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Dosimetric Analysis of a Phase I Study of PSMA-Targeting Radiopharmaceutical Therapy With [^{177}Lu]Ludotadipep in Patients With Metastatic Castration-Resistant Prostate Cancer

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Objective: ^{177}Lutetium [Lu] Ludotadipep is a novel prostate-specific membrane antigen targeting therapeutic agent with an albumin motif added to increase uptake in the tumors. We assessed the biodistribution and dosimetry of [^{177}Lu]Ludotadipep in patients with metastatic castration-resistant prostate cancer (mCRPC).

Materials and Methods: Data from 25 patients (median age, 73 years; range, 60–90) with mCRPC from a phase I study with activity escalation design of single administration of [^{177}Lu]Ludotadipep (1.85, 2.78, 3.70, 4.63, and 5.55 GBq) were assessed. Activity in the salivary glands, lungs, liver, kidneys, and spleen was estimated from whole-body scan and abdominal SPECT/CT images acquired at 2, 24, 48, 72, and 168 h after administration of [^{177}Lu]Ludotadipep. Red marrow activity was calculated from blood samples obtained at 3, 10, 30, 60, and 180 min, and at 24, 48, and 72 h after administration. Organ- and tumor-based absorbed dose calculations were performed using IDAC-Dose 2.1.

Results: Absorbed dose coefficient (mean ± standard deviation) of normal organs was 1.17 ± 0.81 Gy/GBq for salivary glands, 0.05 ± 0.02 Gy/GBq for lungs, 0.14 ± 0.06 Gy/GBq for liver, 0.77 ± 0.28 Gy/GBq for kidneys, 0.12 ± 0.06 Gy/GBq for spleen, and 0.07 ± 0.02 Gy/GBq for red marrow. The absorbed dose coefficient of the tumors was 10.43 ± 7.77 Gy/GBq.

Conclusion: [^{177}Lu]Ludotadipep is expected to be safe at the dose of 3.7 GBq times 6 cycles planned for a phase II clinical trial with kidneys and bone marrow being the critical organs, and shows a high tumor absorbed dose.

Keywords: PSMA; mCRPC; Radiopharmaceutical therapy; Dosimetry; Albumin

INTRODUCTION

The prostate-specific membrane antigen (PSMA) is a transmembrane protein highly expressed in prostate cancer cells [1]. PSMA functions as a folate hydrolase and glutamate carboxypeptidase, and although it is associated with more aggressive prostate cancer, its role in prostate cancer progression is not completely understood [2,3]. Numerous glutamate-ureido-lysine (GUL)-based compounds that bind with high affinity to the substrate recognition

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site of PSMA have been developed for imaging and therapy. Following clinical trials demonstrating improved survival outcomes, ^{177}Lutetium [Lu]Lu-labeled PSMA-targeting radiopharmaceuticals are now a treatment option for patients with metastatic castration-resistant prostate cancer (mCRPC).

Dosimetry of the commercially available [^{177}Lu]Lu-PSMA-617 showed rapid clearance from the blood pool as could be expected from small molecules, with a mean total body time-integrated activity coefficient of 37.9 ± 14.6 hours (h) reported [4,5]. Up to 6 cycles were administered in clinical trials that demonstrated clinical benefit of [^{177}Lu]Lu-PSMA-617 (7.4 GBq in the VISION trial and 6.0–8.5 GBq in the TheraP trial) [6,7]. To overcome the limitations of small-molecule radiopharmaceutical compounds that wash out quickly, various albumin-binding PSMA targets have been developed to prolong circulation time [8-13]. [^{177}Lu]Ludotadipep is a novel PSMA inhibitor labeled with [^{177}Lu]Lu, and its 4-(4-iodophenyl) butanoly moiety functions as an albumin binder to extend the blood circulation time (Fig. 1). In the PC3-PIP animal model, tumor uptake increased over 72 h, and tumor growth was inhibited in mice treated with 4 or 6 MBq of [^{177}Lu]Ludotadipep [14].

This study aimed to assess the biodistribution and dosimetry of single administration of [^{177}Lu]Ludotadipep in patients with mCRPC.

