

Clinical Experience with [^{225}Ac]Ac-PSMA Treatment in Patients with [^{177}Lu]Lu-PSMA–Refractory Metastatic Castration-Resistant Prostate Cancer

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For patients with advanced-stage metastatic castration-resistant prostate cancer (mCRPC) who do not respond to [^{177}Lu]Lu-PSMA therapy, there are limited treatment options. Clinical results obtained with [^{225}Ac]Ac-PSMA are promising. We retrospectively analyzed the outcomes of patients treated with [^{225}Ac]Ac-PSMA between December 2018 and October 2022. **Methods:** We evaluated the treatment results of 23 patients (mean age, 70.3 ± 8.8 y) with mCRPC who were refractory to treatment with [^{177}Lu]Lu-PSMA (2–9 cycles). The safety profile was assessed according to Common Technology Criteria for Adverse Events version 5.0. Treatment efficacy was assessed using prostate-specific membrane antigen PET progression criteria and prostate-specific antigen (PSA) response according to Prostate Cancer Working Group 2 criteria after the first cycle of [^{225}Ac]Ac-PSMA treatment.

Results: All patients received androgen-deprivation therapy, whereas 22 (96%) and 19 (83%) patients received chemotherapy and second-generation antiandrogen therapy, respectively. One patient received 4 cycles, 2 received 3 cycles, 8 received 2 cycles, and 12 received 1 cycle of [^{225}Ac]Ac-PSMA. The median interval between cycles was 13 wk (range, 8–28 wk). [^{225}Ac]Ac-PSMA was administered with a mean activity of 7.6 MBq (range, 6.2–10.0 MBq) in each cycle. Patients were at an advanced stage of disease, and tumor burden was very high. Although the best PSA response was observed in 5 patients (26%) after [^{225}Ac]Ac-PSMA treatment, there was at least some level of decline in PSA observed in 11 patients (58%; $n = 19$). Treatment response was assessed in patients who underwent [^{68}Ga]Ga-PSMA PET/CT imaging. After the first cycle of treatment ($n = 18$), 50% of patients ($n = 9$) showed disease progression according to prostate-specific membrane antigen PET progression criteria, and the disease control rate was calculated to be 50%. Median progression-free survival was 3.1 mo, and median overall survival was 7.7 mo. Grade 3 hematologic toxicity occurred in 1 patient, and grade 3 nephrotoxicity was observed in another patient. Parotid SUV_{max} decreased by 33%, although all patients complained of dry mouth before treatment. **Conclusion:** We observed that [^{225}Ac]Ac-PSMA therapy was safe and showed potential even in cases with advanced-stage mCRPC in which all other treatment options were completed.

Key Words: [^{225}Ac]Ac-PSMA; actinium-targeted α -therapy; PSMA; [^{177}Lu]Lu-PSMA; prostate cancer

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Prostate cancer is the most common malignancy in men and the second leading cause of cancer-related deaths (1). In the last decade, several new agents have been approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Current standard treatment options for mCRPC include taxane-based chemotherapy (docetaxel and cabazitaxel) (2,3), novel androgen axis drug treatment (abiraterone or enzalutamide) (4,5), and bone-seeking [^{223}Ra]RaCl₂ therapy (6), which are approved by the European Medicines Agency and the U.S. Food and Drug Administration.

Prostate-specific membrane antigen (PSMA) is a glycoprotein overexpressed on prostate cancer cells. Radiolabeled PSMA inhibitors have been used for theranostic applications in the last decade. [^{177}Lu]Lu-PSMA, which emits β -particles, has been shown to be effective and safe in the treatment of mCRPC (7,8). An international multicenter phase III (VISION) clinical trial of [^{177}Lu]Lu-PSMA-617 demonstrated prolonged overall survival (OS) in patients with advanced PSMA-positive mCRPC and has been approved by the European Medicines Agency and U.S. Food and Drug Administration (9). However, currently, there are limited treatment options for patients with advanced-stage mCRPC who do not respond to treatment with [^{177}Lu]Lu-PSMA.

Radionuclides with high linear energy transfer have a cell-killing effect many times greater than that of particles with low linear energy transfer. Targeted α -therapy has the advantage of targeting any metastatic tissue and offers a good application perspective in small tumors, scattered cancers, and micrometastases (10,11).

^{225}Ac is an α -emitting radionuclide that can be successfully labeled with a variety of theranostic agents (12). The clinical results obtained with [^{225}Ac]Ac-PSMA are promising. Recent clinical trials using ^{225}Ac -labeled PSMA ligands ([^{225}Ac]Ac-PSMA-617 or [^{225}Ac]Ac-PSMA-I&T) have achieved remarkable therapeutic results. Therefore, [^{225}Ac]Ac-PSMA radioligand therapy may be an effective option for mCRPC that is resistant to β -emitting [^{177}Lu]Lu-PSMA (13–21).

