Original Article

Health-Related Quality-of-Life Outcomes with Actinium-225-Prostate-Specific Membrane Antigen-617 Therapy in Patients with Heavily Pretreated Metastatic Castration-Resistant Prostate Cancer

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Abstract

Aims: Actinium-225 (^{225}Ac) labeled prostate-specific membrane antigen (PSMA)-617 is a novel treatment modality in the management of metastatic castration-resistant prostate cancer (mCRPC). The present study was conducted to assess the impact of ^{225}Ac-PSMA-617 therapy on the quality-of-life of patients with heavily pretreated mCRPC using the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Prostate Symptom Index-17 (NCCN-FACT-FPSI-17) questionnaire. **Materials and Methods:** This was a retrospective single-center study where data of consecutive heavily pretreated mCRPC patients treated with ^{225}Ac-PSMA-617 from January 2019 to February 2020, was collected and analyzed for the biochemical response, quality-of-life outcomes and treatment-related toxicity. **Results:** Eleven heavily pretreated mCRPC patients received a median cumulative dose of 8.3 MBq (interquartile range [IQR] 5.6–20.4 MBq) ^{225}Ac-PSMA-617 over 1–4 cycles. 5/11 patients (46%) showed a ≥50% decline in Prostate Specific Antigen (PSA), while stable values and PSA progression were observed in 3/11 (27%) patients each. Pre- and post-therapy NCCN-FACT-FPSI-17 questionnaires revealed statistically significant improvement in the total FPSI score (P = 0.003) as well as the disease-related symptoms-physical (P = 0.004) and disease-related symptoms-emotional (P = 0.046) subscores. Among the physical symptoms, significant improvement was noted with respect to pain, difficulty in urination, bone pain, fatigue, and restriction in physical activity. No significant change was noted in the treatment side-effects subscore. Of the treatment-related adverse effects, Grade 3 dryness of the mouth, anemia, and nephrotoxicity was observed in 1/11 patients (9%) each and Grade 3 thrombocytopenia in 2/11 patients (18%). **Conclusion:** Health-related quality-of-life of the mCRPC patients improved significantly with ^{225}Ac-PSMA-617 despite extensive pretreatment and advanced nature of the disease.

Keywords: *Actinium-225-prostate-specific membrane antigen-617, castration-resistant prostate cancer, prostate-specific membrane antigen, quality-of-life*

Introduction

Prostate cancer (PCa) is ranked currently as the second most frequent cancer and the fifth leading cause of cancer-related death in males with an estimated 1.3 million new cases and 359,000 related deaths globally in 2018.[1] While localized PCa is reported to have a better prognosis,[2] it is the metastatic disease that accounts for the substantial proportion of PCa related morbidity and mortality.[3] Metastatic PCa can arise in the castration-resistant setting defined by castrate serum testosterone <50 ng/dl or 1.7 nmol/l with a radiological and biochemical progression.[4] So far, only six drugs have been shown to have a survival benefit in metastatic castration-resistant PCa (mCRPC).[5-10] Docetaxel has most commonly been the first-line treatment for such patients.[5,11] Other options in pre- or post-docetaxel setting are cabazitaxel, abiraterone, enzalutamide, radium-223, and sipuleucel-T, usually reserved for more progressive disease (PD).[6-10,12] However, with improved survival, quality of life becomes an essential patient-centric issue, given that a wide range of disease-related symptoms and treatment-related adverse effects are associated with mCRPC. In this setting, there is a need for alternative effective and safer therapeutic options that can also improve the quality of life for such patients.

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Targeted radionuclide therapy with actinium-225 (^{225}Ac) labeled prostate-specific membrane antigen (PSMA) has recently emerged as a novel and promising treatment modality in the management of mCRPC. Retrospective studies with ^{225}Ac-PSMA-617 have shown remarkable treatment efficacy in both heavily pretreated as well as chemotherapy naïve patients with mCRPC.[13,14] Furthermore, the treatment was tolerated well with minimal treatment-related toxicity.[14] Given the excellent efficacy and safety profiles associated with ^{225}Ac-PSMA-617, it is reasonable to assume a favorable impact on the quality of life of these patients. However, there exists a need to definitively evaluate their health-related quality of life using appropriate and validated self-reported quality of life tools. In this study, we intended to retrospectively assess the impact of ^{225}Ac-PSMA-617 therapy on the quality of life of patients with heavily pretreated mCRPC using the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Prostate Symptom Index-17 (NCCN-FACT-FPSI-17) questionnaire.[15]

