

## Original Article

# Efficacy and safety of <sup>177</sup>Lutetium-prostate-specific membrane antigen therapy in metastatic castration-resistant prostate cancer patients: First experience in West Asia – A prospective study

## ABSTRACT

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is highly expressed on the surface of prostate cancer (PC) cells, making it an excellent radiotracer for both therapeutic and diagnostic purposes. In this prospective study, we investigated the efficacy and toxicity of <sup>177</sup>Lutetium (Lu)-PSMA in metastatic castration-resistant PC (mCRPC) patients for the establishment and approval of this therapy in Iran. Fourteen mCRPC patients (mean age 70.57 ± 7.3 years) were treated with a single dose of <sup>177</sup>Lu-PSMA. Complete blood count, liver function tests (aspartate aminotransferase and alanine aminotransferase), alkaline phosphatase levels, renal function tests (urea and creatinine), and prostate-specific antigen (PSA) levels were obtained for the patients at baseline and every 2 weeks. A majority of the patients (11 patients, 64.2%) experienced a decline in their PSA levels; in 5 (45.4%) of these patients, the PSA levels declined > 50%. The severity of pain decreased in 8 (57.1%) patients, and performance status was improved in 5 (45.4%) patients. The treatment was well tolerated, and no severe hematological or nonhematological side effects were observed. Our findings show that <sup>177</sup>Lu-PSMA had a high efficacy and a low toxicity in an Iranian population and is a promising treatment option for PC patients.

**Keywords:** <sup>177</sup>Lutetium, metastatic castration-resistant prostate cancer, prostate cancer, prostate-specific membrane antigen, radionuclide therapy, theranostic

## INTRODUCTION

Prostate cancer (PC) is the second most common cancer in men in the world; in Iran, it is the third most common cancer in men and the sixth most common cancer in the country.<sup>[1]</sup> The American Cancer Society estimates that there will be 164,690 new cases of PC and 29,430 deaths in the United States in 2018.<sup>[2]</sup>

Metastatic castration-resistant PC (mCRPC) is a lethal disease with a 5-year survival rate of about 31%.<sup>[3]</sup> mCRPC is defined as disease progression despite castrated levels of testosterone and may present with a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of preexisting disease, and/or the appearance of new metastases.<sup>[4]</sup> Therefore, it is important to develop new therapies. The approved therapies for mCRPC include

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abiraterone and enzalutamide, as well as, chemotherapy with docetaxel, cabazitaxel, and radium-223.<sup>[5-10]</sup>

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, is a type II transmembrane protein that is highly expressed on prostate adenocarcinoma cells,<sup>[11,12]</sup> particularly on dedifferentiated tumors.<sup>[13,14]</sup> This unique characteristic makes PSMA a suitable radiopharmaceutical for PC diagnosis and therapy.

<sup>177</sup>Lutetium (Lu)-PSMA radioligand therapy (RLT) was first introduced by the German Cancer Research Centre at the University Hospital Heidelberg in 2015.<sup>[15]</sup> Initial studies have shown promising results with <sup>177</sup>Lu-PSMA RLT for patients in advanced stages of PC.<sup>[16-27]</sup> Most of the published efficacy and safety data on <sup>177</sup>Lu-PSMA have been derived from retrospective analyses. To our knowledge, only one prospective trial has investigated this treatment's efficacy and toxicity.<sup>[28]</sup> Since this is a new treatment option, and a limited number of studies have been conducted outside Europe, further studies are needed, especially in different ethnic groups. The aim of this study was to prospectively evaluate the toxicity and response to this novel therapeutic treatment in Iranians for the establishment and approval of this therapy in Iran.

## MATERIALS AND METHODS

### Patient selection and preparation

#### Inclusion criteria

1. mCRPC patients with distant metastases and progressive disease (as determined by PSA levels) after standard treatment (second-line antiandrogen treatment, if the patient could afford it, and chemotherapy, if the patient was medically eligible)
2. PSMA-positive metastases identified in pretherapeutic low-dose <sup>177</sup>Lu-PSMA imaging; and
3. An Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or lower and a life expectancy > 12 weeks.

#### Exclusion criteria

1. Patients with urinary obstructive disease
2. White blood cell count  $\leq 2000/\mu\text{l}$ , platelet count  $\leq 75 \times 10^3/\mu\text{l}$ , and creatinine > 2 mg/dl; and
3. Chemotherapy or external radiation therapy within the last 4 weeks.

