Human Absorbed Dose Estimation of ^{111}In-DOTA-PR81 as a Novel High Potential Agent for Breast Cancer Imaging

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Abstract

Purpose: In this study, the human absorbed dose of ^{111}In-DOTA-PR81 as a new radioimmunoconjugate for single-photon emission computed tomography (SPECT) imaging of MUC1 + breast cancer was determined. **Materials and Methods:** The complex was prepared at optimized conditions in about 1 h and 38°C. The radiochemical purity of the tracer was investigated using the instant thin-layer chromatography method method, showing purity of higher than 96%. After evaluating the stability of the product in human serum and room temperature, the biological distribution of the radiolabeled compound was studied in normal rats and tumor-bearing mice. Finally, the human absorbed dose of the complex was estimated based on animals' data using radiation dose assessment resource and Spark *et al*. methods. **Results:** High uptake of the complex in MUC1 + breast tumors compared to other nontarget organs shows that the radioimmunoconjugate is a beneficial agent for SPECT imaging of MUC1 + breast cancer. Human organs absorbed dose estimation of the complex demonstrated the highest amounts of the absorbed dose are in the liver and kidneys with 0.384 and 0.245 mGy/MBq, respectively. **Conclusions:** ^{111}In-DOTA-PR81 radioimmunoconjugate is a high potential agent for MUC1 + breast cancer SPECT imaging and estimated absorbed dose values could helpfully use for the determination of the maximum injectable dose.

Keywords: Absorbed dose, anti-MUC1, breast cancer, indium-111, radiation dose assessment resource

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Introduction

The early diagnosis of high prevalence breast cancer is one of the most critical issues in treatment management. New diagnostic approaches such as radioimmunoscintigraphy (RIS) can take advantage of antibody specificity to tumor surface antigens as well as noninvasive emitted radiation from a radioisotope to the other nontarget organs.[1] MUC1, a transmembrane protein expressed on somatic cells of the secretory system, is overexpressed in the human breast ovary and other adenosarcomas[2-4] and can be a suitable target to detect this type of cancer.[4]

MUC1 is recognized by a series of antibodies, including PR81 which, was introduced by Paknejad *et al*.[3] PR81 and other monoclonal antibodies are the main category of molecules in targeted therapy of cancers. PR81 has high specific reactivity and also a high affinity to two peptides of TSA-P1-24 and A-P1-15.[3] While, PR81 labeled ^{99}mTc indicated good efficiency, the complex suffered from low immunoreactivity and *in vitro* stability in human serum.[5]

^{111}In, a cyclotron-produced radionuclide, is an exciting radioisotope to radiopharmaceutical goals because of its physical properties, easy production, and availability.[6] It emits gamma photons of 173 and 247 keV; 89% and 94% intensity, respectively. Conformity of ^{111}In and the monoclonal antibodies biological half-life makes this radionuclide as a favorable option for single photon emission computed tomography (SPECT).[7-9] The SPECT results of ^{111}In labeled bombesin, HIgG, DOTMP, and BPAMD show the usefulness of this radionuclide in the imaging detection process of SPECT.[6-10]

Radiation absorbed dose defined as the amount of energy deposited in a unit mass of any organs, plays a significant role in evaluating the risks associated with the administration of radiopharmaceuticals and also in determining the maximum

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amount of administrated activity.[11] After the development of the medical internal radiation absorbed dose method, as the primary method for calculating the absorbed dose, nowadays, some resources are available for this purpose. The radiation dose assessment resource (RADAR) is the most common source for the calculation of the absorbed dose.[12]

In this piece of research work, the human absorbed dose of ^{111}In-DOTA-PR81, a newly developed RIS tracer, was estimated based on biodistribution studies in animals by the RADAR method. For this purpose, ^{111}In-DOTA-PR81 was prepared in optimal condition and its radiochemical purity, and *in vitro* and *in vivo* stabilities were studied. The final radiolabeled compound was injected into normal rats and tumor-bearing mice, and the biodistribution of the radioimmunoconjugate was assessed at different intervals up to 72 h postinjection. Finally, the human absorbed dose of the radiotracer was estimated based on the gathered data in animals according to the standard methods.

