could enhance the quality of life for these patients[8]. Moreover, reducing tumor volume may positively impact patients' immune status through immunomodulation, potentially resulting in improved responses to systemic treatments[38]. Furthermore, contemporary approaches such as local androgen deprivation therapy (ADT) have emerged as accepted modalities for treating patients with oligometastatic cancer[39]. There were two imaging findings that were remarkable. One patient (patient #4) showed a complete response on PSMA-PET. The treated lymph node in this patient was not detectable on the follow-up . This may suggest that 177Lu-PSMA could have a prolonged genotoxic effect to the tumors with tracer uptake, or that 177Lu-PSMA could induce an immunogenic cell death.

Even though our findings regarding both toxicity and efficacy are performed in a small cohort of selected patients, the results suggest a favorable outcome after 177Lu- PSMA in patients with metastatic prostate cancer. Therefore, we assume that higher treatment activity dosages or more treatment cycles are now feasible, with potentially better results. Our study will contribute to the growing body of evidence on the use of PSMA-based therapies in hormone-sensitive prostate cancers with widespread metastasis and will provide important information on the potential benefits of combining radical prostatectomy with PSMA-based therapy for patients with metastatic prostate cancer. This is a pilot study with a limited sample size, there is a pressing need for larger prospective randomized multicenter trials to substantiate the efficacy of first-line 177Lu-PSMA treatment in patients with metastatic prostate cancer.

In conclusion, radical prostatectomy and bilateral orchiectomy in combination with 177Lu-PSMA-617 may have a role in the management of select patients with castrate-sensitive metastatic prostate cancer, but further research is needed to define its optimal use in this setting. Implementing a collaborative teamwork strategy for their care is critical.

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