Materials and Methods

Patient population

This was a retrospective, single-center observational study. Data of consecutive patients with heavily pretreated mCRPC (PD despite ≥2 prior treatments received) having initiated treatment with ^{225}Ac-PSMA-617, from January 2019 to March 2020, was collected and analyzed. All the patients underwent ^{68}Ga-PSMA-11 positron emission tomography/computed tomography (PET/CT) at baseline. Complete blood count (CBC), renal function test (RFT), glomerular filtration rate (GFR as estimated by ^{99m}Tc-DTPA scintigraphy), liver function test (LFT), serum testosterone, and prostate-specific antigen (PSA) values were obtained within 2 weeks before initiation of therapy. Principal eligibility criteria for ^{225}Ac-PSMA-617 therapy included: Histopathologically confirmed adenocarcinoma prostate; documented castration-resistant PCa with distant metastatic disease; PD despite ≥2 prior treatment options and tracer avid lesion (s) on ^{68}Ga-PSMA-11 PET/CT (SUVmax of lesion being at least 1.5 times greater than that of the normal liver). PD at baseline was defined by imaging-based progression (according to Response Evaluation Criteria In Solid Tumors 1.1, RECIST 1.1) and/or biochemical progression (according to PCa Clinical Trials Working Group 3 criteria). Additional inclusion criteria included: Hemoglobin ≥9 g/dL; total leukocyte count ≥3000/mcL; neutrophils≥1500/mcL; platelets≥75000/mcL; GFR≥30 mL/min; serum albumin ≥2.5 g/dL, and the Eastern Cooperation of Oncology Group performance scores 0–2. Patients with sarcomatous/spindle cell/small cell differentiation on histology, nontracer-avid lesions, secondary malignancies, and those on concurrent anti-tumor medications were not eligible for the therapy [Table 1]. Informed written consent was obtained from each patient before initiation of therapy. The study was approved by the Institutional Ethics Committee INT/IEC/2020/000439 and followed the guidelines enshrined in the Declaration of Helsinki.

Table 1: Eligibility criteria for patients of metastatic castration resistant prostate cancer in this study

Patients eligible for ^{225}Ac-PSMA-617 therapy
Histopathologically confirmed adenocarcinoma prostate
Documented castration resistant prostate cancer with distant metastatic disease
Progressive disease despite ≥2 prior treatment options
Tracer avid lesion (s) on 68Ga-PSMA-11 PET/CT (SUVmax of lesion being at least 1.5 times greater than that of normal liver)
Stable haematological parameters: Haemoglobin ≥9 g/dL; Total leucocyte count ≥3000/mcL; Neutrophils ≥1500/mcL; Platelets ≥75,000/mcL
GFR ≥30 mL/min
Serum albumin ≥2.5 g/dL
ECOG performance 0-2
Patients ineligible for ^{225}Ac-PSMA-617 therapy
Sarcomatous/spindle cell/small cell differentiation on histology
Nontracer avid lesions or tracer avidity less than that of liver
Second malignancies
Patients on concurrent anti-tumour medications

GFR: Glomerular filtration rate; SUVmax: Standardized Uptake Value – maximum, ECOG: Eastern Cooperation of Oncology Group, PSMA: Prostate Specific Membrane Antigen, ^{225}Ac: Actinium-225, PET-CT: Positron emission tomography - computed tomography

Treatment characteristics

^{225}Ac was obtained from ITG, Garching, Germany, and PSMA peptide was procured from ABX (GmBH, Radeberg, Germany). In-house radiolabeling of PSMA with ^{225}Ac was then carried out in our hospital radiopharmacy, as described previously in the literature.[13] The radiochemical purity of the labeled ^{225}Ac-PSMA-617 was performed using thin-layer chromatography, and a labeling efficiency of >96% was considered necessary for the administration to the patients.

^{225}Ac-PSMA-617 was administered intravenously over 1–2 min, approximately 100 kBq/kg/cycle, maximum up to 4 cycles, at 8–12 weeks intervals. Pretreatment hydration was achieved with 1.5–2 l of oral fluid, and ondansetron and dexamethasone were given as antiemetics. Patients were monitored for 24 h for any adverse event. Patients on prior treatment (s) with androgen deprivation therapy, bone modifying agents and/or opioid analgesics were advised to continue the same.

