



^{68}Ga -DOTA-DiPSMA PET/CT Imaging: Biodistribution, Dosimetry, and Preliminary Application in Prostate Cancer

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Specialty section:

This article was submitted to
Nanobiotechnology,
a section of the journal
Frontiers in Bioengineering and
Biotechnology

Received: 09 November 2021

Accepted: 17 December 2021

Published: 28 January 2022

Citation:

Zhang J, Lin Z, Zhang X, Lin R, Cui M,
Miao W and Yao S (2022) ^{68}Ga -DOTA-
DiPSMA PET/CT Imaging:
Biodistribution, Dosimetry, and
Preliminary Application in
Prostate Cancer.
Front. Bioeng. Biotechnol. 9:811972.
doi: 10.3389/fbioe.2021.811972

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

Methods: Five healthy volunteers and ten PCa patients were injected with an intravenous bolus of ^{68}Ga -DOTA-DiPSMA. They 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 and whole-body PET were performed with 2 min per bed position in 40 min post-injection. Absorbed organ doses and effective doses were calculated using OLINDA/EXM. Normal organ uptake and tumor lesion uptake 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 ($114.46 \pm 29.28 \mu\text{Sv/MBq}$), followed by the urinary bladder wall ($100.82 \pm 46.22 \mu\text{Sv/MBq}$) in accordance with the expected Prostate-Specific Membrane Antigen (PSMA) renal excretion of the tracer. The mean effective dose was $19.46 \pm 1.73 \mu\text{Sv/MBq}$. The SUV_{max} of ^{68}Ga -DOTA-DiPSMA PET/CT for PCa lesions, bone metastases, and lymph node metastases was 4.41 ± 2.72 , 2.95 ± 1.11 , and 3.26 ± 1.20 , respectively.

Conclusion: Injection of ^{68}Ga -DOTA-DiPSMA is safe and associated with low absorbed and effective doses. ^{68}Ga -DOTA-DiPSMA shows favorable kinetics and imaging characteristics in patients who warrant further head-to-head comparison to validate ^{68}Ga -DOTA-DiPSMA as an alternative for gallium-68-labeled PSMA clinical PET. Low nonspecific uptake in normal organs of ^{68}Ga -DOTA-DiPSMA indicates potential radioligand therapy (RLT) application when labeled with ^{177}Lu , ^{90}Y , or ^{225}Ac .

Keywords: prostate cancer, ^{68}Ga -DOTA-DiPSMA, biodistribution, dosimetry, PET/CT

INTRODUCTION

Prostate cancer (PCa) is one of the most frequently diagnosed cancers in men and the lethal malignant diseases leading to male cancer-related death worldwide (Attard et al., 2016). The accurate presence and location of primary or recurrent tumors are critical for planning effective patient management (Mottet et al., 2021).

The diagnostic capability of conventional anatomic imaging such as MRI and CT to determine PCa is limited in metastases and specificity (Vos et al., 2013). Only prostate biopsy is the definitive way to confirm PCa (Attard et al., 2016). Multiple needle biopsies will increase the positive rate of lesion determination significantly. However, it is difficult to determine distant metastases and increase the risk of complications resulting from biopsy operation (Attard et al., 2016). There has been an unmet need for more advanced imaging modalities to determine primary and metastatic lesions that can be helpful to PCa patient management (observation, salvage local therapy, and systemic therapy). PET with ¹⁸F-FDG is effective for most malignant tumors, but it lacks sensitivity for PCa. Therefore, it is urgent to discover new nuclear medicine imaging agents with more specificity for PCa.

Prostate-Specific Membrane Antigen (PSMA) is a transmembrane glycoprotein enzyme selectively overexpressed in PCa cells, with its expression increasing in higher-grade malignancy (Bouchelouche et al., 2010). PET imaging with PSMA probes targeting various PCa-specific markers will provide additional molecular information to facilitate lesion detection and staging (Perera et al., 2020).