The efficacy and safety of treatments with [^{225}Ac]Ac-PSMA, including chemotherapy and [^{177}Lu]Lu-PSMA-naïve patients, have been reported in the literature. The purpose of this retrospective

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study is to evaluate the efficacy and safety of treatment with [^{225}Ac]Ac-PSMA in mCRPC patients who have not responded to chemotherapy and [^{177}Lu]Lu-PSMA treatment.

MATERIALS AND METHODS

Patients

From December 2018 to October 2022, 23 patients treated with [^{225}Ac]Ac-PSMA were enrolled in this single-center retrospective study. Inclusion criteria for [^{225}Ac]Ac-PSMA treatment were completion of first- and second-line therapies such as abiraterone, enzalutamide, and taxane-based chemotherapy and disease progression after at least 2 cycles of [^{177}Lu]Lu-PSMA treatment. Disease progression was verified by a more than 30% increase in prostate-specific antigen (PSA), a worsening of the patient's clinical condition such as pain or weight loss, or observation of new lesions on [^{68}Ga]Ga-PSMA PET/CT scans. All patients had an Eastern Cooperative Oncology Group performance status of 3 or lower, a white blood cell count of more than 2,000/ μL , a red blood cell count of more than 3,000,000/ μL , a hemoglobin value greater than 6 g/dL, and a serum creatinine level of less than 2 mg/dL. All patients had a high uptake in all of their metastatic lesions with [^{68}Ga]Ga-PSMA PET/CT, which was higher than liver uptake. Treatment with [^{225}Ac]Ac-PSMA was discussed individually by three experienced nuclear medicine physicians and recommended by a tumor board.

Exclusion criteria included urinary tract obstruction and bone marrow suppression as defined by Common Terminology Criteria for Adverse Events version 5.0. All patients were informed of the potential adverse events, including xerostomia, bone marrow suppression, and renal impairment. All patients gave written informed consent for treatment with [^{225}Ac]Ac-PSMA. The study was approved by the institutional ethics committee (reference no. 1736).

Preparation of [^{225}Ac]Ac-PSMA-617

[^{225}Ac]AcCl₃ and [^{225}Ac]Ac(NO₃)₃ were provided by Oak Ridge National Laboratory and the Institute of Physics and Power Engineering, respectively. In-house radiolabeling was performed in a hot cell using ^{225}Ac (1 MBq/16 nmol PSMA-617) with 0.1-M Tris buffer and 20% ascorbic acid. Radiolabeling was performed at 95°C for 20 min. After the reaction vessel cooled to room temperature, 0.3 mL of sterile diethylenetriaminepentaacetic acid solution (3 mg mL⁻¹ of diethylenetriaminepentaacetic acid in saline) was added to the reaction vessel. The solution was sterilized and filtered (0.22 μm) under aseptic conditions, and the total volume was increased to 4–5 mL with sterile saline. The integrity of the filter was checked by a bubble-point test. The radiochemical yield was determined by instant thin-layer chromatography silica gel with 0.05 M citric acid as the solvent. The radiochemical yield was determined by measuring the activity of the 218-keV γ -emission from ^{221}Fr using a Captus 3000 well-type γ -counter (Capintec Inc.) after 45 min of labeling. The measured radiochemical yields of [^{225}Ac]Ac-PSMA were greater than 97% after 45 min of labeling.

Stability of [^{225}Ac]Ac-PSMA

In saline at 37°C, 1 MBq of [^{225}Ac]Ac-PSMA was incubated for up to 6 h ($n = 3$). At specific time points, a sample from the incubating solution was analyzed with reversed-phase high-pressure liquid chromatography (RP-HPLC) to evaluate the in vitro stability of [^{225}Ac]Ac-PSMA. HPLC fractions were measured in the γ -counter at least 20 h after collection. Fractions measured with 440-keV γ -emission from ^{213}Bi were plotted in agreement with the tube numbers from the RP-HPLC analysis. We used blood samples collected at 0–10 min and urine samples collected up to 3 h after injection to assess the in vivo stability in 3 patients. Blood samples collected from patients were precipitated with acetonitrile (1:1) and then vortexed. The precipitate was separated by a 5-min centrifugation. For RP-HPLC analysis, the

supernatant was diluted with double-distilled water (1:1) and then injected into the RP-HPLC tube. Collected urine samples from patients were diluted with double-distilled water, filtered, and immediately analyzed using RP-HPLC. The measured counts of the fractions were plotted according to their tube number from the RP-HPLC analysis.