Treatment endpoints

The primary endpoint of this study was the health-related quality-of-life score. The same was assessed using the NCCN-FACT-FPSI-17 (version 2.0) (FACIT.org, Ponte Vedra, Florida, USA) questionnaire which includes a total of 17 items under four separate domains: Disease-related

symptoms-physical (FPSI-DRS-P, ten items), disease-related symptoms-emotional (FPSI-DRS-E, one item), treatment side-effects (FPSI-TSE, four items) and function/well-being (FPSI-F/WB, two items).[15] The questionnaire was filled up by each patient before the initiation of therapy and 6 weeks following the last cycle of therapy. Each question was given a response ranging from 0 ('not at all') to 4 ('very much'). Reversal of each item response was performed as per the NCCN-FACT-FPSI-17 (version 2.0) scoring guidelines, and the resultant individual item scores were summed to obtain a total score. The missing data were handled as per the specifications in the scoring guidelines. A high score was considered as good with a score of zero indicative of a severely symptomatic patient.

The patients were also followed up every 3 weeks with laboratory values of CBC, RFT, LFT, and PSA. Secondary endpoints included treatment-related toxicity and PSA response. Treatment-related toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. PSA response was assessed at 6 weeks following the last cycle of therapy as follows: ≥50% decline in PSA from baseline was considered partial response (PR); ≥25% increase in PSA was considered a PD and any change in PSA between the above-mentioned thresholds was considered as stable disease (SD). Patients with PR and SD were considered as responders, while those with PD were considered to be nonresponders.

Statistical analysis

Descriptive statistics were used for analysis using IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, NY, USA. Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as the median and Inter-quartile range (IQR). Wilcoxon Signed-Rank test was used to test the significance of the difference between the pre- and post-therapy quality of life scores. The median changes in scores from the baseline were also compared across the categories of PSA response using the Kruskal-Wallis test. A two-tailed $P < 0.05$ was considered to be statistically significant.

Results

Eleven males (median age 68 years, range: 57–81 years) with heavily pretreated mCRPC received treatment with ^{225}Ac-PSMA-617 at our center. All the patients had documented disease progression at baseline despite ≥2 prior treatment options. Prior treatments included: Androgen deprivation therapy: Medical/surgical (11 patients); novel anti-androgens like abiraterone (7 patients) and enzalutamide (4 patients); docetaxel (10 patients); cabazitaxel (3 patients); palliative radiotherapy (4 patients) and bone-modifying agents like bisphosphonates or denosumab (11 patients). 5/11 patients (46%) had also received prior radionuclide therapy with ^{177}Lu-PSMA-617 (2–3 cycles) in view of PD despite chemotherapy and/or novel anti-androgens. On the baseline ^{68}Ga-PSMA-11 PET/CT, all the eleven patients had distant skeletal metastases, with nine of them also presenting with locoregional lymph nodal disease. There was no case of visceral metastasis. Twenty-five cycles of ^{225}Ac-PSMA-617 were administered to the 11 patients (3 patients received 4 cycles, 1 patient received 3 cycles, 3 patients received 2 cycles whereas 4 patients received 1 cycle each). The patients received a median cumulative activity of 8.3 MBq (IQR 5.6–20.4 MBq) ^{225}Ac-PSMA-617 over 1–4 cycles (at 8–12 weeks intervals). On follow-up, five out of eleven patients (46%) showed a ≥50% decline in PSA, while stable values were observed in 3/11 (27%) patients. PD was limited to three out of eleven (27%) patients. The patient characteristics, treatment details, and response outcomes are summarized in Table 2 and Figure 1.

