Original Article

Determination of Critical Organ Doses with ^{177}Lu Prostate-specific Membrane Antigen Dosimetry in Metastatic Prostate Cancer Treatment

Gulcihan Yilidir, Mustafa Demir

Department of Nuclear Medicine, Cerrahpaşa Faculty of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey

Abstract

Aim: This study aimed to perform dosimetry in patients with metastatic prostate cancer treated with ^{177}Lutetium (Lu) prostate-specific membrane antigen (PSMA)-617 radiopharmaceutical, calculating organ blood clearance and consequently determining the maximum tolerable treatment activity. **Materials and Methods:** Eighteen patients with metastatic prostate cancer were enrolled in the study. Patients were administered 5.55 gigabecquerel (GBq) of ^{177}Lu-PSMA-617 radiopharmaceutical per treatment cycle through infusion. Blood samples (2 mL each) were collected at 2, 4, 6, 8, 18, 24, 36, and 44 h postinjection to assess the bone marrow absorbed dose. Organ doses were calculated using the OLINDA/EXM software based on scintigraphic images of the 18 patients who received ^{177}Lu-PSMA-617. **Results:** The blood clearance of ^{177}Lu-PSMA-617 radiopharmaceutical was determined to be bi-exponential. The mean absorbed doses for the parotid glands, kidneys, bone marrow, and liver were found to be 1.18 ± 0.27, 1.05 ± 0.3, 0.07 ± 0.05, and 0.31 ± 0.2 Gy/GBq, respectively. The radiation dose to the bone marrow was significantly lower than that to the kidneys and parotid glands. No dose limitations were necessary for kidneys and bone marrow in any of the patients. **Conclusions:** Our dosimetry results indicate that ^{177}Lu-PSMA-617 therapy is safe in terms of radiation toxicity.

Keywords: ^{177}Lutetium-prostate-specific membrane antigen treatment, internal dosimetry, organ doses, prostate cancer, radionuclide dosimetry

Received on: 19-01-2024 **Review completed on:** 11-03-2024 **Accepted on:** 23-03-2024 **Published on:** 25-06-2024

Introduction

Prostate cancer remains the fourth most commonly diagnosed cancer among men. In 2023, there were 288,300 new cases of prostate cancer reported, resulting in a total of 34,700 deaths.[1] Common treatment modalities for prostate cancer include radical prostatectomy and external radiation therapy for localized disease and hormone therapy, androgen deprivation therapy, and chemotherapy for metastatic prostate cancer. Current medical guidelines recommend antimitotic chemotherapy with docetaxel.[2] Due to the low survival rates of patients with metastatic prostate cancer, the effective treatment of this condition represents an unmet clinical need in modern oncology.[3] For a long period, the role of nuclear medicine in prostate cancer was limited to bone scintigraphy and the palpation of certain bone metastases. However, in the last decade, significant progress has been made in the diagnosis and treatment of prostate cancer with the labeling of the J591 antibody composition, which binds to the extracellular epitope of prostate-specific membrane antigen (PSMA), with radionuclides.[4] Organ tolerance doses in radionuclide therapy are generally determined by referencing doses in radiotherapy applications. In this study, organ tolerance doses for parotid glands, kidneys, and liver were determined as 25 Gy, 20 Gy, and 30 Gy, respectively.[5]

PSMA, alternatively referred to as glutamate carboxypeptidase II or folate hydrolase, is a transmembrane glycoprotein that finds expression in prostate cells.[6] Prostate cancer cells manifest elevated levels of PSMA expression compared to their benign counterparts, thereby presenting a relatively specific target for individuals diagnosed with this neoplasm. Notably,

Access this article online

Quick Response Code:

Website: www.jmp.org.in

DOI: 10.4103/jmp.jmp_12_24

Address for correspondence: Dr. Mustafa Demir, Department of Nuclear Medicine, Cerrahpaşa Faculty of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey.
E-mail: demirm@istanbul.edu.tr.

How to cite this article: Yilidir G, Demir M. Determination of critical organ doses with ^{177}Lu prostate-specific membrane antigen dosimetry in metastatic prostate cancer treatment. J Med Phys 2024;49:304-10.