Treatment

Patients received a fluid infusion of 1,000 mL of 0.9% saline for 30 min before treatment. [^{225}Ac]Ac-PSMA was injected via slow infusion over 5 min. The amount of injected activity was 100 kBq/kg (13). Whole-body images were obtained between 4 and 24 h after injection using γ -rays of ^{221}Fr (218 keV) and ^{213}Bi (440 keV) with an energy window of 20%. A Discovery NM/CT 670 Pro (GE Healthcare) system with high-energy general-purpose collimators was used to obtain the images. The imaging method was a step and shoot with 15 min per step. The patients

TABLE 1
Patient Characteristics

Characteristic	Value
Age (y)	70.3 $\pm$ 8.8
PSA (ng/mL)	103.79 (0.349–727.8)
ALP (U/L)	95 (45–1,184)
LDH (U/L)	268.5 (98–2,374)
Hemoglobin (g/dL)	10.1 (7.0–12.2)
Platelet (count/ μL)	154,500 (12,000–385,000)
WBC (count/ μL)	5,740 (3,200–14,140)
ISUP grade group ($n = 23$)	
Group 1	0%
Group 2	9%
Group 3	26%
Group 4	9%
Group 5	43%
Undefined	13%
Sites of metastasis ($n = 23$)	
Bone	91%
Lymph node	56%
Liver	13%
Lung	22%
Leptomeningeal	4%
Subcutaneous metastasis	4%
Prior therapies ($n = 23$)	
Radical prostatectomy	48%
EBRT	70%
ADT	100%
Abiraterone or enzalutamide	83%
Docetaxel	96%
Cabazitaxel	43%
[^{177}Lu]Lu-PSMA	100%

ALP = alkaline phosphatase; LDH = lactate dehydrogenase; WBC = white blood cell; ISUP = International Society of Urological Pathology; EBRT = external-beam radiation therapy; ADT = androgen-deprivation therapy.

Continuous data are median and range or mean $\pm$ SD.

were observed every 60 min for 5 h to record vital signs such as blood pressure, body temperature, and pulse rate. Additionally, patients were monitored for any complaints of pain, vomiting, and nausea for 24 h according to the standard institutional protocol for all in-patient treatments.

Response Evaluation, Survival, and Toxicity

Response to [^{225}Ac]Ac-PSMA treatment was determined from serial measurements of serum PSA levels 1 wk before and every 4 wk after [^{225}Ac]Ac-PSMA treatment and by [^{68}Ga]Ga-PSMA PET/contrast-enhanced CT within 4 wk before and 8–12 wk after treatment. Response was assessed according to Prostate Cancer Clinical Trials Working Group 2 criteria (22) as a PSA decrease of at least 50% and a decrease from baseline. [^{68}Ga]Ga-PSMA PET/CT was repeated 8–12 wk after each treatment cycle and until disease progression or death. Radiologic evidence of disease progression was assessed according to PSMA PET progression criteria (23). Progression-free survival (PFS) and OS were calculated from the date of the first [^{225}Ac]Ac-PSMA administration to disease progression or death. Adverse events were documented according to Common Terminology Criteria for Adverse Events version 5.0. The total tumor volume (TTV) was determined from [^{68}Ga]Ga-PSMA PET/CT images using LIFEx version 7.2.0 (LIFExsoft) (24). A SUV threshold of at least 3.0 was used for tumor segmentation. The mean SUV_{max} of the parotid glands at baseline and at follow-up [^{68}Ga]Ga-PSMA PET/CT scans was calculated using a threshold value of 42% of maximum pixel value.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM). PFS and OS with a 95% CI were estimated by the Kaplan–Meier method. Multivariate analysis was performed using Cox regression analysis in sequential order of statistical significance, variables that were found to be significant in the univariate analysis, followed by the interactive terms. Baseline factors included age, cumulative [^{225}Ac]Ac-PSMA activity, International Society of Urological Pathology grade group classification, baseline PSA levels, a PSA level with at least a 50% decline, lymph node, bone, visceral, and liver metastases, TTV, baseline hemoglobin levels, white blood cell counts, platelet counts, alkaline phosphatase levels, and lactic dehydrogenase levels. We also dichotomized the following clinical covariates: International Society of Urological Pathology grade group, PSA decline of at least 50%, and the presence of lymph node, bone, and liver metastasis. A *P* value of less than 0.05 was considered statistically significant. A Wilcoxon signed-rank test was performed to reveal changes in both TTV and SUV_{max} of the salivary glands before and after treatment with [^{68}Ga]Ga-PSMA PET/CT.

RESULTS

Patient Characteristics

All patients treated in the study were in advanced stages of mCRPC. The mean age of the patients was 70.3 ± 8.8 y. According to the International Society of Urological Pathology grade group classification, most patients were diagnosed as grade group 5. Descriptions of patient characteristics are shown in Table 1.

All patients had undergone a median of 4.5 cycles (range, 2–9 cycles) of [^{177}Lu]Lu-PSMA treatment. All patients did not respond to [^{177}Lu]Lu-PSMA treatment and had

disease progression according to PSA levels and [^{68}Ga]Ga-PSMA PET/CT images obtained before [^{225}Ac]Ac-PSMA treatment. Patients who had experienced biochemical and clinical progression after [^{177}Lu]Lu-PSMA treatment were discussed with the hospital tumor board, and [^{225}Ac]Ac-PSMA treatment was decided. The mean interval between [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA treatment was 10 wk (range, 6–26 wk).