Table 2: Patients' characteristics, treatment details and response outcomes

Characteristics	Value
Total number of patients, *n* (%)	11 (100)
Age, median (IQR)	68 years (62-76)
Gleason score at diagnosis, median (IQR)	8 (7-9)
ECOG performance status, *n* (%)	
0	2 (18)
1	4 (36)
2	5 (46)
Prior treatments, *n* (%)	
ADT	11 (100)
Abiraterone	7 (64)
Enzalutamide	4 (36)
Docetaxel	10 (91)
Cabazitaxel	3 (27)
Palliative radiotherapy	4 (36)
^{177}Lu-PSMA-617	5 (46)
Bisphosphonate or denosumab	11 (100)
Disease extent at baseline, *n* (%)	
Local nodes	9 (82)
Distant nodes	3 (27)
Skeletal	11 (100)
Visceral	0 (0)
On opioid analgesia for pain	11 (100)
Pretherapy PSA (median, IQR)	158 (35-840) ng/mL
Cumulative activity of ^{225}Ac-PSMA-617, (median, IQR)	8.3 (5.6-20.4) MBq
Number of cycles (range)	1-4
PSA response, *n* (%)	
PR	5 (46)
SD	3 (27)
PD	3 (27)

ADT: Androgen deprivation therapy; ECOG: Eastern cooperation of oncology group; IQR: Interquartile range (1st – 3rd quartiles); PSA: Prostate specific antigen; PD: Progressive disease; PR: Partial response; SD: Stable disease, PSMA: Prostate Specific Membrane Antigen, ^{225}Ac: Actinium-225

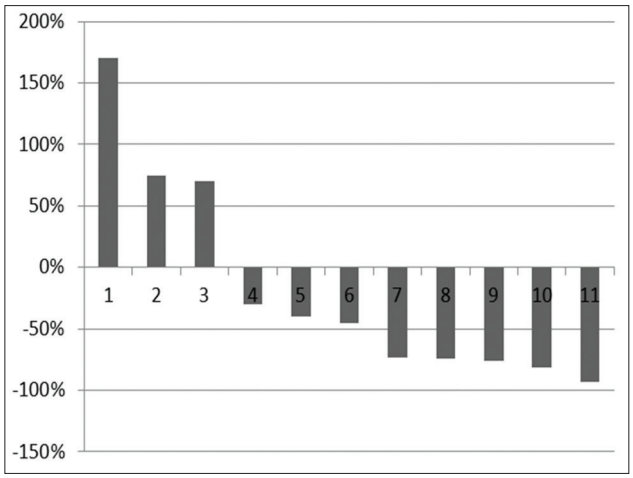

Figure 1: Waterfall plot showing PSA response at 6 weeks following the last cycle of 225Ac-PSMA-617 therapy (*n* = 11)

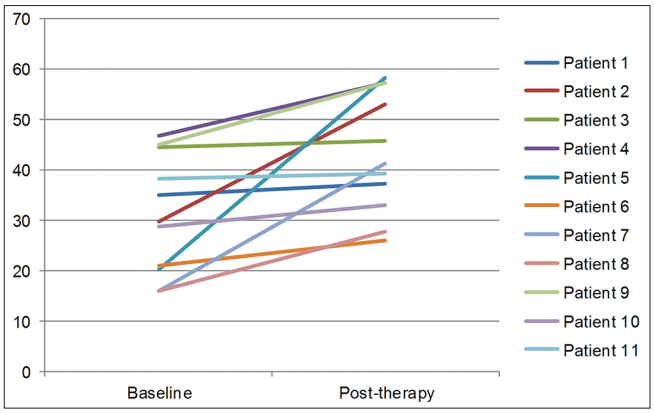

Figure 2: Line diagram showing change in total FPSI-17 scores from baseline to post 225Ac-PSMA-617 therapy for the individual patients (*n* = 11)

Pre- and post-therapy NCCN-FACT-FPSI-17 questionnaires were filled up by all the patients. The median total FPSI-17 score at baseline was 29.8 (IQR 20.2–44.6), which improved significantly to 41.3 (IQR 32.9–57.4) post-^{225}Ac-PMSA-617 therapy (P = 0.003). The separate domain-based analysis revealed statistically significant improvement in the FPSI-DRS-P (median pretherapy score of 16 versus a post-therapy score of 22, P = 0.004) and FPSI-DRS-E (median pretherapy score of 1 versus a posttherapy score of 3, P = 0.046) scores. Among the physical symptoms, significant improvement was noted with respect to pain (P = 0.003), difficulty in urination (P = 0.020), bone pain (P = 0.007), fatigue (P = 0.016) and restriction in physical activity (P = 0.016). No significant change was noted in the scores for the rest of the domains, i. e., TSE and F/WB. The changes in the total FPSI-17 and individual domain-based scores are depicted in Table 3 and Figure 2. Further, the median changes from baseline for the total FPSI-17 score and the individual domain-based DRS-P and DRS-E scores were not significantly different across the different categories of PSA response (P = 0.109, P = 0.091 and P = 0.282 respectively).

