68Ga-DOTA-DiPSMA PET/CT Imaging: Biodistribution, Dosimetry and First Comparison with 68Ga-PSMA-11 in Prostate Cancer

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Abstract

Purpose

This prospective trial aimed to evaluate the safety, dosimetry, biodistribution, and diagnostic efficacy of a novel theranostic probe ^{68}Ga -DOTA-DiPSMA. Also, we have performed the first comparison with ^{68}Ga -PSMA-11 in prostate cancer (PCa) patients.

Methods

Five healthy volunteers and ten PCa patients with a previous clinical ^{68}Ga -PSMA-11 PET/CT were injected with an intravenous bolus of ^{68}Ga -DOTA-DiPSMA with a dose of 1.85MBq/kg. Healthy volunteers received serial whole-body PET scans from the time of injection up to 60 min post-injection, with a second PET/CT scanning at 120 min post-injection. In PCa patients, low-dose CT scan, whole-body PET was performed with 2 min per bed position in 40 min post-injection. In addition, ^{68}Ga -PSMA-11 scanning was performed on PCa patients within 10 days under the same acquisition procedure. Absorbed organ doses and effective doses were calculated using OLINDA/EXM. Normal organ uptake and tumor lesion uptake (SUV_{max}) were measured. A lesion-by-lesion analysis was performed.

Results

^{68}Ga -DOTA-DiPSMA administration was safe and well-tolerated. The kidneys received the highest absorbed dose ($114.46 \pm 29.28 \text{ uSv/MBq}$), followed by the urinary bladder wall ($100.82 \pm 46.22 \text{ uSv/MBq}$) in accordance with the expected PSMA renal excretion of the tracer. The mean effective dose was $19.46 \pm 1.73 \text{ }\mu\text{Sv/MBq}$. The SUV_{max} of ^{68}Ga -PSMA-11 and ^{68}Ga -DOTA-DiPSMA PET/CT for PCa lesions, bone metastases, and lymph node metastases were 11.2 ± 10.76 vs. 4.41 ± 2.72 , 7.6 ± 1.58 vs. 2.95 ± 1.11 and 4.86 ± 1.94 vs. 3.26 ± 1.2 , respectively.

Conclusion

Injection of ^{68}Ga -DOTA-DiPSMA is safe and associated with low absorbed and effective doses. Compared to ^{68}Ga -PSMA-11, ^{68}Ga -DOTA-DiPSMA shows comparable pharmacokinetics and detection ability in PCa patients that warrant further head-to-head comparison. Low non-specific uptake in salivary glands and kidneys of ^{68}Ga -DOTA-DiPSMA indicates potential radioligand therapy (RLT) application when labeled with ^{177}Lu , ^{90}Y , or ^{225}Ac .

Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer in men and one of the lethal malignant diseases leading to male cancer-related death worldwide [1]. The accurate presence and location of primary or recurrent tumors are critical for planning effective patient management [2].

The diagnostic capability of conventional anatomic imaging such as MRI and CT to determine prostate cancer is limited in metastases and specificity [3]. Only prostate biopsy is the definitive way to confirm prostate cancer [1]. Multiple needle biopsy will increase the positive rate of lesions determination significantly. However, it is difficult to determine distant metastases and increase the risk of complications resulting from biopsy operation [1]. There has been an unmet need for more advanced imaging modalities to determine primary and metastatic lesions that can be helpful to prostate cancer patient management (observation, salvage local therapy, systemic therapy). PET with ^{18}F -FDG is effective for most malignant tumors, but it has insufficient specificity for prostate cancer and is prone to have false-positive results. Therefore, it is urgent to discover new nuclear medicine imaging agents with more specificity for prostate cancer.

Prostate-Specific Membrane Antigen (PSMA) is a transmembrane glycoprotein enzyme selectively overexpressed in prostate cancer cells, with its expression increasing in higher-grade malignancy [4]. PET imaging with PSMA probes targeting various prostate cancer-specific markers will provide additional molecular information to facilitate lesion detection and staging [5].