One patient received 4 cycles, 2 received 3 cycles, 8 received 2 cycles, and 12 received 1 cycle of [^{225}Ac]Ac-PSMA (a total of 34 cycles). The median interval between [^{225}Ac]Ac-PSMA treatment cycles was 13 wk (range, 8–28 wk). The mean administered activity of [^{225}Ac]Ac-PSMA was 7.6 MBq (range, 6.2–10.0 MBq) in each cycle. Although the interval between cycles was planned to be 8–10 wk, some patients were unable to initiate treatment in a timely manner because of ^{225}Ac supply shortages and travel restrictions during the coronavirus disease 2019 pandemic.

Stability of [^{225}Ac]Ac-PSMA

RP-HPLC analyses of the saline incubation samples showed a single radioactivity peak corresponding to [^{225}Ac]Ac-PSMA. However, a slight decrease of the in vitro stability of [^{225}Ac]Ac-PSMA was observed after 6 h in the saline incubation (Figs. 1A and 1B). A slight decrease of the in vitro stability was also observed with instant thin-layer chromatography, but still the radiochemical yield was higher than 95%.

RP-HPLC analyses of the blood and urine samples showed a single radioactivity peak corresponding to [^{225}Ac]Ac-PSMA; however, a slight decrease of the in vivo stability was also observed in the blood and urine after the injection (Figs. 1C and 1D). Stability in the blood could be checked only 10 min after the injection, and [^{225}Ac]Ac-PSMA remained stable for up to 10 min.

Toxicity and Side Effects

[^{225}Ac]Ac-PSMA administration was well tolerated. We did not observe any complications during the injection. No changes in blood pressure, body temperature, or pulse rate were observed for 5 h.

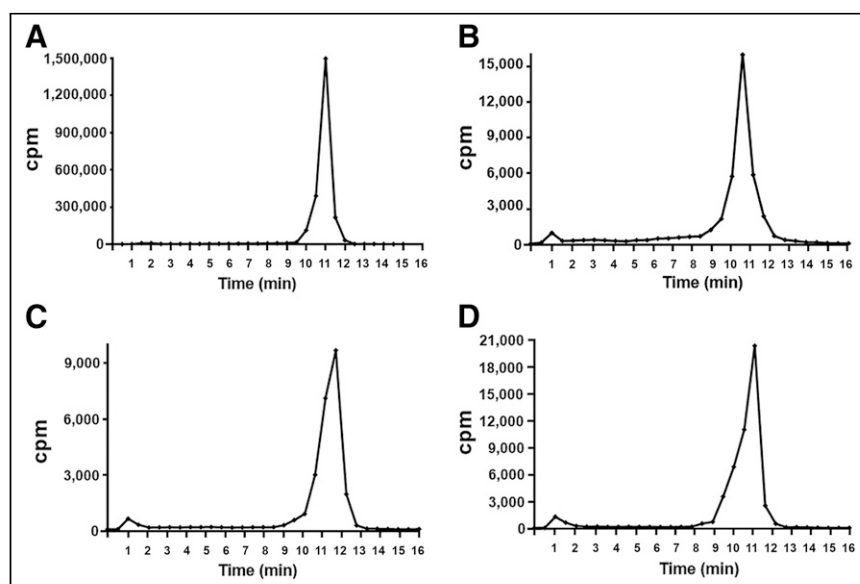


FIGURE 1. RP-HPLC profiles of 1 MBq of [^{225}Ac]Ac-PSMA from reaction vial (A), incubated in saline at 6 h (B), in blood after 8-MBq injection of radioligand in patient at 0–10 min (C), and in urine after 8-MBq injection of radioligand in patient at 3 h (D). cpm = counts per minute.

Before the [^{225}Ac]Ac-PSMA therapy, 2 patients had grade 3 nephrotoxicity; the remaining patients had grade 1 or 2 hematologic toxicity, and 4 patients had grade 1 or grade 2 nephrotoxicity due to previous treatments. In 1 patient, grade 1 to grade 3 hematologic toxicity was observed after 3 cycles of treatment. In 3 patients, grade 1 to grade 2 hematologic toxicity was observed after the first cycle of treatment. In 1 patient, grade 1 to grade 3 nephrotoxicity was observed after 2 cycles of treatment. The nephrotoxicity rate was 7%, and the total hematotoxicity rate was 28%.

All patients complained of dry mouth before and after treatment, but none of them complained from dysphagia as defined in Common Terminology Criteria for Adverse Events version 5.0. Mean parotid SUV_{max} was 12.2 ± 3.9 before treatment and decreased to 8.2 ± 2.8 (33% decrease) after the first cycle of [^{225}Ac]Ac-PSMA treatment ($n = 18$, $P = 0.001$).