The majority of the treatment-related adverse events were of grade 1/2, which was in line with the observation that there was no significant change in FPSI-TSE scores. The most commonly encountered symptomatic adverse event was grade 1/2 dryness of the mouth (7/11 patients, 64%). Only one patient experienced Grade 3 dryness of mouth, requiring feeds through a nasogastric tube. Other frequent symptomatic adverse events reported were fatigue and loss of appetite. Grade 1/2 anemia was the most commonly observed treatment-related adverse effect among the laboratory parameters (7/11 patients, 64%). Leucopenia and thrombocytopenia of any grade were observed in 5/11 (46%) patients, respectively. Serious hematological adverse events, namely grade 3 anemia and thrombocytopenia were observed in 1/11 (9%) and 2/11 (18%) patients, respectively. The hematological toxicities were observed to be transient in most patients with values normalizing between 8 and 12 weeks posttherapy. The patient with grade 3 anemia received a single transfusion of packed red blood cells, following which his hemoglobin level returned to the baseline level. However, the two patients with grade 3 thrombocytopenia experienced persistently low platelet counts after two and three cycles, respectively, thereby leading to discontinuation of further treatment cycles. The patients died subsequently due to treatment-related toxicity (grade 5). One patient also experienced grade 3 nephrotoxicity. This particular patient had baseline deranged renal function (grade 1) with further deterioration after one cycle of therapy to grade 3 nephrotoxicity. The patient was put on dialysis; however, the patient died 2 months later due to multi-organ failure (grade 5). The treatment-related toxicity profile is elucidated in Table 4.

Discussion

In the era of multiple chemotherapies, targeted therapies and immunotherapies in the setting of mCRPC, health-related quality of life is an important parameter to assess the patients' subjective experience with the disease and its treatment.[16] The majority of the patients with mCRPC have skeletal metastases, thereby leading to significant morbidity in the form of bony pain and skeletal-related events such as spinal cord compression and pathological fractures.[17] In addition, the patients also develop a multitude of general symptoms such as fatigue, anorexia, anxiety, bladder and bowel disturbances, loss of weight, nausea, vomiting, and sleep disturbances.[18,19] Furthermore, a host of treatment-related adverse effects can lead to a greater degree of deterioration in the quality of life of these patients. In this scenario, regulatory trials for any new therapeutic agent not only require a demonstration of its survival benefit but also its impact on the quality of life of the patients. Our study demonstrated that treatment with ^{225}Ac-PSMA-617 significantly improved the health-related quality of life of the patients with mCRPC despite extensive pretreatment and advanced nature of the

Table 3: Pre- and post-therapy health-related quality of life scores as measured with National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Prostate Symptom Index-17 questionnaire

Scale (maximum score)	Pre-therapy score[a]	Post-therapy score[a]	Change in score from baseline[a]	*P*[b]
DRS-P (40)	16 (9-26)	22 (19-32)	6 (5-15)	0.004
Lack of energy (4)	1 (0-2)	2 (1-3)		0.130
Pain (4)	1 (0-2)	3 (3-4)		0.003
Difficulty urinating (4)	2 (1-4)	3 (2-4)		0.020
Loss of weight (4)	3 (1-4)	2 (1-4)		0.773
Bone pain (4)	1 (0-2)	3 (3-4)		0.007
Fatigue (4)	2 (0-2)	2 (2-3)		0.016
Weakness in legs (4)	1 (0-2)	2 (1-3)		0.079
Restriction in activity (4)	1 (1-3)	3.5 (1.8-4)		0.016
Appetite (4)	2 (1-4)	2 (1-3)		0.713
Sleep (4)	3 (2-3)	3 (2-3)		1.000
DRS-E (4)	1 (1-3)	3 (2-3)	1 (0-1)	0.046
TSE (16)	8 (6.7-13.3)	10.7 (7-13.3)	0 (−1.4-2.7)	0.672
F/WB (8)	4 (3-5)	5 (3-8)	0 (−1-3)	0.136
Total FPSI-17 (68)	29.8 (20.2-44.6)	41.3 (32.9-57.4)	10.6 (2.1-23.3)	0.003

