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ORIGINAL RESEARCH ARTICLE

Evaluating the response and side effects of [^{177}Lu]Lu-PSMA therapy in mCRPC patients: A single-center experience from Iran

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ABSTRACT

Introduction: To evaluate clinical and laboratory findings in patients undergoing [^{177}Lu]Lu-PSMA treatment for metastatic castration-resistant prostate cancer (mCRPC).

Methods: This cross-sectional study included mCRPC patients treated with [^{177}Lu]Lu-PSMA. Patients underwent regular evaluations by a nuclear medicine specialist, with laboratory tests (CBC, serum PSA, creatinine, and liver functions) conducted before each treatment cycle and at 1-, 4-, and 8-weeks post-treatment. Treatment cycles were repeated every 8-10 weeks to assess response and side effects. Patients received [^{177}Lu]Lu-PSMA intravenously, followed by a 6-hour monitoring period. A pre-designed checklist was used to collect demographic data, clinical manifestations (pain assessment via VAS), treatment complications, and laboratory parameters. The relationships among PSA level changes, age, and radiopharmaceutical dosage were analyzed, along with side effects related to blood cell counts and serum creatinine levels.

Results: This study evaluated the efficacy and safety of [^{177}Lu]Lu-PSMA treatment in 133 metastatic castration-resistant prostate cancer (mCRPC) patients. PSA level decreases in 122 patients (92%), with 39 (29%) achieving a ≥50% reduction. Disease stabilization occurred in 79 patients (59%), while 34 patients (26%) experienced disease progression. Bone pain relief in 41% of 72 patients complaining of baseline pain. Hematological toxicity was observed mostly as grade 1 (67%) and as grade 2 (34%) of the patients. No renal or hepatic complications were observed.

Conclusion: The results suggest that [^{177}Lu]Lu-PSMA treatment is effective in managing metastatic castration-resistant prostate cancer, with a favorable therapeutic response and limited side effects.

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INTRODUCTION

Prostate cancer, currently the second most frequently diagnosed cancer and sixth leading cause of cancer-related deaths among men globally. It is projected to nearly double in incidence by 2040 [1]. Despite the anticipated increase in global incidence, many countries have recently experienced a decline or stabilization in prostate cancer incidence and mortality rates, attributed in part to decreased prostate-specific antigen testing and advancements in treatment options [2]. The improvement in treatment outcomes is attributed to substantial progress in chemotherapy, hormonal therapy, and particularly targeted therapy options for patients with castration-resistant prostate cancer [3]. Of the approximately 1.3 million new cases of prostate cancer diagnosed annually, around 30% will progress to metastatic disease, with some cases advancing to metastatic-castration resistant prostate cancer (mCRPC), a condition characterized by a poor prognosis and a median survival rate of 9-13 months. Currently, the prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein receptor, has revolutionized prostate cancer care, offering new opportunities for diagnosis and treatment [4]. Androgen deprivation therapy (ADT) remains the cornerstone of treatment for metastatic and recurrent prostate cancer, although it is inevitable that nearly all patients will eventually progress to castration-resistant disease. PSMA is drastically overexpressed in prostate cancer cells - with levels reaching up to 1000 times than those found in normal prostate cells. This receptor is typically expressed in specific tissues, including the renal tubules and duodenum, where it plays a crucial role in the uptake and processing of dietary folates. Additionally, PSMA is found in the brain, where it is involved in modulating glutamate signaling [5, 6]. Although PSMA is not exclusively specific to prostate cancer cells, its significant overexpression in tumor cells compared to healthy tissues makes it an attractive target for both imaging and therapeutic applications. The relatively low toxicity of PSMA-targeted approaches to healthy tissues, which exhibit limited uptake, further supports its potential as a target for cancer treatment and diagnosis [7]. The radiometal ^{177}Lu, which is produced in a reactor, is characterized by its emission of low-energy gamma rays at two distinct energy levels: 208 keV (with an abundance of 10%) and 113 keV (with an abundance of 6%). ^{177}Lu is also a medium-energy beta emitter, with a maximum energy of 0.5 MeV. Notably, its tissue penetration is limited to less than 2 mm. This shorter beta range of ^{177}Lu enables more effective irradiation of small tumors, which is advantageous compared to the longer beta range of ^{90}Y [8]. The favorable characteristics of [^{177}Lu]Lu-PSMA have contributed to its growing adoption in therapeutic approaches. Currently, numerous studies are investigating the residual effects of this emerging treatment, including its adverse effects and impact on PSA responses. We aim to share our experience in our center.

METHODS

This retrospective study included all patients with metastatic castration-resistant prostate cancer who were referred to the Nuclear Medicine Center of Ghaem Hospital for [^{177}Lu]Lu-PSMA therapy between 2020 and 2022. A total of 133 patients were enrolled in this study.

