Am J Nucl Med Mol Imaging 2017;7(2):53-62
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0051623

*Original Article*

# A phase one, single-dose, open-label, clinical safety and PET/MR imaging study of $^{68}$Ga-DOTATOC in healthy volunteers

Shadi A Esfahani[1], Stephanie Salcedo[1], Pedram Heidari[1], Onofrio A Catalano[1], Rachel Pauplis[2], Jacob Hesterman[2], James F Kronauge[2], Umar Mahmood[1]

*[1]Athinoula A Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]InviCRO LLC, 27 Drydock Ave., Boston 02210, MA, USA*

Received February 24, 2017; Accepted March 17, 2017; Epub April 15, 2017; Published April 30, 2017

**Abstract:** This prospective pilot study provides a dynamic whole body PET/MR image database, clinical safety, biodistribution profile and dosimetry of $^{68}$Ga-DOTATOC in healthy subjects, to establish a baseline and standard reference for its use in diagnosis and treatment response evaluation among patients with somatostatin receptor expressing neoplastic diseases. Dynamic whole body PET/MR imaging was performed in 12 healthy subjects (male/female: 8/4) after injection of 242.39 ± 53.38 MBq (mean ± SD) $^{68}$Ga-DOTATOC. Images were acquired 15, 60, 120, and 240 minutes post injection. Subjects were assessed at baseline and after $^{68}$Ga-DOTATOC PET/MR by monitoring vital signs, 12-lead electrocardiograms, complete blood count, comprehensive metabolic panel, and urinalysis. Adverse events were monitored for one week after injection. Organ dosimetry was estimated using OLINDA/EXM 1.1 software. Radiotracer was exclusively eliminated via urinary tract (18.8 ± 1.0% of injected dose within 4 hours) and no redistribution was observed. Bladder wall, spleen and kidneys received the highest radiation exposure (0.64 ± 0.1 mSv/MBq, 0.29 ± 0.14 mSv/MBq, and 0.1 ± 0.02 mSv/MBq, respectively). Mean effective dose yielded 0.048 ± 0.007 mSv/MBq. No adverse events were reported during the one-week follow-up period. Follow-up laboratory tests and electrocardiograms showed no changes compared to the baseline. The use of MRI provided valuable anatomical information and eliminated the risk of radiation exposure compared to CT.

**Keywords:** $^{68}$Ga, DOTATOC, PET/MR, somatostatin receptor, dosimetry, safety

## Introduction

Radiolabeled octreotide derivatives have been widely studied for diagnostic molecular imaging and targeted systemic radionuclide therapy in various types of cancers that overexpress somatostatin receptors (SSTR), such as neuroendocrine tumors (NETs) [1-3]. DOTA-conjugated octreotide analogs readily chelate metal ions in stable +3 oxidation state including $^{68}$Gallium and $^{64}$Copper for diagnostic imaging, as well as $^{86}$Yttrium, $^{177}$Lutetium and $^{111}$Indium for peptide receptor radionuclide therapy (PRRT) [4-7]. The favorable characteristics of $^{68}$Gallium such as its 68-minute half-life, accessibility and relative ease of radiolabeling has led to great interest for the use of $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE in research studies worldwide [8, 9].

Human dosimetry, biodistribution and safety of $^{68}$Ga-labelled octreotide analogs in healthy subjects are required to serve as reference for image interpretation and accurate assessment of lesion uptake in cancer patients. To date there has been a few studies assessing the dosimetry and biodistribution of these $^{68}$Ga-labelled octreotide analogs as PET imaging probes in patients with SSTR overexpressing neoplastic disease [10-12]; however, to our knowledge there has been no report of dosimetry of these PET imaging probes, in particular of $^{68}$Ga-DOTATOC in healthy human subjects.

In this phase-1, open-label study we evaluated clinical safety, biodistribution profile and dosimetry of $^{68}$Ga-DOTATOC in twelve healthy subjects. We have also provided a whole-body PET/MR image database to establish a baseline for

**Table 1.** Subjects' enrollment criteria

| |
|---|
| Inclusion Criteria |
| Age of 18-65 years |
| Normal or normal variant ECG |
| Clinical laboratory tests (CBC, CMP, UA) within normal limits |
| If female, not of childbearing potential or negative serum β-hCG pregnancy test just prior to radiotracer injection |
| Agreement on using an acceptable form of birth control for 6 hours (more than 5 half-lives) after injection of the radiotracer |
| Exclusion Criteria |
| History of head trauma, Meniere's disease, or claustrophobia |
| Other MRI contraindications such as non-MR compatible devices, implants and tattoos |
| Inadequate venous access |
| Received an investigational compound and/or medical device within 30 days prior to imaging |
| Received external beam therapy or chemotherapy within the last 30 days |
| Documented history of significant drug allergy that required medical intervention or known allergy to medications |
| Ongoing medical condition, taking medications, or other circumstances which would significantly decrease the chances of obtaining reliable data, or completing the study and/or post-injection follow-up examinations |

ECG: electrocardiogram, CBC: complete blood count, CMP: comprehensive metabolic panel (including serum electrolytes, liver and renal function tests), UA: urinalysis.

use in clinical management of a range of oncologic and non-oncologic diseases in various capacities, including diagnosis, treatment planning, surveillance, and assessment of response to therapy.

## Materials and methods

### *Enrollment of subjects*

The study was approved by our Institutional Review Board (IRB). Of 14 evaluated volunteer participants, 12 healthy subjects met the enrollment criteria and were entered into this pilot study between January and May 2016. The written informed consent was obtained from all volunteers on the screening day. Subjects' health status was evaluated by reviewing their medical history, list of current medications, vital signs (including blood pressure, pulse rate, respiratory rate and temperature), thorough physical examination, 12-lead electrocardiogram (ECG), and laboratory tests including complete blood count (CBC), complete metabolic panel (CMP), and urinalysis (UA). The subjects who met the inclusion criteria were enrolled in the study (**Table 1**).