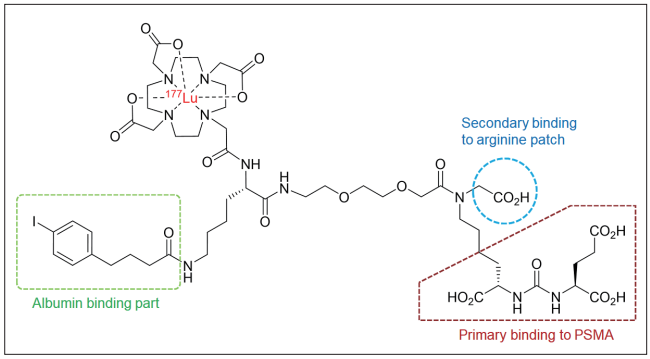

Fig. 1. [^{177}Lu]Ludotadipep structure. [^{177}Lu]Lutetium(III) 2,2′,2″-(10-((4S,20S,24S)-20,24,26-tricarboxy-15-(carboxymethyl)-4-(4-(4-(4-iodophenyl)butanamido)butyl)-2,5,14,22-tetraoxo-9,12-dioxa-3,6,15,21,23-pentaazahexacosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate. The iodophenylbutanoly group (in green box) acts as an albumin binder, and increases circulation time and target uptake of the radiopharmaceutical. PSMA = prostate-specific membrane antigen

MATERIALS AND METHODS

Study Design

This study was approved by the hospital's Institutional Review Board (IRB No. KC20MDSF0483) and the Korean Ministry of Food and Drug Safety (KMFDS). Written informed consent was obtained from all participants and the study was conducted in compliance with the Declaration of Helsinki and local regulations (ClinicalTrials.gov Identifier: NCT04509557). In this phase I clinical trial, patients with mCRPC (blood testosterone level < 50 ng/dL) who progressed after standard treatment were enrolled [15]. [^{177}Lu]Ludotadipep doses of 1.85, 2.78, 3.70, 4.63, and 5.55 GBq were administered once in each subject and safety assessments were made at 2-, 3-, 4-, 6-, 8-, and 12-weeks post-injection (p.i.). In this activity escalation design, patient enrollment for the next dose began only if dose-limiting toxicity (grade 4 thrombocytopenia, grade 4 neutropenia, grade 3 febrile neutropenia, and other grade 3 or 4 non-hematological toxicities persisting for 5 days or more) was observed at 8 weeks in two or less of each group of six subjects.

Subjects were screened with [^{18}F]Florastamin PSMA PET/CT [16] for lesions with PSMA-reporting and data systems (RADS)-4 or 5 [17]. All screened patients had a history of disease progression following taxane-based chemotherapy and androgen receptor-targeted agents. A total of six subjects were included in each of the five dose groups, but one did not receive [^{177}Lu]udotadipep and four subjects did not have p.i. images for assessment (n = 4 due to COVID19 restrictions, and n = 1 for emergency surgery), and a total of 25 subjects were assessed for biodistribution and dosimetry.

Radiopharmaceuticals

[^{18}F]Florastamin was manufactured using an automatic synthesizer as previously described [16]. A good manufacturing practice-grade lutetium no-carrier-added product (Isotopia Molecular Imaging) approved by the Food and Drug Administration and European Medicines Agency was used for the radiolabeling of [^{177}Lu]Ludotadipep. [^{177}Lu]$LuCl_3$ solution was added to a reaction vial containing 1M NaOAc/HCl buffer (pH 4.88), L-ascorbic acid, and the Ludotadipep precursor solution. The reaction mixture was heated at 90°C for 5–10 min. The solid-phase purification was performed using a C-18 light cartridge. Tests were performed on the appearance and particle size, pH, identification (radioisotope, radiochemistry), purity

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(radiochemical, residual solvent, chemical), bacterial endotoxin (limulus amebocyte lysate test), and sterility to confirm the quality of [^{18}F]Florastamin and [^{177}Lu] Ludotadipep.

[^{18}F]Florastamin PSMA PET/CT

To evaluate adequate PSMA expression in tumors, [^{18}F] Florastamin, which has the same primary binding domain consisting of Glu-urea-Lys as that of [^{177}Lu] Ludotadipep, was used as a diagnostic radioligand. [^{18}F]Florastamin PSMA PET/CT was performed at screening, 4 weeks p.i., and 8 weeks p.i. using a dedicated PET/CT scanner (Discovery 710, GE Healthcare, Chicago, IL, USA). PET/CT images were acquired 90 min after the intravenous injection of 185 ± 19 MBq of [^{18}F]Florastamin. The static images were reconstructed using the ordered-subset expectation maximization and point-spread function (VPFX-S) method. The pre-treatment tumor maximum standardized uptake value (SUVmax) was measured using screening [^{18}F]Florastamin PSMA PET/CT. Additionally, the total PSMA-expression-positive tumor burden was defined and measured: total PSMA-tumor burden = (SUV mean)·(total tumor volume), applying fixed threshold of SUV 2.5 for segmentation of all visible tumor lesions on the [^{18}F]Florastamin PSMA PET/CT using LIFEx software v.7.0.16 [18]. [^{18}F]-Fluorodeoxyglucose PET/CT was not performed.