Materials and Methods

^{111}In was produced in Radiation Application Research School, Karaj, Iran, by ^{112}Cd (p, 2n) ^{111}In reaction. DOTA-NHS was purchased from Macrocyclics (NJ, USA). Fetal Bovine Albumin, RPMI-1640 medium, and L-Glutamine were bought from Gibco Co. (Dublin, Ireland). PD10 De-salting column was inquired from Amersham Pharmacia Biotech; additional chemicals were purchased from Sigma Chemical Co. (MO, USA). Sprague-Dawley rats were obtained from Pasteur Institute (Tehran, Iran). A Bioscan AR-2000 radio thin-layer chromatography (TLC) scanner instrument (Bioscan, Paris, France) was used for Radio-chromatography purposes. A p-type coaxial high-purity germanium (HPGe) detector (model: EGPC 80–200R) coupled with a multichannel analyzer card system and a dose calibrator ISOMED 1010 (Dresden, Germany) were utilized for the measurement of the activity. Calculations were carried out based on the 245 keV peak for ^{111}In. The United Kingdom Biological Council's Guidelines on the Use of the Living Animals in Scientific Investigations, 2nd edition was used to determine the framework of animal experiments. Achieved results are displayed as mean ± standard deviation (mean ± standard deviation), and Student's *t*-test was used to compare the data based on statistical significance defined as $P < 0.05$.

Production and quality control of $^{111}InCl_3$

Indium-111 was produced according to the previously reported procedure.[13] Briefly, cadmium was electroplated on a copper surface to be used as a target and irradiated by a 22 megaelectron volt (MeV) proton at a 30 MeV cyclotron for 100 µAh to produce ^{111}In. Indium-111 was eluted with 1 N Hydrochloric acid (HCl) (25 ml) as $^{111}InCl_3$ for labeling use. Radionuclidic purity of the final solution was measured by the HPGe detector. Chemical purity control was carried out to ensure that the amounts of cadmium (from target material) and copper (from target support) ions in the final solution are acceptable regarding the internationally accepted limits. Chemical purity was studied by differential-pulsed anodic stripping polarography. The radiochemical purity of the $^{111}InCl_3$ solution was also measured by the instant thin-layer chromatography method (ITLC) with two solvent systems, 1 mM diethylenetriaminepentaacetic acid (DTPA) and 10% ammonium acetate: methanol mixture.

Preparation and quality control of ^{111}In-DTPA-PR81

DOTA-NHS was conjugated with the PR81 according to the previously published method.[14] For the preparation of ^{111}In-DOTA-PR81 complex at optimized condition, 74 MBq of ^{111}In-$InCl_3$ (in 0.2 M HCl) was added to conical vials, and dried under a flow of nitrogen and gentle heating. Then, pH was arranged to 5.5 by ammonium acetate buffer. A total of 400 µg of the bioconjugate was added to the vial and the sample was taken for 1 h at 38°C. The radiolabeling step was terminated by adding ethylenediaminetetraacetic acid (EDTA) to their solution mentioned above, and it was allowed to react for 5 min. The addition of EDTA also resulted in the production of the In-EDTA complex, which makes it more applicable for better removal with the help of the size exclusion method. The radiochemical purity of the final product was studied by ITLC using a radio TLC scanner (Whatman no. 2; 1 mM DTPA).

Stability tests

About 18.5 MBq of the final radioimmunoconjugate was added to the Phosphate Buffered Saline (PBS) buffer and freshly prepared human serum while keeping at 4°C and 37°C, respectively. Samples were taken from the complex up to 72 h after preparation, and the stability of the final complex in PBS buffer and human serum was assessed by measuring radiochemical purity.

A mouse model with breast tumor

A few BALB/c mice with grade II/III invasive ductal carcinoma were provided from Pasteur Institute, Tehran, Iran. These mice breast tumor models were used for the development of the tumor allograft in other healthy BALB/c mice. The tumor was established by subcutaneous implantation of spontaneous breast tumor fragments (2–3 mm^3) in the right side of the abdominal region (Flank) of inbred female BALB/c mice (16–25 g, 6–8 weeks old). The bio-distribution and imaging studies were performed when the tumor volume reached 70–80 mm^3. All the animal experiments were approved by the Animal Care Committee of Tarbiat Modares University.

