Potential application of lutetium-177-labeled prostate-specific membrane antigen-617 radioligand therapy for metastatic castration-resistant prostate cancer in a limited resource environment: Initial clinical experience after 2 years

ABSTRACT
In recent years, lutetium-177 ($^{177}$Lu)‑labeled prostate‑specific membrane antigen (PSMA)‑617 has become a promising new therapeutic agent in patients with metastatic castration‑resistant prostate cancer (mCRPC). In this study, we report on an early experience of $^{177}$Lu‑PSMA therapy with an evaluation of its efficacy and safety in mCRPC patients. Twenty‑one mCRPC patients with a mean age of 70.3 ± 9.6 (54–88)‑year‑old were treated with one to four therapy cycles (median two cycles) and administered activity of 3.7–29.6 GBq (mean of 15.4 GBq). A prostate‑specific antigen (PSA) decline 50% was considered to be a biochemical response (BCR). To evaluate the clinical response, the Eastern Cooperative Oncology Group (ECOG) status was used. Within 2 weeks before and 1 and 2 months after each therapy cycle, hematology, renal function, liver status, alkaline phosphatase, and PSA were checked. The Common Terminology Criteria for Adverse Events was used for grading adverse events induced by $^{177}$Lu‑PSMA. Furthermore, overall survival (OS) was calculated and analyzed. During the treatment, a BCR was seen in 62% of patients; 19% of patients showed progression and 19% of patients showed stable disease. ECOG status was improved after treatment, and OS was 62.7 weeks. After the treatment, two patients showed Grade II toxicity of white blood cells, Grade I thrombocytopenia was observed in two patients, one patient showed Grade II toxicity in serum creatinine and transient Grade I toxicity in creatinine was seen in two patients. In total, our initial experience demonstrates that $^{177}$Lu‑PSMA therapy has the potential to positively affect the development and maturation of radioligand practices in selected mCRPC patients, even in resource limited, developing country environments. However, some challenges, such as practitioner training, poor initial acceptance by colleagues and financial concerns, particularly in developing nations, still exist.

Keywords: Biochemical response, lutetium‑177‑prostate‑specific membrane antigen, prostate cancer, radioligand therapy, toxicity

Majid Assadi, Samira Rezaei, Esmail Jafari, Seyed Javad Rekabpour, Mohammad Reza Ravanbod, Farshad Zohrabi, Abdullatif Amini, Saied Keshmiri, Habibollah Dadgar, Hojjat Ahmadvandehfar

Department of Molecular Imaging and Radionuclide Therapy (MIRT), The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, 1Department of Oncology, Bushehr Medical University Hospital, Bushehr University of Medical Sciences, 2Department of Urology, Bushehr Medical University Hospital, Bushehr University of Medical Sciences, 3Department of Cardiology, Bushehr Medical University Hospital, Bushehr University of Medical Sciences, 4Department of Anesthesiology (Division of Pain Management), Bushehr Heart Medical Center, Bushehr University of Medical Sciences, Bushehr; 5Cancer Research Center, RAZAVI Hospital, Imam Reza International University, Mashhad, Iran; 6Department of Nuclear Medicine, University Hospital Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany

Address for correspondence: Prof. Majid Assadi, Department of Molecular Imaging and Radionuclide Therapy (MIRT), Bushehr Medical University Hospital, The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran. E-mail: assadipoya@yahoo.com, asadi@bpums.ac.ir

Submitted: 13-Mar-2019, Accepted: 29-Jun-2019, Published: 27-Feb-2020

How to cite this article: Assadi M, Rezaei S, Jafari E, Rekabpour SJ, Ravanbod MR, Zohrabi F, et al. Potential application of lutetium-177-labeled prostate-specific membrane antigen-617 radioligand therapy for metastatic castration-resistant prostate cancer in a limited resource environment: Initial clinical experience after 2 years. World J Nucl Med 2020;19:15-20.
INTRODUCTION