^{177}Lu-Imaging and Blood Sampling

To evaluate organ level dosimetry, both whole body scan (WBS) and abdomen SPECT/CT (SymbiaT6, Siemens, Healthineers, Erlangen, Germany) were obtained at 2, 24, 48, 72, and 168 h p.i. WBS were acquired with medium energy collimator, 20% energy window centered on the energy peak of 208 keV (187.2–228.8 keV) and scan speed of 17 cm/min. In the subset of subjects administered with 5550 MBq, WBS was acquired with the following dual energy window (photopeak window 187.2–228.8 keV, scatter window 153.9–187.2 keV). A vial of the calibration source containing 3.7 MBq ^{177}Lu was placed between the knees at each time point to calibrate the images with attenuation and scatter correction. SPECT/CT images were acquired with a medium-energy collimator, 187.2–228.8 keV energy window, step and shoot for 60 frames, 15 s/frame, at a 180° angle, and reconstructed with CT-based attenuation correction and scatter correction according to the manufacturer's standard reconstruction method. To evaluate bone marrow dosimetry, 1–3 mL of peripheral venous blood samples was obtained from the arm opposite the radiopharmaceutical injection site at 3, 10, 60, 180 min, 24, 48, and 72 h p.i.

Dose Calculations

The salivary glands, lungs, liver, kidneys, spleen, and red marrow were defined as accumulating organs. The activities of the liver, kidneys, and spleen at each time point were estimated from SPECT/CT images, whereas the activities of the salivary glands and lungs were estimated from the WBS. Red marrow activity was estimated from the blood samples. Lesions that were definite tumors based on all available data (previous anatomical images, [^{18}F]Florastamin PET/CT, and pathology results when available) and lesions with uptake that could reliably be accounted for by the tumor alone (i.e., lesions with uptake that could be clearly distinguished from the background activity on WBS and SPECT/CT) were selected to estimate the tumor absorbed dose. Lesions > 2 cm^3 in volume were selected to minimize the partial volume effect. The SUV on [^{18}F]Florastamin PET/CT was not considered during selection.

QDOSE software v.1.1.18 (ABX-CRO, Dresden, Germany) was used to draw the region of interest (ROI) on the WBS and SPECT images, time-activity curve (TAC) fitting, and dose calculation. The ROI of the source tissues was drawn by sequential automatic segmentation using the fuzzy c-mean algorithm with the following settings: three clusters, 1.1 of weight exponent, and 3–4 included regions volume/activity, after co-registration of images for each time point. When necessary, an experienced nuclear medicine physician adjusted the ROI manually. The 2-dimentional activity calculations, including attenuation, scatter, and background corrections for the measurement of activity A_j for each source tissue ROI, were done referencing MIRD pamphlets 16 and 26 [19,20].

Bone marrow dosimetry was calculated using the venous blood samples. The intravenously administered [^{177}Lu] Ludotadipep was assumed to be uniformly distributed within the plasma and extracellular fluid spaces of the red marrow. A standardized solution of ^{177}Lu with 3.7 MBq/mL at the time of [^{177}Lu]Ludotadipep administration was diluted by x 3, x 10, x 100 a week later and used to calibrate the gamma well counter. Red marrow-to-blood activity concentration ratio (RMBLR) of 1.0 was used [21,22]. Details of the dosimetry methods applied in this study are presented in the Supplementary Methods.

TAC Fitting and Absorbed Dose Analysis

The TAC of the source tissue was calculated using bi-

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exponential fitting, except for the salivary glands. For the salivary glands and tumor lesions, the peaks were observed at later time points (24, 48, or 72 h p.i.), and the area under the curve was calculated by combining the trapezoidal method up to the peak and the mono-exponential function after the peak. The absorbed dose of the normal organs was calculated according to IDAC-Dose 2.1 implemented in the QDOSE software. The absorbed dose of tumor was calculated using a spherical model, assuming a density of 1 g/cm^3 after measuring the volume from [^{18}F]Florastamin PSMA PET by applying SUV threshold of 40% of maximum for tumor segmentation, which corresponded well to the anatomical margin seen on the CT images. The effective dose was calculated using the International Commission on Radiological Protection publication 103 weighting factors.

Statistical Analysis

Spearman's correlation test was performed to test the linear correlation between 1) pre-treatment tumor SUVmax and tumor absorbed dose coefficient and 2) total PSMA-tumor burden and absorbed doses of the salivary glands and kidneys. A partial correlation test was applied to control for the effect of tumor mass as a covariate, in addition to the correlation test between pre-treatment tumor SUVmax and tumor absorbed dose. A two-sided *P*-value less than 0.050 was considered statistically significant. Statistical analyses were performed using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

Data from 25 male (median age 73 years, range 60–90 years) were analyzed. No dose-limiting toxicities were observed. The average of total PSMA-tumor burden was 2620 cm^3 [25.1–28000 cm^3], and the 5.55 GBq dose group had the highest total PSMA-tumor burden of 8830 cm^3 [1790–28000 cm^3]. Patient characteristics are presented in Table 1. Images of a representative case are shown in Figure 2.