The decision to apply this therapy was made by an interdisciplinary tumor board according to the Iranian guidelines.<sup>[29]</sup>

<sup>99m</sup>Tc-DTPA renal scintigraphy was performed to rule out obstructive disease. Patients with urinary obstructions were referred to the urologist before therapy.

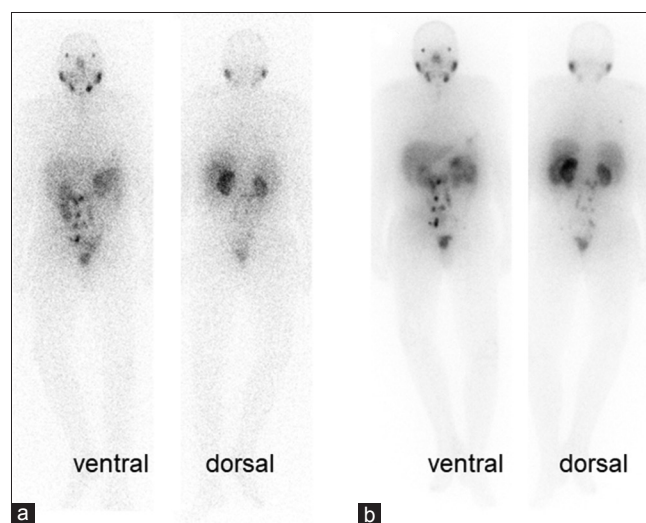
Blood samples were obtained at baseline and every 2 weeks up to 8 weeks of therapy for the following evaluations: complete blood count (CBC), liver function tests (including aspartate aminotransferase [AST] and alanine transaminase [ALT]), alkaline phosphatase level, renal function tests (urea and creatinine), 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.

### Pretherapeutic imaging

Pretherapeutic low-dose <sup>177</sup>Lu-PSMA imaging was performed on all patients to ensure adequate PSMA expression on the tumoral lesions. Whole-body images were obtained 24 h after intravenous injection of 185 MBq of <sup>177</sup>Lu-PSMA-617 [Figure 1].

### <sup>177</sup>Lutetium-prostate-specific membrane antigen preparation

PSMA-617 precursor (Advanced biochemical compounds, ABX, Germany) was radiolabelled with no-carrier added Lu-177 chlorides (Isotope technologies garching (ITG), Germany) in Pars Isotope radiopharmaceutical company, according to the manufacturer's instructions. Quality control was performed by an expert radiochemist before the administration of each dose and double-checked by the attending physician.



**Figure 1:** Patient number 8: <sup>177</sup>Lutetium-prostate-specific membrane antigen whole-body scans in anterior and posterior projection 24 h after injection of diagnostic dose of 185 MBq (a) and therapeutic dose of 6 GBq (b) of <sup>177</sup>Lutetium-prostate-specific membrane antigen, which are comparable in showing multiple lymph node involvement in the abdomen and pelvic cavity. He is a 78-year-old man who had undergone radical prostatectomy and radiation therapy. He could not afford second-line hormone therapy (abiraterone and enzalutamide) and was not a suitable candidate for chemotherapy. The baseline prostate-specific antigen = 3.1 ng/ml declined to 0.43 ng/ml after radioligand therapy

### <sup>177</sup>Lu-PSMA administration

<sup>177</sup>Lu-PSMA was administered 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 <sup>177</sup>Lu-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 then discharged.

### Posttherapeutic <sup>177</sup>Lu-PSMA imaging

At least one whole-body scintigraphic imaging was performed within 24 h of the <sup>177</sup>Lu-PSMA administration to ensure uptake of the <sup>177</sup>Lu-PSMA by the tumoral lesions.

### Patient follow-up

All patients were seen every 2 weeks for at least 2 months. CBC, liver function tests (AST and ALT), alkaline phosphatase levels, renal function tests (urea and creatinine), and PSA levels were subsequently recorded.

A treatment response was defined by a decline in the patient's PSA levels and pain score according to the Visual Analog Scale. The ECOG status score was also documented at baseline and 8 weeks after therapy.

### Toxicity

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

### Ethical issues

This study was approved by the ethics committee of the University of Medical Sciences (ethic code: ir.sbm.u.rec.1396.135), and all local regulations for radiation protection were followed. Before initiating the therapy, a written informed consent for therapy and imaging studies was obtained from each patient. All patients received a consult from a nuclear medicine physician and were informed of the side effects and harms of this new therapy. The patients received this therapy under a compassionate use.