Biodistribution of ^{111}In-DOTA-PR81 in normal and tumor-bearing animals

3.7 MBq of ^{111}In-DOTA-PR81 was injected intravenously into Sprague-Dawley rats (140–160 g, 8–10 weeks' age) and tumoral BALB/c mice. It should be noted that while most studies in normal rodents are performed on normal rats, creating tumors in rats are very difficult and require difficult conditions. Therefore, for the study of tumoral cases, BALB/c mice was used to investigate the specialized uptake and accumulation of the labeled compound in the tumor containing the MUC1 receptor. The rats were sacrificed at 12, 24, 48, and 72 h postinjection ($n = 4$). Their organs, including blood, liver, spleen, kidneys, stomach, small and large intestines, heart, lungs, muscle, skin, bone, and tumor were taken, rinsed with normal saline, weighted, and their activity was measured by a p-type coaxial HPGe detector. The activity of each tissue was calculated using Equation 1:[15]

$$A = \frac{N}{\in \gamma\, t_s\, m\, k_1\, k_2 k_3\, k_4\, k_5} \quad (1)$$

where ε is the efficiency at photopeak energy, γ is the emission probability of the gamma line corresponding to the peak energy, t_s is the lifetime of the sample spectrum collection in seconds, m is the mass (kg) of the measured sample, k_1, k_2, k_3, k_4 and k_5 are the correction factors for the nuclide decay from the time the sample is collected to start the measurement, the nuclide decay during the counting period, self-attenuation in the measured sample, pulses loss due to random summing and the coincidence, respectively. N is the corrected net peak area of the corresponding photopeak given as:

$$N = N_s - \frac{t_s}{t_b} N_b \quad (2)$$

where N_s is the net peak area in the sample spectrum, N_b is the corresponding net peak area in the background spectrum, and t_b is the lifetime of the background spectrum collection in seconds.

Accumulated activity calculation for animal organs

The nondecay corrected percentage of the injected activity versus time for different animal organs was plotted according to Equation 3.

$$\tilde{A} = \int_{t_1}^{\infty} A\,(t)\,dt \quad (3)$$

where *A (t)* is the activity of each organ at time t.

To calculate the cumulative activity for each source organ, according to Equation 3, it is necessary to calculate the area under the time-activity curves in the time interval of Zero to infinity. For this purpose, two curves were plotted. The first curve was drawn based on the obtained data from the activity of each animal's organ and the second one was extrapolated to infinity by fitting the tail of each curve to a monoexponential curve with the exponential coefficient equal to the physical decay constant of the indium-111 radionuclide. Whereas the activity of blood at $t = 0$ was considered the total amount of the injected activity, the activity of all other organs was assumed to be zero at that time.

Estimation of accumulated activity for human organs

Sparks *et al*. method was used to scale the cumulated activity for animal organs to the cumulated activity for human organs (Equ 4).[16] The standard mean weights for each human organ were utilized for the extrapolation.[17]

$$\tilde{A}_{Human\ organ} = \tilde{A}_{Animal\ organ} \times \frac{Organ\ mass_{human} / Body\ mass_{human}}{Organ\ mass_{animal} / Body\ mass_{animal}} \quad (4)$$

Absorbed dose calculation

The absorbed dose in human organs, D, was calculated utilizing the RADAR formalism and based on biodistribution data in rats:

$$D = \tilde{A} \times DF \quad (5)$$

where $\tilde{A}$ is the accumulated activity for each human organ, and dose factor (DF) (in mGy = MBq s) represents the physical decay characteristics of the radionuclide, the range of the emitted radiations, and the organ size and configuration and defined as:

$$DF = \frac{k \sum_i n_i E_i \phi_i}{m} \quad (6)$$

In this equation, n_i is the number of radiations with energy E emitted per nuclear transition, E_i is the energy per radiation (MeV), ϕ_i is the fraction of energy emitted that is absorbed in the target, *m* is the mass of the target region (kg), and *k* is some proportionality constant ($\frac{\text{mGy.kg}}{\text{MBq.s.MeV}}$). In this research, DFs presented in OLINDA/EXM software were employed.[18]

Calculation of effective absorbed dose

The effective absorbed dose was calculated using Equation 7.

$$E = \sum_T W_T H_T \quad (7)$$

where H_T is the equivalent absorbed dose which is the product of the absorbed dose for each organ (D) and the radiation weighting factors and W_T is the tissue-weighting factor that obtained from the reported value in International Commission On Radiological Protection (ICRP 103).[19]

Results and Discussion

Quality control of ^{111}In chloride solution

The HPGe spectrum of $^{111}InCl_3$ showed the presence of 171 and 245 keV gamma energies, all originating from ^{111}In. The radionuclidic purity of >99.9% was demonstrated. The result of polarography showed the concentrations of cadmium and copper were below the internationally accepted levels, i.e., 0.1 ppm.[20] The radiochemical purity of the ^{111}InCl3 sample was more than 99% [Figure 1].