PSMA is not restricted to prostate cancer and benign prostate epithelium; its expression extends to various tissues, including the proximal renal tubules of the kidneys, brain, intestines, and neovasculature of most solid neoplasms.[7]

In recent years, the development of novel therapeutic agents targeting PSMA has garnered significant attention in the field of prostate cancer treatment. Among these agents, ^{177}Lutetium (^{177}Lu)-PSMA-617 has emerged as a promising radiopharmaceutical for both imaging and therapy of metastatic castration-resistant prostate cancer (mCRPC). ^{177}Lu-PSMA-617 exhibits characteristics such as rapid blood clearance, low hepatic uptake, high binding affinity in radiopharmaceutical labeling, effective internalization into prostate cancer cells, and renal clearance within 24 h postinjection. These attributes contribute to excellent imaging quality and efficient targeted therapy. In addition, it has been reported that ^{177}Lu-PSMA-617 is safe for the treatment of mCRPC patients from a dosimetric perspective.[8]

Through the use of small-molecule ligands of PSMA, gallium-68 (^{68}Ga) is employed for imaging prostate cancer recurrences and metastases, whereas ^{177}Lu-PSMA-617, labeled with radionuclides, serves as a therapeutic target for the treatment of metastatic prostate adenocarcinoma.[9] In ^{177}Lu-PSMA-617 treatments, salivary and lacrimal glands demonstrate the highest accumulation of PSMA in normal tissues.[10] For salivary glands, immunohistochemistry has revealed focal expression of PSMA, and it is believed that the high uptake of ^{177}Lu-PSMA-617 is a result of both specific and nonspecific uptake mechanisms.[11] Treatment with ^{177}Lu-PSMA-617 can provide exceptional clinical benefits for some patients, as evidenced by occasional complete radiological and biochemical responses. However, the treatment does not completely eradicate the disease in most patients due to the high expression of PSMA by hormone-resistant and metastatic prostate cancer, which also increases tumor aggressiveness as PSMA expression levels rise.[12]

Increased PSMA expression in prostate cancer is associated with a higher tumor stage and an increased risk of disease progression defined by biochemical recurrence after radical prostatectomy. Various other cancer types, such as follicular lymphoma, multiple myeloma, papillary and follicular thyroid carcinoma, pancreatic neuroendocrine tumor, gastrointestinal stromal tumor, and squamous cell carcinoma of the oropharynx, also exhibit high PSMA expression.[13] Since PSMA is not exclusive to the prostate, the use of ^{177}Lu-PSMA-617 radionuclide treatment carries the risk of uptake by other organs. Therefore, performing dosimetry is crucial to consider the side effect profile of PSMA-targeted therapy and understand the safest radioisotope dose that can be administered to the patient without causing significant radiation damage to nontarget organs.[14]

The aim of this study is to calculate blood clearance and organ doses in patients with metastatic prostate cancer treated with ^{177}Lu PSMA-617 radiopharmaceutical, with the subsequent estimation of the maximum treatment activity based on tolerance doses of dose-limiting organs.

Materials and Methods

Eighteen patients with metastatic prostate cancer (mean age: 64.9 ± 6.5 years) treated with ^{177}Lu-PSMA-617 at Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Department of Nuclear Medicine, were included in this study. The study received approval from the Istanbul University Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (document number: 83045809/604/5855).

Gleason scoree and ^{177}Lutetium-prostate-specific membrane antigen blood clearance

The Gleason score graded prostate cancer based on cellular appearance and ranged from 2 to 10. Lower scores indicated less aggressiveness and better differentiation, whereas higher scores indicated more aggressive cancer. For this purpose, 18 patients were included in the study. All patients had a histopathological diagnosis of prostate cancer. Their ages ranged from 55 to 76 (mean age: 64.9 ± 6.5). Thirteen patients had undergone prostate surgery, and 15 had received radiotherapy. All patients had received hormone therapy, and their blood prostate-specific antigen (PSA) levels had increased. Gleason scores ranged from 6 to 9. Blood PSA levels varied between 19 and 121 ng/mL (mean 73 ± 31) [Table 1]. Each patient received 5.55 GBq (150 mCi) of ^{177}Lu-PSMA activity per treatment cycle through infusion. For blood clearance rate and bone marrow dosimetry, 2 mL blood samples were collected at 2, 4, 6, 8, 18, 24, 36, and 44 h postinfusion. All radioactive counting procedures related to the preparation and quality control of ^{177}Lu-PSMA-617 were performed using a model: AtomLab, brand: Biodex well counter 187–246 well-type NaI (Tl) detector. Baseline and window settings were adjusted at 208 and 100 keV, respectively, to count the highest efficiency gamma radiations of ^{177}Lu. Time-count changes were extracted semi-logarithmically, and the blood clearance rate of ^{177}Lu-PSMA-617 was calculated. Equation 1 for bone marrow dosimetry is given by Wessels *et al*. method was used.[15]