Data collection

Patients underwent routine medical evaluations and laboratory tests, including PSA, complete blood count (CBC), creatinine, and liver function tests, before treatment and at 1, 4, and 8 weeks after treatment. The treatment response was evaluated, and potential adverse effects were monitored. Adverse events reported by patients were documented both within 24 hours and at 8 weeks following the therapy. The [^{177}Lu]Lu-PSMA therapy was administered intravenously in 250-500 mL of normal saline, and patients were observed for 6 hours at the Nuclear Medicine Center.

Demographic information, clinical manifestations (including pain scores using the Visual Analog Scale (VAS)), treatment-related adverse effects, and laboratory parameters (PSA, CBC, creatinine, and liver function tests) were extracted from patients' medical records using a pre-designed checklist.

Biochemical response evaluation

Biochemical response was evaluated by measuring PSA levels at 1 and 2 months after treatment. According to the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria, a biochemical response was defined as a decrease in PSA of ≥50%. Stable disease was defined as a PSA decrease of <50% or a <25% increase. Progressive disease was defined as a PSA increase of ≥25%.

Toxicity evaluation

Hematological and renal toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Other potential acute and chronic adverse effects were recorded and reported.

Statistical analysis

The collected data were analyzed using SPSS software. Descriptive statistics were used to summarize the data and were reported in tables and figures using appropriate indices of dispersion and central tendency; also, the Kolmogorov-Smirnov test was used to evaluate the normality of quantitative data. Mean and standard deviation were used to describe normally distributed data, while median and interquartile range were used to describe non-normally distributed data. Frequency (percentage) was used to describe categorical variables. A repeated-measures ANOVA or its nonparametric equivalent (Friedman test) was used to compare quantitative variables. A significance level of <0.05 was considered statistically significant.

RESULTS

Patients

In a cross-sectional study at Ghaem Hospital Medical Center, 133 patients with hormone-resistant metastatic prostate cancer were treated with [^{177}Lu]Lu-PSMA-617 between 2020 and 2022. The mean age of the patients was 69.49 years (ranging from 50 to 88). Most patients (49.6%) had an ECOG Performance Status (PS) of 0, 43.2% had an ECOG PS of 1 or 2, and the remaining patients had an ECOG PS of 3 or 4. Gleason scores were available for 91 patients, with a median score of 9, and 51% of these patients had a score greater than 8. Bone was the most common site for metastasis, affecting 96.2% of patients, while lymph node and visceral metastases were present in 38.3% and 15.2% of patients, respectively. Previous treatments included chemotherapy (47.4%), surgical orchiectomy (8.3%), external beam radiotherapy (42.1%), first-line androgen deprivation therapy (90.8%), and second-line ADT (59.4%) (Figure 1). All patients received at least one cycle of [^{177}Lu]Lu-PSMA-617, with an average dose of 181 mCi (range: 100-250 mCi). Patients' characteristics are shown in Table 1.

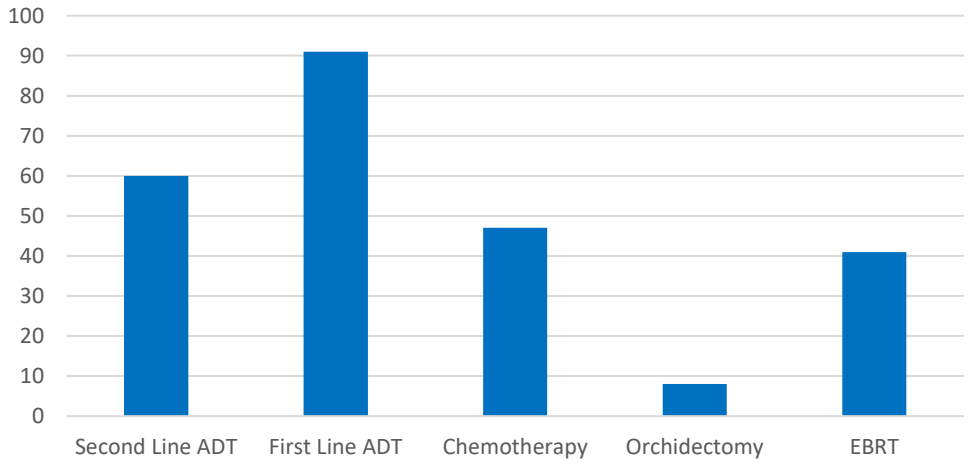

Figure 1. Overview of prior treatments administered to patients

Biochemical values before treatment

The lower limit of normal (LLN) for hemoglobin (Hb) was defined as 14 g/dL. Baseline Hb results were available for 128 out of 133 patients (range: 7.3 to 16.1, mean: 11.5, standard deviation: 2). Toxicity grades were as follows: 61% had grade 1, 25% had grade 2, and 0.07% had grade 3 toxicity; 13% of patients had no toxicity when considering the LLN of 14. For platelets, the LLN was set at 150K. Baseline platelet results were available for 128 patients (range: 85K to 574K, mean: 259.3K, standard deviation: 100.6K). Grade 1 toxicity was observed in 9% of patients, while the remaining patients had normal platelet counts. For white blood cells (WBC), the LLN was defined as 4K. Baseline WBC results were available for 129 patients (range: 2100 to 33200, mean: 7480, standard deviation: 3900). In 6% of patients, grade 1 toxicity occurred, in 1.5% grade 2, and the remaining patients had normal WBC counts.