### *Safety monitoring*

On the day of imaging, the subjects underwent another round of physical examination, vital sign assessment, and baseline 12-lead ECG. A serum beta human chorionic gonadotropin (ß-hCG) test for all females of childbearing potential was performed to exclude the possibility of pregnancy. Within 1-5 minutes after radiotracer injection and after each PET/MR imaging, vital signs and repeat 12-lead ECGs were obtained, and subjects were monitored for any possible adverse events. Twenty-four hours after $^{68}$Ga-DOTATOC injection, the subjects underwent repeat physical examination and 12-lead ECG, and samples were again taken for CBC, CMP, and UA. One week after injection of the radiotracer, a follow up phone call was carried out to ask for and assess any experienced adverse events.

### *$^{68}$Ga-DOTATOC preparation*

$^{68}$Ga-DOTATOC was synthetized under a physician sponsored, extended access IND approval. The commercial $^{68}$Ge/$^{68}$Ga generator (Isotope Technologies Garching (ITG) GmbH, Germany) was eluted with 0.5 M hydrochloric acid in 3 fractions and the second fraction containing 2 ml of the eluent (as $^{68}$Ga-chloride) was taken for probe preparation. The radiopharmaceutical was produced using the previously described custom made automated $^{68}$Ga-labeling synthesis unit [9]. Briefly, the eluent was mixed with lyophilized DOTATOC and sodium acetate kit (InviCRO LLC, Boston, MA) at 100°C for 15 minutes. Following rapid cooling of the mixture at 30°C, it was pushed through the solid-phase extraction cartridge (Sep-Pak, Waters, Milford, MA). Ethanol was

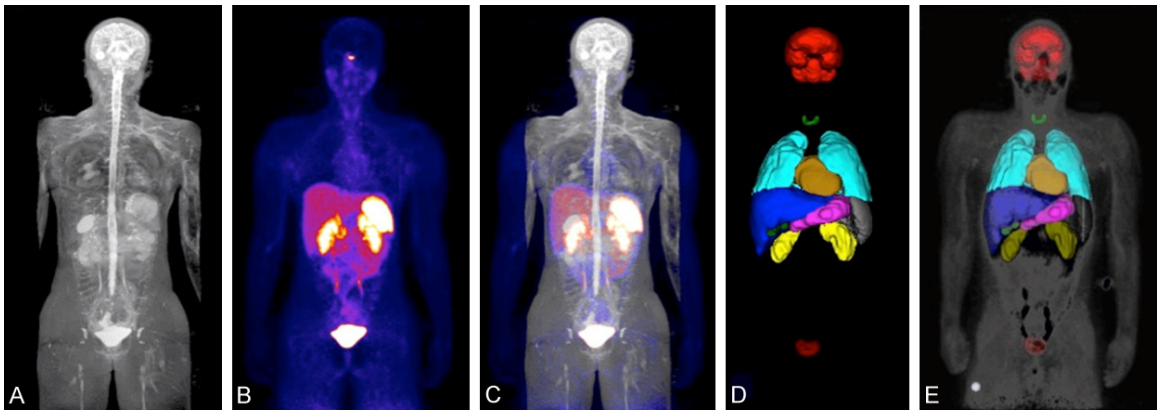


**Figure 1.** Representative maximum-intensity projection images of simultaneously acquired body MRI (A), $^{68}$Ga-DOTATOC PET (B), overlaid PET/MRI (C), volume of interest analysis (D) and overlaid volume of interest on representative PET image (E).

added to elute the product of the column. The product ethanol content was adjusted to 10% by adding normal saline (Hospira, Lake Forest, IL). The final drug product $^{68}$Ga-DOTATOC solution was immediately sterilized by terminal filtration followed by QC release testing and then dispensed into a unit-dose for administration in imaging suites. Subjects received one dose of $^{68}$Ga-DOTATOC with the mean activity of 242.39 ± 53.38 MBq (range 156.5-334.2 MBq) in total volume of 10 ml containing 80 μg of DOTATOC.

*PET/MR acquisition*

The PET/MR image acquisitions were started at 15, 60, 120, and 240 minutes after intravenous injection of $^{68}$Ga-DOTATOC. Images were acquired using a 3 Tesla Biograph mMR-PET scanner (Siemens Medical Solutions, Knoxville, TN). MR acquisition was performed using a 16-channel head and neck surface coil and three to five 12-channel body coils, with the number of used coils depending on the participant's height. PET acquisition was performed in 4-6 bed positions depending on the subjects' height with 30% overlap between adjacent table stations. Simultaneous MRI and PET images were acquired for all the subjects starting from base of the skull to the level of proximal thighs (**Figure 1A-C**). Automatic attenuation correction was performed using attenuation maps generated from the twopoint Dixon sequence. The mean total time for the PET/MR imaging was 30 ± 3 minutes.

*Data analysis*

Whole organ 3D segmentation was performed to draw the regions of interest (ROIs) based on the anatomical imaging data for each organ from MRI. When due to respiratory motion the co-registration of MR and PET was less than optimal, ROIs were adjusted to match the PET data in areas without good alignment. The time activity curves were subsequently measured by the input from the whole organ 3D ROIs including from brain, thyroid, heart, lungs, liver, gallbladder, spleen, kidneys, bladder, and stomach (**Figure 1D**, **1E**). The dose to the portions of the lower extremities that were not included in the field of view was estimated by calculating the approximate volume not imaged using the body weight multiplied by the activity in the thigh muscle.

Time-activity curves were fit to single- and bi-exponential models. The corrected Akaike Information Criterion (AICc) was used for model selection. Trapezoidal integration was used for AUC calculation, using decay corrected activity from the 1$^{st}$ scan at time zero, and assuming only physical decay after the final measured time point. Dosimetry was calculated in various organs using OLINDA/EXM (version 1.1) software using 73.7 kg adult male and 56.9 kg female phantom models.