### Statistical analysis

Statistical analyses were performed with the SPSS Statistics program version 21 (IBM Corp., Armonk, NY, USA). Data are shown as medians and ranges or as frequencies. The Kolmogorov–Smirnov test demonstrated that the variable

**Table 1: Patient characteristics at baseline (n=14)**

Characteristics	Data
Age (year)	70.57 ± 7.3 (60-83)
Previous therapies, n (%)	
Second-line antiandrogen	11 (78.6)
Chemotherapy	11 (78.6)
Docetaxel + cabazitaxel	5 (35.7)
Docetaxel	6 (42.8)
External-beam radiation therapy	8 (57.1)
Prostatectomy	12 (78.5)
Gleason score (median)	7.5 (4-10)
PSA (ng/ml)	217.31 ± 395.8 (0.4-1533)
Hemoglobin (g/dL)	11.41 ± 1.88 (7.3-13.3)
WBC (/dL)	5475.7 ± 1145.02 (2900-7000)
Platelets (×10 <sup>3</sup> /dL)	224.86 ± 55.752 (104.0-308.0)
Creatinine (mg/dL)	1.0 (0.7-2.0)
Aspartate aminotransferase (U/L)	21.0 (15.0-44.0)
Alanine transaminases (U/L)	13.0 (7.0-25.0)
Pain (visual analog scale score)	
No pain	5
Mild pain (1-3)	5
Moderate-to-severe pain (4-10)	4
ECOG performance status	
0	3
1	6
2	5

Qualitative data are expressed as numbers, followed by percentages in parentheses; continuous data are expressed as median, followed by range in parentheses.

Pain (Visual Analog Scale score) is defined by score under 2, or 2 and more.

PSA: Prostate-specific antigen; WBC: White blood cell; ECOG: Eastern Cooperative Oncology Group

distribution was skewed, so the Wilcoxon's signed rank test was used to compare the different groups.  $P \leq 0.05$  was considered statistically significant.

## RESULTS

Between May 2017 and May 2018, among the 24 patients with mCRPC who were referred to the Nuclear Medicine department, 15 patients were eligible for enrollment in this study according to the inclusion and exclusion criteria. The patients' characteristics are shown in Table 1. All the 15 patients received at least one cycle of <sup>177</sup>Lu-PSMA with an average dose of 5.7 GBq (range, 4.4–6.6 GBq). Seven patients agreed to continue treatment (receiving 2–6 further treatments). Two patients died during the study due to extensive metastatic disease: one patient died during the 7<sup>th</sup> week and one patient died during the 12<sup>th</sup> week after treatment (patient number 5). The first patient's data were excluded from the study because the 8-week follow-up was not completed. To our knowledge, the death of these patients was not related to the <sup>177</sup>Lu-PSMA therapy. Table 2 shows the detailed characteristics of the 14 included patients.

Table 2: Characteristic of 14 included patients with summary of therapeutic result

n	Age	Cycles	GS	Previous therapy			Known metastases				PSA		Pain score		ECOG		Hematologic toxicity		Others	
				SUR	RT	CTx	Enz/Ab	Bone	LN	Lung	Liver	Brain	Pre	Post	Pre	Post	Pre	Post		PLT
1	66	6	8	+	+	D/C	Enz	+	+	+	+	0.4	0.05	0	0	2	1	-	-	G1
2	81	2	7	-	+	D	Enz/Ab	+	-	+	+	243	166	5	1	2	1	G2	G1	G2
3	69	1	4	-	-	D/C	Enz	+	-	-	-	47	24	0	0	0	0	-	-	G1
4	69	1	6	+	-	-	-	+	-	-	-	14	12	2	1	0	0	G1	-	G1
5	61	1	9	+	-	D	Ab	+	-	-	-	300	384	9	9	2	2	G1	G2	G2
6	83	1	9	+	+	D	Ab	+	-	-	-	19	3.6	3	0	1	1	-	-	-
7	60	1	10	+	+	D	-	+	-	-	-	59	34	3	1	1	1	-	-	-
8	78	1	6	+	-	-	-	+	-	-	-	3.1	0.43	0	0	0	0	-	-	-
9	71	3	7	-	-	D/C	Ab	+	-	-	-	218	100	0	0	1	1	-	-	G1
10	65	2	10	+	+	D/C	Ab	+	-	-	-	1533	2394	3	2	1	1	-	-	G2
11	67	3	7	+	-	D	Enz	+	-	-	-	138	31.9	3	0	1	1	-	-	G1
12	77	2	7	+	+	-	Enz	+	-	-	-	1.9	1.2	6	3	1	1	-	-	G1
13	76	1	9	+	+	D	Ab	+	-	-	-	325	283	0	0	1	1	-	-	G1
14	65	2	9	+	+	D/C	Enz/Ab	+	-	-	-	141	357	8	5	2	1	G1	-	G2