Nephrotoxicity was assessed using an upper limit of normal (ULN) for creatinine of 1.4. Baseline creatinine results were available for 126 patients (range: 0.5-2.37, mean: 1.1, standard deviation: 0.33). 7% of patients had grade 1 toxicity and 3% had grade 2 toxicity, with the rest having normal creatinine levels. Increased alkaline phosphatase (ALP) toxicity was assessed with an ULN of 147. Baseline ALP results were available for 99 patients (range: 24 to 11440, median: 317, interquartile range: 790). Patients were categorized into toxicity grades as follows: 42% in grade 1, 12% in grade 2, 28% in grade 3, and 4% in grade 4; 13 patients had normal ALP levels. Baseline PSA results were available for 132 patients (range: 0.3 to 9773, median: 99.8, interquartile range: 226.7). Baseline biochemical values are shown in Table 2.

Table 1. Patients' characteristics

	Mean	IQR
Age	69.49	50-88
ECOG	N	Percentage (%)
0	62	49.6%
1	36	28.8%
2	18	14.4%
3	7	5.6%
4	2	1.6%
Gleason Score	N	Percentage (%)
6	3	3.3%
7	13	14.3%
8	28	30.8%
9	39	42.9%
10	8	8.8%
Metastasis	N	Percentage (%)
Bone	128	96.2%
Lymph Node	51	38.3%
Visceral	20	15.2%
Previous Treatment	N	Percentage (%)
Chemotherapy	63	47.4%
Orchidectomy	11	8.3%
EBRT	56	42.1%
First Line ADT	119	90.8%
Second Line ADT	76	59.4%

Table 2. Baseline biochemical values

Variable	Normal Limits	Available	Range	Mean	SD	Toxicity
Hb	LLN=14	N=128	7.3-16.1	11.5	2	Grade I: 61% Grade II: 25% Grade III: 0.007%
Plt	LLN=150	N=128	85-547	259	100.6	Grade I: 0.09%
WBC	LLN=4000	N=128	2100-33200	7.48	3900	Grade I: 0.06% Grade II: 0.01%
Cr	ULN=1.4	N=126	0.5-2.37	1.10	0.33	Grade I: 0.07% Grade II: 0.03%
Alk	ULN=147	N=99	24-11440	813	Interquartile range: 790	Grade I: 42% Grade II: 12% Grade III: 28% Grade IV: 0.04%
PSA	-	N=132	0.3-9773	99.8	Interquartile range: 226.7	-

LLN: Lower limit of normal; ULN: Upper limit of normal

Hematologic toxicity with radioligand therapy (RLT)

Among the 119 patients with available hemoglobin results after the first cycle, 56% had grade 1 toxicity, 28% had grade 2 toxicity, 6.7% had grade 3 toxicity, and 0.02% had grade 4 toxicity; 0.07% patients had no blood-related complications. Of the 84 patients who received the second dose of lutetium and had available hemoglobin results, 69% had grade 1 toxicity, 18% had grade 2 toxicity, 0.02% had grade 3 toxicity, and 0.02% had grade 4 toxicity; 0.08% of patients had no Hb-related complications (Figure 2). Of the 121 patients treated with available baseline and follow-up WBC results after the first cycle of RLT, 13% had grade 1 toxicity, 5% had grade 2 toxicity, and 0.8% had grade 3 toxicity; 80% patients had normal WBC counts. Of the 83 patients who received the second dose of lutetium and had available WBC results, 18% had grade 1 toxicity and 2% had grade 2 toxicity; 79% patients had normal WBC counts (Figure 3). Of the 120 patients treated with available baseline and follow-up platelet results after the first cycle of RLT, 18%had grade 1 toxicity, 0.02% had grade 2 toxicity, and 0.02%had grade 3 toxicity; 76% patients had normal platelet counts. None of the patients with platelet counts of 77K or less received a second treatment cycle. Among the 83 patients who received the second dose of lutetium and had available platelet results, 9.6% had grade 1 toxicity, 2.4% had grade 2 toxicity, and 1.2% had grade 3 toxicity; 86% patients had normal platelet counts (Figure 4).