Biodistribution

Blood clearance of [^{177}Lu]Ludotadipep was relatively prolonged, falling to 70.7% ± 7.0% of the injected dose at 3 min p.i., 24.0% ± 9.2% at 1 h p.i., 7.5% ± 3.3% at 24 h p.i., 4.7% ± 1.7% at 48 h p.i., and 4.2% ± 1.0% at 72 h p.i. (Fig. 3). The half-times of the distribution phase and clearance phase were calculated as 27.0 ± 7.1 min

Table 1. Patient characteristics

	Group 1 of 1.85 GBq (n = 3)	Group 2 of 2.78 GBq (n = 6)	Group 3 of 3.70 GBq (n = 6)	Group 4 of 4.63 GBq (n = 6)	Group 5 of 5.55 GBq (n = 4)	Total (n = 25)
Administered activity, GBq	1.87 ± 0.02	2.85 ± 0.04	3.80 ± 0.04	4.83 ± 0.10	5.60 ± 0.04	-
Age, yrs	65 [63–78]	73.5 [63–83]	76.5 [64–90]	68 [60–86]	77.5 [73–83]	73 [60–90]
Gleason score	8 [8–10]	8 [7–9]	9 [7–9]	7.5 [7–9]	7.5 [7–10]	8 [7–10]
PSA, ng/mL	120 [7.9–125]	119 [18.7–545]	63.3 [5.3–149]	114 [58.7–3190]	790 [230–2990]	123 [5.3–2990]
Total PSMA tumor burden, g	418 [35.7–6280]	2890 [25.1–10000]	339 [49.2–3170]	4240 [618–5750]	8830 [1790–28000]	2620 [25.1–28000]

Data are mean ± standard deviation or median [range].
PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen

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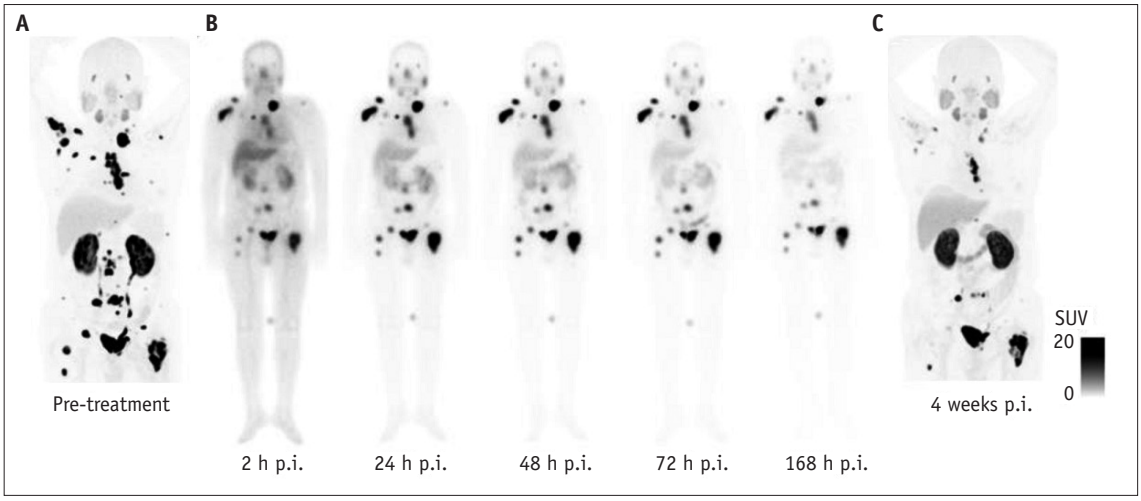

Fig. 2. A representative case. **A:** Pre-treatment [^{18}F]Florastamin PSMA PET/CT image of a patient with multiple bone and lymph node metastases. **B:** Serial whole body scans following administration of 4.63 GBq of [^{177}Lu]Ludotadipep demonstrate high uptakes in the sites corresponding to metastases seen on the PET/CT images. **C:** Post-radiopharmaceutical therapy [^{18}F]Florastamin PSMA PET/CT images show decreased intensity and extent of the tumors. PSMA = prostate-specific membrane antigen, p.i. = post-injection, SUV = standardized uptake value