Renal clearance half time was assumed to be the whole-body clearance over the same time frame. The voiding bladder model (using a 2-h void time) in OLINDA 1.1 was used. To deter-

**Table 2.** Demographic characteristics of the study subjects

| Age (years) | Gender | Race/Ethnicity | Weight (kg) | Active Disease | Active Medications | Injected Activity (MBq) | AEs | CBC, CMP, UA | | ECG | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Pre-injection | 24 h Post-injection | Pre-injection | 5 min-24 h Post-injection |
| 24 | F | Caucasian/Non-Hispanic | 67.1 | Mild cutaneous psoriasis | Clobetasol topical cream 0.05% | 207.94 | None | WNL | | WNL | |
| 27 | M | African American/Non-Hispanic | 104.3 | None | None | 241.98 | None | Mild microcytic anemia | Mild microcytic anemia* | WNL | |
| 33 | F | African American/White, Hispanic | 59 | None | None | 156.51 | None | Mild normocytic anemia | Mild normocytic anemia* | WNL | |
| 19 | M | Caucasian/Non-Hispanic | 62.1 | Intermittent Asthma, acne | Doxycycline | 222.74 | None | AST: 76 | AST: 49* | WNL | |
| 21 | M | Caucasian/Hispanic | 68 | None | None | 196.47 | None | WNL | | WNL | |
| 35 | M | Caucasian/Non-Hispanic | 83.9 | None | None | 249.75 | None | Asymptomatic 1+ bacteriuria | 1+ bacteriuria (unchanged)* | WNL | |
| 24 | F | Caucasian/Non-Hispanic | 61.2 | Sinusitis, Seasonal allergy | Calcium, Zyrtec | 231.25 | None | WNL | | WNL | |
| 23 | M | Caucasian/Non-Hispanic | 88.5 | None | None | 321.9 | None | WNL | | RBBB Otherwise WNL | RBBB (unchanged)* |
| 29 | M | Asian/Non-Hispanic | 81.6 | None | None | 306.73 | None | WNL | | WNL | |
| 29 | M | Caucasian/Non-Hispanic | 83.9 | None | None | 297.295 | None | WNL | | WNL | |
| 31 | M | Caucasian/Non-Hispanic | 76.20 | None | None | 228.66 | None | WNL | | WNL | |
| 29 | F | Caucasian/Non-Hispanic | 66.22 | None | None | 208.31 | None | WNL | | WNL | |

PMH: past medical history, AE: adverse events, CBC: complete blood count, CMP: comprehensive metabolic panel, UA: urinalysis, ECG: electrocardiogram, WNL: within normal limits. *Subjects were notified of the results and advised to follow up with their primary care physicians.