Efficacy and Survival

According to the [^{68}Ga]Ga-PSMA PET/CT images obtained 8–12 wk after the first treatment cycle ($n = 18$), 50% of patients ($n = 9$) showed disease progression according to the PSMA PET progression criteria, and the disease control rate was calculated to be 50%. [^{68}Ga]Ga-PSMA PET/CT was not available to 5 patients because of an immediate deterioration of their clinical condition. After the first cycle of treatment, a decrease in PSA was observed in 11 of 19 patients (58%), and a decrease in PSA of more than 50% was observed in 5 of 19 patients (26%) (Fig. 2A).

The median baseline TTV ($n = 17$) on [^{68}Ga]Ga-PSMA PET/CT was $1,265 \text{ cm}^3$ (range, 99–6,450 cm^3), whereas the TTV after the first cycle of [^{225}Ac]Ac-PSMA treatment was $1,085 \text{ cm}^3$ (range, 85–5,170 cm^3). The change in TTV is shown in Figure 2B. The total number of patients in this analysis was 17 because the baseline images of 1 patient could not be processed with LIFEx software.

Univariate analysis showed that decreases in PSA of more than 50%, the presence of visceral and liver metastases, baseline TTV, baseline hemoglobin levels, and alkaline phosphatase and lactic dehydrogenase levels were significantly associated with OS ($P < 0.05$, 95% CI). Multivariate analysis showed that baseline TTV remained an individual predictor of OS ($P = 0.038$, 95% CI). On the other hand, the International Society of Urological Pathology grade group, baseline PSA levels, and bone metastases were found to be related to PFS ($P < 0.05$, 95% CI; Table 2).

For all patients, based on the first [^{225}Ac]Ac-PSMA treatment, the median PFS and median OS were 3.1 and 7.7 mo, respectively (Fig. 3). The estimated median OS plots for the selected parameters of the univariate analysis are shown in Figure 4.

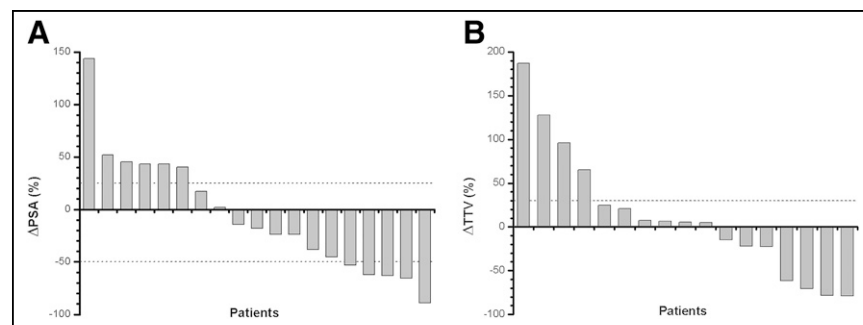


FIGURE 2. Waterfall plot demonstrating percentage change of PSA (A) and TTV (B) after first cycle of [^{225}Ac]Ac-PSMA treatment.

TABLE 2
Univariate Analysis of Correlation Between Analyzed Variables and Survival

Variable	<i>P</i>	
	PFS	OS
Age (y)	0.341	0.994
Cumulative activity	0.395	0.233
ISUP grade group	0.010*	0.591
Baseline PSA level	0.033*	0.391
PSA $\geq$ 50% decline	0.081	0.005*
Lymph node metastasis	0.518	0.125
Bone metastasis	0.029*	0.461
Visceral metastasis	0.431	0.021*
Liver metastasis	0.170	<0.001*
TTV	0.058	<0.001*
Hemoglobin	0.359	0.007*
White blood cell count	0.964	0.964
Platelet count	0.226	0.330
ALP	0.058	0.016*
LDH	0.108	0.038*

*Statistically significant.

ISUP = International Society of Urological Pathology; ALP = alkaline phosphatase; LDH = lactate dehydrogenase.

DISCUSSION

Treatment with α -particle radiation has distinct advantages over treatment with β -particles, including a shorter range and a high linear energy transfer property. In addition, α -emitting isotopes are less dependent on the oxygen content of the tumor. These biologic advantages may explain why targeted α -therapy is superior to β -therapy. However, because of the short range of α -particles, the cross-fire effect may be less than with β -particles. Combination therapy with α - and β -particles may compensate for the lack of a cross-fire effect (25). The radiobiologic properties of ^{225}Ac for labeling with the PSMA molecule may provide a reasonable alternative. In this study, we investigated the in vivo and in vitro stability of [^{225}Ac]Ac-PSMA. The radiolabeling process of [^{225}Ac]Ac-PSMA is very similar to that of [^{177}Lu]Lu-PSMA and remains quite stable in vivo and in vitro. The in vitro stability of [^{225}Ac]Ac-PSMA decreased slightly in saline, but the radiochemical yield was still higher than 95% after 6 h of incubation in saline. [^{225}Ac]Ac-PSMA remained stable for up to 10 min in the blood and for up to 3 h in urine. In addition, we observed no side effects during injection and no change in patients' vital signs for at least 5 h after injection of [^{225}Ac]Ac-PSMA.