Prostate cancer (PC) is considered the second-most prevalent malignancy and the fifth greatest cause of death due to cancer worldwide.\(^1\) In the local PC, the 5-year survival rate approaches 100%, but in metastatic PC, the survival rate is significantly lower (30%).\(^2\) Metastatic castration-resistant PC (mCRPC) is defined as a progressive disease and metastatic invasion despite androgen deprivation therapy, and it is known as the most lethal type of PC. Although several new life-prolonging treatments have been approved, about 250,000 men die annually due to PC worldwide.\(^3\) Several treatments, including chemotherapy, new generation hormone therapies, and radionuclide therapy with radium-223 have been used for the treatment of mCRPC.\(^4,5\) Developing further effective treatments to improve the patient condition, including decreasing symptoms, prolonging life, and improving quality of life, should continue to be a priority for these patients.\(^6\)

On prostate epithelial cells, prostate-specific membrane antigen (PSMA) is overexpressed and up-regulated in PC. There is a direct relationship between PSMA expression levels and PC progression, metastasis, and androgen independence. Therefore, PSMA can be used as an interesting diagnostic and therapeutic target for advanced PC. Recently, targeted radionuclide therapy with lutetium-177 (\(^{177}\)Lu)-PSMA-617 (Lu-PSMA) binding with high affinity to PSMA has been introduced as an effective therapeutic agent for mCRPC patients.\(^7,8\) In addition to therapy purposes, \(^{177}\)Lu-PSMA could be used as a pretherapeutic imaging agent in countries with limited access to positron emission tomography (PET).\(^9\) In several studies, improving quality of life and promising overall and progression-free survival, besides the favorable toxicity profile of this agent, have been reported.\(^7,10-13\) The most prevalent \(^{177}\)Lu-PSMA-related side effects affect the dose-limiting organs, including the bone marrow, salivary and lacrimal glands, and kidneys.\(^14\)

Recently, due to its suitable physical features, \(^{177}\)Lu has become a popular therapeutic radionuclide. These features include its relatively long half-life (6.6 days), its optimal medium energy beta radiation (490 Kev) with 1 mm path length, which leads to the delivery of high radiation to cancer cells while delivering minimal radiation to surrounding normal cells and its gamma radiation (113, 208 Kev). These features make it a favorable choice for use in imaging.\(^15\)

In this prospective study, we report our preliminary experience and evaluate safety, efficacy, toxicity, and quality of life of \(^{177}\)Lu-PSMA-617 treatment in mCRPC patients with progression under standard treatments.
imaging. The exclusion criteria included clinically significant impairment of the liver, kidneys or bone marrow, white blood cell (WBC) count lower than 2000/µl, platelet count lower than 60 × 10⁹/l, and creatinine > 2 mg/dl. All patients underwent imaging with ⁶⁸Ga-PSMA PET or ¹⁷⁷Lu/⁹⁹mTc-PSMA scintigraphy before treatment to confirm adequate PSMA expression.

In each patient, the decision to perform the treatment was made by an interdisciplinary tumor board. The study protocol was approved by the Regional Ethics Committee (IR.BPU.MS.REC.1395.152) and was in accordance with the Declaration of Helsinki. The study protocol and its possible adverse effects were explained to all patients, and written informed consent was provided before treatment.

Treatment
The commercially available precursor PSMA-617 was radiolabeled with ¹⁷⁷Lu chloride according to the manufacturer’s instructions (Pars Isotope Co., Iran). ¹⁷⁷Lu-PSMA (3.7–7.4 GBq) was injected intravenously followed by 1000 ml normal saline. The patients were encouraged to apply ice compress packs to the salivary glands from 30 min before to 4 h after administration to decrease adverse effects. To avoid any contamination, a urinary catheter was used for patients with urinary incontinence during the first 48 h after treatment. The patients were discharged when radiation emission was below 9 microSievert/h at 2 m, which is usually reached two to 4 h after the first void.