[a]Variables expressed as median and interquartile range (1st quartile – 3rd quartile), [b]Comparison of pre- and post-therapy scores: *P* value calculated using Wilcoxon Signed Rank test. DRS-E: Disease-related symptoms – emotional, DRS-P: Disease-related symptoms – physical, FPSI: FACT Prostate Symptom Index, F/WB: Function/well-being, TSE: Treatment side-effects

Table 4: Summary data of adverse events as per CTCAE v5.0

Type of adverse event	Any grade, *n* (%)	Grade ≥3/4, *n* (%)
Nausea	2 (18)	0 (0)
Vomiting	1 (9)	0 (0)
Diarrhoea	1 (9)	0 (0)
Constipation	2 (18)	0 (0)
Fatigue	3 (27)	0 (0)
Dryness of mouth	8 (73)	1 (9)
Pain abdomen	1 (9)	0 (0)
Loss of weight	2 (18)	0 (0)
Loss of appetite	3 (27)	0 (0)
Haematological		
Anaemia	8 (73)	1 (9)
Leucopenia	5 (46)	0 (0)
Thrombocytopenia	5 (46)	2 (18)[a]
Nephrotoxicity	1 (9)	1 (9)[a]
Hepatotoxicity		
Decreased serum albumin	1 (9)	0 (0)

[a]Patients died subsequently due to treatment-related toxicity (grade 5). CTCAE: Common Terminology Criteria for Adverse Events

disease. This improvement was most prominent concerning the physical symptoms of the patients, namely pain, difficulty in urination, fatigue, and restriction in physical activity. Further, there was no significant deterioration in the quality of life due to treatment-related adverse effects.

In this study, we used the NCCN-FACT-FPSI-17 questionnaire for assessing the health-related quality of life of our patients. This tool is a robust measure to evaluate the patients' symptom-specific responses to treatment and is particularly well-suited in routine clinical settings that require brief but clinically appropriate assessment of the health-related quality of life.[20] The questionnaire was recently validated in the setting of mCRPC by Beaumont *et al*. using data from the phase 3 alpharadin in symptomatic PCa Patients (ALSYMPCA) trial. The study also suggested clinically meaningful difference ranges for the NCCN-FACT-FPSI-17 tool: 4–6 points for the FPSI-17 total score, 2–3.5 points for FPSI–disease-related symptoms–Physical, 0.5 points for FPSI–disease-related symptoms–emotional, 1–1.5 points for FPSI–treatment side effects, and 0.5–1 point for FPSI-F/WB.[21] Our results with ^{225}Ac-PSMA-617, thus, showed clinically essential differences for FPSI-17 total score as well as the DRS-P and DRS-E subscores, as evident in Table 3.

Prior studies with ^{225}Ac-PSMA-617 have shown remarkable treatment efficacy and safety in both heavily pretreated as well as chemotherapy naïve patients with mCRPC.[13,14] In this study, approximately three-quarters of patients achieved a biochemical response. Interestingly, however, the improvement in the quality of life scores did not differ significantly across the categories of the PSA response. Patients continued to have a relatively better quality of life with ^{225}Ac-PSMA-617 therapy irrespective of biochemical response.

Treatment-related adverse effects were not clinically significant in most of the patients. This was further reflected in the relatively unchanged pre- and post-therapy TSE subscores. Nevertheless, the TSE domain includes only four items, namely nausea, bowel disturbance, sexual dysfunction, and botheration about side-effects in general. This may, at times, fail to grasp the entire spectrum of treatment-related adverse effects afflicting the patient. Definitive and pointed enquires for the

^{225}Ac-PSMA-617-related-specific adverse effects must, therefore, be made simultaneously in routine clinical practice to have a better understanding of the patients' quality of life.

The present study is not without limitations. The retrospective nature of this study, the limited number of cases included and a lack of long-term follow-up limit the strength of our observations. Approximately one-third of the patients received a single cycle of ^{225}Ac-PSMA-617, as a result of which the full impact of therapy on the quality-of-life cannot be reliably ascertained. Future prospective trials evaluating the role of ^{225}Ac-PSMA-617 in mCRPC should include health-related quality-of-life as a definite trial endpoint, which would add credence to our observations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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