GS: Gleason score; SUR: Surgery; RT: Radiation therapy; CTx: Chemotherapy; D: Docetaxel; C: Cabazitaxel; LN: Lymph node; Lung: Lung metastases; Liver: Liver metastases; Brain: Brain metastases; Bone: Bone metastases; Enz: Enzyme; Ab: Antibody; Pre: Pre-treatment; Post: Post-treatment; Change (%): Percentage change in PSA; Pain score: Pain score; ECOG: Eastern Cooperative Oncology Group performance; Hematologic toxicity: Hematologic toxicity; PLT: Platelet; WBC: White blood cell; Hb: Hemoglobin; G: Grade; +: Positive; -: Negative

Table 3: Site of metastases

Tissue or organ	Number of patients (%)
Skeletal system	13 (92.9)
Lymph node	6 (42.8)
Brain	2 (14.3)
Liver	1 (7.1)
Lung	1 (7.1)

Of the patients included in the study, 11 (78.6%) had previously undergone prostatectomy and 11 (78.6%) had received chemotherapy (docetaxel and cabazitaxel in 7 [50%] and only docetaxel in 4 [28.5%] patients). The mean and median PSA levels prior to the therapy commencement were 217.3 and 59.8 ng/ml, respectively (range, 0.4–1533 ng/ml).

The extent of the patients' metastases is shown in Table 3. All but 1 (92.9%) of the patients had bone metastases based on previous conventional imaging (computed tomography scan, whole-body bone scan, magnetic resonance imaging, and PSMA scan). Lymph node metastases in three (21.4%) patients, lung metastases in two patients (14.3%), and brain and liver in one (7.1%) patient were detected.

Five patients (35.7%) were taking analgesics prior to the <sup>177</sup>Lu-PSMA therapy. The Visual Analog Scale score for pain severity was 2 or more in eight patients. The blood, renal, and liver parameters before treatment are shown in Table 1.

### Scintigraphy with <sup>177</sup>Letetium-prostate-specific membrane antigen after therapy

As the radiopharmaceutical is primarily excreted through the kidneys, physiologic uptake was observed in the kidneys and the bladder as well as in the lacrimal and salivary glands and the liver, spleen, and the small intestine. Higher uptake of <sup>177</sup>Lu-PSMA was detected in sites with metastases and residual tumors [Figures 2 and 3].

### Response evaluation 2 months after therapy Biochemical response

Over the 8-week follow-up period, PSA levels declined in 11 out of 14 (78.6%) patients, with PSA levels declining by 50% or more in 5 (45.4%) patients. Progressive disease, defined by more than a 25% rise in PSA, occurred in three (21.4%) patients. Figure 4 displays waterfall plots that indicate the percentage change in PSA at the 8-week follow-up. A subset of seven patients received repeated treatment, and five of those (patient numbers 1, 2, 9, 11, and 12) had a further PSA reduction (91.2%, 35.5%, 83.5%, 94.2%, and 81%, respectively).



The two nonresponders (numbers 10 and 14) did not show any response during re-treatment and a continued PSA rise was recorded. However, one of these patients (patient number 14) had an improved pain score and a reduced analgesic consumption. In summary, 27 cycles were conducted [Table 2].

The mean serum alkaline phosphatase level declined from 569.5 U/L (range, 79–2667 U/L) to 498.4 U/L (range, 59–2023 U/L), but the difference was not statistically significant ( $P = 0.17$ ).

### Clinical symptoms

At baseline, nine (64.3%) patients with bone metastases reported skeletal bone pain. Among these, pain improved in eight (88.9%) patients after treatment. One patient showed no significant change in pain severity and required the continued use of analgesics (patient number 5). The remaining five patients had no pain complaints at the beginning of the study and did not complain of pain throughout the treatment.