Recently, a relatively new nuclear imaging modality ^{68}Ga -PSMA PET/CT imaging with good PCa diagnosis and staging performance, has become increasingly utilized to evaluate PCa aggressiveness, especially in patients with biochemical recurrence after surgery [6-8]. PSMA can be coupled with different chelators and labeled with corresponding radionuclides for different purposes. The most widely used PSMA ligands in clinical examination are PSMA-11 and PSMA-617 containing different linkers and chelators. According to the previously published papers, ^{68}Ga -PSMA-11 and ^{177}Lu -PSMA-617 are molecular-pair in metastatic castration-resistant PCa (mCRPC) diagnosis and radioligand therapy (RLT) [9,10]. However, considering the high nonspecific uptake in the salivary, kidney, and bone marrow of ^{68}Ga -PSMA-11 and ^{177}Lu -PSMA-617, novel PSMA tracers with low accumulation in normal organs are urgently needed.

We have discovered a PSMA dimer (DOTA-DiPSMA, Fig. 1), and proved its imaging ability and low unspecific uptake (salivary, kidney) in preclinical experiments, which will be published later. In this study, we aimed to evaluate the safety, biodistribution and dosimetry of ^{68}Ga -DOTA-DiPSMA in healthy volunteers. Furthermore, a head-to-head comparison of ^{68}Ga -DOTA-DiPSMA vs. ^{68}Ga -PSMA-11, including lesion detection rate, tumor uptake, and biodistribution in PCa patients were performed.

Methods

Healthy Volunteers and Patients

This study was approved by the Independent Ethics Committee of First Affiliated Hospital of Fujian Medical University (No. MRCTA, ECFAH of FMU[2019]293). All subjects gave written informed consent and were registered at ClinicalTrials.gov (NCT04525612). Five healthy volunteers and ten patients were enrolled (Table 1; Fig. 2). Five healthy volunteers (5 men, age range 42-76 y mean age $\pm$ SD, 59.83 ± 11.65

y]; weight range, 55.0-78.0 kg [mean weight $\pm$ SD, 70.27 $\pm$ 13.05 kg]) were enrolled to validate the safety, biodistribution and radiation dosimetry of ^{68}Ga -DOTA-DiPSMA in this study. Exclusion criteria consisted of mental illness conditions, severe liver or kidney disease with serum creatinine greater than 3.0 mg/dL (270 μM), or any hepatic enzyme level 5 times or more than the standard upper limit. Participants were also excluded if they were known to have severe allergy or hypersensitivity to intravenous radiographic contrast or claustrophobia during PET/CT scanning.

A total of 10 patients who were newly diagnosed as having prostate cancer by sextant core-needle biopsy and had not received any prior therapy were enrolled with written informed consent. The inclusion criteria were being between 40 and 80 years old, having a prostate neoplasm identified by ultrasound or MRI, being diagnosed by needle biopsy as having prostate cancer. The exclusion criteria included claustrophobia, kidney or liver failure, and inability to fulfill the study. The demographics of healthy volunteers and patients are listed in Table 1. All the patients underwent ^{68}Ga -PSMA-11 PET/CT, and ^{68}Ga -DOTA-DiPSMA PET/CT for comparison within 1 week. MRI or enhanced CT and MDP (methylene diphosphonate) bone scintigraphy were performed within 2 weeks for comparison.

Subject age averaged 73.6 ± 4.6 years (median 74.5 years; range 67-80 years), and body mass averaged 65.2 ± 11 kg (median 65.4 kg; range 51.8-92.4 kg). Serum PSA values averaged 22.3 ± 17.6 ng/ml (median 13.9 ng/ml; range 6.27-60.1 ng/ml). The reported serum PSA levels were the most recent clinical values at the time of ^{68}Ga -PSMA imaging. The interval between ^{68}Ga -PSMA-11 and ^{68}Ga -DOTA-DiPSMA PET/CT imaging averaged 1.3 ± 0.5 days (median 1 day; range 1-2 days). Subjects are numbered chronologically in the order of imaging with ^{68}Ga -DOTA-DiPSMA.