Treatment with [^{177}Lu]Lu-PSMA is well established in mCRPC patients. However, many of these patients become resistant to [^{177}Lu]Lu-PSMA treatment, and there are limited treatment options left for this patient group. [^{225}Ac]Ac-PSMA treatment is a new

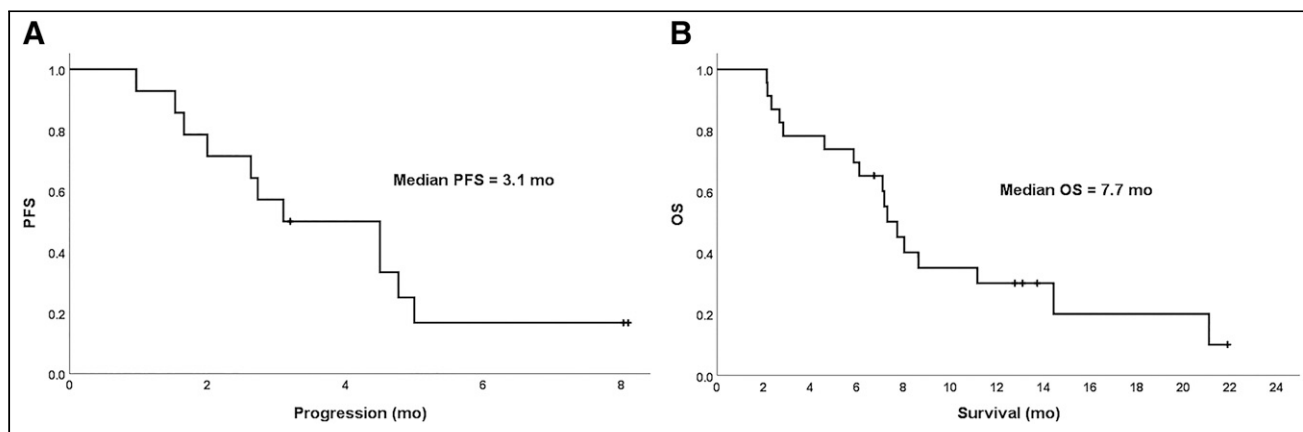


FIGURE 3. PFS (A) and OS (B) estimates from Kaplan–Meier analysis based on first [^{225}Ac]Ac-PSMA treatment date.

radionuclide treatment option, but there are very few publications in the literature on the topic. In the first report of [^{225}Ac]Ac-PSMA therapy, which included 2 patients, the serum PSA levels were shown to have decreased below detectable levels with limited toxicity in both patients, and both patients responded completely to [^{68}Ga]Ga-PSMA imaging (13). This early observation is promising in this area. In the analysis of 38 patients, some PSA decline was observed in 33 patients (87%), and there was a PSA decline of more than 50% in 24 patients (63%) (26). The median duration of tumor control was 9 mo. In another study of 73 patients with mCRPC, some PSA decline was observed in 60 patients (82%), and there was

a PSA decline of more than 50% in 51 patients (70%) (17). The estimated median PFS and OS were 15.2 and 18 mo, respectively. In our study, after the first cycle of [^{225}Ac]Ac-PSMA treatment, a PSA response of at least 50% was observed in 5 patients (26%) (Fig. 5), with some decline in PSA in 11 patients (58%). The survival times were shorter, and the PSA response rates were relatively lower. We believe that the explanation for the lower response rate is related to patient-selection criteria. These studies included chemotherapy or [^{177}Lu]Lu-PSMA-naïve patients. In our study, all patients underwent all standard treatment options and also showed disease progression after at least 2 cycles of [^{177}Lu]Lu-PSMA treatment. On the contrary,