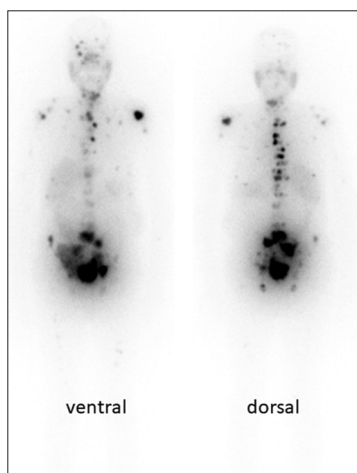


Figure 2: Patient number 11: <sup>177</sup>Lutetium-prostate-specific membrane antigen scan 24 h after administration of the radiotracer (4440 MBq). He is a 67-year-old man with widespread bone metastases. He had undergone prostatectomy and been treated with docetaxel and enzalutamide. Gleason score = 7, prostate-specific antigen = 138, and creatinine = 0.8. Note the patient's nonfunctioning native kidneys and the transplanted kidney in the right hemipelvis

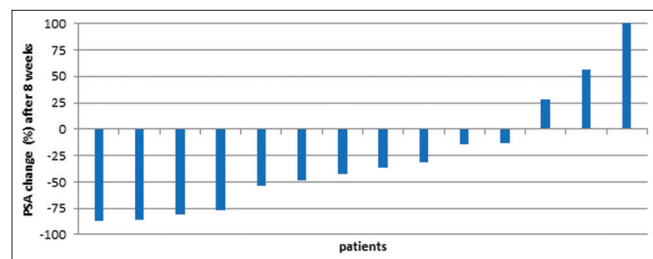


Figure 4: Waterfall curve showing percentage change in prostate-specific antigen values. Prostate-specific antigen increase >100% was cropped due to simplification

The ECOG performance score improved in five (35.7%) patients. One patient's score worsened after therapy (patient number 5).

### Toxicity and side effects

#### Complaints

There were no adverse effects immediately after the <sup>177</sup>Lu-PSMA injections. No concerning changes in body temperature or blood pressure were recorded. There were no side effects in nine (64.2%) patients. During the 1<sup>st</sup> week after injection, one (7.1%) patient experienced myalgia; this was successfully treated with two 400-mg doses of ibuprofen administered daily for 1 week. Mild nausea was experienced by three (21.4%) patients and was the most common side effect within the first 2 days after injection. Ondansetron

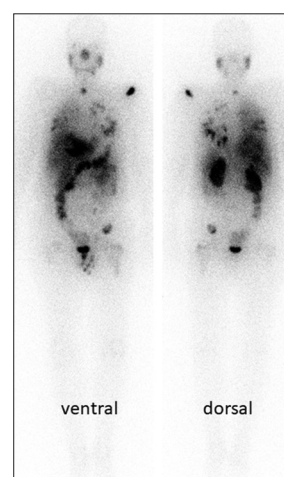


Figure 3: Patient number 1: <sup>177</sup>Lutetium-prostate-specific membrane antigen scan 24 h after administration of the radiotracer (6.6 GBq). He is a 66-year-old man with multiple metastases in his lungs, bones, liver, and lymph nodes. His brain metastases had been treated by surgery and radiotherapy before radioligand therapy. He had also undergone treatment with docetaxel, cabazitaxel, abiraterone, and enzalutamide. Despite the diffuse metastases, the patient's baseline prostate-specific antigen dropped to 0.4 ng/ml, indicating a significant decline (-87.5%) after radioligand therapy

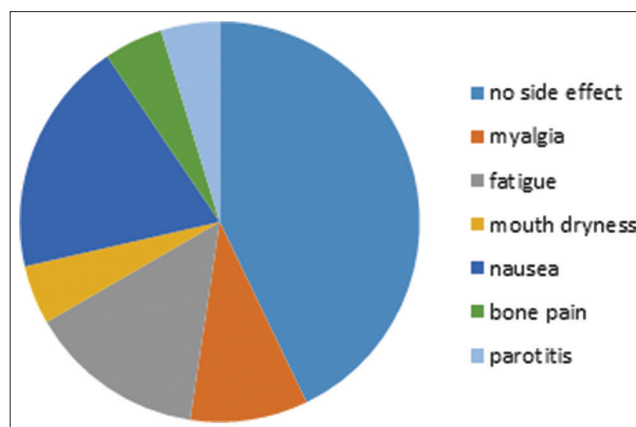


Figure 5: Bar chart shows complaints of patients after administration of <sup>177</sup>Lutetium-prostate-specific membrane antigen