Safety Assessment

Patient safety was assessed and graded according to Common Terminology Criteria for Adverse Events (version 5.0), electrocardiograms, physical examination, and vital signs (blood pressure, respiratory rate, heart rate, body temperature). Within the first 72 h after ^{68}Ga -DOTA-DiPSMA injection, the research team kept phone contact with each subject monitoring their adverse event (AE) responses.

Radiopharmaceutical Preparation

Precursors were supplied by Prof. Cui from Key Laboratory of Radiopharmaceuticals, Ministry of Education, Beijing Normal University. $^{68}\text{Ga}^{3+}$ was eluted from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator (JSC Isotope, Russian) using 0.1 M HCl and mixed with 1.25 M NaOAc buffer to adjust pH to around 4.0. Radiolabeling of DiPSMA-DOTA-COOH was performed in a sterile hot cell. The radiochemical purity of the product ^{68}Ga -DOTA-DiPSMA exceeded 99%. ^{68}Ga -PSMA-11 was synthesized following a procedure reported previously [12].

Examination Procedures

For healthy volunteers, the blood pressure, pulse, respiratory frequency, and temperature were measured, and routine blood and urine tests, liver function, and renal function were examined immediately before and 24 h after the scan. In addition, any possible side effects during ^{68}Ga -DOTA-DiPSMA PET/CT scanning and within 1 week after the examination were collected and analyzed. No specific subject preparation was requested on the day of ^{68}Ga -DOTA-DiPSMA PET/CT. For the volunteers, after the whole-body low-dose CT scan, 111-222 MBq (3-6 mCi) of ^{68}Ga -DOTA-DiPSMA were injected intravenously, followed by serial whole-body PET acquisitions. The whole body (from the top of the skull to the middle of the femur) of each volunteer was covered by 6 bed positions. The acquisition duration was 2 min/bed position at 5, 15, 30, 45, 60, and 120 min after injection.

For the patients, ^{68}Ga -DOTA-DiPSMA PET/CT scanning was performed at 40 min after tracer administration. For each patient, 1.85 MBq (0.05 mCi) of ^{68}Ga -DOTA-DiPSMA per kilogram of body weight was injected intravenously. After a low-dose CT scan, whole-body PET was performed with 2 min per bed position (5–6 bed positions depending on the patient's height). The emission data were corrected for randoms, dead time, scattering, and attenuation. The conventional reconstruction algorithm was used, and the images were zoomed with a factor of 1.2. The images were transferred to an MMWP workstation (Siemens) for analysis. All patients who were newly diagnosed with prostate cancer underwent ^{68}Ga -PSMA-11 PET/CT for comparison within 1 week. For each patient, 1.85 MBq (0.05 mCi) of ^{68}Ga -PSMA-11 per kilogram of body weight were injected intravenously. The imaging procedure and data analysis were the same as those for ^{68}Ga -DOTA-DiPSMA PET/CT.

Biodistribution Assessment and Dosimetry

Image analysis was performed using MIM v6.9.4 (MIM Software Inc., Cleveland, Ohio, USA). VOIs were drawn over healthy organs on all ^{68}Ga -DOTA-DiPSMA PET images, and SUVmean in these VOIs was determined to obtain the biodistribution of this tracer. Tumor lesions were evaluated in consensus by two nuclear medicine physicians.

All source organs with relevant detectable activity were delineated on the PET images with CT guidance for the healthy volunteers, using MIM software v6.9.4. Time-integrated activity coefficients (normalized cumulated activity; NCA) were calculated for each source organ by integrating their time-activity curves through curve fitting and normalizing the cumulated activity to the injected activity. Based on the time-integrated activity coefficients, individual absorbed organ doses and the effective dose were determined using OLINDA/EXM v1.1 (Vanderbilt University, Nashville, Tennessee, USA). Calculations were performed with modeling of urinary bladder voiding. Parameters representing the fraction leaving the body via urine and biologic half-time were obtained from the fit and used to model urinary bladder voiding. Urinary bladder voiding models with voiding intervals of 1 h were applied. The 70-kg adult male models were used. Organ-absorbed doses, effective doses, and effective dose equivalents were calculated as mean $\pm$ SD across subjects.