Posttherapy imaging
Twenty-four and 48 h after treatment, a whole-body scan (and single-photon emission computed tomography if needed) was acquired using a dual-head gamma camera (Philips [ADAC] Vertex Plus), and a whole-body scan was simultaneously acquired in anterior and posterior views with a speed of 14 cm/min and matrix of 256 × 1024 pixels.

Laboratory tests
Within 2 weeks before treatment, hematology, renal function (creatinine), liver status (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), alkaline phosphatase (ALP), and prostate-specific antigen (PSA) were checked at baseline and were repeated at one and 2 months after each therapy cycle.

The Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) were used for grading causality assigning adverse events from the 1st to 3rd month after the final injection of Lu-PSMA.

Lu-PSMA treatment was stopped if follow-up imaging revealed no or minimal uptake of PSMA in the tumor. In addition, for patients in whom adequate organ function was not obtained (neutrophil > 1.5 × 10⁹/L, platelets > 75,000 × 10⁹/L), the treatment was stopped until the organ function recovered to acceptable levels.

Treatment response
According to the PC Clinical Trials Working Group 3 (PCWG3) criteria, the primary treatment response of the study was PSA response rate. A decrease of 50% or more in the PSA level compared to baseline was considered to be a biochemical response (BCR). In addition, any decline in PSA level was evaluated and analyzed. Progressive disease was defined as an increase in the PSA level ≥30%. Neither progression nor BCR was considered a stable disease. Complete BCR was considered to be a decrease in serum PSA to < 4 ng/ml. Since the patients received different numbers of treatment cycles, the focus of this study was on the best PSA level alteration compared to the baseline during the treatment.

In addition, overall survival (OS) was measured from the date of the first cycle and defined as the time interval from starting treatment to death from any reason. Levels of ALP and PSA at baseline were correlated with OS.

Statistical analysis
In this study, descriptive statistics, continuous variables, and categorical variables were reported as median, interquartile range and frequencies, respectively. Significance change of parameters during the treatment was determined by nonparametric tests. Kaplan–Meier estimator and log-rank tests were used to evaluate OS and impact of multiple parameters on OS. P ≤ 0.05 was considered statistically significant. The analysis was performed with SPSS Statistics 21 (IBM Corporation, Somers, NY, USA).

RESULTS
Twenty-one mCRPC patients with a mean age of 70.3 ± 9.6 (54–88)-year-old participated in this study. Table 1 presents the detailed demographic data of all patients. The patients underwent Lu-PSMA therapy with a median of two cycles (number of cycles: One: n = 5, two: n = 7, three: n = 6, four: n = 3). The mean cumulative administered activity was 15.4 ± 7.5 GBq, with a range of 3.7–29.6 GBq.

During the follow-up (median: 9 months, ranged from 1 to 25 months), 7 patients (33.3%) died.
Biochemical response
The median baseline serum PSA level during a mean follow-up of 32.7 weeks was 135 ng/ml (range: 4–1702), and the median value following the first cycle of therapy was 36.5 ng/ml (range: 0.15–2354), which was a statistically significant decrease \((P = 0.03)\). The median of the best PSA decline during the therapy period was 26.5 ng/ml (0.15–2354), which was a statistically significant decline compared to baseline \((P = 0.03)\).

Any PSA decline was observed in 16/21 (76%) patients. According to the PCWG3 criteria, after the first cycle, BCR (>50% PSA decline) was seen in 13/21 (62%) patients. Progressive disease was observed in 4/21 (19%) patients, and 4/21 (19%) patients had stable disease [Figure 1]. The same results were seen for the best PSA decline during the therapy. Complete BCR was seen in 3/21 (14%) patients [Figure 2]. There was no significant relationship between BCR and age, Gleason score, prior history of prostatectomy, chemotherapy/radiotherapy, bisphosphonate treatment, number of cycles, and administered activity.