**Table 3.** Organ-specific radiation dose estimation

| Organ | Subject | | | | | | | | | | | | Mean dose (mSv/MBq) | Dose SD (mSv/MBq) | Male/Female |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | | |
| Adrenals | 0.0136 | 0.011 | 0.0106 | 0.0104 | 0.0119 | 0.0102 | 0.0105 | 0.0092 | 0.0098 | 0.0127 | 0.0088 | 0.0137 | 0.011 | 0.0016 | 1/1.29† |
| Brain | 0.0024 | 0.0024 | 0.0026 | 0.0025 | 0.0038 | 0.0019 | 0.0023 | 0.0025 | 0.0023 | 0.0041 | 0.0022 | 0.0032 | 0.0027 | 0.0007 | 0.23/0.33† |
| Breasts | 0.0074 | 0.0065 | 0.0056 | 0.006 | 0.008 | 0.0065 | 0.0056 | 0.0052 | 0.0059 | 0.0075 | 0.0057 | 0.0074 | 0.0064 | 0.0009 | 0.58/0.75† |
| Gallbladder Wall | 0.0199 | 0.0169 | 0.013 | 0.0138 | 0.0177 | 0.0151 | 0.0143 | 0.016 | 0.0162 | 0.0167 | 0.0122 | 0.0234 | 0.0163 | 0.0031 | 1.46/1.94† |
| LLI Wall | 0.0172 | 0.0137 | 0.0126 | 0.0132 | 0.0179 | 0.0136 | 0.0127 | 0.0126 | 0.0132 | 0.0166 | 0.0136 | 0.0165 | 0.0145 | 0.002 | 1.31/1.7† |
| Small Intestine | 0.0127 | 0.0106 | 0.0096 | 0.0101 | 0.013 | 0.0105 | 0.0096 | 0.0092 | 0.0099 | 0.0124 | 0.0098 | 0.0124 | 0.0108 | 0.0014 | 0.99/1.26† |
| Stomach Wall | 0.026 | 0.0344 | 0.0213 | 0.0185 | 0.0316 | 0.0273 | 0.0214 | 0.0211 | 0.0236 | 0.0362 | 0.0219 | 0.0277 | 0.026 | 0.0057 | 2.36/3.03 |
| ULI Wall | 0.0123 | 0.0102 | 0.0092 | 0.0096 | 0.0126 | 0.0101 | 0.0091 | 0.0087 | 0.0094 | 0.0121 | 0.0092 | 0.0122 | 0.0104 | 0.0015 | 0.94/1.23† |
| Heart Muscle | 0.0135 | 0.0126 | 0.0116 | 0.0124 | 0.0165 | 0.0115 | 0.0111 | 0.0116 | 0.0104 | 0.014 | 0.0092 | 0.0157 | 0.0125 | 0.0021 | 1.13/1.49† |
| Kidneys | 0.133 | 0.108 | 0.163 | 0.0871 | 0.0857 | 0.0924 | 0.1 | 0.0938 | 0.0737 | 0.133 | 0.0731 | 0.0852 | 0.102 | 0.0274 | 9.88/10.9 |
| Liver | 0.0444 | 0.0426 | 0.0414 | 0.0385 | 0.0336 | 0.0395 | 0.0423 | 0.0408 | 0.0394 | 0.0543 | 0.0267 | 0.0611 | 0.0421 | 0.0088 | 3.89/4.83 |
| Lungs | 0.0131 | 0.013 | 0.0173 | 0.0106 | 0.0147 | 0.0101 | 0.0113 | 0.0172 | 0.0137 | 0.0205 | 0.0114 | 0.0108 | 0.0136 | 0.0032 | 1.3/1.47 |
| Muscle | 0.0103 | 0.0087 | 0.0078 | 0.0083 | 0.0106 | 0.0087 | 0.0078 | 0.0074 | 0.0081 | 0.01 | 0.008 | 0.0101 | 0.0088 | 0.0011 | 0.81/1.02† |
| Ovaries** | 0.0169 | N/A | N/A | N/A | 0.0176 | N/A | N/A | N/A | N/A | 0.0164 | N/A | 0.0162 | 0.0167 | 0.0006 | N/A |
| Pancreas | 0.0166 | 0.0133 | 0.0126 | 0.0131 | 0.0129 | 0.0113 | 0.0142 | 0.0111 | 0.012 | 0.0138 | 0.0101 | 0.0174 | 0.0132 | 0.0021 | 1.22/1.51† |
| Red Marrow | 0.0084 | 0.0073 | 0.0066 | 0.0069 | 0.0086 | 0.0072 | 0.0066 | 0.0062 | 0.0067 | 0.0083 | 0.0066 | 0.0082 | 0.0073 | 0.0009 | 0.67/0.83† |
| Osteogenic Cells | 0.0127 | 0.0103 | 0.0089 | 0.0097 | 0.0137 | 0.0104 | 0.0089 | 0.0083 | 0.0094 | 0.0127 | 0.0094 | 0.0126 | 0.0106 | 0.0018 | 0.94/1.29† |
| Skin | 0.0076 | 0.0066 | 0.0057 | 0.0062 | 0.0081 | 0.0067 | 0.0057 | 0.0054 | 0.0061 | 0.0075 | 0.006 | 0.0075 | 0.0066 | 0.0009 | 0.60/0.76† |
| Spleen | 0.478 | 0.264 | 0.299 | 0.355 | 0.133 | 0.123 | 0.471 | 0.252 | 0.266 | 0.175 | 0.146 | 0.538 | 0.292 | 0.142 | 27.2/33.1 |
| Testes* | NA | 0.0106 | 0.0096 | 0.0102 | NA | 0.0107 | 0.0097 | 0.0096 | 0.0102 | NA | 0.0105 | NA | 0.0101 | 0.0004 | N/A |
| Thymus | 0.0081 | 0.0071 | 0.0061 | 0.0066 | 0.0089 | 0.0072 | 0.006 | 0.0057 | 0.0064 | 0.0083 | 0.0063 | 0.0081 | 0.0071 | 0.001 | 0.64/0.83† |
| Thyroid | 0.0159 | 0.0101 | 0.017 | 0.005 | 0.0125 | 0.0212 | 0.0118 | 0.0136 | 0.0108 | 0.0239 | 0.0096 | 0.0146 | 0.0138 | 0.0052 | 1.23/1.67 |
| Bladder Wall | 0.813 | 0.561 | 0.562 | 0.596 | 0.816 | 0.541 | 0.575 | 0.614 | 0.58 | 0.765 | 0.616 | 0.757 | 0.647 | 0.107 | 58 /78.7† |
| Uterus** | 0.0255 | N/A | N/A | N/A | 0.0126 | N/A | N/A | N/A | N/A | 0.0245 | N/A | 0.0243 | 0.0217 | 0.006 | N/A |
| Total Body | 0.0135 | 0.0111 | 0.0105 | 0.0106 | 0.0136 | 0.0105 | 0.0106 | 0.0097 | 0.0102 | 0.0129 | 0.0095 | 0.0137 | 0.0113 | 0.0015 | 1.03/1.34† |
| Effective Dose | 0.059 | 0.0443 | 0.0435 | 0.042 | 0.0576 | 0.041 | 0.043 | 0.045 | 0.0435 | 0.0578 | 0.043 | 0.056 | 0.0482 | 0.0071 | 4.34/5.77† |

LLI: lower large intestine, ULI: upper large intestine, SD: standard deviation. *Average for testes was calculated using only the 8 male subjects. **Averages for ovaries and uteri were calculated using only the 4 female subjects. †*P* value < 0.05. Columns 1, 5, 10 and 12 show the data in female subjects.

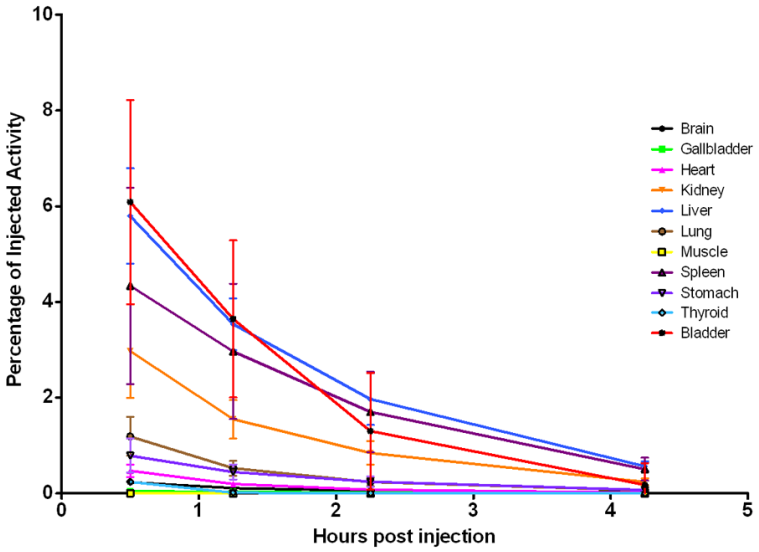


**Figure 2.** Time-activity curves of selected organs in 12 subjects 30 minutes to 255 minutes after $^{68}$Ga-DOTATOC administration.