$$\widehat{A}_{rm} = \left(\frac{RMECFF}{1-HCT}\right) \times \widehat{A}_{blood} \times \frac{M_{rm}}{M_{blood}} \quad (1)$$

$\tilde{A}_{rm}$: Cumulative activity in red marrow, RMECFF: Red marrow extracellular fluid fraction, $\tilde{A}_{blood}$: Cumulative activity in blood, M_{rm}: Bone marrow mass, M_{blood}: Blood mass, HCT: Hematocrit.

Preparation of ^{177}Lutetium-prostate-specific membrane antigen-617 and ınfusion method

^{177}Lu-PSMA-617 was prepared according to established protocols. Briefly, lutetium-177 chloride (^{177}LuCl3) was obtained from a commercial supplier and labeled with PSMA-617 using a standardized procedure. Quality control tests were performed to ensure the radiochemical purity and stability of the radiopharmaceutical. Before infusion, the

Table 1: Demographic information of patients and absorbed radiation doses (Gy/GBq)

Patient number	Age	GS	PSA (ng/mL)	Parotid gland	Kidneys	Bone marrow	Liver
1	65	8	48	1.66	0.760	0.025	0.27
2	61	7	98	1.27	0.89	0.087	0.54
3	76	6	78	0.98	1.54	0.043	0.19
4	55	6	45	1.53	1.43	0.04	0.21
5	72	9	98	0.98	1.32	0.098	0.98
6	62	9	110	1.08	0.96	0.076	0.23
7	49	8	79	1.66	0.76	0.025	0.27
8	63	9	23.5	1.07	0.69	0.058	0.34
9	69	8	87	1.34	1.0	0.099	0.34
10	66	8	89	1.05	1.03	0.099	0.24
11	71	8	69	1.43	1.54	0.076	0.29
12	65	7	89	1.48	0.52	0.021	0.25
13	67	7	66	1.03	1.43	0.09	0.34
14	69	7	101	0.89	1.25	0.079	0.16
15	57	8	19	0.94	0.98	0.037	0.23
16	70	8	19	0.8	0.51	0.022	0.18
17	67	8	121	1.07	0.99	0.034	0.23
18	65	9	78	1.25	1.03	0.03	0.22
Mean±SD	64.9±6	7.7±0.9	73±31	1.18±0.27	1.05±0.3	0.07±0.05	0.31±0.2

GS: Gleason score, SD: Standard deviation, PSA: Prostate-specific antigen, GS: Gleason score

radiolabeled compound was diluted in a sterile saline solution to achieve the desired activity concentration. Infusion was carried out using standard techniques under strict aseptic conditions, with continuous monitoring of vital signs and patient comfort.

Scintigraphic ımaging and dosimetry

Before treatment, all patients underwent ^{68}Gallium (Ga)-PSMA-11 positron emission tomography/computed tomography (PET/CT) (General Electric Discovery 710 PET/CT) scanning to assess the PSMA expression status of metastases. Volumes of organs and tumors, necessary for dosimetry, were calculated using the CT dataset from ^{68}Ga-PSMA PET/CT scans. Planar whole-body images of ^{177}Lu-PSMA were performed at 4, 24, 48, and 72 h using Siemens Symbia T16 single-photon emission computed tomography/CT with medium-energy parallel-hole collimators. Scintigraphic images were acquired at the 208 keV energy peak of ^{177}Lu with a 15% window, dual detectors, 180° projections, 128 × 128 matrix, and a step duration of 20 s. Images were obtained with a 1024 × 256 matrix, pixel size of 2.4 mm × 2.4 mm, and a total scan duration of 20 min, and regions of interest (ROIs) were drawn on the images [Figure 1]. Individual patient-absorbed doses for parotid glands, kidneys, liver, and bone marrow were evaluated following the medical ınternal radiation dose (MIRD) schema and guidelines recommended by the European Association of Nuclear Medicine Dosimetry Committee and MIRD Handbook No 20.[15,16]

The formulation is given by equation (2), where D_h represents the target organ dose, $\tilde{A}_k$ is the cumulative activity, and S (h ← k) is the S-value from the source organ to the target organ.