Results

Patient Safety

^{68}Ga -DOTA-DiPSMA was found to be safe and well-tolerated in all subjects. No adverse events or serious adverse events occurred after ^{68}Ga -DOTA-DiPSMA injection for all the healthy volunteers and patients. No apparent changes in vital signs or clinical laboratory tests were found before and after the injection of ^{68}Ga -DOTA-DiPSMA.

Biodistribution

Fig. 3, 4 illustrates the biodistribution of ^{68}Ga -DOTA-DiPSMA as a function of time in healthy volunteers. The whole-body background of ^{68}Ga -DOTA-DiPSMA was low. The highest uptake was observed in the kidney with a SUV_{mean} of 43.4 ± 26.8 at 5 min p.i. and further decreased to 11.4 ± 6.5 at 120 min p.i. The spleen, liver, salivary gland, and small intestine showed moderate uptake, with SUV_{mean} of 2.90 ± 1.5 , 1.89 ± 0.75 , 2.30 ± 0.87 , and 2.42 ± 0.64 at 30 min after injection, respectively. Low background uptake was observed in the brain, lungs, muscle, red marrow, heart, thyroid, gall bladder, pancreas, stomach, bone, and large intestine. The rapid presence in the kidneys, followed by a passage toward the urinary bladder, illustrates the tracer's fast and mainly renal excretion.

Dosimetry

The average estimated absorbed organ in healthy volunteers was summarized in Table 2. The highest absorbed dose was received by the kidneys (114.46 ± 29.28 uSv/MBq), followed by the urinary bladder wall (100.82 ± 46.22 uSv/MBq). The mean effective dose was 19.46 ± 1.73 $\mu\text{Sv/MBq}$.

Detection of Primary Prostate Cancer

For the 10 patients with primary prostate cancer, ^{68}Ga -DOTA-DiPSMA PET/CT showed 27 positive findings—including 16 prostate lesions, 4 bone metastases, 5 lymph node metastases and 2 seminal vesicle metastases. The primary lesions were confirmed by needle biopsy. SUV_{max} for prostate lesions, bone metastases, and lymph node metastases were 4.41 ± 2.72 , 2.95 ± 1.11 and 3.26 ± 1.2 , respectively. For ^{68}Ga -PSMA-11 PET/CT, all lesions were positive, with the SUV_{max} of 11.2 ± 10.76 , 7.6 ± 1.58 , and 4.86 ± 1.94 , respectively (Table 3, Fig. 5). Comparing normal tissues and organs background between ^{68}Ga -DOTA-DiPSMA and ^{68}Ga -PSMA-11 in Pca patients at 40 min p.i., significantly lower uptake was observed in the salivary glands (SUV_{max} 4.88 ± 2.04 vs. 12.15 ± 1.90 , $p = 0.000$), liver (2.92 ± 1.05 vs. 5.64 ± 1.19 , $p = 0.000$), kidney (23.40 ± 11.27 vs. 41.48 ± 11.02 , $p = 0.005$) and spleen (3.16 ± 0.64 vs. 7.78 ± 1.99 , $p = 0.000$) in ^{68}Ga -DOTA-DiPSMA, respectively (Table 4, Fig. 6).

Discussion

To our knowledge, this is the first human study to evaluate the novel tracer ^{68}Ga -DOTA-DiPSMA in healthy volunteers and patients with PCas. This tracer is a new type of Ga-68-labeled dimer PSMA imaging agent with a simple structure, easy synthesis, and low synthesis cost. ^{68}Ga -DOTA-DiPSMA can be prepared by a one-step labeling reaction in high yield greater than 95% between $^{68}\text{Ga}^{3+}$ ions eluted from a germanium-gallium generator and the precursor DiPSMA-DOTA-COOH.