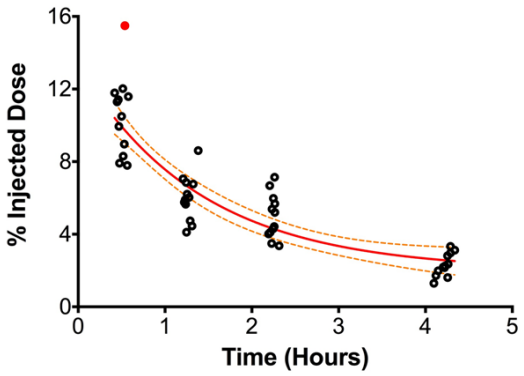


**Figure 3.** Urine clearance during 4 hours after injection of $^{68}$Ga-DOTATOC. The outlier is marked in red.

mine urine clearance, the urine activity at each time point was divided by the whole-body activity and was fit to bi-exponential model.

*Statistical analysis*

Statistical analysis was performed using GraphPad Software (ver. 7.01, CA, USA). Descriptive statistics for continuous variables (number, mean, standard deviation, median, minimum and maximum) or for categorical variables (counts, percentages) was used as appropriate.

Differences between absorbed doses in male and female subjects were assessed using Mann-Whitney U test. A $p$ value of less than 0.05 was considered significant. The scan time points in the graphs reflect the average time from injection of the radiotracer to mid-point of scan at each scan time point.

## Results

*Enrolled subjects*

Twelve subjects fulfilled the inclusion criteria including 8 men and 4 women (Male/Female ratio: 2, age range 19-35 years, median 28 years). Subjects' demographics, laboratory test and ECG results, and the injected dose of $^{68}$Ga-DOTATOC are summarized in **Table 2**. All subjects tolerated $^{68}$Ga-DOTATOC injection and PET/MR scanning well. No immediate adverse reaction related to radiotracer injection was reported. There was no significant change in the vital signs, ECGs, and laboratory results at any time point after the injection of radiopharmaceutical compared to baseline. The subjects reported no adverse events from the time of radioisotope injection until one week after the imaging. A male participant showed isolated 1+ bacteriuria (most likely secondary to sample contamination), with no urinary symptoms or other abnormalities in the UA or metabolic panel. Another male participant was found to have mild microcytic anemia and a female subject was found to have mild anemia on both screening and follow up CBC, with no significant change between the results of the two time points. These subjects were informed of the results and advised to follow up with their primarycare physicians for further evaluation.

*Dosimetry*

Organ dosimetry for each individual subject is shown in detail in **Table 3** and the time-activity curve for multiple organs are shown in **Figure 2**. Our results indicate that the urinary bladder receives the greatest dose, followed by spleen, kidneys and liver in descending order. Prior dosimetry of $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE in cancer patients showed spleen and bladder as the organs, which receive the greatest dose which are consistent with our findings [10, 11].

**Table 4.** Comparison of $^{68}$Ga-DOTATOC dosimetry with prior reports on $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE

| Organ | DOTATOC Dose (mSv/MBq) | DOTATOC dose (mSv/MBq) (Sandstrom *et al*) [11] | DOTATATE dose (mSv/MBq) (Sandstrom *et al*) [11] | DOTATOC dose (mSv/MBq) (Hartmann *et al*) [10] | DOTATATE dose (mSv/MBq) (Walker *et al*) [8] |
|---|---|---|---|---|---|
| Adrenals | 0.0110 ± 0.0016 | 0.077 ± 0.028 | 0.086 ± 0.052 | | 0.0146 ± 0.0005 |
| Brain | 0.0027 ± 0.0007 | | | | 0.0097 ± 0.0006 |
| Breasts | 0.0064 ± 0.0009 | | | | 0.0097 ± 0.0004 |
| Gallbladder Wall | 0.0163 ± 0.0031 | 0.015 ± 0.0001 | 0.016 ± 0.002 | | 0.0149 ± 0.0007 |
| LLI Wall | 0.0145 ± 0.0020 | | | | 0.0129 ± 0.0008 |
| Small Intestine | 0.0108 ± 0.0014 | | | | 0.0138 ± 0.0026 |
| Stomach Wall | 0.0260 ± 0.0057 | | | | 0.0138 ± 0.0007 |
| ULI Wall | 0.0104 ± 0.0015 | | | | 0.0129 ± 0.0004 |
| Heart Muscle | 0.0125 ± 0.0021 | | | | 0.0123 ± 0.0004 |
| Kidneys | 0.1023 ± 0.0274 | 0.082 ± 0.020 | 0.093 ± 0.016 | 0.22 | 0.0921 ± 0.0284 |
| Liver | 0.0421 ± 0.0088 | 0.041 ± 0.014 | 0.050 ± 0.015 | 0.074 | 0.0450± 0.0152 |
| Lungs | 0.0136 ± 0.0032 | 0.007 ± 0.001 | 0.006 ± 0.001 | | 0.0115 ± 0.0004 |
| Muscle | 0.0088 ± 0.0011 | | | | 0.0113 ± 0.0005 |
| Ovaries* | 0.0167 ± 0.0006 | | | | 0.0131 ± 0.0008 |
| Pancreas | 0.0132 ± 0.0021 | | | | 0.0167 ± 0.0014 |
| Red Marrow | 0.0073 ± 0.0009 | 0.016 ± 0.003 | 0.015 ± 0.003 | | 0.0096 ± 0.0004 |
| Osteogenic Cells | 0.0106 ± 0.0018 | | | | 0.0155 ± 0.0007 |
| Skin | 0.0066 ± 0.0009 | | | | 0.0097 ± 0.0004 |
| Spleen | 0.2916 ± 0.1424 | 0.108 ± 0.065 | 0.077 ± 0.028 | 0.24 | 0.2820 ± 0.1210 |
| Testes* | 0.0101 ± 0.0004 | | | | 0.0112 ± 0.0007 |
| Thymus | 0.0071 ± 0.0010 | | | | 0.0109 ± 0.0005 |
| Thyroid | 0.0138 ± 0.0052 | | | | 0.0187 ± 0.0105 |
| Bladder Wall | 0.6474 ± 0.1069 | 0.119 ± 0.058 | 0.098 ± 0.048 | 0.07 | 0.125 ± 0.0618 |
| Uterus* | 0.0217 ± 0.006 | | | | 0.0147 ± 0.0016 |
| Total Body | 0.0113 ± 0.0015 | 0.014 ± 0.002 | 0.014 ± 0.002 | | 0.0134 ± 0.0003 |
| Effective Dose** | 0.0482 ± 0.0071 | 0.021 ± 0.003 | 0.021 ± 0.003 | 0.023 | 0.0257 ± 0.0029 |