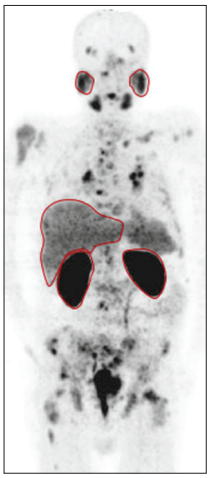

Figure 1: Regions of interests drawn on ^{177}Lutetium-prostate-specific membrane antigen-617 whole-body scintigraphic image

$$D_h = \sum_k \tilde{A}_k s(h \leftarrow k) \quad (2)$$

The total counts for the source organ in scintigraphic images were determined using the geometric background subtraction method as defined in MIRD Handbook No 16.[17] This formulation is given by equation (3).

$$A_k = \sqrt{\frac{I_A I_P}{e^{-\mu e t}}} \frac{f_k}{C} F_k \quad (3)$$

A_k: Cumulative activity, I_A I_p: Anterior and posterior counts, F_k: ^{177}Lu attenuation correction factor, μ_e: Linear attenuation coefficient, t: Time, C: Gamma camera calibration factor, and f_k: Background counts.

Counts in ROIs were converted to activity by multiplying with the calibration factor. The absorbed doses in the target region were calculated using the OLINDA/EXM (version 1.1) software according to the methodology outlined in MIRD Handbook No 20.[18]

Statistical evaluation

Due to the relatively small sample size and the data not conforming to a normal distribution, the Mann–Whitney *U* test was applied to compare the means of two independent groups. The Mann–Whitney *U*-test was employed to assess the significance levels between absorbed doses of parotid glands, kidneys, bone marrow, and liver. A significance level of $P < 0.05$ was considered statistically significant.

Results

Demographic information of patients who underwent radionuclide dosimetry is presented in Table 1. The patients had an average Gleason score of 7.7 ± 0.92, and their serum PSA levels ranged from 19 to 235 ng/mL (mean 73 ± 31 ng/mL). The temporal changes in counts obtained from gamma counting of blood samples taken at 2, 4, 6, 8, 18, 24, 36, and 44 h postinjection from patients treated with ^{177}Lu-PSMA-617 are depicted in Figure 2. The figure illustrates that the clearance of radioactivity from the blood slowed down after the 8th h, showing a biexponential clearance pattern in the subsequent period. The half-life of the blood clearance phase was calculated as 8.1 ± 1.8 h in the first phase and 14.9 ± 2.3 h in the second phase. Patients were monitored in their rooms in the nuclear medicine department for 24 h following the infusion of ^{177}Lu-PSMA-617. No acute side effects (blood pressure, heart rate, body temperature, etc.) were detected, and the patients tolerated the administered radiopharmaceutical very well.

Eighteen patients who underwent ^{177}Lu-PSMA-617 treatment had dosimetry performed on selected organs based on their scintigraphic images, and the absorbed doses are provided in Table 1. According to the dosimetry results, the amounts of activity (GBq) that critical organs can tolerate for each patient are shown in Table 2. A comparison of organ doses obtained in this study with various literature data is presented in Table 3.[10,19-22]

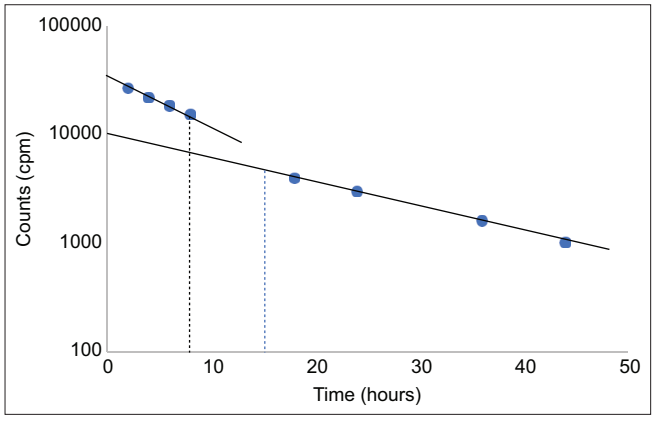

Figure 2: Biexponential blood clearance curve of ^{177}Lutetium-prostate-specific membrane antigen-617