Preparation and quality control of ^{111}In-DOTA-PR81

^{111}In-DOTA-PR81 was prepared with radiochemical purity of >96%at optimized conditions. ITLC chromatograms of ^{111}In and ^{111}In-DOTA-PR81 are indicated in Figure 2. While the free cation migrates to higher R_f (0.8), the radiolabeled compound remains at the origin [Figure 2].

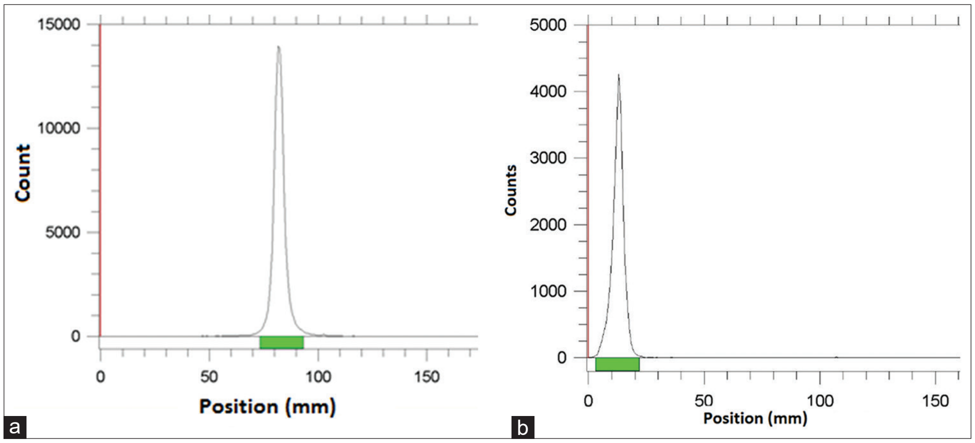

Figure 1: Instant thin-layer chromatography method chromatograms of $^{111}InCl_3$ in Diethylenetriaminepentaacetic acid solution (a) and 10% ammonium acetate: methanol mixture (1:1) solution (b) using Whatman no. 2

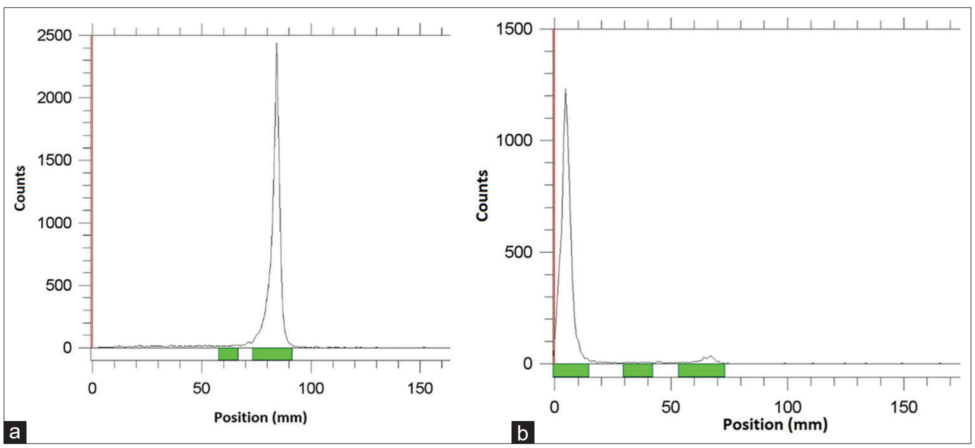

Figure 2: Radiochromatogram of free $^{111}In^{3+}$ (a) and ^{111}In-DOTA-PR81 (b) using Whatman No. 2 in 1 mM DTPA pH 5.0 (n = 3)

Biodistribution of the complex in normal and tumor-bearing animals

The percentage of the injected dose per gram in animal organs was calculated up to 72 h after injection of ^{111}In-DOTA-PR81. The nondecay corrected clearance curves from the main organ sources of the animals for the radiolabeled compound are shown in Figure 3 that indicated high uptake of the tumor compared to other nontarget organs.