Recently, a relatively new nuclear imaging modality ⁶⁸Ga-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 (Sachpekidis et al., 2016; Koerber et al., 2017; Wang et al., 2020). PSMA can be coupled with different chelators and labeled with corresponding radionuclides for different purposes. The most widely used PSMA ligands in the clinical examination

are PSMA-11 and PSMA-617 containing different linkers and chelators. According to the previously published papers, ⁶⁸Ga-PSMA-11 and ¹⁷⁷Lu-PSMA-617 are a molecular pair in metastatic castration-resistant PCa (mCRPC) diagnosis and radioligand therapy (RLT) (Rahbar et al., 2017; Sun et al., 2020; Violet et al., 2020). However, considering the high nonspecific uptake in the salivary, kidneys, and bone marrow of ⁶⁸Ga-PSMA-11 and ¹⁷⁷Lu-PSMA-617, novel PSMA tracers with lower accumulation in normal organs are urgently needed.

We have discovered a new PSMA dimer (DOTA-DiPSMA, **Figure 1**). The Prof. Cui group from Beijing Normal University will discuss the discovery and preclinical experiments, which will be published elsewhere. Preclinical experiments proved its good imaging ability and low nonspecific uptake in normal organs including the liver, kidneys, spleen, and salivary glands. In addition, the affinity of DiPSMA-DOTA-COOH to the PSMA receptor can reach 1.56 nM. This was the first study in humans, following the abovementioned preclinical studies. In this study, we aimed to evaluate the safety, biodistribution, and dosimetry of ⁶⁸Ga-DOTA-DiPSMA in healthy volunteers and its diagnostic efficacy in PCa patients.

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 in this study. Five healthy volunteers [5 men, age range 42–76 years (mean age ± SD, 59.83 ± 11.65 years); weight range, 55.0–78.0 kg (mean weight ± SD, 70.27 ± 13.05 kg)] were enrolled to validate the safety, biodistribution, and radiation dosimetry of ⁶⁸Ga-DOTA-DiPSMA in this study. Exclusion criteria consisted of mental illness conditions, severe liver or kidney disease with

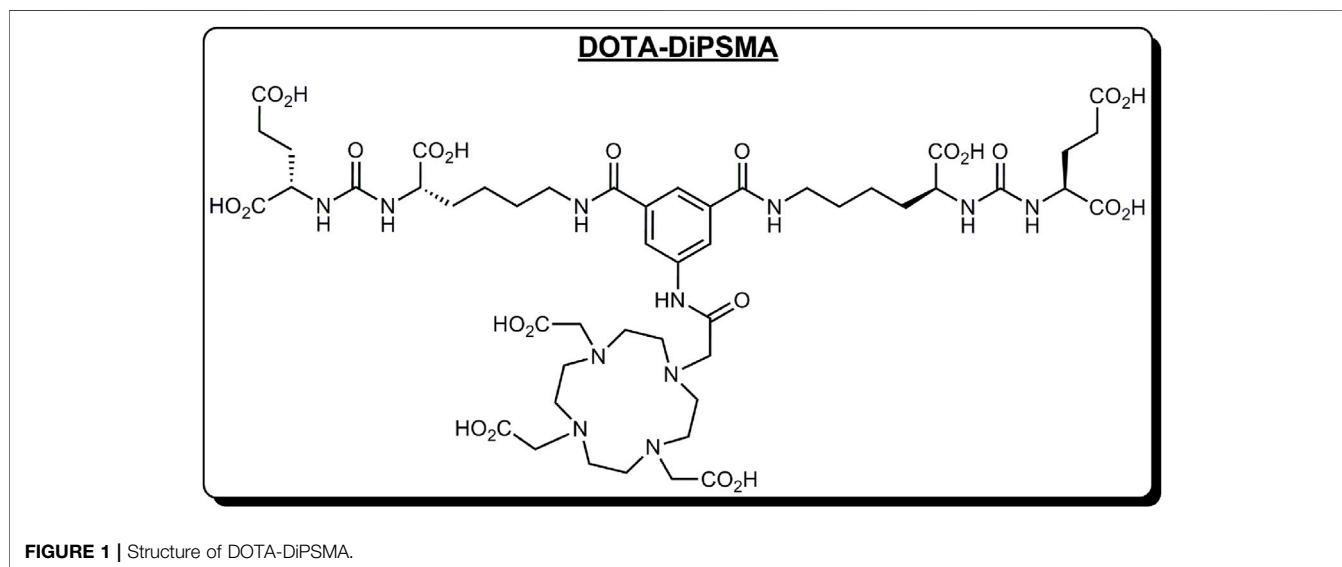


TABLE 1 | Summary of the healthy volunteer and patient characteristics and PET findings in ten newly diagnosed prostate cancer patients with ⁶⁸Ga-DOTA-DiPSMA.