Here, we presented the results of an independently performed first clinical evaluation of ^{68}Ga -DOTA-DiPSMA in five healthy volunteers, including biodistribution, dosimetry and safety. Also, we have performed the head-to-head lesion comparison of ^{68}Ga -DOTA-DiPSMA to ^{68}Ga -PSMA-11 in ten PCa patients.

The results showed that this tracer displayed favorable biodistribution, dosimetry features and well-tolerated in all patients. Both ^{68}Ga -DOTA-DiPSMA and ^{68}Ga -PSMA-11 showed high PSMA affinity. The biodistribution of ^{68}Ga -DOTA-DiPSMA was similar to that of ^{68}Ga -PSMA-11. The highest uptake was observed in the kidney and rapidly cleared through urinary system in both tracers, consistent with the published ^{68}Ga -PSMA-11 results [13-15]. ^{68}Ga -DOTA-DiPSMA PET/CT images showed lower uptake in normal organs, including salivary glands, liver and spleen than ^{68}Ga -PSMA-11.

The dosimetry data of ^{68}Ga -DOTA-DiPSMA showed a little lower yet comparable effective dose than ^{68}Ga -PSMA-11 (0.019 mSv/MBq vs. 0.022/0.023 mSv/MBq) [14,15], salivary glands (0.024 mSv/MBq vs. 0.089 /mSv/MBq), kidney (0.114 mSv/MBq vs. 0.240 mSv/MBq), liver (0.0240 mSv/MBq vs. 0.053/MBq), spleen (0.031 mSv/MBq vs. 0.046mSv/MBq), respectively [15]. We thought the lower liver and spleen dose of ^{68}Ga -DOTA-DiPSMA might be attributed to the dosimetry methodology.

It is crucial to reduce the radiation dose of non-specific organs and tissues in the field of radionuclide therapy (RLT) [16]. ^{177}Lu -PSMA-617 RLT is a promising option for patients with metastatic castration-resistant prostate cancer (mCRPC) [17-20]. Based on the lower non-specific uptake of ^{68}Ga -DOTA-DiPSMA than ^{68}Ga -PSMA-11. The radiation dosimetry in normal organs seemed to be reduced when DOTA-DiPSMA was labeled with ^{177}Lu for RLT.

A critical finding of our study is the high tumor accumulation of ^{68}Ga -DOTA-DiPSMA, which showed high tumor uptakes with the highest SUV_{max} up to 10.6 on ^{68}Ga -DOTA-DiPSMA. The tumor lesion detection rate of ^{68}Ga -DOTA-DiPSMA was the same as ^{68}Ga -PSMA-11 in this pilot series of newly diagnosed prostate cancer patients. However, ^{68}Ga -DOTA-DiPSMA showed lower uptake (SUV_{max}) in some lesions than ^{68}Ga -PSMA-11, such as primary tumor (4.41 ± 2.72 vs. 11.23 ± 10.76), iliac lymph node (3.26 ± 1.20 vs. 4.86 ± 1.94), bone (2.95 ± 1.11 vs. 7.62 ± 1.58), and seminal vesicle (3.95 ± 2.61 vs. 10.35 ± 7.00), respectively. ^{68}Ga -DOTA-DiPSMA seems to have a lower uptake in small lesions and distant metastasis [21-22]. However, the lower uptake of ^{68}Ga -DOTA-DiPSMA in normal organs than ^{68}Ga -PSMA-11 maybe

its advantage. The small lesion near the urinary bladder would be more apparent with this relatively low background.

The primary limitation of our study is the sample size which did not enable accurate multivariate regression analysis about comparing ^{68}Ga -DOTA-DiPSMA to ^{68}Ga -PSMA-11. Besides, neither blood nor urine samples were collected in our study, which will allow for the stability test in vivo. Further detailed and head-to-head comparison studies are required.