In Table 3, liver doses ranged from 0.07 to 0.12 Gy/GBq, whereas in this study, it was found to be 0.32 Gy. For the parotid gland, the literature reports doses ranging from 0.53 to 0.72 Gy/GBq, whereas in this study, it was found to be 1.15 Gy. Similarly, for the kidneys, a dose of 0.39 Gy/GBq was reported, whereas in our study, it was found to be 1.08 Gy/GBq. The relatively mild dose elevation per Gy/GBq in our study did not necessitate any modifications to the treatment protocol.

There was no significant difference between parotid glands and kidneys ($P = 0.9124$) and between bone marrow and liver ($P = 0.27134$). However, significant differences were detected between other groups ($P < 0.05$).

Discussion

In this study, calculated absorbed doses showed significant variations among patients. It was determined that ^{177}Lu-PSMA radiopharmaceutical has a high affinity for the parotid glands, even exhibiting uptake comparable to that in the kidneys. The highest absorbed doses were observed in the parotid glands (1.18 ± 0.27 Gy/GBq) and kidneys (1.05 ± 0.3 Gy/GBq), with no statistically significant difference between them.

As ^{177}Lu-PSMA is administered intravenously, the blood elements are the first to be exposed to radiation. Abdominal organs receive irradiation due to specific accumulation or physiological excretion functions in ^{177}Lu-PSMA treatments. Therefore, blood clearance is crucial to avoid exceeding the 2 Gy limit for bone marrow dose.[23] According to the results of this study, ^{177}Lu-PSMA-617 is rapidly cleared from the blood within 4–6 h after administration and relatively slows down in the subsequent period.

Theranostics in nuclear medicine have become increasingly popular for precise diagnosis and treatment, especially in the late-stage detection and treatment of bone metastases.[24,25] In the ^{177}Lu-PSMA-617 treatment of metastatic prostate cancer, kidneys are considered critical organs.[26-29] Our results, as shown in Table 3, are relatively higher than the reported values in the literature. This discrepancy may be due to the two-dimensional (2D)-based kidney dosimetry, which tends to slightly overestimate kidney doses compared to 3D methods due to overlapping abdominal organ radioactivity accumulation.[10] Zhang *et al*. calculated an average kidney dose of 0.816 ± 0.32 Gy/GBq in 80 prostate cancer patients treated with 177 Lu-PSMA-617. They reported no evidence of significant hematological toxicity apart from possible increased background radiation dose due to potential renal dysfunction, and thus, no evidence of possible increased background radiation dose posttreatment attributable to potential renal impairment.[30] The absorbed dose to the kidneys varied depending on individual differences in kidney functions among patients. However, our results remained within the known tolerance dose limits of 20 Gy for kidneys.

Table 2: Cumulative activity amounts calculated to reach absorbed dose limits (GBq)

Patient number	Parotid gland (GBq/25 Gy)	Kidneys (GBq/20 Gy)	Bone marrow (GBq/2 Gy)	Liver (GBq/30 Gy)
1	37.5	44.8	89.7	181.3
2	25.4	36.4	53.2	132.4
3	25.3	45.2	65.2	121.4
4	28.2	23.2	45.3	145.2
5	27.4	26.4	49.2	134.2
6	31.9	23.5	54.2	137.6
7	28.1	33.2	34.3	95.0
8	18.2	30.6	79.6	116.4
9	26.0	23.4	58.5	111.4
10	9.3	43.5	54.2	98.8
11	19.9	37.4	58.9	97.3
12	31.0	13.8	41.9	69.7
13	29.4	25.2	65.2	132.4
14	27.4	17.3	35.1	123.1
15	20.2	44.2	95.7	126.3
16	21.4	45.2	47.5	124.2
17	24.0	22.5	66.0	142.4
18	31.0	35.2	57.4	143.0
Mean±SD	25.6±6.3	31.7±10.3	58.4±18.8	124±24.5

