MATERIALS AND METHODS

This clinical study was approved by the Institute Review Board of the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College and all subjects signed a written informed consent. This study was registered at the NIH ClinicalTrial.gov (NCT01737112).

Healthy Volunteers

To validate the safety and efficacy of ^{68}Ga-NOTA-PRGD2 PET/CT, 7 healthy volunteers (M 3, F 4, 38–65 y, 48 ± 9 y) were enrolled. For healthy volunteers, the blood pressure, pulse, respiratory rate and temperature were measured, and liver function, renal function, routine blood tests, and urine tests were examined immediately before and 24 h after the scan. In addition, any possible side effects during ^{68}Ga-NOTA-PRGD2 PET/CT scan and within 5 days after the examination were collected and analyzed. A Siemens Biograph 128 mCT X was used for ^{68}Ga-NOTA-PRGD2 PET/CT. The volunteers were asked to urinate right before examination. After the whole-body low-dose CT scan (140 kV, 35 mA, pitch 1:1, layer 5 mm, layer spacing 3 mm, matrix 512 x 512, FOV 70 cm), approximately 117.7 ± 37.7 MBq of ^{68}Ga-NOTA-PRGD2 was injected intravenously, followed by immediate serial whole-body dynamic PET acquisitions. The duration was 3 sec/bed position for the 1–8 phases，6 sec/bed position for the 9–14 phases, 60 sec/bed position for the 15–17 phases, 120 sec/bed position for the next several phases and the last phase lasted for 240 sec/bed position. The whole body images were obtained in sequence and the total scanning lasted for 1 to 2 h based on the subject's height and number of phases.

After imaging reconstruction, the regions of interest (ROIs) were outlined over the major organs. The standard uptake values (SUVs) were calculated and time activity curves were analyzed. The OLINDA/EXM1.0 software was used for radiation dose calculation (*1, 2*).

Safety Evaluation

The vital signs and routine blood and urine tests, as well as liver and renal functions of the volunteers were all within normal range before tracer injection and PET imaging, and no significant changes were found 24 h after PET scan ($P > 0.05$). During ^{68}Ga-NOTA-PRGD2 PET/CT scan and within 5 days after the examination, no side effect was reported in all the volunteers.

Biodistribution and Dosimetry

As shown in Supplemental Figure 1, within several minutes after intravenous injection, ^{68}Ga-NOTA-PRGD2 was rapidly cleared from the blood pool and primarily excreted through the urinary system. The images were clear and preferable for diagnostic reading. As shown in Supplemental Table 1, the highest distribution of radioactivity was found in the bladder, kidneys, and ureters. Moderate physiological uptake was found in the spleen, liver, choroid plexus, uterus, intestines, and thyroid. The distribution of ^{68}Ga-NOTA-PRGD2 became relatively stable in most organs starting from 15 min after injection except for the urinary system.

Based on the images obtained from, the average internal radiation dose per MBq dosage of ^{68}Ga-NOTA-PRGD2 was calculated using the OLINDA/EXM 1.0 software and listed in Supplemental Table 2. The organ with the highest radiation dose was the urinary bladder, and the total body effective dose and effective dose equivalent were 22.6 and 27.7 μSv/MBq, respectively.

Without voiding the bladder for 1~2 h after injection, the total body effective dose was comparable to that from routine ^{18}F-FDG PET. The effective dose of target organs and total body would reduce dramatically after urination. The radiation of low-dose CT was approximately 20% less than the standard clinical CT dose, which is about 11.2 mGy for a whole body scan.

Therefore, the exposure to radiation for a ^{68}Ga-NOTA-PRGD2 PET/CT examination is totally acceptable.

References

1. Stabin MG, Brill AB. State of the art in nuclear medicine dose assessment. *Semin Nucl Med.* 2008;38:308-320.

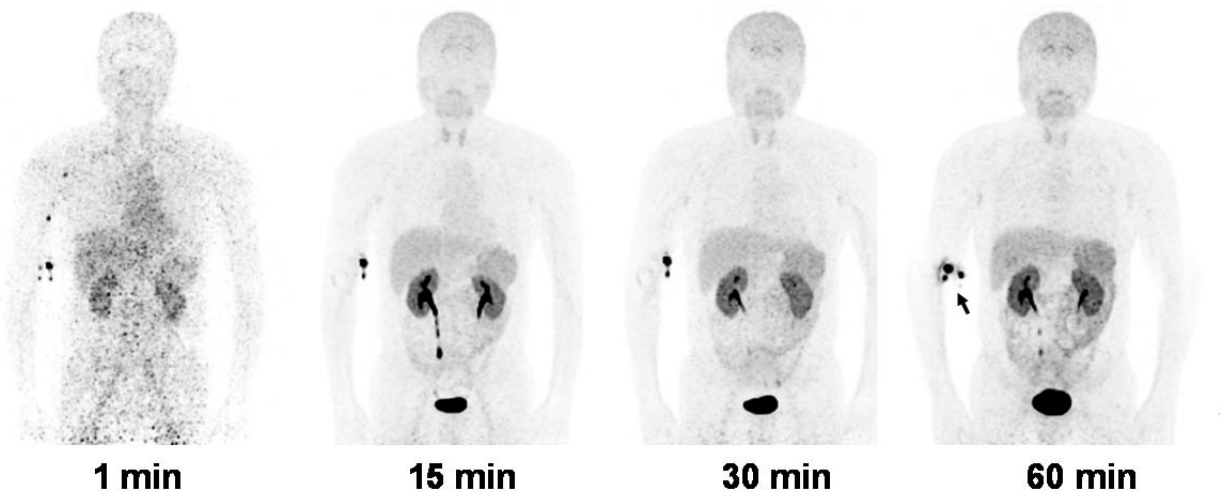
2. Stabin MG, Tagesson M, Thomas SR, Ljungberg M, Strand SE. Radiation dosimetry in nuclear medicine. *Appl Radiat Isot.* 1999;50:73-87.