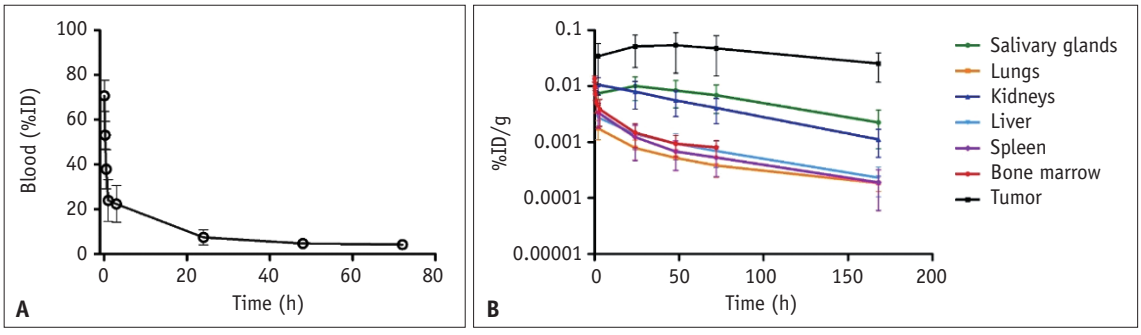

Fig. 3. Time-activity curves of [^{177}Lu]Ludotadipep **(A)** blood clearance and **(B)** normal organs and tumor.

Table 2. Absorbed dose coefficient of the source organs

Group (planned activity)	Absorbed dose coefficient (Gy/GBq)					
	Salivary glands	Lungs	Liver	Kidneys	Spleen	Bone marrow
Group 1 (1.85 GBq)	1.84 ± 1.52	0.04 ± 0.01	0.18 ± 0.09	0.86 ± 0.25	0.14 ± 0.05	NA†
Group 2 (2.78 GBq)	1.17 ± 0.43	0.06 ± 0.01	0.13 ± 0.05	0.78 ± 0.28	0.10 ± 0.02	NA†
Group 3 (3.70 GBq)	1.26 ± 0.69	0.06 ± 0.03	0.15 ± 0.06	0.76 ± 0.27	0.15 ± 0.06	0.09‡
Group 4 (4.63 GBq)	0.89 ± 0.74	0.05 ± 0.01	0.13 ± 0.05	0.65 ± 0.31	0.11 ± 0.08	0.07 ± 0.01
Group 5 (5.55 GBq)	0.97 ± 0.27	NA*	0.12 ± 0.06	0.47 ± 0.25	0.07 ± 0.03	0.06 ± 0.02
All doses	1.17 ± 0.81	0.05 ± 0.02	0.14 ± 0.06	0.77 ± 0.28	0.12 ± 0.06	0.07 ± 0.02

Data are mean ± standard deviation.
*Disseminated rib metastases, †Insufficient blood sample data, ‡Data from one subject.
NA = not assessable

and 60.3 ± 59.0 h, respectively. Among the normal organs, the highest activity level was $1.06 \pm 0.37 \cdot 10^{-2}$%ID/g in the kidneys at 2 h p.i. and $1.00 \pm 0.46 \cdot 10^{-2}$%ID/g in the salivary glands at 24 h p.i. The peaks were lower in the lungs ($0.18 \pm 0.07 \cdot 10^{-2}$%ID/g), liver ($0.28 \pm 0.08 \cdot 10^{-2}$%ID/g), and spleen ($0.34 \pm 0.16 \cdot 10^{-2}$%ID/g), all observed at 2 h p.i. The peak activity of tumor was $5.38 \pm 3.66 \cdot 10^{-2}$%ID/g at 48 h p.i.

Organ and Tumor Dosimetry

Table 2 summarizes the absorbed doses in normal organs. Salivary glands had the highest absorbed dose coefficient of 1.17 ± 0.81 Gy/GBq. The absorbed dose coefficient of kidney

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Table 3. Tumor absorbed dose