No.	Age (year)	Sex	Weight (kg)	Inject dose	Serum PSA (ng/ml)	SUV _{max} for detected lesions	Lesion location
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	26.95	3.3 1.9 4.1 3.7 2.1	Prostate T8 vertebrae Sacrum Iliac Iliac
2	76	M	67.2	3.0	10.5	2.9 2.6	Prostate Prostate
3	67	M	61	4.1	10.3	1.9 1.7 3.7	Prostate Prostate Prostate
4	71	M	92.4	3.05	9.56	6.4 3.8	Prostate Prostate
5	73	M	67	3.06	8.62	4.0	Prostate
6	77	M	65.1	3.85	6.27	2.1 2.3	Prostate Prostate
7	77	M	57.9	2.70	17.22	9.76	Prostate
8	69	M	65.6	2.98	37.9	10.6 3.0 5.8 2.1	Prostate Prostate Seminal vesicle Seminal vesicle
9	78	M	56	2.8	35.72	6.6	Prostate
10	80	M	68	2.8	60.1	5.9 2.6 3.1 4.6 4.3 1.7	Prostate Iliac lymph node Iliac lymph node Iliac lymph node Iliac lymph node Iliac lymph node

Note. PSA, prostate-specific antigen.

serum creatinine greater than 3.0 mg/dl, 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 PCa by sextant core-needle biopsy and had not received any prior therapy were enrolled with written informed consent. The inclusion criteria were those aged between 40 and 80 years, who have a prostate neoplasm identified by ultrasound or MRI, and were diagnosed by needle biopsy as having PCa. 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**.

Subject age averaged 73.6 ± 4.6 years (median 74.5 years; range 67–80 years), and body mass averaged 65.2 ± 11.0 kg (median 65.4 kg; range 51.8–92.4 kg). Serum prostate-specific antigen (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 PET/CT imaging. Subjects were numbered chronologically in the order of imaging with ⁶⁸Ga-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, and body temperature). Within the first 72 h after ⁶⁸Ga-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. Radiolabeling of DiPSMA-DOTA-COOH was performed in a sterile hot cell manually. ⁶⁸Ga³⁺ was eluted from a ⁶⁸Ge/⁶⁸Ga generator (JSC Isotope, Moscow, Russia) using 0.1 M of HCl. The clinical doses of DOTA-DiPSMA (30 μg) were compounded in 1.25 M of NaOAc buffer to adjust pH to around 4.0 and labeled with an average of 585.34 ± 177.97 MBq (15.82 ± 4.81 mCi) of ⁶⁸Ga³⁺ using a reaction temperature of 95°C for 10 min. Our protocol permits the radiochemical purity of the product ⁶⁸Ga-DOTA-DiPSMA to exceed 99% so that we omit the purification step. The final product will pass through a sterile filter membrane (Millipore,

TABLE 2 | Quality control test items.

Test item	Acceptance criteria	Test method
Appearance	Colorless and particle-free	Visual inspection
pH	3.5–6.0	pH strip
Radiochemical purity	—	Radio TLC
⁶⁸ Ga-DOTA-DiPSMA	≥90%	—
Maximum injection volume	≤5 ml	Injector
Sterility	No growth after 14 days of incubation at 37°C	Petri dish inoculation method
Bacterial endotoxins	≤15 EU per ml	LAL test

Note. TLC, thin-layer chromatography; LAL, limulus amoebocyte lysate.

Billerica, MA, United States) and then be diluted to 5 ml in a sterile syringe for injection. The total time required for completion of radiolabeling and quality control averaged approximately 30 min. Quality control items are shown in Table 2.