Supplemental Table 1. Biodistribution of ^{68}Ga-NOTA-PRGD2 in main organs/tissues in healthy volunteers (n = 7, SUV mean ± SD)

	1 min	5 min	15 min	30 min	60 min	120 min
Choroid plexus	0.01±0.02	0.04±0.04	0.87±0.06	0.50±0.30	0.38±0.08	0.19±0.02
Thyroid	2.26±0.60	1.74±0.81	1.53±0.28	2.35±0.85	1.64±0.42	0.98±0.21
Arcus aortae	4.36±0.69	3.82±0.47	2.56±0.50	2.37±0.44	1.87±0.37	0.9±0.19
Myocardium	4.51±1.01	3.66±0.72	2.31±0.81	2.14±0.49	1.84±0.41	0.91±0.22
Lungs	1.11±0.18	1.01±0.13	0.8±0.17	0.76±0.19	0.64±0.15	0.4±0.07
Liver	3.65±0.36	3.37±0.39	2.78±0.19	2.62±0.24	2.21±0.30	1.92±0.07
Spleen	4.57±0.78	4.46±0.48	4.23±0.90	4.11±0.69	3.95±0.81	3.13±0.75
Pancreas	2.86±0.45	2.78±0.50	2.46±0.29	2.82±0.47	2.34±0.28	1.82±0.21
Kidneys	9.28±1.91	10.61±1.87	9.96±1.01	9.58±1.73	7.83±1.31	4.60±0.71
Gastrointestinal	1.02±0.40	1.35±0.42	1.15±0.52	1.25±0.48	1.20±0.50	1.15±0.36
Bladder	0.76±0.40	0.82±0.44	3.55±1.61	7.08±2.17	13.42±4.16	42.93±20.93
Gluteus	0.54±0.29	0.59±0.26	0.56±0.23	0.56±0.20	0.52±0.22	0.35±0.13

Supplemental Table 2. The mean radiation dose and effective dose according to organs and tissues in volunteers (n=7)

Target Organ	*Doses (mSv/MBq)*	*Effective doses (mSv/MBq)*
Brain	5.653E-5±5.968E-5	3.24E-7±2.9E-7
Thyroid	5.731E-3±4.347E-3	3.518E-4±1.903E-4
Lungs	1.893E-2±8.845E-3	2.471E-3±8.863E-4
Breasts	5.826E-4±2.618E-4	3.447E-5±1.662E-5
Thymus	7.846E-4±3.018E-4	4.736E-6±2.283E-6
Heart Wall	9.251E-3±2.428E-3	Not available
Liver	1.479E-2±5.844E-3	9.137E-4±5.489E-4
Gall bladder wall	2.809E-3±1.469E-3	Not available
Spleen	2.516E-2±1.027E-2	1.553E-4±1.153E-4
Adrenals	2.147E-3±1.073E-3	1.318E-5±7.688E-6
Kidneys	6.15E-2±3.37E-2	3.934E-4±2.594E-4
Stomach wall	3.539E-2±3.667E-2	5.184E-3±4.507E-3
Pancreas	8.231E-3±3.807E-3	5.35E-5±4.001E-5
Upper large intestines wall	1.66E-3±1.178E-3	9.813E-6±6.916E-6
Lower large intestines wall	3.186E-3±2.7E-3	4.396E-4±3.605E-4
Small intestine	1.809E-3±1.323E-3	1.057E-5±7.583E-6
Urinary Bladder Wall	2.664E-1±2.248E-1	1.516E-2±1.237E-2
Ovaries (n=4)	3.026E-3±2.471E-3	6.944E-4±5.513E-4
Uterus (n=4)	7.964E-3±5.525E-3	4.493E-5±3.043E-5
Testis (n=3)	2.584E-3±2.818E-3	Not available
Red Marrow	1.187E-3±8.107E-4	1.677E-4±1.162E-4
Osteogenic Cells	8.23E-4±5.288E-4	9.486E-6±6.098E-6
Muscle	1.261E-3±9.13E-4	7.504E-6±5.475E-6
Skin	4.949E-4±3.474E-4	5.874E-6±4.149E-6
Total body		22.6



Supplemental Figure 1. Maximum intensity projection (MIP) of whole-body ^{68}Ga-NOTA-PRGD2 PET images of a patient with lung cancer. The 1-min image was acquired 3 sec/bed-position, while the 15, 30 and 60-min image was acquired in 60, 120 and 240 sec/bed-position. ^{68}Ga-NOTA-PRGD2 was rapidly cleared from the blood pool and primarily excreted through the urinary system. The highest distribution of radioactivity *in vivo* was found in the bladder, kidneys, and ureters. The arrow points the injection site.