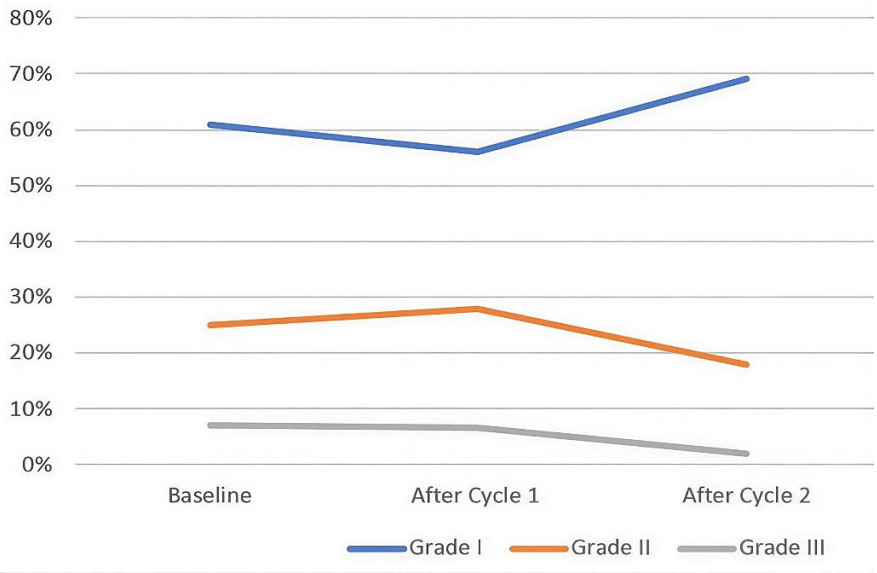

Figure 2. Incidence of anemia before and after RLT

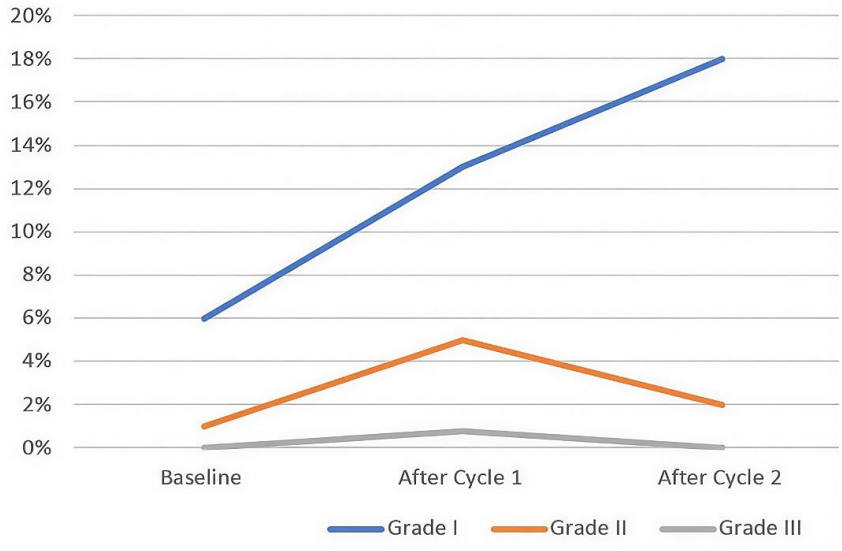

Figure 3. Incidence of leukopenia before and after RLT

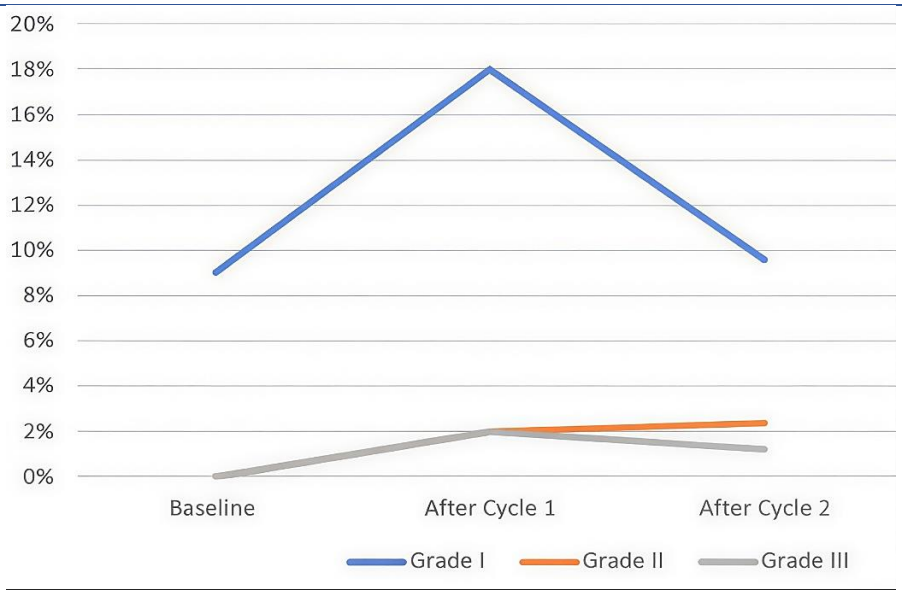

Figure 4. Incidence of thrombocytopenia before and after RLT

Renal toxicity with RLT

Out of the 126 patients treated with available baseline creatinine results, follow-up creatinine results were unavailable for 10 patients. Among the 116 patients with available creatinine results after the first cycle, 6% had grade 1 toxicity and 3% had grade 2 toxicity. Creatinine levels decreased in 51% of patients following treatment, with a reduction of more than 0.5 units in 5% cases, 80% of whom had lymphatic involvement. Among the 116 patients treated and with available creatinine results after the first cycle, 24 did not receive the second dose (17 due to death, three due to unavailability of second cycle creatinine results at the time of analysis, two lost to follow-up, and one who withdrew from further treatment). Of the 92 remaining patients who received the second dose of lutetium, follow-up creatinine results were unavailable for 14 patients. Among the remaining 78 patients, 10% had grade 1 toxicity and 1% had grade 2 