*Average for testes was calculated using only the male subjects and average for ovaries and uteri was calculated using only female subjects. **The effective dose is approximately twice higher when compared to prior reported data, due to using a different bladder-voiding model. The data is presented as mean ± SD.

However, the dynamic bladder model in our study showed significant elimination of the radiotracer through the urinary tract (**Figures 2**, **3**), and resulted in slightly lower total body dose and higher effective dose when compared to prior studies (**Table 4**). The present data resulted in effective dose of 4.8 mSv from 100 MBq injected activity.

During the 4-hour injection, 18.8 ± 1.0% ID (range: 16.8-20.8% ID) of the injected activity was eliminated in the urine, which is slightly higher than an average of approximately 15% urinary elimination reported in patients with neuroendocrine tumors [11].

Representative dynamic PET images of healthy male and female adults are shown in **Figures 4** and **5**. When women and men were analyzed separately, the mean received doses for each organ as well as the effective doses were slightly higher in female compared to male participants ($P < 0.05$; please see **Table 3** for details).

## Discussion

This study, to our knowledge, is the first to provide safety, biodistribution and dosimetry data of $^{68}$Ga-DOTATOC in healthy adult subjects. Our organ specific dosimetry showed urinary bladder wall as the organ receiving the highest absorbed dose, followed by spleen, kidneys, and liver. Overall, the results of organ specific and total body dosimetry of $^{68}$Ga-DOTATOC in healthy subjects in our study were similar to the results in patients with neuroendocrine tumors, which were previously reported by Hartman et al, and Sandström et al [10, 11]. However, we observed a higher bladder dose in our study