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 ⁶⁸Ga-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 ⁶⁸Ga-DOTA-DiPSMA PET/CT. For the volunteers, after the whole-body low-dose CT scan, 111–222 MBq (3–6 mCi) of ⁶⁸Ga-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.

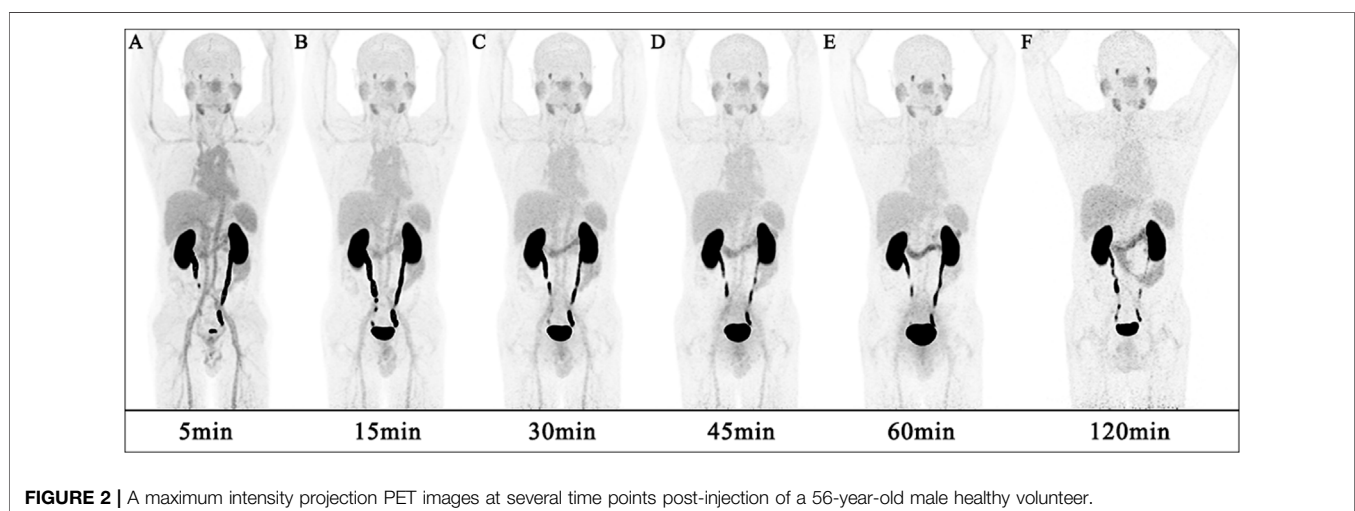
For the patients, ⁶⁸Ga-DOTA-DiPSMA PET/CT scanning was performed at 40 min after tracer administration. For each patient, 103.6–151.7 MBq (2.8–4.1 mCi) of ⁶⁸Ga-DOTA-DiPSMA was injected intravenously. After a low-dose CT scan, whole-body

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 randomness, 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, Erlangen, Germany) for analysis.

Biodistribution Assessment and Dosimetry

Image analysis was performed using MIM v6.9.4 (MIM Software Inc., Cleveland, OH, United States). The volume of interests (VOIs) were drawn over healthy organs on all ⁶⁸Ga-DOTA-DiPSMA PET images, and SUV_{mean} 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, TN, United States).