Lesion number	Administered activity (GBq)	Tumor site	Tumor volume (cm^3)	Pre-treatment PSMA PET SUVmax	Pre-treatment PSMA PET SUVavg	Absorbed dose (Gy)	Absorbed dose coefficient (Gy/GBq)
1	1.86	Lumbar vertebra	7.5	41.6	9.1	19.7	10.6
2	1.86	Pelvic bone	8.1	58.7	15.0	66.7	35.8
3	1.85	Lumbar vertebra	3.8	6.8	3.7	1.8	0.9
4	1.89	Lumbar vertebra	16.7	9.3	3.9	6.7	3.5
5	2.83	Thoracic vertebra	18.3	23.5	8.8	30.4	10.7
6	2.90	Thoracic vertebra	12.0	26.6	11.0	19.9	6.9
7	2.81	Thoracic vertebra	3.0	9.9	4.7	11.0	3.9
8	3.75	Mesenteric lymph node	3.3	7.9	4.2	29.4	7.9
9	3.83	Thoracic vertebra	2.7	21.3	7.5	42.2	11.0
10	3.83	Lumbar vertebra	2.7	23.7	9.5	106.0	27.6
11	3.86	Thoracic vertebra	12.4	8.7	4.3	37.0	9.6
12	4.85	Thoracic vertebra	23.5	23.2	9.1	42.7	8.8
13	4.85	Lumbar vertebra	18.4	29.7	8.5	29.4	6.1
14	4.85	Lumbar vertebra	15.1	27.2	8.5	59.1	12.2
15	4.86	Rib	3.5	15.9	7.0	58.7	12.1
16	4.86	Thoracic vertebra	3.5	13.2	13.2	28.1	5.8
17	4.86	Lumbar vertebra	2.5	22.0	7.8	34.4	7.1
18	4.86	Lumbar vertebra	3.7	33.4	11.5	52.8	10.9
19	4.74	Aortocaval lymph node	4.1	12.5	7.9	25.4	5.4
20	4.66	Lumbar vertebra	50.2	15.1	6.5	39.3	8.9
21	4.66	Lumbar vertebra	39.5	17.2	6.0	41.6	8.9
22	5.59	Lumbar vertebra	14.8	17.2	5.7	38.2	6.8
23	5.63	Lumbar vertebra	5.8	52.1	14.1	39.7	7.0
24	5.63	Thoracic vertebra	2.0	51.3	11.1	123.9	22.0
Median [range]			6.7 [2.0–50.2]	21.7 [6.8–58.7]	8.2 [3.7–15.0]	37.6 [1.8–123.9]	8.9 [0.9–35.8]

PSMA = prostate-specific membrane antigen, SUVmax = maximum standardized uptake value, SUVavg = average standardized uptake value

and bone marrow was calculated as 0.77 ± 0.28 Gy/GBq and 0.07 ± 0.02 Gy/GBq, respectively. Table 3 describes the twenty-four tumor lesions selected for the tumor dosimetry analysis. The average volume was 11.55 ± 12.16 cm^3, and the average absorbed dose coefficient of tumors was computed as 10.43 ± 7.77 Gy/GBq.

Pre-Treatment [^{18}F]Florastamin PSMA PET vs. Absorbed Dose

The absorbed dose coefficient of the salivary glands showed a positive correlation with the SUVmax of the submandibular glands measured on pre-treatment [^{18}F] Florastamin PSMA PET (rho = 0.78, P < 0.001) and parotid glands (rho = 0.42, P = 0.035). There was also a significant positive correlation between the absorbed dose coefficient of individual tumors and the pre-treatment tumor SUVmax (rho = 0.56, P = 0.005) and average standardized uptake value (SUVavg) (rho = 0.46, P = 0.026) (Fig. 4). There was no significant difference in the rho between the SUVmax and SUVavg data (P = 0.66).

Salivary gland doses showed a significant negative correlation with total PSMA-tumor burden (rho = -0.50, P = 0.011) (Fig. 5). The absorbed dose coefficient of other source tissues did not significantly correlate with the total PSMA-tumor burden (P > 0.050).

DISCUSSION

In this first-in-human study of a novel PSMA-targeting radiopharmaceutical [^{177}Lu]Ludotadipep, data from 25 subjects were assessed for biodistribution and dosimetry. Blood clearance of [^{177}Lu]Ludotadipep was prolonged with half-times the distribution phase and clearance phase being 0.45 ± 0.12 h and 60.3 ± 59.0 h, respectively, compared to 0.16 ± 0.09 h and 10.8 ± 2.5 h reported for [^{177}Lu]Lu-PSMA-617 [23]. A peak in the kidneys was observed in

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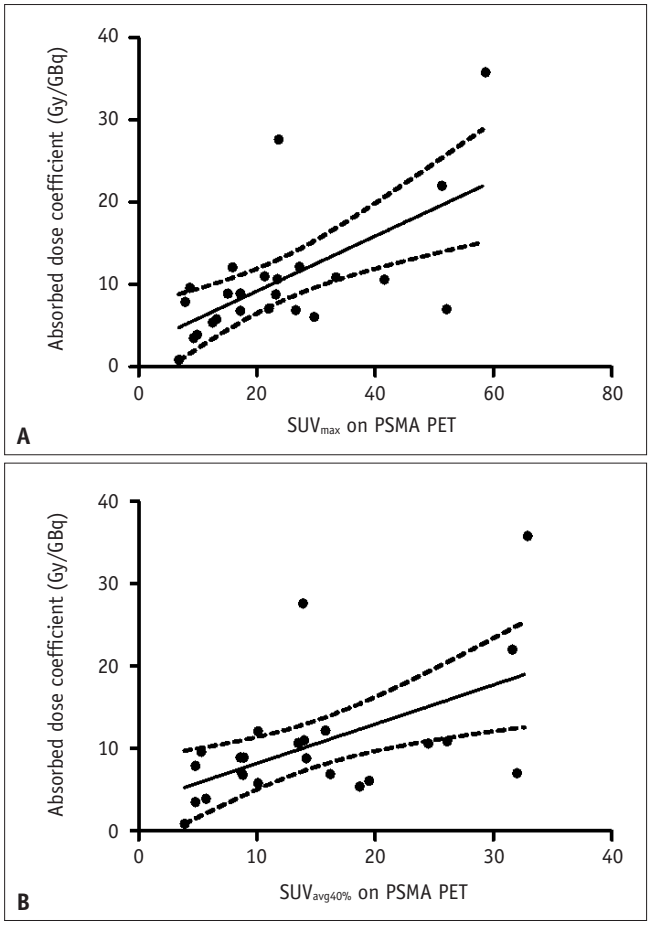