toxicity; 88% patients had normal creatinine levels. Creatinine levels decreased in 43% of patients following treatment, with a reduction of more than 0.5 units in 5% cases, all of whom had lymphatic involvement (Figure 5).

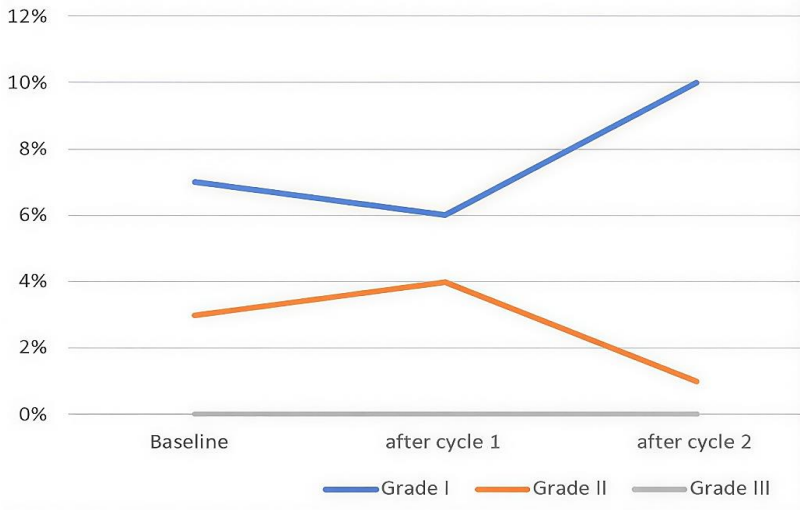

Figure 5. Incidence of renal toxicity before and after RLT

Hepatic toxicity with RLT

Increased ALP CTCAE was defined as above the upper normal limit of 147. Among the 88 patients with available ALP results after the first cycle, the distribution was as follows: 26% in grade 1, 13% in grade 2, 36% in grade 3, and 3% in grade 4; 20% patients had normal ALP levels. Of the 69 patients who received the second dose of lutetium and had available baseline and first-cycle ALP results, follow-up ALP results after the second cycle were unavailable for 12 patients (10 due to death and 2 due to unavailability of results at the time of analysis). Among the remaining 57 patients, the distribution was as follows: 33% in grade 1, 23% in grade 2, and 23% in grade 3; 21% patients had normal ALP levels (Figure 6). Based on the results, the reduction in alkaline phosphatase in the first treatment cycle in patients was significant, but the overall reduction across all treatment cycles was not significant.