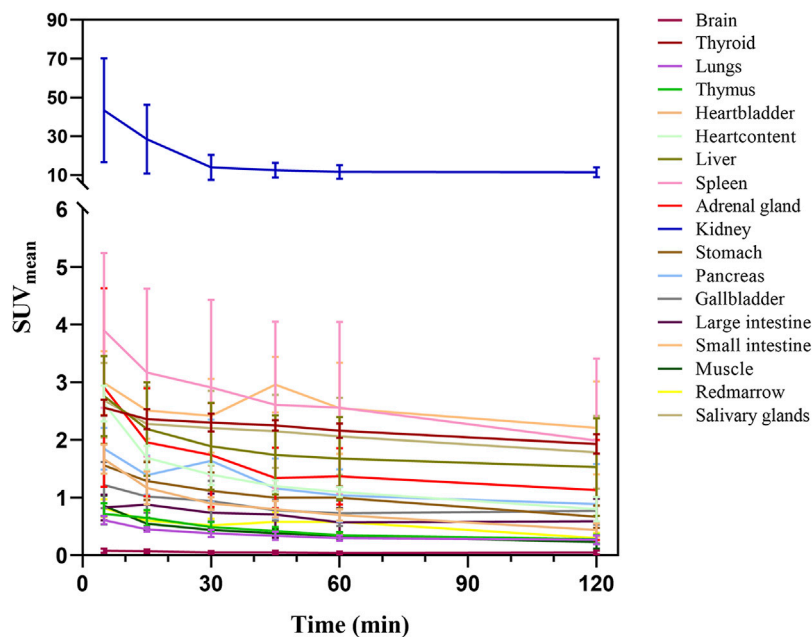


FIGURE 3 | Biodistribution of ⁶⁸Ga-DOTA-DiPSMA in healthy volunteers.

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. SPSS 23.0 Software (IBM SPSS, Chicago, IL, United States) was used for statistical analyses.

RESULT

Patient Safety

⁶⁸Ga-DOTA-DiPSMA was found to be safe and well-tolerated in all subjects. No AEs or serious AEs occurred after ⁶⁸Ga-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 ⁶⁸Ga-DOTA-DiPSMA.

Biodistribution

Figures 2, 3 illustrate the biodistribution of ⁶⁸Ga-DOTA-DiPSMA as a function of time in healthy volunteers. The whole-body background of ⁶⁸Ga-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 uptakes were 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, illustrated the tracer's fast and mainly renal excretion.

TABLE 3 | Estimated absorbed organ doses and effective dose for ⁶⁸Ga-DOTA-DiPSMA in healthy volunteers.

Absorbed dose	Mean (μ Sv/MBq)	SD (μ Sv/MBq)
Adrenals	14.44	0.34
Brain	11.16	0.43
Breasts	10.94	0.42
Gallbladder wall	13.12	3.33
LLI wall	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

Note. LLI, lower large intestine; ULI, upper large intestine.

TABLE 4 | Different organs' SUV_{max} for ⁶⁸Ga-DOTA-DiPSMA in PCa patients.

	SUV _{max}	SD
Thyroid	1.12	0.21
Brain	0.07	0.04
Lung	0.40	0.09
Thymus	0.53	0.19
Heart bladder	1.18	0.21
Heart content	1.94	0.50
Liver	2.92	1.05
Kidney	23.40	11.27
Stomach	0.99	0.57
Adrenal gland	1.76	0.64
Pancreas	1.48	0.43
Spleen	3.16	0.64
Gallbladder	0.97	0.41
Large intestine	0.92	0.33
Small intestine	2.26	1.70
Red marrow	0.44	0.20
Muscle	0.65	0.24
Salivary gland	4.88	2.04
Prostate lesions	4.41	2.72
Lymph node metastasis	3.26	1.20
Bone metastasis	2.95	1.11
Seminal vesicle metastasis	3.95	2.62

Note. PCa, prostate cancer.

Dosimetry

The average estimated absorbed organ in healthy volunteers is summarized in Table 3. The highest absorbed dose was received by the kidneys ($114.46 \pm 29.28 \mu\text{Sv}/\text{MBq}$), followed by the urinary bladder wall ($100.82 \pm 46.22 \mu\text{Sv}/\text{MBq}$). The mean effective dose was $19.46 \pm 1.73 \mu\text{Sv}/\text{MBq}$.

Detection of Primary Prostate Cancer

For the 10 patients with primary PCa, ⁶⁸Ga-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 ± 1.20 , respectively (Table 1; Figure 4). Low background uptake was observed in ⁶⁸Ga-DOTA-DiPSMA (the salivary glands SUV_{max} 4.88 ± 2.04 , liver SUV_{max} 2.92 ± 1.05 , kidneys SUV_{max} 23.40 ± 11.27 , and spleen SUV_{max} 3.16 ± 0.64) (Table 4; Figure 5).