Clinical response
In total, ECOG performance status was used for the assessment of clinical response. In the surviving patients, the mean ECOG score improved significantly from 2.1 ± 1.1 to 1.4 ± 1.1 \((P = 0.02)\).

For the entire cohort, the Kaplan–Meier test revealed a median OS of 62.7 weeks (95% confidence interval: 42.1–83.3). There was no significant difference concerning OS in comparison of patients with a PSA decline ≥50% and <50%, and other factors, including baseline ALP, age, Gleason score, and ECOG, had no impact on OS \((P > 0.05)\) [Figure 3].

Toxicity
In all patients, hematotoxicity factors were analyzed. According to the CTCAE, during the treatment, two patients showed transient Grade II toxicity of WBCs, which resolved within 2 months after therapy. Two patients showed Grade I thrombocytopenia.

According to the CTCAE, one patient showed Grade II toxicity in serum creatinine, and two patients showed transient Grade I toxicity, which resolved 3 months after treatment.

There was no remarkable toxicity according to the CTCAE in AST and ALT Table 2.

DISCUSSION
Up until today, different PSMA antibodies and peptides labeled with \(^{177}\)Lu have been used as therapeutic options in mCRPC patients. Among them, \(^{177}\)Lu−J591 is a monoclonal antibody which has been widely used for therapy in mCRPC patients. Despite its efficacy, it led to significant toxicity, such as myelosuppression. Currently, \(^{177}\)Lu-PSMA-617

| Table 1: Patients characteristics |
|-------------------------------|
| **Characteristics**                   | **Data**          |
| Age (years)                        | Mean±SD 70.3±9.6  |
| Range                              | 54–88            |
| PSA (ng/ml)                        | Median 135       |
| Range                              | 4–1702           |
| Alkaline phosphatase (U/L)         | Median 435       |
| Range                              | 120–1590         |
| Radical prostatectomy, n (%)       | Yes 11 (52.4)    |
|                                    | No 10 (47.6)     |
| Bisphosphonate, n (%)              | Yes 11 (52.4)    |
|                                    | No 10 (47.6)     |
| ADT drug, n (%)                    | Triptorelin 15 (72) |
|                                    | Abiraterone 2 (9) |
|                                    | Leuprolide 2 (9)  |
|                                    | Enzalutamide 1 (5) |
|                                    | Bicalutamide 1 (5) |
| Chemotherapy/radiotherapy, n (%)   | Radiotherapy 2 (9.5) |
|                                    | Chemotherapy 7 (33.3) |
|                                    | Both 9 (42.9)    |
| Gleason score (n=16), n (%)        | Mean±SD 8.2±1.1  |
|                                    | <7 2 (9.5)       |
|                                    | 7 0 (0)          |
|                                    | 8 7 (33.3)       |
|                                    | ≥9 7 (33.3)      |
| Cycle, n (%)                       | Median 2         |
|                                    | 1 5 (23.8)       |
|                                    | 2 7 (33.3)       |
|                                    | 3 6 (28.6)       |
|                                    | 4 3 (14.3)       |
| Dose (GBq)                         | 15.4±7.5         |
| Range                              | 3.7–23.6         |

| SD: Standard deviation; PSA: Prostate-specific antigen; ADT: Androgen deprivation therapy |

| Table 2: Adverse events related to the 177 Lu-prostate-specific membrane antigen therapy according to the common terminology criteria for adverse events |
|-----------------------------------------------|
| **Grade** | **1** | **2** | **3** | **4** |
| Leucopenia | -     | 2     | -     | -     |
| Thrombocytopenia | 2     | -     | -     | -     |
| Renal function | 2     | 1     | -     | -     |
In this study, we report the early results of our experience with $^{177}$Lu-PSMA-617 in 21 mCRPC patients who progressed after standard treatments. In this experience, we observed rapid and clinically hopeful improvements in PSA level (BCR), clinical status, and quality of life. Besides these meaningful results, this therapy was well tolerated, and therapy-related toxicities happened rarely and were usually transient or easily controlled. Our results broadly correlate with previous studies, which collectively propose that $^{177}$Lu-PSMA is a safe and effective treatment option for mCRPC patients.\textsuperscript{[7,10-14]}