Equivalent absorbed dose calculation

In this study, human organ absorbed dose was estimated based on the animals' data which is a prerequisite in radiopharmaceutical development and is suggested in the ICRP 62 recommendations.[21,22] For this purpose, RADAR and Spark *et al*. methods were utilized in similarity to the previously reported literature.[23-25]

In the calculation of the accumulated activity of each organ, two different approaches may be considered. In the first approach, before any decay correction, the measured %ID data are fitted with an appropriate curve. In this case, a linear extrapolation of the data points at 24 h, 48 h, and 72 h can be considered and all negative data resulting from the extrapolation are set to zero. In the case of the tumor, the data points at 24 h, 48 h, and 72 h may be fitted by a mono-exponential curve. Afterward the total curve (= measured and fitted part) are decay corrected and integrated until favorably 5 half-lives. In the second approach, it is assumed that the organ uptake remains constant after 72 h. In this way, the activity integral is calculated just by the time-activity curve of the radionuclide. The second approach may result in some overestimation of the integral. In this study, the second approach was considered for the calculation of the accumulated activity that leads to some overestimation of the absorbed doses. Thus, the actual absorbed doses are less. It seems an overestimation of the radiation dose is better than an underestimation in light of the safety aspect of the patient.

The values of residence time and the absorbed dose in different human organs are shown in Tables 1 and 2, respectively. As seen, the highest amounts of the absorbed dose after injection of the radiolabeled compound was observed in the liver and kidneys with 0.384 and 0.245 mGy/MBq, respectively. Furthermore, the effective absorbed dose in humans after injection of ^{111}In-DOTA-PR81 was estimated as 0.050 mGy/MBq.

Table 1: The residence time(s) calculated for human organs

Tissue	Residence time (s)
Bone	3243
Spleen	1667
Liver	38,220
Kidney	5075
Stomach	982
Lung	16,387
Heart	2252
Intestine	1447
Muscle	79,980
Skin	26,536
Reminder body	15,483

Different radiopharmaceuticals, including ^{18}F-FES, ^{18}F-FDHT, ^{111}In-trastuzumab, and ^{111}In-pentetreotide have been developed and used for breast cancer imaging.[26-29] The values of the effective absorbed dose and the absorbed dose of critical organs (who received the highest amount) after injections of these radiolabeled compounds are presented in Table 3.

As can be seen, while the absorbed dose of critical organs and the effective absorbed dose after injection of ^{111}In-DOTA-PR81 are significant compared to the other radiolabeled compounds of ^{18}F, these amounts are lesser in contrast to the ^{111}In-trastuzumab and ^{111}In-pentetreotide. As a result, this new radiolabeled compound can be regarded as a safe complex and a suitable alternative for SPECT imaging of the MUC1 + breast tumors; however, further studies are still needed.

Table 2: Equivalent and effective absorbed dose delivered into human organs after injection of ^{111}In-DOTA-PR81

Target organs	Equivalent absorbed dose in humans (mGy/MBq)	W_T[a]	Effective absorbed dose in humans (mSv/MBq)
Adrenals	0.096	0.12	0.0115
Brain	0.013	0.01	0.0001
GB wall	0.118	0.12	0.0142
LLI wall	0.065	0.12	0.0078
Small intestine	0.035	0.12	0.0042
Stomach wall	0.066	0.12	0.0079
ULI wall	0.041	0.12	0.0049
Heart wall	0.137	0.12	0.0164
Kidneys	0.245	0.12	0.0294
Liver	0.384	0.04	0.0154
Lungs	0.199	0.12	0.0239
Muscle	0.035	0.12	0.0042
Pancreas	0.088	0.12	0.0106
Red marrow	0.043	0.12	0.0052
Bone surf	0.048	0.01	0.0005
Spleen	0.150	0.12	0.0180
Testes	0.020	0.12	0.0024
Thymus	0.041	0.12	0.0050
Thyroid	0.021	0.04	0.0008
UB wall	0.017	0.04	0.0007
Total body	0.050		0.050

[a]Tissue weighting factors according to ICRP 103 (2007). ICRP: International Commission On Radiological Protection, GB: Gallbladder wall, LLI: Lower large intestine, ULI: Upper large intestine, UB Wall: Urinary bladder wall

Table 3: The values of the effective absorbed dose and the absorbed dose of organs received the highest dose after injection of ^{18}F-FES, ^{18}F-FDHT, ^{111}In-trastuzumab, ^{111}In-pentetreotide and ^{111}In-DOTA-PR81