SD: Standard deviation

Table 3: Comparison of absorbed doses calculated in this study with literatüre

Organs	This study (Gy/GBq)	Delker *et al*. (Gy/GBq)	Okamoto *et al*. (Gy/GBq)	Hohberg *et al*. (Gy/GBq)	Violet *et al*. (Gy/GBq)	Kamaldep *et al*. (Gy/GBq)
Kidneys	1.08±0.34	0.60±0.18	0.72±0.21	0.60±0.18	0.39±0.15	0.49±0.17
Bone marrow	0.059±0.028	0.01±0.01	-	-	0.11±0.10	0.03±0.02
Liver	0.32±0.19	0.10±0.06	0.12±0.06	-	0.10±0.05	0.07±0.04
Parotid glands	1.15±0.24	-	0.55±0.14	0.72±0.14	0.58±0.43	0.53±0.20

^{177}Lu-PSMA is retained in the salivary glands through transmembrane receptor binding mechanisms and exhibits very high uptake. When planning for PSMA-targeted therapies, nuclear medicine specialists' concern lies in the irreversible salivary gland damage due to radiation toxicity. Damage to the salivary glands and the development of xerostomia as a side effect of radionuclide therapy diminishes the patient's quality of life. In some recent studies, the use of an ice-pack collar during ^{177}Lu-PSMA-617 therapy has been suggested to induce vasoconstriction and reduce PSMA binding to the salivary glands.[31] Despite not being considered a critical organ, a significant uptake of ^{177}Lu-PSMA-617 in the parotid glands was observed in scintigraphic images. The tolerance doses for the parotid and kidneys are 25 Gy and 20 Gy, respectively, which are somewhat close values. Therefore, in dosimetry, it is important not only to consider kidney doses but also the dose exposure of the parotid glands.

The liver is not considered a critical organ at risk for ^{177}Lu-PSMA-617 treatments.[32] However, in simultaneous treatments and in the treatment of larger molecules such as ^{177}Lu-labeled monoclonal antibodies, monitoring the liver is essential.[26] Classic radiation-induced liver disease develops a few weeks after irradiation and shows the typical pathological appearance of veno-occlusive disease in the central lobule and small branches of hepatic veins.[33] Our results demonstrated that absorbed doses for the liver were significantly below the reported tolerance dose limit of 30 Gy.

Although there was no significant difference in absorbed doses between parotid glands and kidneys, a significant difference was found between liver and bone marrow doses. This suggests a high affinity of ^{177}Lu-PSMA-617 radiopharmaceutical for parotid glands.

Since ^{177}Lu-PSMA is administered intravenously, blood elements are the first to be exposed to radiation, and the dose exposure to bone marrow should be below 2 Gy to prevent bone marrow suppression.[28,29] According to Delker *et al*., it is unlikely to encounter bone marrow toxicity with ^{177}Lu-PSMA-617 within the expected activity ranges per treatment course.[19] However, according to Kabasakal *et al*., dose prediction for bone marrow using blood-based dosimetry models may underestimate the absolute dose due to the presence of highly avid lesions that increase the dose to the bone marrow. In addition, intense treatments with chemotherapy and radiotherapy in advanced prostate cancer patients may potentially increase the risk of hematotoxicity, even with lower radiation doses to the bone marrow.[14] Furthermore, bone marrow dosimetry relies on

image-based estimation rather than blood-based dosimetry due to retrospective data collection. According to our study, ^{177}Lu-PSMA-617 provided an average bone marrow dose of 0.059 ± 0.028 Gy/GBq. However, when evaluated alongside literature data, the administration of up to 5.55 GBq activity appeared to be safe. The rapid clearance of ^{177}Lu-PSMA-617 from the bloodstream ensures treatment safety and efficacy for the patient. Addressing the challenges and limitations in accurately predicting bone marrow dosimetry is crucial, as it can lead to potential inaccuracies in absorbed dose estimation, especially due to highly avid lesions. This scenario may increase the risk of hematotoxicity, particularly in patients with a history of extensive chemotherapy or radiotherapy.

^{177}Lu-PSMA offers promising results in patients with castration-resistant prostate cancer, presenting as a treatment option with minimal accompanying toxicity observed in both treatment-naïve and heavily pretreated patients.