In our study, BCR was seen in 13 (62%) patients, and any PSA decline occurred in 76% of patients. The progressive and stable disease was observed in 4 (19%) patients each. Complete BCR occurred in three patients. In two patients, complete response was achieved after one cycle. Baseline serum PSA was 17 and 49 ng/ml which after 3.7 and 7.4 GBq Lu-PSMA, dropped to 0.15 and 2.68 ng/ml, respectively. In addition, an improvement in the ECOG status (1-0 and 3-1, respectively) was documented. In another patient, a complete response was obtained after three cycles (cumulative activity: 18.5 GBq), and serum PSA dropped from 1100 to 0.76 ng/ml. These results correlate relatively well with available studies.\textsuperscript{[4,19]} Yadav \textit{et al.} reported a BCR in 64% of patients. In 35% of them, the serum PSA reduced by more than 90%, and in 65%, it reduced by more than 50%.\textsuperscript{[19]} In addition, according to a meta-analysis, any PSA decline occurred in two-thirds of mCRPC patients, and a more than 50% PSA decline was reported in one-third of patients.\textsuperscript{[15]} The PSA decline of more than 50% seen in 62% of the patients in our study is hopeful, especially in comparison with the results of conventional agents, such as 39% with cabazitaxel.\textsuperscript{[20]} In addition, it has been shown that a PSA decline of more than 50% was observed in only 32% of patients undergoing enzalutamide after abiraterone therapy.\textsuperscript{[21]}

Some clinical and paraclinical factors did not correlate well with BCR after treatment, which may be due to the small number of cases in our study. In a German multicenter study, it was shown that prior chemotherapy did not significantly influence the response rate, but acute promyelocytic leukemia <220 U/L and the number of therapy cycles were relevant independent predictors of BCR.\textsuperscript{[10]}

In the present study, ECOG status was used for clinical evaluation. In correlation with Yadav \textit{et al.},\textsuperscript{[19]} ECOG status improved after treatment, which proved the effective impact of Lu-PSMA therapy on the clinical condition and quality of life of mCRPC patients.

According to the CTCAE, transient Grade II toxicity of WBCs occurred in two patients and resolved later, while two patients showed Grade I thrombocytopenia. In one study, rates of thrombocytopenia and anemia of 4% and 10%, respectively, were reported.\textsuperscript{[10]} Considering that PSA is not expressed in normal bone marrow, this Lu-PSMA-related hemotoxicity may be due to the result of damage to adjacent marrow in patients with severe bone involvement.\textsuperscript{[22]} It can be noted that Lu-PSMA therapy leads to fewer adverse events compared to other treatments. The TROPIC study revealed a grade ≥3 leukopenia in 68% of patients treated with cabazitaxel and in 42% of patients treated with mitoxantrone as second-line chemotherapy.\textsuperscript{[20]}

In an evaluation of nephrotoxicity, according to the CTCAE, one patient showed Grade II and two patients showed transient Grade I toxicity in creatinine. There was no remarkable hepatotoxicity. Very similar observations were made by previous studies.\textsuperscript{[8,19]}

This study is accompanied by some limitations. First, the small number of treated patients is the principal limitation. Second, the relatively short follow-up of patients limited our results. Another limitation of the current study was the lack of follow-up diagnostic scans for the assessment of metabolic response rate in the included patients and consideration of serum PSA values as the standard of reference for the treatment response, as PSA values have been demonstrated to be not always trustworthy enough for monitoring disease activity in mCRPC cases.
In summary, we report our first experience with 177Lu-PSMA therapy in 21 mCRPC patients. BCR was observed in 62%, and the median OS was 62 weeks. Compared to conventional therapies, no serious adverse toxicity was reported.