Radiolabeled compound	Absorbed dose (mGy/MBq)	Effective absorbed dose (mSv/MBq)	Reference
^{18}F-FES	Liver: 0.13 Gallbladder: 0.10 Urinary bladder: 0.05	0.022	[27]
^{18}F-FDHT	Urinary bladder: 0.061	0.020	[28]
^{111}In-trastuzumab	Liver: 0.598 Spleen: 0.360	0.185	[29]
^{111}In-pentetreotide	Spleen: 0.57 Kidneys: 0.41 Liver: 0.1	0.054	[30]
^{111}In-DOTA-PR81	Liver: 0.376 Kidneys: 0.237 Spleen: 0.143	0.044	This study

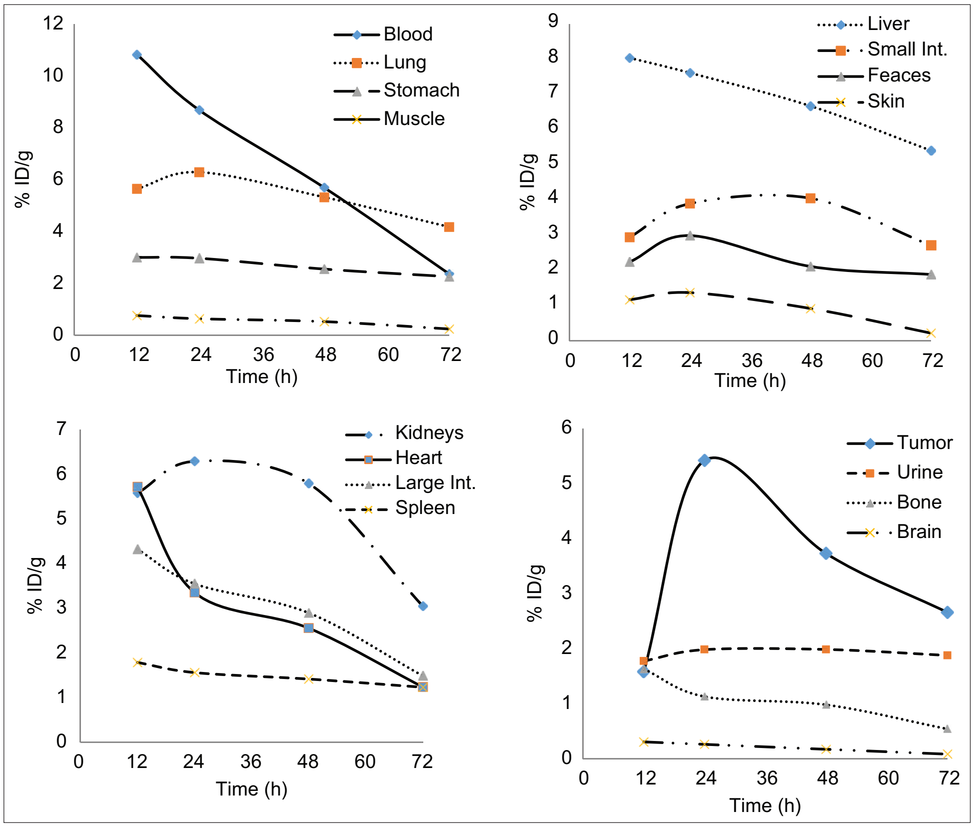

Figure 3: Non-decay corrected clearance curves of the animals' organs after injection of ^{111}In-DOTA-PR81 complex

Conclusions

In this study, ^{111}In-DOTA-PR81 was prepared with radiochemical purity of >96%. High uptake of the complex in MUC1 + breast tumors compared to other nontarget organs shows that the radioimmunoconjugate is a beneficial agent for SPECT imaging of MUC1 + breast cancer. Human organs absorbed dose of the complex was estimated based on animals' data according to the RADAR and Spark *et al.* methods. The highest amounts of the absorbed dose are in the liver (0.384 mGy/MBq) and kidneys (0.245 mGy/MBq, respectively. ^{111}In-DOTA-PR81 radioimmunoconjugate is a high potential agent for MUC1 + breast cancer SPECT imaging and estimated absorbed dose values could helpfully utilize for determining the maximum injectable dose.

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Conflicts of interest

There are no conflicts of interest.

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