**Table 4: Toxicity based on Common Toxicity Criteria For Adverse Events, version 4.0**

Event	Baseline				Post-RLT			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade4
Hemoglobin (%)	8 (57.1)	2 (14.2)	0 (0.0)	0 (0.0)	7 (50.0)	4 (28.5)	0 (0.0)	0 (0.0)
WBCs (%)	1 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)	4 (28.5)	1 (7.1)	0 (0.0)	0 (0.0)
Platelets (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.1)	1 (7.1)	0 (0.0)	0 (0.0)
Creatinine (%)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.2)	0 (0.0)	0 (0.0)	0 (0.0)

WBCs: White blood cells

was used to effectively control the nausea. Mouth dryness was experienced by one (7.1%) patient; the condition showed significant improvement by the 8-week follow-up. Fatigue was reported in two (14.2%) patients. One patient complained of multiple side effects (nausea, fatigue, bone pain, myalgia, and parotiditis). Diarrhea did not occur in any patient. None of the patients asked to skip future doses due to intolerable side effects [Figure 5].

#### Hematotoxicity

Table 4 illustrates the patients' toxicity values based on version 4.03 of the Common Toxicity Criteria for Adverse Events. There was no significant change in hemoglobin values (median  $\pm$  standard deviation [SD]; prior to therapy:  $11.7 \pm 1.8$  g/L; after therapy:  $11.2 \pm 1.8$  g/L;  $P = 0.20$ ). Three patients needed packed red blood cells prior to or after the therapy due to extensive bone metastases. Only two (14.2%) patients worsened one grade. None of the patients decreased more than one grade.

There was no statistically significant change in the white blood cell counts (median  $\pm$  SD; prior to therapy:  $5.4 \pm 1.1 \times 10^3$ /dL; after therapy:  $4.6 \pm 1.6 \times 10^3$ /dL;  $P = 0.10$ ) or the platelet counts (median  $\pm$  SD; prior to therapy:  $233.8 \pm 55.7 \times 10^3$ /dL; after therapy:  $178.0 \pm 78.4 \times 10^3$ /dL;  $P = 0.10$ ). Grade 1 or 2 leukocytopenia was observed in five (35.8%) patients. At the baseline, all patients had normal platelet counts, but after treatment, three (21.4%) patients with Grade 1 thrombocytopenia and one (7.1%) patient with Grade 2 thrombocytopenia were detected. None of the patients reported significant hemorrhagic episodes.

#### Nephrotoxicity and hepatotoxicity

There were no significant changes in the median values for serum creatinine or for the liver parameters as follows: serum creatinine (median  $\pm$  SD; prior to therapy:  $1.00 \pm 0.34$  mg/dL; after therapy:  $0.91 \pm 0.41$  mg/dL;  $P = 0.38$ ), AST (median  $\pm$  SD; prior to therapy:  $21.0 \pm 8.6$  U/L; after therapy:  $19.5 \pm 10.8$  U/L;  $P = 0.97$ ), and ALT (median  $\pm$  SD; prior to therapy:  $13.0 \pm 4.8$  U/L; after therapy:  $12.5 \pm 3.2$  U/L;  $P = 0.26$ ). Only one (7.1%) patient developed Grade 1 nephrotoxicity after therapy. Notably, one patient (number 11) had received a kidney transplant 9 years earlier. This patient was treated with three

cycles of  $^{177}\text{Lu}$ -PSMA, with a cumulative activity of 13.3 GBq, and no change in the patient's creatinine value was noted during the follow-up period.

#### DISCUSSION

Cumulative data have confirmed the promising response rates and favorable safety profile of  $^{177}\text{Lu}$ -labeled PSMA ligands for the treatment of mCRPC patients, but this therapy has not yet received clinical approval.<sup>[11,30]</sup> Additional prospective studies are needed to make  $^{177}\text{Lu}$ -PSMA a first-line therapeutic.