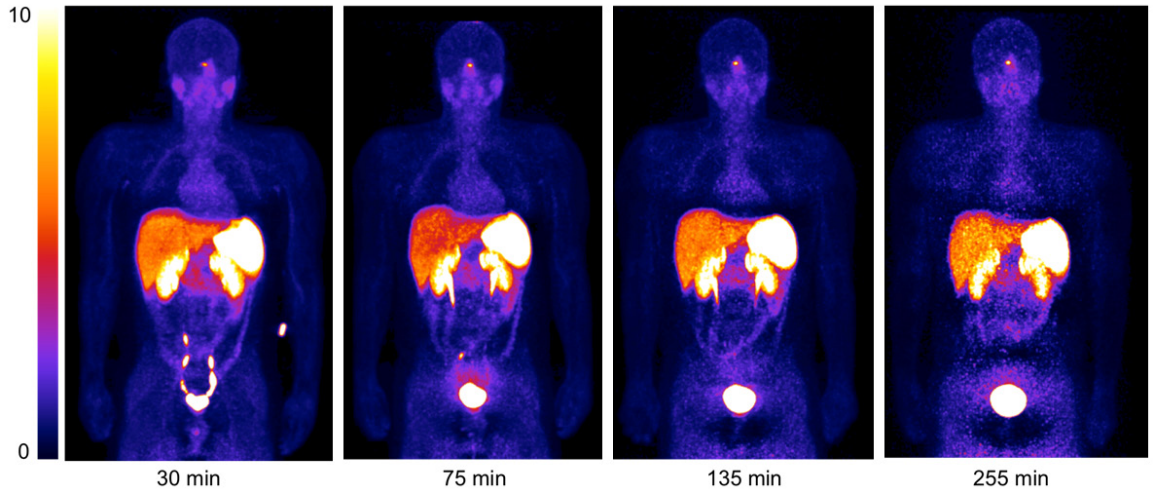


**Figure 4.** Representative dynamic PET images of male subject during 4 hours after injection of $^{68}$Ga-DOTATOC.

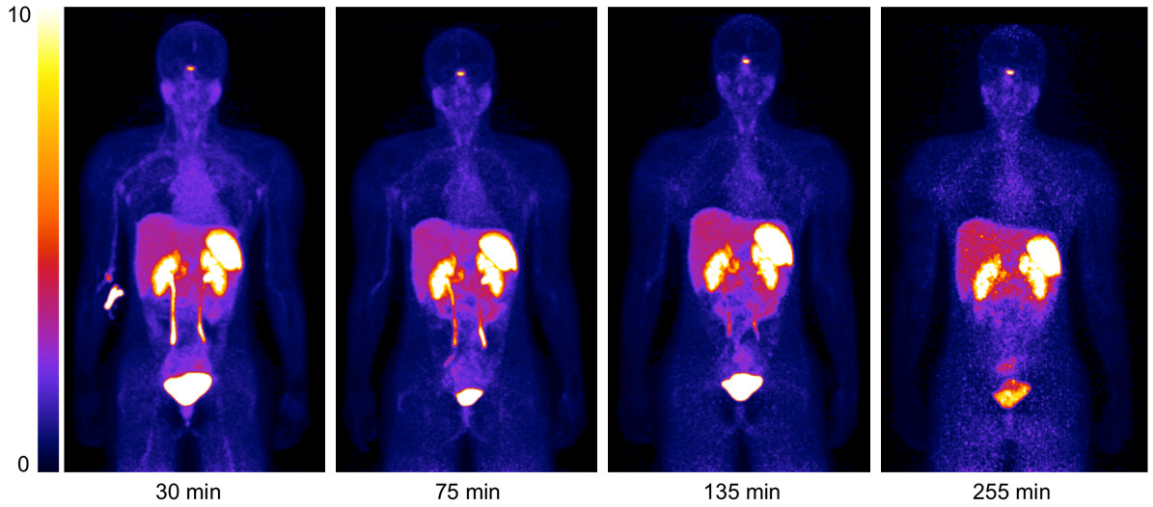


**Figure 5.** Representative anterior 3-dimensional maximum-intensity projection demonstrating normal physiologic biodistribution of $^{68}$Ga-DOTATOC during 4 hours post injection in female subject.

compared to prior reports, which may be explained by higher percentage of urinary elimination of the radiotracer compared to previous reports (**Table 4**). This could likely be explained by very low SSTR2 receptor burden in healthy subjects in contrast to patients with NETs where the tumor tissue with high SSTR2 expression acts as a radiotracer sink. A review of $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE dosimetry showed minor differences between organ specific doses. The effective dose for a single $^{68}$Ga-DOTATOC scan is less than 5 mSv, which by comparison is lower than an estimated effective dose per scan of 6 mSv for $^{111}$In-DTPA-octreotide and of 7 mSv for $^{18}$F-FDG [8]. Comparison of total body dosimetry of female and male subjects showed overall higher doses in female compared to male subjects (total dose: 0.013 vs. 0.01 mSv/MBq, $P < 0.05$; effective dose: 0.057 vs. 0.043 mSv/MBq, $P < 0.05$, respectively). This is best explained by smaller body size of female compared to male subjects, which results in proportionally larger dose as expected.

This PET imaging probe was well tolerated by all the participants, and no immediate or delayed adverse reaction was reported by the subjects during the one week follow up after the probe injection. There was no significant change in

the subjects' physical examination, ECG or laboratory results at baseline compared to the follow up. Growing body of evidence from clinical studies around the globe mostly focused on the imaging efficacy, tumor detection and characterization, and they have reported no side effects from $^{68}$Ga-DOTATOC administration [13-20]. Intravenously administered doses of $^{68}$Ga-DOTATOC up to 307 MBq have been shown to be tolerated, with no acute or chronic side effects [16, 19, 21]. DOTATOC labeled with ß-emitting radiometals such as $^{90}$Yttrium and $^{177}$Lutetium have shown renal and hematological toxicities, which are believed to occur secondary to cytotoxic effects of ß-emitting long-lived radionuclides rather than DOTATOC itself [6, 22, 23]. $^{68}$Gallium with half-life of 68 minutes is devoid of such hazardous side effects and no toxicities have been reported for its use in diagnostic PET imaging. Non-radioactive octreotide injection given in intravenous bolus dose of 1 mg to healthy volunteers, or 30 mg given over 20 minutes and 120 mg over 8 hours to patients has not shown any serious side effect. The reported safety margin of cold octreotide analogs is very high and reported to be approximately 150-450 µg/day for immediate release and 10-30 mg/month for extended release preparations [24]. The single dose mass of DOTATOC in the final radiopharmaceutical product is less than 50 µg, which accounts for approximately one third to one fourth of the active pharmaceutical ingredient in a single day dose of the therapeutic agent and thus amounts to a very low likelihood of side effects risk.

## Conclusion

This study successfully demonstrated the safety and dosimetry of $^{68}$Ga-DOTATOC as well as PET/MR images in healthy human subjects. The results showed that single organ and effective doses are within acceptable ranges and no side effect was observed in one week after administration of this PET imaging agent. The use of MRI provided valuable anatomical information and eliminated the risk of ionizing radiation exposure compared to CT. The normal $^{68}$Ga-DOTATOC PET/MR image database is intended to serve as a normal distribution atlas to develop an automated segmentation algorithm to quantitate total tumor burden in NET patients. The data may also be accessed as standard reference for adopting amended INDs and as negative control for $^{68}$Ga-DOTATOC image interpretations at Society of Nuclear Medicine and Molecular Imaging (SNMMI) clinical trial network, and other independent academic institutions. Copies of all the anonymized image data can be accessed for free on the inviCRO website (www.invicro.com).

## Acknowledgements

The authors would like to thank Shirely Hsu, and Grea Arabas for image acquisition. This study was supported by NIH grants R01CA-166582 and R44CA157090.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Umar Mahmood, Athinoula A Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, 02129, MA, USA. Tel: 617-726-6477; Fax: 617-726-7422; E-mail: umahmood@mgh.harvard.edu

## References

[1] Breeman WA, de Blois E, Sze Chan H, Konijnenberg M, Kwekkeboom DJ and Krenning EP. (68)Ga-labeled DOTA-peptides and $^{68}$Ga-labeled radiopharmaceuticals for positron emission tomography: current status of research, clinical applications, and future perspectives. Semin Nucl Med 2011; 41: 314-321.

[2] Reubi JC and Maecke HR. Peptide-based probes for cancer imaging. J Nucl Med 2008; 49: 1735-1738.

[3] Breeman WA, Kwekkeboom DJ, de Blois E, de Jong M, Visser TJ and Krenning EP. Radiolabelled regulatory peptides for imaging and therapy. Anticancer Agents Med Chem 2007; 7: 345-357.

[4] Pfeifer A, Knigge U, Mortensen J, Oturai P, Berthelsen AK, Loft A, Binderup T, Rasmussen P, Elema D, Klausen TL, Holm S, von Benzon E, Hojgaard L and Kjaer A. Clinical PET of neuroendocrine tumors using $^{64}$Cu-DOTATATE: first-in-humans study. J Nucl Med 2012; 53: 1207-1215.