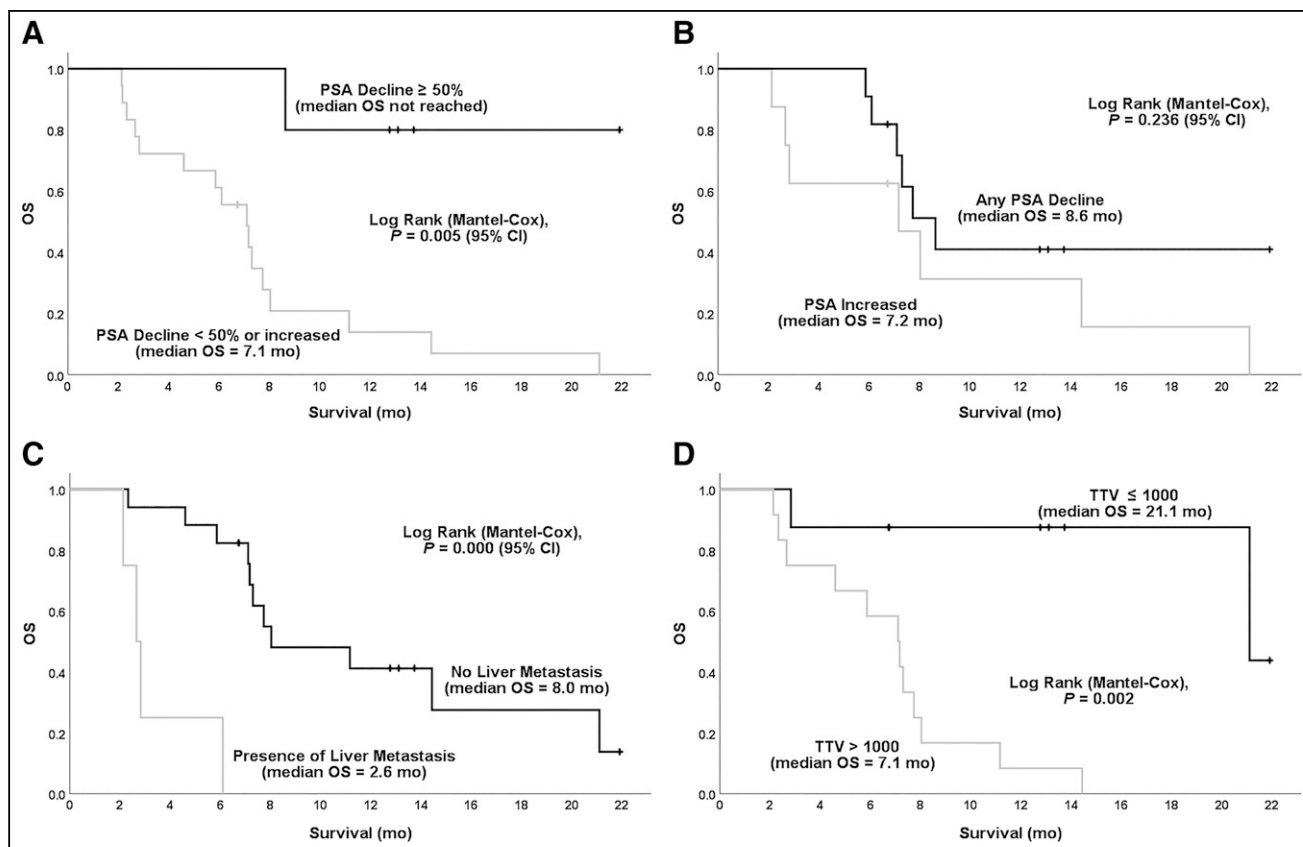


FIGURE 4. Survival analysis of patients who showed more than 50% PSA decline (A), any PSA decline (B), liver metastasis (C), and TTV of more than 1,000 cm^3 (D).

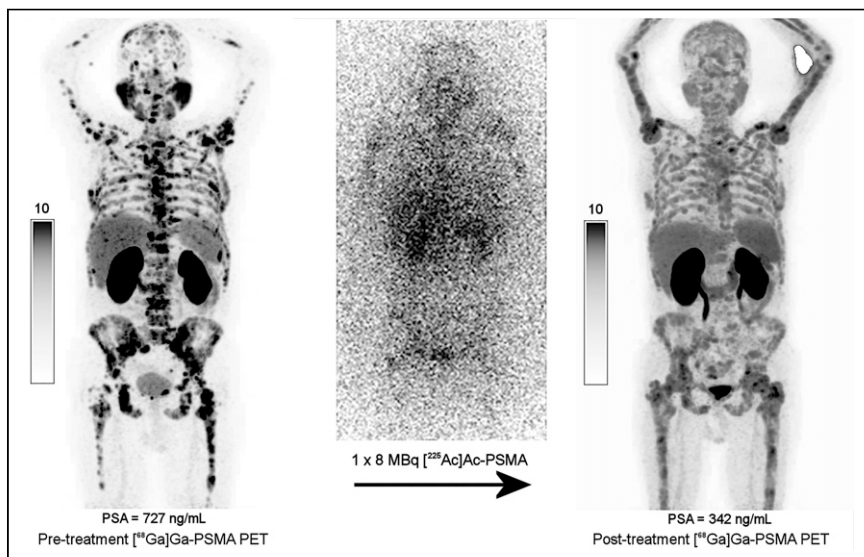


FIGURE 5. Pretreatment and posttreatment [^{68}Ga]Ga-PSMA PET maximum-intensity projection images of patient showing partial response.

the study by Feurecker (20), which treated a cohort of patients similar to that in our study, showed that the median PSA PFS, clinical PFS, and OS were 3.5, 4.1, and 7.7 mo, respectively, which were similar to our study. Consistent with our study, they also showed that liver metastases were associated with shorter PSA PFS (median, 1.9 vs. 4.0 mo; $P = 0.02$), clinical PFS (median, 1.8 vs. 5.2 mo; $P = 0.001$), and OS (median, 4.3 vs. 10.4 mo; $P = 0.01$) (Figs. 3 and 4).