In our study, PSA levels declined in a majority of patients (11 patients, 78.6%) after a single dose of  $^{177}\text{Lu}$ -PSMA therapy, and 5 (45.4%) of these patients experienced a PSA decline of more than 50%. In addition to the demonstrated efficacy and improved quality of life,  $^{177}\text{Lu}$ -PSMA was well tolerated, and no high-grade toxicity was recorded. Since a majority of the patients were anemic (Grades 1 or 2) at the beginning of the study, possibly due to progressive disease and extensive skeletal metastases, anemia (Grades 1 or 2) was commonly seen in the patients.

Since the primary excretion route of  $^{177}\text{Lu}$ -PSMA is through the kidneys, nephrotoxicity is a potential side effect. An optimal agent for renal protection is not yet available, since the routine use of nephroprotective agents for the blocking of PSMA binding sites in the kidneys has not been established in clinical studies.<sup>[31]</sup> In our study, repeated RLT cycles were well tolerated even in a patient with a transplanted kidney.

Previous retrospective studies on  $^{177}\text{Lu}$ -PSMA have reported similar results. Ahmadzadehfard *et al.* reported that 70% of ten patients experienced a decrease in PSA levels; of those, 71.4% experienced more than a 50% decline. Severe hematotoxicity (Grade 3 or 4) and Grade 2 leukopenia was only seen in one case, and these side effects were attributed to the patient's compromised bone marrow.<sup>[17]</sup> Another study by the same group investigated the efficacy and toxicity of repeated  $^{177}\text{Lu}$ -PSMA therapy on mCRPC patients and reported that PSA levels declined in 79.1% of the patients, with the PSA levels in 41.6% of these patients decreasing more than 50%. No severe hemato- or nephro-toxicity effects were detected

except in two patients who experienced Grade 3 anemia.<sup>[16]</sup> A multicentric retrospective study by Rahbar *et al.* analyzed the data of 74 mCRPC patients treated with a single dose of <sup>177</sup>Lu-PSMA. They found that PSA levels declined in 64% of the patients; in 31% of these patients, the PSA levels declined more than 50%. Again, no high-grade toxicity was reported.<sup>[23]</sup> A German multicentric study<sup>[20]</sup> investigated 145 patients with advanced PC; the data for 99 of these patients were available for analysis. The researchers found that after the first cycle of <sup>177</sup>Lu-PSMA, 66% of the patients experienced a decline in PSA levels, while 40% of these patients experienced a decrease of more than 50%. After the second cycle, 72% of the patients experienced a decline in PSA levels and 57% experienced a PSA decline of more than 50%. This study also evaluated factors affecting the patients' biochemical response. The presence of visceral metastases and alkaline phosphatase levels of >220 resulted in lower biochemical response, whereas higher number of treatment cycles was associated with higher biochemical response.<sup>[20]</sup> In a recently published prospective trial, Hofman *et al.*<sup>[28]</sup> studied thirty patients with PSMA-avid mCRPC who had failed standard therapies and received up to four cycles of <sup>177</sup>Lu-PSMA-617 every 6 weeks. This study found high response rates and low toxicity with improved quality of life and pain reduction in men with mCRPC who had failed conventional therapies.<sup>[28]</sup>

In accordance with the previous studies, our study confirmed the safety of <sup>177</sup>Lu-PSMA treatment and demonstrated a favorable biochemical response and a low toxicity profile of RLT in patients with advanced PC. This efficacy and low toxicity may be due to the radiotracer's specific targeting of the tumor cells.

This prospective study was the first to investigate RLT with <sup>177</sup>Lu-PSMA in mCRPC patients in our region. Most of the previous <sup>177</sup>Lu-PSMA studies were conducted in Europe and Australia. Therefore, there is a need for more regional studies to evaluate the treatment response in different ethnic groups. The main limitation of our study was the lack of a control group. This would have allowed us to investigate whether the observed side effects were due to the therapy or whether they could be attributed to the disease progression.

Our patients entered this study after all the other available therapies had failed; therefore, they were at the end stage of the disease. Further studies should investigate the use of RLT in patients at earlier stages of the disease. Important questions should be addressed in future studies, including the optimal number of treatment cycles as well as the effect of patient characteristics (such as age, baseline PSA level, metastasis sites, type of bone metastases, Gleason score, and prior therapies) on the therapeutic response.

## CONCLUSION

This prospective study demonstrated that treatment with <sup>177</sup>Lu-PSMA was a safe and effective therapy in patients with mCRPC.

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## Conflicts of interest

There are no conflicts of interest.

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