Conclusions

In this study, it was determined that reaching the tolerance doses of 20 Gy for kidneys and 2 Gy for bone marrow would only be possible with 31.7 ± 10.3 GBq and 58.4 ± 18.8 GBq of ^{177}Lu PSMA activity, respectively. This result underscores the critical importance of kidneys as a vital organ in ^{177}Lu PSMA therapy. It is anticipated that absorbed doses resulting from the total treatment activity that can be administered to metastatic prostate cancer patients with ^{177}Lu-PSMA-617 will be lower than tolerance doses in critical organs such as kidneys and bone marrow. Nevertheless, the significant variability in organ-absorbed doses among patients emphasizes the importance of patient-specific dosimetry.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Fendler WP, Rahbar K, Herrmann K, Kratochwil C, Eiber M. (177) Lu-PSMA radioligand therapy for prostate cancer. J Nucl Med 2017;58:1196-200.
3. Sadaghiani MS, Sheikhbahaei S, Werner RA, Pienta KJ, Pomper MG, Solnes LB, *et al*. A systematic review and meta-analysis of the effectiveness and toxicities of lutetium-177-labeled prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. Eur Urol 2021;80:82-94.
4. Akyel R, Özaraslan İA, Urhan M. Radionuclide therapy applications in the treatment of prostate cancer. Turk Clin J Med Oncol Spec Top 2017;10:P398-403.
5. Emami B. Tolerance of normal tissue to therapeutic radiation. Rep Radiother Oncol 2013;1:P123-7.
6. Carter RE, Feldman AR, Coyle JT. Prostate-specific membrane antigen is a hydrolase with substrate and pharmacologic characteristics of a neuropeptidase. Proc Natl Acad Sci U S A 1996;93:749-53.
7. Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS, Gaudin PB. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res 1999;59:3192-8.
8. Yadav MP, Ballal S, Bal C, Sahoo RK, Damle NA, Tripathi M, *et al.* Efficacy and safety of 177Lu-PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer patients. Clin Nucl Med 2020;45:19-31.
9. Weineisen M, Schottelius M, Simecek J, Baum RP, Yildiz A, Beykan S, *et al.* 68Ga- and 177Lu-Labeled PSMA I and T: Optimization of a PSMA-targeted theranostic concept and first proof-of-concept human studies. J Nucl Med 2015;56:1169-76.
10. Okamoto S, Thieme A, Allmann J, D'Alessandria C, Maurer T, Retz M, *et al.* Radiation dosimetry for (177)Lu-PSMA I and T in metastatic castration-resistant prostate cancer: Absorbed dose in normal organs and tumor lesions. J Nucl Med 2017;58:445-50.
11. Rupp NJ, Umbricht CA, Pizzuto DA, Lenggenhager D, Töpfer A, Müller J, *et al.* First clinicopathologic evidence of a Non-PSMA-related uptake mechanism for (68)Ga-PSMA-11 in salivary glands. J Nucl Med 2019;60:1270-6.
12. Kabasakal L, Toklu T, Yeyin N, Demirci E, Abuqbeitah M, Ocak M, *et al.* Lu-177-PSMA-617 prostate-specific membrane antigen ınhibitor therapy in patients with castration-resistant prostate cancer: Stability, bio-distribution and dosimetry. Mol Imaging Radionucl Ther 2017;26:62-8.
13. Perner S, Hofer MD, Kim R, Shah RB, Li H, Möller P, *et al.* Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Pathol 2007;38:696-701.
14. Kabasakal L, AbuQbeitah M, Aygün A, Yeyin N, Ocak M, Demirci E, *et al.* Pre-therapeutic dosimetry of normal organs and tissues of (177) Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2015;42:1976-83.
15. Wessels BW, Bolch WE, Bouchet LG, Breitz HB, Denardo GL, Meredith RF, *et al.* Bone marrow dosimetry using blood-based models for radiolabeled antibody therapy: A multiinstitutional comparison. J Nucl Med 2004;45:1725-33.
16. Hindorf C, Glatting G, Chiesa C, Lindén O, Flux G, EANM Dosimetry Committee. EANM dosimetry committee guidelines for bone marrow and whole-body dosimetry. Eur J Nucl Med Mol Imaging 2010;37:1238-50.
17. Siegel JA, Thomas SR, Stubbs JB, Stabin MG, Hays MT, Koral KF, *et al.* MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. J Nucl Med 1999;40:37S-61S.
18. Wessels BW, Konijnenberg MW, Dale RG, Breitz HB, Cremonesi M, Meredith RF, *et al.* MIRD pamphlet No. 20: The effect of model assumptions on kidney dosimetry and response – İmplications for radionuclide therapy. J Nucl Med 2008;49:1884-99.
19. Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, *et al.* Dosimetry for (177)Lu-DKFZ-PSMA-617: A new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging 2016;43:42-51.
20. Hohberg M, Eschner W, Schmidt M, Dietlein M, Kobe C, Fischer T, *et al.* Lacrimal glands may represent organs at risk for radionuclide therapy of prostate cancer with [(177)Lu] DKFZ-PSMA-617. Mol Imaging Biol 2016;18:437-45.
21. Violet J, Jackson P, Ferdinandus J, Sandhu S, Akhurst T, Iravani A, *et al.* Dosimetry of (177)Lu-PSMA-617 in metastatic castration-resistant prostate cancer: Correlations between pretherapeutic ımaging and whole-body tumor dosimetry with treatment outcomes. J Nucl Med 2019;60:517-23.
22. Kamaldeep K, Wanage G, Sahu SK, Maletha P, Adnan A, Suman S, *et al.* Examining absorbed doses of ındigenously developed (177) Lu-PSMA-617 in metastatic castration-resistant prostate cancer patients at baseline and during course of peptide receptor radioligand therapy. Cancer Biother Radiopharm 2021;36:292-304.
23. Kramer V, Fernández R, Lehnert W, Jiménez-Franco LD, Soza-Ried C, Eppard E, *et al.* Biodistribution and dosimetry of a single dose of albumin-binding ligand [(177)Lu] Lu-PSMA-ALB-56 in patients with mCRPC. Eur J Nucl Med Mol Imaging 2021;48:893-903.