Rosar et al. (27) examined the importance of assessing early molecular-imaging response based on total viable tumor burden and its relationship to OS. Alkaline phosphatase levels, Eastern Cooperative Oncology Group classification, and biochemical and molecular-imaging response assessments were all significantly associated with OS according to univariate analysis. They showed that molecular-imaging response assessment, high alkaline phosphatase levels of at least 220 U/L, and an Eastern Cooperative Oncology Group of 2 or higher remained independent predictors of OS, with hazard ratios of 2.76, 3.08, and 2.21, respectively. Similarly, we demonstrated that the presence of liver metastasis, a high total tumor burden, and the absence of a PSA response decline of more than 50% shortened OS. Disease progression occurred earlier in patients with bone metastases and high baseline PSA levels. In our study, tumor burden was quite high (median TTV, 1,265 cm^3), which was due to our end-stage patient population. Accordingly, multivariate analysis showed that baseline TTV remained an independent predictor of OS ($P < 0.05$, 95% CI). This finding may suggest that an early treatment decision may be beneficial, and better outcomes may be achieved when patients with lower TTV receive [^{225}Ac]Ac-PSMA therapy.

In the safety analysis, no relevant hematologic toxicity was observed, and xerostomia was the only clinical side effect worth mentioning (13). On the other hand, in a recent metaanalysis (28), the rate of hematotoxicity after [^{225}Ac]Ac-PSMA treatment was calculated to be 30%, which is comparable to that in our study. We observed grade 3 and grade 2 hematotoxicity in 7% and 21% of patients, respectively. As for nephrotoxicity, grade 3 nephrotoxicity was observed in 1 patient (7%) in our study. In the same metaanalysis, a nephrotoxicity rate of 21% was reported.

Regarding nephrotoxicity, our results were quite low when compared with the metaanalysis.

In a recent article, Lawal et al. (21) also reported low hematologic toxicity in patients with extensive skeletal metastases and a relatively high TTV. They found that age, number of treatment cycles, and the presence of renal dysfunction predicted hematologic toxicity. Although prior therapies such as chemotherapy or [^{177}Lu]Lu-PSMA therapies had an impact on the occurrence of hematologic toxicity in univariate analysis, it did not appear to be a predictive factor in multivariate analysis in their study. Our toxicity results were similar to those reported in their study. However, the average number of treatment cycles with [^{225}Ac]Ac-PSMA was lower in our study. Therefore, the toxicity results should be interpreted with caution.

The most common reason for discontinuation of [^{225}Ac]Ac-PSMA treatment was xerostomia, which may affect up to 10% of

patients, according to published studies (13). We observed that salivary gland uptake in [^{68}Ga]Ga-PSMA PET/CT images decreased significantly after the first cycle of treatment. Cooling of the salivary glands with ice has been widely used to prevent xerostomia (29). However, the beneficial effect of cooling in the prevention of xerostomia has not yet been reported in the literature. Therefore, we did not use cooling, which is quite uncomfortable for patients. None of our patients discontinued treatment because of xerostomia, and we did not observe the patients to have any swallowing problems. However, all patients complained of dry mouth before and after treatment.

The main limitations of this study are that it is a retrospective study of a single center and the cohort is small. The toxicity results of this study should be interpreted with caution because a substantial number of patients were treated with only 1 cycle of [^{225}Ac]Ac-PSMA therapy. On the other hand, most of these patients had very large TTVs and were treated intensively before [^{225}Ac]Ac-PSMA therapy. Nevertheless, these patients did not develop significant toxicity. Long-term toxicity is also unknown because of the limited duration of the follow-up. Because of the pandemic and a group of patients who had to travel from abroad, follow-up data were lacking for some patients. However, the available data were sufficient to draw a conclusion for the short-term period.

CONCLUSION

We observed that [^{225}Ac]Ac-PSMA therapy was safe and effective, and toxicities were manageable. The treatment has potential even in advanced-stage mCRPC patients in whom almost all treatment options were completed. In patients with liver metastases and high TTV, an association with low OS was noted, and the benefits and risks of [^{225}Ac]Ac-PSMA treatment should be carefully weighed.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is treatment with [²²⁵Ac]Ac-PSMA safe and effective in patients with mCRPC who are refractory to [¹⁷⁷Lu]Lu-PSMA?

PERTINENT FINDINGS: Treatment with [²²⁵Ac]Ac-PSMA appears to be safe and may be particularly effective in patients with low TTV and in patients without liver metastases.

IMPLICATIONS FOR PATIENT CARE: [²²⁵Ac]Ac-PSMA treatment may be an alternative for patients who have no other options.

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