CONCLUSION

In total, our initial experience demonstrates that 177Lu-PSMA therapy has the potential to positively affect the development and maturation of radioligand practices in selected mCRPC patients, even in resource-limited, developing country environments. However, some challenges, such as practitioner training, poor initial acceptance by colleagues and financial concerns, particularly in developing nations, still exist. The necessity for emerging programs to promote change in the management of patients with mCRPC, especially in developing nations, should be encouraged and supported as a distinct discipline in the era of precision medicine.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
3. Center MM, Jemal A, Lorret-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012;61:1079-92.
4. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [177Lu]-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): A single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19:825-33.
5. Wei Q, Li M, Fu X, Tang R, Na Y, Jiang M, et al. Global analysis of differentially expressed genes in androgen-independent prostate cancer. Prostate Cancer Prostatic Dis 2007;10:167-74.
6. Gillessen S, Attard G, Beer TM, Beltran H, Bossi A, Bristow R, et al. Management of patients with advanced prostate cancer: The report of the advanced prostate cancer consensus conference APCCC 2017. Eur Urol 2018;73:178-211.
7. Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, et al. PSMA targeted radioligandtherapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging 2018;45:12-9.
8. Ahmadzadehfar H, Rahbar K, Kürpıp S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: A two-centre study. EJNMMI Res 2015;5:114.
9. Assadi M, Nabipour I. The evolving role of molecular imaging in transforming reactive to proactive (P4) medicine: Predictive, preventive, personalized and participatory. J Nucl Med 2014;55 Suppl 1:1310.
10. Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med 2017;58:85-90.
11. Ahmadzadehfar H, Eppard E, Kürpıp S, Fimmers R, Yordanova A, Schlenkoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. Oncotarget 2016;7:12477-88.
12. Ahmadzadehfar H, Schlolaut S, Fimmers R, Yordanova A, Hirzebruch S, Schlenkoff C, et al. Predictors of overall survival in metastatic castration-resistant prostate cancer patients receiving [177Lu] Lu-PSMA-617 radioligand therapy. Oncotarget 2017;8:103108-16.
13. Ahmadzadehfar H, Wegen S, Yordanova A, Fimmers R, Kürpıp S, Eppard E, et al. Overall survival and response pattern of castration-resistant metastatic prostate cancer to multiple cycles of radioligand therapy using [177Lu] Lu-PSMA-617. Eur J Nucl Med Mol Imaging 2017;44:1448-54.
14. Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and tolerability of a single dose of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: A multicenter retrospective analysis. J Nucl Med 2016;57:1334-8.
15. Kim YJ, Kim YI. Therapeutic responses and survival effects of 177Lu-PSMA-617 radioligand therapy in metastatic castrate-resistant prostate cancer: A meta-analysis. Clin Nucl Med 2018;43:728-34.
16. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol 2016;34:1402-18.
17. Tagawa ST, Akhtar NH, Nikolopoulou A, Kaur G, Robinson B, Kahn R, et al. Bone marrow recovery and subsequent chemotherapy following radiolabeled anti-prostate-specific membrane antigen monoclonal antibody J591 in men with metastatic castration-resistant prostate cancer. Front Oncol 2013;3:214.
18. Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wiessalla S, et al. [177Lu]-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: Safety and efficacy. J Nucl Med 2016;57:1006-13.
19. Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. 177Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: Safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging 2017;44:81-91.
20. de Bono JS, Oudard S, Ozuguroglu M, Hansen S, Machiels JP, Kokch I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. Lancet 2010;376:1147-54.
21. Antonarakis ES, Lu C, Wang H, Lubner B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028-38.
22. Bräuer A, Grubert LS, Roll W, Schrader AJ, Schäfers M, Bögemann M, et al. 177Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2017;44:1663-70.
23. Tagawa ST, Milowsky MI, Morris M, Vallabhajosula S, Christops P, Akhtar NH, et al. Phase II study of lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res 2013;19:5182-91.