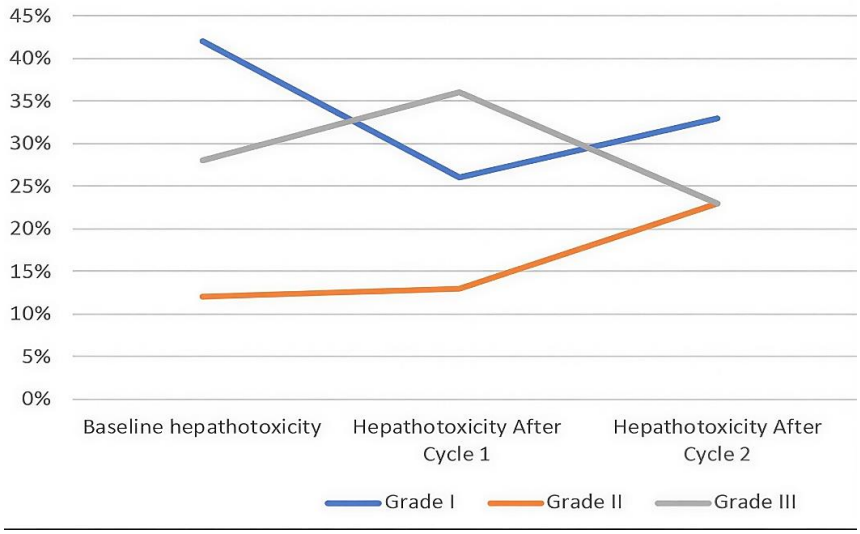

Figure 6. Incidence of hepatotoxicity before and after RLT

PSA change

Among 122 patients after one cycle of RLT, a PSA decline of any extent was observed in 79 (65%) patients with available PSA results, with a maximal PSA decline of at least 50% in 39 (32%) patients. In contrast, 34(28%) patients had PSA progression of at least 25% (Table 3). Of the 122 patients with accessible PSA results after the first treatment cycle, 99 received the second dose of lutetium, with PSA results unavailable for 15 patients. Of the remaining 84 patients with accessible PSA results after the second treatment cycle, a PSA decrease of any magnitude was observed in 56(66%) patients, with a reduction of more than 50% in 29 (34%) patients, while 20 (24%) patients had PSA progression. Of the remaining 84 patients, 71 received the third dose of lutetium, and PSA results were unavailable for 6. Among the 65 remaining patients, a PSA decrease of any magnitude was observed in 31 (48%), with a decline of more than 50% in 11 (17%), while 30 (46%) had PSA progression (Table 3).

Of the 34 patients who had PSA progression after the first treatment cycle, nine patients did not receive a second dose of treatment (6 deaths, one withdrawal from continuing treatment, one still on the following treatment cycle list at the time of data analysis, and one lost to follow-up). Four other patients also died after receiving the second dose and before the PSA results were available (a total of 13 deaths). Of the remaining 21 patients, a second cycle of [^{177}Lu]Lu-PSMA therapy was injected, and the PSA results after treatment were available. Any PSA reduction and PSA reduction greater than 50% were seen in 12 and 4 patients, respectively. Also, despite the initial PSA rise, in 5 patients, a consistent PSA reduction (i.e., a continuous decrease in PSA level after the second and third cycles) was observed, which can be considered an initial flare (Table 4).

All patients with bone pain at the beginning of treatment reported a noticeable reduction in pain within 10 to 14 days after injection. The most common side effect after treatment was fatigue and transient weakness, which did not require special intervention. No patient had nausea or vomiting side effects during treatment. Dry mouth was seen transiently after injection. In most patients, no specific side effects were observed. The possibility of liver, kidney, and hematological (anemia) toxicity after treatment was assessed according to the International Cancer Institute CTCAE v 4.03 criteria in patients two months after injection (Table 5).

Table 3. Biochemical response to treatment

Response to treatment	N (%)	
PSA decline ≥50%	39 (32%)	P Value 0.19
PSA decline <50% and progression <25%	49 (40%)	
PSA progression ≥25%	34 (28%)	

Table 4. Overview of PSA values

Variable	Number	Mean	SD	P Value
PSA at baseline	132	447	1096	0.1
PSA after treatment	123	285	561	0.019

Table 5. Toxicity 2 months after the first cycle of treatment

Variable	Toxicity Grade	Number	Percentage
Anemia	Grade I	67	56%
	Grade II	34	28%
	Grade III	8	6.7%
Hepatoxicity	Grade I	12	9.37%
Nephrotoxicity	Grade I	22	17%

DISCUSSION

The primary focus of our study was on the safety and efficacy of the therapy protocol, as well as the response rate and clinical outcomes observed in the patients who received treatment. In the treatment period, 83 patients (62.4%) died.

According to the World Health Organization and statistical data, the life expectancy at birth for Iranian men is 74.7 years, whereas in Australia, it stands at 81.3 years. Consequently, the mortality rate in Iran can be somewhat expected, particularly since it should be considered that the patients were end-stage and had complications from previous treatments when referred for [^{177}Lu]Lu-PSMA therapy. It can be suggested that the delayed referral may have contributed to the mortality observed in these patients.

The treatment method with the radiopharmaceutical [^{177}Lu]Lu-PSMA demonstrates considerable therapeutic benefits, such as an effective therapeutic response and minimal side effects. This makes it a viable and safe option for the widespread treatment of patients with metastatic prostate cancer resistant to hormone therapy.

Our study's findings align with previous research, identifying fatigue, nausea, and dry mouth as common adverse effects of [^{177}Lu]Lu-PSMA-617 treatment. Additionally, we observed more frequent decline in hematological parameters, particularly anemia, which is a known risk factor for poor outcomes in mCRPC patients.