Fig. 4. Correlation of SUV from pre-treatment [^{18}F]Florastamin PSMA PET/CT with absorbed dose coefficient for tumor lesions. Correlation plots with SUVmax **(A)** and SUVavg using 40% of SUVmax as a fixed threshold **(B)**. SUV = standardized uptake value, PSMA = prostate-specific membrane antigen, SUVmax = maximum standardized uptake value, SUVavg = average standardized uptake value

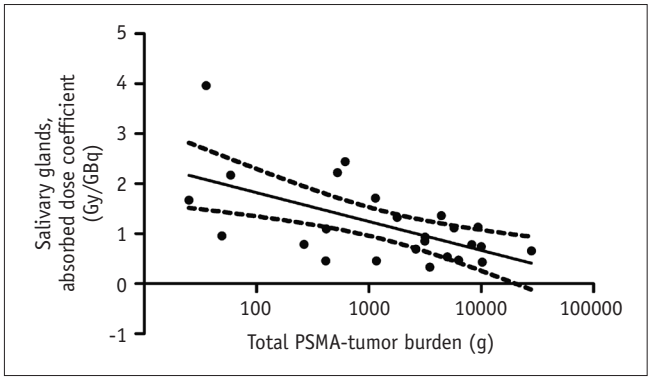

Fig. 5. Tumor sink effect observed as negative correlation between total PSMA-positive tumor burden and absorbed dose of the salivary glands. PSMA = prostate-specific membrane antigen

the first set of images obtained 2 h p.i. The mean tumor-absorbed dose coefficient was 13.6 times higher than the mean absorbed dose coefficient of the kidneys and 8.7 times higher than that of the salivary glands. As previously reported, a tumor sink effect was observed in the salivary glands of the study population [24]. Overall, the absorbed dose coefficients in various normal organs were comparable for the different activities of [^{177}Lu]Ludotadipep administered.

The red marrow was a dose limiting organ with absorbed dose coefficient of 0.07 Gy/GBq, and applying the RMBLR of 1.0 and limit of 2 Gy, the maximum injectable activity of [^{177}Lu]Ludotadipep was projected as 29.85 GBq per patient. The kidneys, another dose limiting organ with absorbed dose coefficient of 0.77 Gy/GBq and applying limit of 23 Gy derived from data of external beam radiation therapy (EBRT), allows similar maximum injectable activity of 29.87 GBq per patient. A higher maximum injectable activity can be considered if a biologically effective dose of 40 Gy is applied as the renal dose limit in radioligand therapy, considering its low radiation dose rate compared with EBRT [25,26]. The mean absorbed dose coefficient in the tumors selected for assessment in this study was 10.43 ± 7.77 Gy/GBq, which may be high compared to the reported values for [^{177}Lu]Lu-PSMA-617, I&T, or J591 [27-29]. It should be noted that the pre-treatment PSMA SUVmax of the tumors selected for dosimetry was relatively low (< 10.0) in 5 out of 24 assessed lesions in our study. However, as only [^{177}Lu]Ludotadipep was used in this study, and considering the wide variability of inter- and intra-patient tumor PSMA expression, dosimetry profiles, and dosimetry computation methods [30-32] it would be injudicious to directly compare the reported tumor absorbed dose values of various PSMA-targeting compounds were directly compared. Full therapeutic efficacy can only be appreciated after long-term clinical outcome data are available.

[^{177}Lu]Ludotadipep has an iodophenylbutanoly group incorporated for affinity to serum albumin [14]. A couple of other PSMA-targeting radiopharmaceuticals that were modified to increase tumor uptake by increasing albumin binding have published dosimetry data obtained from patients with mCRPC. Evans blue (EB), the dye that binds to serum albumin with moderate affinity [33], and [^{177}Lu]Lu-PSMA-617 with a truncated EB molecule, [^{177}Lu]Lu-EB-PSMA-617, showed a longer circulation time and improved tumor uptake than [^{177}Lu]Lu-PSMA-617 [10]. [^{177}Lu]Lu-PSMA-ALB-56 contains a PSMA ligand with a p-tolyl-entity that shows lower background activity in mice [34]. In this study, the computed radiation to the kidneys with [^{177}Lu]Ludotadipep was 0.77 ± 0.28 Gy/GBq, which may be low