Conclusion

^{68}Ga -DOTA-DiPSMA is safe and well-tolerated and shows favorable dosimetry and biodistribution in healthy volunteers and detection performances in PCa patients. Lesion detection rate and tumor-to-background ratios were comparable to ^{68}Ga -PSMA-11. The lower background of ^{68}Ga -DOTA-DiPSMA showed its potential application for RLT when labeled with ^{177}Lu . DOTA-DiPSMA is a promising novel theranostics tracer both for PCa patient diagnosis and RLT. Further validation by head-to-head comparisons in more extensive clinical trials is warranted.

Declarations

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Conflict of interest The authors declare that they have no conflict of interest.

Availability of data and materials Not applicable.

Code availability Not applicable.

Ethics approval All procedures involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any experiments with animals.

Consent to participate Informed consent was obtained from all individual participants included in the study.

ClinicalTrials.gov identifier: NCT04525612

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Tables

Table 1. Summarizes the healthy volunteers and patient characteristics.

No	Age (year)	Sex	Weight (kg)	Inject dose
HV1	55	M	73.8	3.3
HV2	42	M	92.3	5.5
HV3	67	M	60.2	3.8
HV4	56	M	74.3	5.44
HV5	50	M	65.9	5.5
1	68	M	51.8	3.6
2	76	M	67.2	3.0
3	67	M	61	4.1
4	71	M	92.4	3.05
5	73	M	67	3.06
6	77	M	65.1	3.85
7	77	M	57.9	2.70
8	69	M	65.6	2.98
9	78	M	56	2.8
10	80	M	68	2.8

Table 2. Estimated absorbed organ doses and effective dose for ^{68}Ga -DOTA-DiPSMA in healthy volunteers.

Absorbed dose	Mean (uSv/MBq)	SD (uSv/MBq)
Adrenals	14.44	0.34
Brain	11.16	0.43
Breasts	10.94	0.42
Gallbladder Wall	13.12	3.33
LLI Wal	12.47	3.71
Small Intestine	12.36	3.61
Stomach Wall	11.74	3.51
ULI Wall	12.18	3.57
Heart Wall	11.38	3.48
Kidneys	114.46	29.28
Liver	24.76	5.38
Lungs	12.12	0.41
Muscle	12.24	0.30
Ovaries	14.26	0.13
Pancreas	14.56	0.31
Red Marrow	11.38	3.74
Osteogenic Cells	14.53	5.46
Skin	10.68	0.33
Spleen	30.98	7.76
Testes	12.38	0.13
Thymus	12.14	0.48
Thyroid	12.04	0.48
Urinary Bladder Wall	100.82	46.22
Uterus	15.54	0.61
Salivary glands	24.32	7.11
Total Body	9.71	4.93
Effective Dose Equivalent	26.42	3.68
Effective Dose	19.46	1.73

Table 3. Comparison of PET findings with ^{68}Ga -DOTA-DiPSMA and ^{68}Ga -PSMA-11 in the initial ten subject study of ^{68}Ga -DOTA-DiPSMA in prostate cancer patients with newly diagnosed.

Subject	Age	Serum PSA (ng/ml)	Site(s) of recurrence detected by		SUV _{max} values for detected lesions		Lesion location
			PSMA-11	DiPSMA	PSMA-11	DiPSMA	
1	68	26.95	yes	yes	7.4	3.3	prostate
			yes	yes	6.0	1.9	T8 vertebrae
			yes	yes	9.6	4.1	Sacrum
			yes	yes	6.8	3.7	Iliac
			yes	yes	8.1	2.1	Iliac
2	76	10.5	yes	yes	5.6	2.9	prostate
			yes	yes	4.1	2.6	prostate
3	67	10.3	yes	yes	5.9	1.9	prostate
			yes	yes	2.9	1.7	prostate
			yes	yes	4.0	3.7	prostate
4	71	9.56	yes	yes	18.9	6.4	prostate
			yes	yes	4.5	3.8	prostate
5	73	8.62	yes	yes	20.4	4.0	prostate
6	77	6.27	yes	yes	3.1	2.1	prostate
			yes	yes	2.6	2.3	prostate
7	77	17.22	yes	yes	14.5	9.76	prostate
8	69	37.9	yes	yes	44.9	10.6	prostate
			yes	yes	13.3	3.0	prostate
			yes	yes	15.3	5.8	Seminal vesicle
			yes	yes	5.4	2.1	Seminal vesicle
9	78	35.72	yes	yes	14	6.6	prostate
10	80	60.1	yes	yes	13.5	5.9	prostate
			yes	yes	7.3	2.6	Iliac lymph node
			yes	yes	4.4	3.1	Iliac lymph node