Hematological deterioration is common in patients with progressive mCRPC and predicts poor outcomes. Up to 10–25% of men had a Grade 1–2 reduction in hemoglobin or platelets. However, it was aligned with a meta-analysis that showed Grade 1/2 anemia was the most common adverse effect of [^{177}Lu]Lu-PSMA therapy, affecting about 50% of patients, while grade 3/4 toxicities in other categories were rare, occurring in under 10% of cases [9].

The relationship between myelotoxic complications and predisposing factors in patients treated with [^{177}Lu]Lu-PSMA-617 is not well understood and requires further investigation. Risk factors for myelosuppression during radionuclide therapy include pre-existing hematologic disorders, a history of myelotoxic treatments, prior Peptide receptor radionuclide therapy (PRRT), and the extent of bone tumor infiltration. RLT may also exacerbate hematopoietic dysfunction due to bone marrow irradiation.

The data regarding hemoglobin baseline levels and the grades of intra- and post-therapeutic hematologic toxicity, as assessed by CTCA v5, were entirely consistent with the findings of the study conducted by Groener et al. [10].

In our study, the prevalence of thrombocytopenia, lymphopenia, and leukopenia across all grades was closely aligned

with the trend observed in the Vision trial [11]. Our findings on the efficacy and safety of [^{177}Lu]Lu-PSMA therapy in mCRPC patients closely align with those reported in major international trials, with some expected differences. The biochemical response in our group, with 32% of patients achieving ≥50% PSA decline after the first cycle, aligns with the established profile of this treatment. This rate was about 44% ≥50% PSA response reported in the landmark VISION trial, given that our patients were heavily pre-treated and most received only 1 or 2 cycles. In contrast, patients in the VISION trial had a median of 4 cycles.

Most of our patients completed two cycles of treatment, whereas most data from other studies relate to three or four cycles. As a result, it is anticipated that the percentage of PSA decline observed in our study is lower than that reported in other studies, although it follows a comparable decreasing trend. The median serum PSA levels measured 1 month after completion of the initial cycle of [^{177}Lu]Lu-PSMA radioligand therapy showed a notable decline compared with levels observed before treatment initiation. After the first cycle, 32% of patients experienced a PSA reduction exceeding 50%; this increased to 34% after the second cycle and decreased to 17% after the third cycle. These findings align with a study by Gupta, which found that approximately 36.4% of patients had a 30% or greater decrease in PSA levels after one cycle of treatment. Numerous studies, predominantly retrospective, have demonstrated a notable PSA response following [^{177}Lu]Lu-PSMA radioligand therapy, particularly after multiple treatment cycles [12].

Hematologic adverse events from radioligand therapy (RLT) have an acceptable and often reversible incidence. Key risk factors for significant myelosuppression include a high burden of bone tumors, prior taxane-based chemotherapy, and pre-existing grade 2 cytopenia. Additional pre-treatment factors that may increase myelosuppression risk include existing hematologic deficiencies, prior myelotoxic treatments, and the extent of bone tumor involvement [13].

However, some studies showed that the cumulative activity of RLT and prior treatment with ^{223}Ra-dichloride does not significantly affect incidence rates [10].

Variations in tumor stage among the treated patients, along with differences in the therapies administered prior to the PSMA-RLT, contributed to the observed discrepancies.

Grade I and II nephrotoxicity was observed in less than 9% of our patients, which was consistent with the study by Gupta et al. [14]. No instances of grade 3 or 4 nephrotoxicity were observed in any of the patients.

Due to the nature and requirements of this research, which focuses on the initiation of this new treatment for patients in our department and the fact that most patients received only one treatment session, limiting direct comparison with studies involving multiple treatment cycles. However, all patients in this study were closely monitored to ensure that they could receive subsequent treatment cycles at appropriate times as determined by the treatment team. In a study, Ferdinandus et al. examined predictors of response to [^{177}Lu]Lu-PSMA-617 radioligand therapy in mCRPC [15]. It included 40 patients with hormone-resistant PC and progressive disease based on PSA levels. Factors negatively affecting therapeutic response in univariate analysis included younger age, higher γ-glutamyl transferase levels, lower pre-treatment hemoglobin, higher Gleason score, higher platelet count, higher C-reactive protein, regular need for pain medication, and higher lactate dehydrogenase levels. The most significant independent factors were platelet count and regular need for pain medication. The response was independent of PSMA uptake and other measured factors. A favorable response rate (PSA reduction >50%) was significantly observed in patients without regular need for pain medication.