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when compared to the published data for [^{177}Lu]Lu-PSMA-ALB-56 (2.54 ± 0.94 Gy/GBq) and [^{177}Lu]Lu-EB-PSMA-617 (2.38 ± 0.69 Gy/GBq) [8,10]. The favorable renal dosimetry of [^{177}Lu]Ludotadipep could be attributed to the earlier peak renal activity at 2 h p.i. compared to that of [^{177}Lu]Lu-PSMA-ALB-56 (24 h p.i.) and [^{177}Lu]Lu-EB-PSMA-617 (72 h p.i.). The computed dose to the red marrow for [^{177}Lu]Ludotadipep (0.07 ± 0.02 Gy/GBq) was higher than [^{177}Lu]Lu-EB-PSMA-617 (0.05 ± 0.01 Gy/GBq) and lower than [^{177}Lu]Lu-ALB-56 (0.29 ± 0.07 Gy/GBq), while the salivary gland findings were reversed ([^{177}Lu]Lu-ALB-56 0.86 ± 0.42 Gy/GBq, vs. [^{177}Lu]Ludotadipep 1.17 ± 0.81 Gy/GBq, vs. [^{177}Lu]Lu-EB-PSMA-617 6.41 ± 1.40 Gy/GBq) [8,10]. The absorbed dose to the kidneys observed in this study was about twice the preclinical dose that was estimated based on biodistribution in mice, which had been calculated as 0.03 Gy/GBq, reflecting the difference between the species and highlighting the difficulty of estimating human dose and variability that comes from different masses. Newer radiopharmaceuticals with albumin binders, such as [^{177}Lu]HTK03121 reported a 2.9 fold improvement in the tumor-to-kidney absorbed dose ratio compared to [^{177}Lu]Lu-PSMA-617 in animal LNCaP tumor-bearing mice [35], and it remains to be seen if this advantage is retained in patients.

In our study, up to 5.6 GBq of [^{177}Lu]Ludotadipep was administered once to patients without immediate complications or an incidence of grade 3 or 4 toxicity. In a study with patients in three escalating activities (1.2, 2.1, and 3.5 GBq) of up to 3 cycles of [^{177}Lu]Lu-EB-PSMA-617 radiopharmaceutical therapy at 8-week intervals, 2.1 GBq was shown to be safe and adequate in tumor treatment [36]. Data are currently being collected for a more comprehensive assessment of the clinical safety profile and the efficacy of [^{177}Lu]Ludotadipep. Based on the available data so far, the KMFDS has approved phase II clinical trial with up to 3.7 GBq x 6 cycles of [^{177}Lu]Ludotadipep. In a multicycle clinical trial, positively charged amino acid infusion was added to the protocol for kidney protection. We used a more conservative RMBLR (1.0) for the estimation of the bone marrow dose, as recommended for both [^{177}Lu]Lu-SSRT and [^{177}Lu]Lu-PSMA [22], but a lower RMBLR could be more appropriate for [^{177}Lu]Ludotadipep considering its albumin-binding character. Additionally, 3 Gy as the marrow dose limit instead of 2 Gy should be cautiously tested in the future to better understand normal tissue tolerance to radiopharmaceutical therapy [37,38].

This pilot dosimetry study of [^{177}Lu]Ludotadipep had several limitations. Whole-body scans were acquired in different energy windows, and blood sampling was performed in only half of the patients. Instead of the total tumor burden, a selected minority of the tumor lesions was assessed for the absorbed dose, and the majority were vertebral metastases. Real-life scenarios, such as impaired renal function or constipation of the patient, spillover from bone and paravertebral metastases to the bone marrow, changes in tumor PSMA expression, and total tumor volume over the therapeutic period, could create room for discrepancy from dosimetry estimates based on blood samples and images, especially for multiple cycles of therapy.

In conclusion, [^{177}Lu]Ludotadipep showed a dosimetry profile that is expected to be safe at a dose of 6 cycles of 3.7 GBq planned for a phase II clinical trial, with kidneys and bone marrow as the critical organs. At the projected maximum injected activity, the tumor-absorbed dose in human subjects was computed to be comparably high for [^{177}Lu]Ludotadipep as for various [^{177}Lu]Lu-labeled PSMA-targeting radiopharmaceuticals reported in the literature.

Supplement

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Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Chansoo Park is an employee of FutureChem Co., Ltd., and Dae Yoon Chi is its chief executive officer. Seunggyun Ha has consultant agreement with FutureChem. Joo Hyun O has consultant agreements with FutureChem and Novartis, and as a member of the editorial board of the *Korean Journal of Radiology*, she was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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