24. Afshar-Oromieh A, Babich JW, Kratochwil C, Giesel FL, Eisenhut M, Kopka K, *et al.* The rise of PSMA ligands for diagnosis and therapy of prostate cancer. J Nucl Med 2016;57:79S-89S.
25. Afshar-Oromieh A, Hetzheim H, Kübler W, Kratochwil C, Giesel FL, Hope TA, *et al.* Radiation dosimetry of (68)Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. Eur J Nucl Med Mol Imaging 2016;43:1611-20.
26. Lassmann M, Chiesa C, Flux G, Bardiès M, EANM Dosimetry Committee. EANM dosimetry committee guidance document: Good practice of clinical dosimetry reporting. Eur J Nucl Med Mol Imaging 2011;38:192-200.
27. Brabander T, van der Zwan WA, Teunissen JJ, Kam BL, de Herder WW, Feelders RA, *et al.* Pitfalls in the response evaluation after peptide receptor radionuclide therapy with [(177)Lu-DOTA(0), Tyr(3)] octreotate. Endocr Relat Cancer 2017;24:243-51.
28. Pichard A, Marcatili S, Karam J, Constanzo J, Ladjohounlou R, Courteau A, *et al.* The therapeutic effectiveness of (177)Lu-lilotomab in B-cell non-hodgkin lymphoma involves modulation of G2/M cell cycle arrest. Leukemia 2020;34:1315-28.
29. Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, *et al.* Radiation-associated liver injury. Int J Radiat Oncol Biol Phys 2010;76:S94-100.
30. Zhang J, Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Langbein T, *et al.* (177)Lu-PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer patients with a single functioning kidney. J Nucl Med 2019;60:1579-86.
31. Yilmaz B, Nisli S, Ergul N, Gursu RU, Acikgoz O, Çermik TF. Effect of external cooling on (177)Lu-PSMA uptake by the parotid glands. J Nucl Med 2019;60:1388-93.
32. Sandström M, Garske-Román U, Granberg D, Johansson S, Widström C, Eriksson B, *et al.* Individualized dosimetry of kidney and bone marrow in patients undergoing 177Lu-DOTA-octreotate treatment. J Nucl Med 2013;54:33-41.
33. Hagmarker L, Svensson J, Rydén T, van Essen M, Sundlöv A, Gleisner KS, *et al.* Bone marrow absorbed doses and correlations with hematologic response during (177)Lu-DOTATATE treatments are ınfluenced by ımage-based dosimetry method and presence of skeletal metastases. J Nucl Med 2019;60:1406-13.