DISCUSSION

To our knowledge, this was the first human study to evaluate the novel tracer ⁶⁸Ga-DOTA-DiPSMA in healthy volunteers and patients with PCa. This tracer is a new type of ⁶⁸Ga-labeled dimer PSMA imaging agent with a simple structure, easy synthesis, and low synthesis cost. ⁶⁸Ga-DOTA-DiPSMA can be prepared by a one-step labeling reaction in a high yield greater than 95% between ⁶⁸Ga³⁺ 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 ⁶⁸Ga-DOTA-DiPSMA in five healthy volunteers, including biodistribution, dosimetry, and safety. Also, we have performed the first initial application with ⁶⁸Ga-DOTA-DiPSMA in PCa patients. The results showed that this tracer displayed favorable biodistribution and dosimetry features and was well-tolerated in all patients. ⁶⁸Ga-DOTA-DiPSMA showed

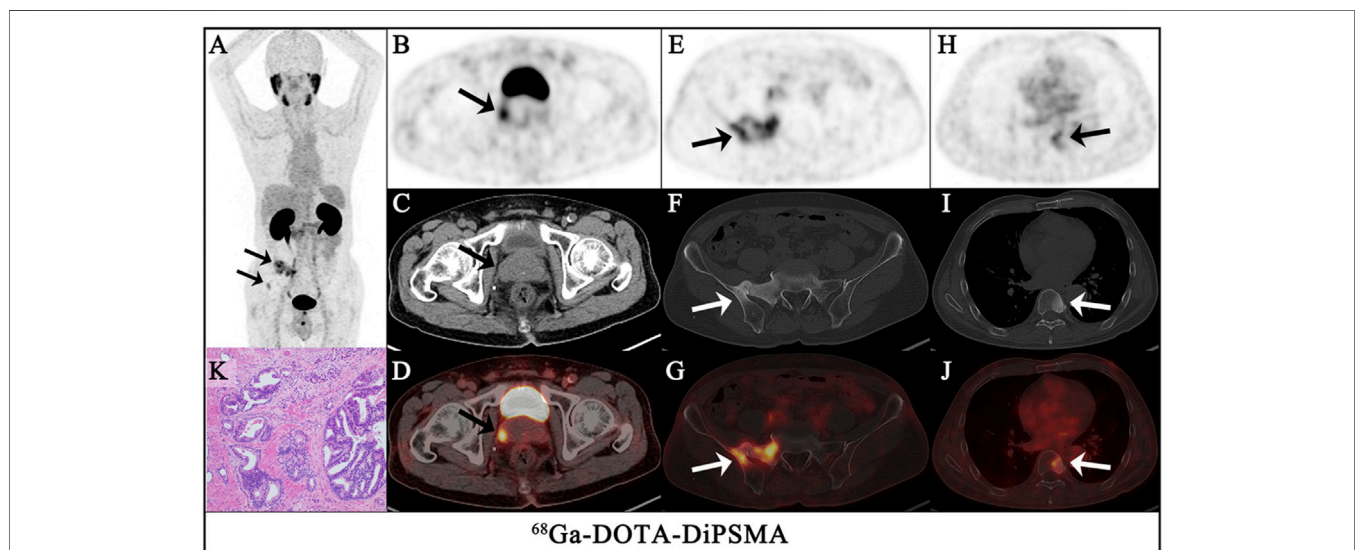


FIGURE 4 | A 68-year-old man had confirmed prostate cancer after a needle biopsy of the prostate for 1 week. The maximum intensity projection (MIP) of ⁶⁸Ga-DOTA-DiPSMA PET/CT [(A), arrows] showed significantly abnormal uptake in the image. Axial views of the prostate (top, PET; middle, CT; bottom, fusion image) show intense uptake (SUV_{max} 3.3) in the isodense nodule of the prostate [(B–D), arrows]. In the other level axial views, increased ⁶⁸Ga-DOTA-DiPSMA uptake was observed in the sacrum and iliac [(E–G), arrows] and the 8th thoracic vertebrae lesions [(H–J), arrows], which were concomitant with bone density increased. Postoperative pathology confirmed it as adenocarcinoma of the prostate (K).