	yes	yes	4.1	4.6	Iliac lymph node
	yes	yes	6.2	4.3	Iliac lymph node
	yes	yes	2.3	1.7	Iliac lymph node

Table 4. Comparison of normal organs SUV_{max} with ^{68}Ga -DOTA-DiPSMA and ^{68}Ga -PSMA-11

	SUV_{max} (Mean $\pm$ SD)		<i>P</i> -value
	PSMA-11	DiPSMA	
Thyroid	1.62 $\pm$ 0.50	1.12 $\pm$ 0.21	0.013*
Brain	0.08 $\pm$ 0.05	0.07 $\pm$ 0.04	0.364
Lung	0.48 $\pm$ 0.12	0.40 $\pm$ 0.09	0.151
Thymus	0.66 $\pm$ 0.16	0.53 $\pm$ 0.19	0.257
Heart bladder	1.13 $\pm$ 0.35	1.18 $\pm$ 0.21	0.762
Heart content	1.53 $\pm$ 0.35	1.94 $\pm$ 0.50	0.041*
Liver	5.64 $\pm$ 1.19	2.92 $\pm$ 1.05	0.000*
Kidney	41.48 $\pm$ 11.02	23.40 $\pm$ 11.27	0.005*
Stomach	2.36 $\pm$ 2.60	0.99 $\pm$ 0.57	0.049*
Adrenal gland	3.34 $\pm$ 2.32	1.76 $\pm$ 0.64	0.016*
Pancreas	2.80 $\pm$ 2.29	1.48 $\pm$ 0.43	0.004*
Spleen	7.78 $\pm$ 1.99	3.16 $\pm$ 0.64	0.000*
Gallbladder	2.19 $\pm$ 1.11	0.97 $\pm$ 0.41	0.002*
Large intestine	1.29 $\pm$ 0.23	0.92 $\pm$ 0.33	0.028*
Small intestine	7.18 $\pm$ 5.38	2.26 $\pm$ 1.70	0.028*
Red marrow	0.59 $\pm$ 0.24	0.44 $\pm$ 0.20	0.186
Muscle	0.51 $\pm$ 0.16	0.65 $\pm$ 0.24	0.406
Salivary gland	12.15 $\pm$ 1.90	4.88 $\pm$ 2.04	0.000*

* $P \leq 0.05$.

Figures

Figure 1

Structure of DOTA-DiPSMA.

Figure 2

Study flowchart with excluded healthy volunteers and patients.

Figure 3

Biodistribution of 68Ga-DOTA-DiPSMA in healthy volunteers. A maximum intensity projection PET images at several time points post-injection of a 56-year-old male healthy volunteer.

Figure 4

Mean SUVmean as a function of time for all healthy volunteers.

Figure 5

A 78-year-old-man confirmed prostate cancer for 1 week. The MIP of ^{68}Ga -PSMA-11 PET/CT (A, arrows) showed significantly intense uptake in the prostate. Axial views of the prostate (B, PET; C, CT; D, fusion image) showed intense uptake (SUVmax 14) in the isodense nodule of the prostate (arrows). In ^{68}Ga -DOTA-DiPSMA PET/CT (E, MIP; F, PET; G, CT; H, fusion image), the lesion showed moderate increased uptake of the tracer (SUVmax 6.6).

Figure 6

Normal organs SUVmax (Average in 10 patients) of ^{68}Ga -DOTA-DiPSMA as compared with ^{68}Ga -PSMA-11