In another study, Groener et al (2021) investigated the occurrence, severity, and reversibility of hematologic side effects in patients undergoing RLT with [^{177}Lu]Lu-PSMA-617 for mCRPC. The study involved 140 patients receiving a total of 497 cycles. The average administered dose per cycle was 6.9 ± 1.3 GBq of [^{177}Lu]Lu-PSMA-617, with a cumulative dose of 24.6 ± 15.9 GBq. Hematologic parameters were measured initially, before each treatment cycle, 2 to 4 weeks post-treatment, and during follow-up. Hematologic side effects post-RLT were generally acceptable and often reversible. High bone tumor burden, prior taxane-based chemotherapy, and grade 2 cytopenia before treatment were identified as risk factors for developing bone marrow suppression. In contrast, cumulative RLT dose and prior ^{223}Ra-dichloride treatment did not significantly contribute to the incidence rate [10]. Ahmadzadehfar et al. (2015), in a study conducted in Germany, analyzed side effects and response rates in 24 patients with mCRPC

treated with ^{177}Lu-PSMA-DKFZ-617 ([^{177}Lu]Lu-PSMA). The patients, aged 64-82 years with progressive disease and distant metastases, with a median PSA level of 522 ng/ml (range: 17-2360). A total of 46 cycles of [^{177}Lu]Lu-PSMA were administered, with 22 patients receiving two cycles. Eight weeks after the first treatment cycle, 79.1% of patients experienced a PSA reduction. Eight weeks after the second cycle, 68.2% of patients had a PSA reduction compared to baseline. Aside from two cases of grade 3 anemia, there were no grade 3 or 4 hematologic or renal toxicities, confirming [^{177}Lu]Lu-PSMA as a safe treatment option for mCRPC patients with a favorable therapeutic response in about 70% of cases [16].

In a study conducted by Prasad Yadav in 2021, 121 out of 135 patients with mCRPC met the eligibility criteria and were included in the final analysis. These patients received an average of 3 cycles of [^{177}Lu]Lu-PSMA-617 radioligand therapy (RLT) at intervals of 6 to 12 weeks. The primary endpoint was overall survival (OS), while secondary endpoints included progression-free survival (PFS), predictors of OS and PFS, PSA response rate, molecular response, clinical response, and toxicity assessment. The study demonstrated short-term safety and efficacy, high response rates, long-term PFS and OS, improved quality of life, and low treatment-related toxicity in patients treated with [^{177}Lu]Lu-PSMA-617.

Given the high incidence of prostate cancer worldwide, finding the most effective treatment methods can significantly reduce the problems faced by these patients. The results of this study could potentially decrease mortality rates among these patients and pave the way for future research on the impact of [^{177}Lu]Lu-PSMA treatment on the lives of patients with metastatic prostate cancer resistant to hormone therapy [17].

Our research supports previous studies, indicating that severe adverse effects following PRLT are rare [18, 19]. One strength of this study is its novel approach and methodology, as not many similar studies are available. The imaging criteria employed in our trial facilitate the administration of life-extending therapy to patients with PSMA-positive metastatic castration-resistant prostate cancer, which rely on conventional imaging methods.

The primary differences between our results and those of larger trials are primarily attributable to patient population characteristics and treatment patterns. The lower overall PSA response rate in our study compared to some cohorts is likely multifactorial, stemming from the delayed referral of patients in our center, who presented with more advanced disease and a higher baseline disease burden, as evidenced by the high prevalence of bone metastases (96.2%) and the fact that many patients did not proceed beyond the first cycle. In our study, 78.4% of patients had an ECOG score of 0 or 1, whereas in the VISION trial, this value was 91.6%. In contrast, trials like VISION [11] and TheraP [20] enrolled patients who were typically earlier in their mCRPC diagnosis time and received a more standardized, multi-cycle treatment regimen. Despite the higher response rate in patients with better performance scores in the VISION trial (32% vs. 46% response rate, 78.4% vs. 91.6% ECOG of 0 or 1) the rate of overall and severe adverse events in the VISION trials were higher (negligible severe hematology adverse events vs. 31% of at least grade 3 hematologic adverse events, respectively).

Study limitations

Our study had several limitations, including the necessity for larger sample sizes. In some studies, health-related quality of life was evaluated with a questionnaire that explored disease-related symptoms, functional well-being, prostate cancer-specific symptoms, and treatment-related side effects from both emotional and physical viewpoints. The variation in results can be attributed to differences in tumor stage among the treated patients, as well as to discrepancies in therapies administered prior to the PSMA-RLT. Future studies should include long-term follow-ups and ensure that most patients receive at least three cycles of the drug. Additionally, recent studies suggest that starting treatment before chemotherapy may reduce mortality and complications.

CONCLUSION

The results suggest that [^{177}Lu]Lu-PSMA treatment is effective in managing metastatic castration-resistant prostate cancer, with a favorable therapeutic response and limited side effects.

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