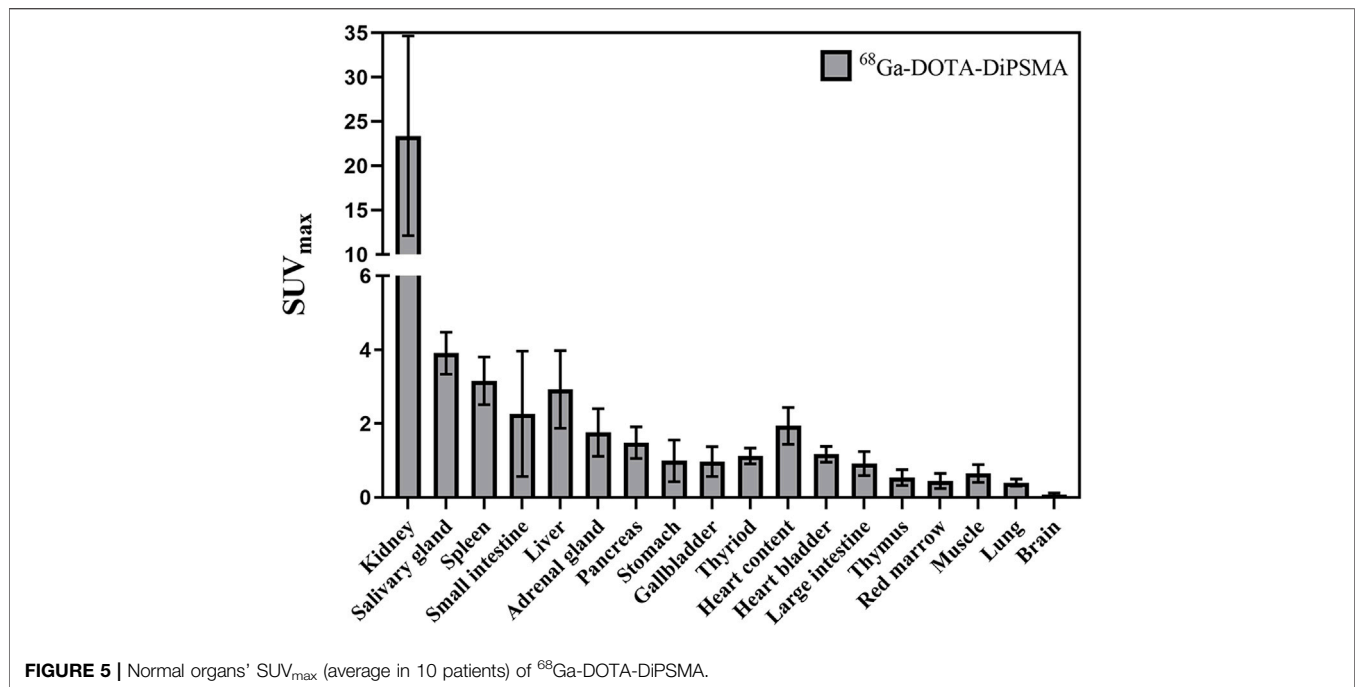


FIGURE 5 | Normal organs' SUV_{max} (average in 10 patients) of ⁶⁸Ga-DOTA-DiPSMA.

high PSMA affinity. The biodistribution of ⁶⁸Ga-DOTA-DiPSMA was similar to that of ⁶⁸Ga-PSMA-11 (Pfoh et al., 2016). The rapid presence in the kidneys, followed by a passage toward the urinary bladder, illustrates the tracer's fast and mainly renal excretion. The highest uptake was observed in the kidneys and rapidly cleared through the urinary system in both tracers, consistent with the published ⁶⁸Ga-PSMA-11 results (Afshar-Oromieh et al., 2016; Zamboglou et al., 2016; Chen et al., 2019; Sandgren et al., 2019). However, ⁶⁸Ga-DOTA-DiPSMA observed SUV_{mean} values at 60 min for the kidneys, liver, spleen, and parotids (11.93 ± 3.54 , 1.68 ± 0.72 , 2.56 ± 1.49 , and 2.16 ± 0.89 , respectively) were in general lower than ⁶⁸Ga-PSMA-11 (30.1 ± 6.6 , 3.3 ± 0.6 , 5.2 ± 2.5 , and 9.4 ± 2.0 , respectively) (Green et al., 2017).