[5] Kwekkeboom DJ, Kooij PP, Bakker WH, Macke HR and Krenning EP. Comparison of $^{111}$In-DOTA-Tyr3-octreotide and 111In-DTPA-octreotide in the same patients: biodistribution, kinetics, organ and tumor uptake. J Nucl Med 1999; 40: 762-767.

[6] Villard L, Romer A, Marincek N, Brunner P, Koller MT, Schindler C, Ng QK, Macke HR,

Muller-Brand J, Rochlitz C, Briel M and Walter MA. Cohort study of somatostatin-based radiopeptide therapy with [$^{90}$Y-DOTA]-TOC versus [$^{90}$Y-DOTA]-TOC plus [$^{177}$Lu-DOTA]-TOC in neuroendocrine cancers. J Clin Oncol 2012; 30: 1100-1106.

[7] Al-Nahhas A, Win Z, Szyszko T, Singh A, Nanni C, Fanti S and Rubello D. Gallium-68 PET: a new frontier in receptor cancer imaging. Anticancer Res 2007; 27: 4087-4094.

[8] Walker RC, Smith GT, Liu E, Moore B, Clanton J and Stabin M. Measured human dosimetry of $^{68}$Ga-DOTATATE. J Nucl Med 2013; 54: 855-860.

[9] Heidari P, Szretter A, Rushford LE, Stevens M, Collier L, Sore J, Hooker J and Mahmood U. Design, construction and testing of a low-cost automated (68)Gallium-labeling synthesis unit for clinical use. Am J Nucl Med Mol Imaging 2016; 6: 176-184.

[10] Hartmann H, Zophel K, Freudenberg R, Oehme L, Andreeff M, Wunderlich G, Eisenhofer G and Kotzerke J. [Radiation exposure of patients during $^{68}$Ga-DOTATOC PET/CT examinations]. Nuklearmedizin 2009; 48: 201-207.

[11] Sandstrom M, Velikyan I, Garske-Roman U, Sorensen J, Eriksson B, Granberg D, Lundqvist H, Sundin A and Lubberink M. Comparative biodistribution and radiation dosimetry of $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE in patients with neuroendocrine tumors. J Nucl Med 2013; 54: 1755-1759.

[12] Pettinato C, Sarnelli A, Di Donna M, Civollani S, Nanni C, Montini G, Di Pierro D, Ferrari M, Marengo M and Bergamini C. $^{68}$Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. Eur J Nucl Med Mol Imaging 2008; 35: 72-79.

[13] Hofmann M, Maecke H, Borner R, Weckesser E, Schoffski P, Oei L, Schumacher J, Henze M, Heppeler A, Meyer J and Knapp H. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med 2001; 28: 1751-1757.

[14] Todorovic-Tirnanic MV, Gajic MM, Obradovic VB and Baum RP. Gallium-68 DOTATOC PET/CT in vivo characterization of somatostatin receptor expression in the prostate. Cancer Biother Radiopharm 2014; 29: 108-115.

[15] Combs SE, Welzel T, Habermehl D, Rieken S, Dittmar JO, Kessel K, Jakel O, Haberkorn U and Debus J. Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and $^{68}$Ga-DOTATOC-PET. Acta Oncol 2013; 52: 514-20.

[16] Afshar-Oromieh A, Giesel FL, Linhart HG, Haberkorn U, Haufe S, Combs SE, Podlesek D, Eisenhut M and Kratochwil C. Detection of cranial meningiomas: comparison of $^{68}$Ga-DOTATOC PET/CT and contrast-enhanced MRI. Eur J Nucl Med Mol Imaging 2012; 39: 1409-1415.

[17] Thorwarth D, Muller AC, Pfannenberg C and Beyer T. Combined PET/MR imaging using $^{68}$Ga-DOTATOC for radiotherapy treatment planning in meningioma patients. Recent Results Cancer Res 2012; 194: 425-439.

[18] Poeppel TD, Binse I, Petersenn S, Lahner H, Schott M, Antoch G, Brandau W, Bockisch A and Boy C. 68Ga-DOTATOC versus 68Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. J Nucl Med 2011; 52: 1864-1870.

[19] Kumar R, Sharma P, Garg P, Karunanithi S, Naswa N, Sharma R, Thulkar S, Lata S and Malhotra A. Role of $^{68}$Ga-DOTATOC PET-CT in the diagnosis and staging of pancreatic neuroendocrine tumours. Eur Radiol 2011; 21: 2408-2416.

[20] Velikyan I, Sundin A, Sorensen J, Lubberink M, Sandstrom M, Garske-Roman U, Lundqvist H, Granberg D and Eriksson B. Quantitative and qualitative intrapatient comparison of $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE: net uptake rate for accurate quantification. J Nucl Med 2014; 55: 204-210.

[21] Al-Ibraheem A, Bundschuh RA, Notni J, Buck A, Winter A, Wester HJ, Schwaiger M and Scheidhauer K. Focal uptake of $^{68}$Ga-DOTATOC in the pancreas: pathological or physiological correlate in patients with neuroendocrine tumours? Eur J Nucl Med Mol Imaging 2011; 38: 2005-2013.

[22] Bodei L, Cremonesi M, Grana C, Rocca P, Bartolomei M, Chinol M and Paganelli G. Receptor radionuclide therapy with $^{90}$Y-[DOTA]0-Tyr3-octreotide ($^{90}$Y-DOTATOC) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2004; 31: 1038-1046.

[23] Otte A, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, Maecke HR and Muller J. Yttrium-90 DOTATOC: first clinical results. Eur J Nucl Med 1999; 26: 1439-1447.

[24] Chieffo C, Cook D, Xiang Q and Frohman LA. Efficacy and safety of an octreotide implant in the treatment of patients with acromegaly. J Clin Endocrinol Metab 2013; 98: 4047-4054.