The dosimetry data of ⁶⁸Ga-DOTA-DiPSMA showed a little lower yet comparable effective dose than ⁶⁸Ga-PSMA-11 (0.019 vs. 0.022/0.023 mSv/MBq) (Afshar-Oromieh et al., 2016; Sandgren et al., 2019), salivary glands (0.024 vs. 0.089 mSv/MBq), kidney (0.114 vs. 0.240 mSv/MBq), liver (0.0240 vs. 0.053 mSv/MBq), and spleen (0.031 vs. 0.046 mSv/MBq) (Sandgren et al., 2019). We thought that the lower liver and spleen dose of ⁶⁸Ga-DOTA-DiPSMA might be attributed to the dosimetry methodology.

It is crucial to reduce the radiation dose of nonspecific organs and tissues in the field of radionuclide therapy (RLT) (ICRP, 2002). ¹⁷⁷Lu-PSMA-617 RLT is a promising option for patients with mCRPC (Delker et al., 2016; Kratochwil et al., 2016; Paganelli et al., 2020; Rasul et al., 2020). Based on the lower nonspecific uptake and effective dose of ⁶⁸Ga-DOTA-DiPSMA, the radiation dosimetry in normal organs seemed to be reduced when DOTA-DiPSMA was labeled with ¹⁷⁷Lu for RLT. Low background uptakes were observed in the brain, lungs, muscle, red marrow, heart, thyroid, gall bladder, pancreas, stomach, bone,

and large intestine. The low uptake of the dimer DOTA-DiPSMA in the parotid glands and the clearance in the kidneys were impressive, which could be an advantage for RLT.

A critical finding of our study is the high tumor accumulation of ⁶⁸Ga-DOTA-DiPSMA, which showed high tumor uptakes with the highest SUV_{max} up to 10.6 on ⁶⁸Ga-DOTA-DiPSMA. The primary lesions showed the highest uptake (SUV_{max} 4.41 ± 2.72). For metastasis lesions, the highest uptake was shown in a seminal vesicle (SUV_{max} 3.95 ± 2.61), followed by the iliac lymph node (SUV_{max} 3.26 ± 1.20), and the lowest uptake was observed in the bone (SUV_{max} 2.95 ± 1.11). However, the lower uptake of ⁶⁸Ga-DOTA-DiPSMA in normal organs may be its advantage (Afshar-Oromieh et al., 2015; Fendler et al., 2017). The study on ⁶⁸Ga-DOTA-DiPSMA provided a new radiotracer targeting PSMA to diagnose PCa. It was conducive to the accuracy of PCa staging. The small lesion near the urinary bladder would be more apparent with this relatively low background. The mechanism of DOTA-DiPSMA in reducing the uptake in the salivary gland and kidney was still unknown, which needs further studies to confirm.

The primary limitation of our study is the sample size, which did not enable accurate multivariate regression analysis in comparing the diagnosis efficacy of ⁶⁸Ga-DOTA-DiPSMA with ⁶⁸Ga-PSMA-11, which is the next work in our research group. 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

⁶⁸Ga-DOTA-DiPSMA is safe and well-tolerated and shows favorable dosimetry and biodistribution in healthy volunteers

and detection performances in PCa patients. The low uptake of the dimer DOTA-DiPSMA in the parotid glands and the clearance in the kidneys were impressive. The lower background of ⁶⁸Ga-DOTA-DiPSMA showed its potential application for RLT when labeled with ¹⁷⁷Lu. DOTA-DiPSMA is a promising novel theranostic tracer for both PCa patient diagnosis and RLT. Further validation by head-to-head comparison is warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Independent Ethics Committee of First Affiliated

Hospital of Fujian Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MC, WM, and SY: research design. JZ, ZL, XZ, and RL: acquisition of data. All were involved in the analysis and/or interpretation of data and drafting the article or revising it critically. All approved the submitted and final version.

FUNDING

This study was funded in part by the Joint Funds for the Innovation of Science and Technology, Fujian Province (2020Y9101), National Natural Science Foundation of China (82171982), Natural Science Foundation of Fujian (2020J05249), and Fujian Provincial Health Technology Project (2020GGA045).

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