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Compartmental modeling and absorbed dose assessment of ^{188}Re-HYNIC-PSMA according to the rats' biodistribution data

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► ***Original article***

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ABSTRACT

***Background*:** PSMA is known as a suitable marker for imaging and targeted therapy of malignant tumors, especially prostate cancer. While; ^{177}Lu-labeled PSMA is recognized as a promising compound for the treatment of metastatic castration-resistant prostate cancer patients, deployment of radionuclides with higher beta energy, including ^{188}Re, can be useful for larger-sized tumors. However, the absorbed dose of the PSMA radiolabeled compound is substantial according to the considerable accumulation in the kidney. ***Materials and Methods*:** In this study; the biodistribution of ^{188}Re-HYNIC-PSMA was studied in Wistar rats. ANACOMP software was utilized for compartmental modeling. The human absorbed dose of this new agent was assessed according to the rats' biodistribution data using the RADAR method. ***Results*:** The highest accumulation of activity in Wistar rats' organs were observed in the kidney. The human organs that received the highest absorbed dose were the kidneys and bladder wall with 0.69 and 0.46 mSv/MBq, respectively. ***Conclusion*:** The absorbed dose of ^{188}Re-PSMA-617 in critical organs is comparable to the values of ^{177}Lu-PSMA-617. ^{188}Re-HYNIC-PSMA can be considered a safe compound for the treatment of PSMA expressing tumors.

INTRODUCTION

Prostate-Specific Membrane Antigen (PSMA) is a transmembrane Glycoprotein that is widely expressed in the majority of prostate cancers [1,2]. Expression of PSMA in the neovasculature of the other cancers, including renal cell carcinoma (RCC) [3], breast [4], thyroid [5], bladder [6], lung [7], gastric and colorectal cancers [8] made it a suitable marker for imaging and therapy of not only prostate but also the other malignant tumors.

Recently, the clinical trials of ^{68}Ga-PSMA-11 (PSMA-HBED-CC) demonstrated its efficacy in the detection of prostate cancers and obtained approval from the U.S. Food and Drug Administration as the first radiopharmaceutical for PET imaging of PSMA$^+$ lesions [9]. Besides, radiolabeling of different molecules for binding to PSMA with ^{177}Lu, ^{131}I, ^{90}Y and ^{161}Tb for therapeutic purposes has been reported [10-11]. While the clinical trials of some of these radiolabeled compounds, such as ^{177}Lu- PSMA- R2, ^{177}Lu- PSMA I&T, and ^{177}Lu- CTT-1403, are in process [12], Phase III VISION study of ^{177}Lu-PSMA-617 indicated significant improvement in overall survival for patients with metastatic castration-resistant prostate cancer (mCRPC) [13].

Previous studies have shown that the pharmacokinetics properties of the radiolabeled compounds, including PSMA inhibition potencies, cellular internalization, and the biodistribution, can be affected by the modification of the linker [14]. To date, Different molecules for PSMA binding such as PSMA-11, PSMA-617, and PSMA-D4, have been synthesized with HBED-CC, DOTA, and HYNIC chelators for combination with different radionuclides [14, 15].

The radiolabeled complexes of PSMA-D4 with ^{177}Lu, ^{90}Y, ^{47}Sc, and ^{225}Ac indicated large aggregation in LNCaP tumor xenografts and rapid removal from blood, where replacement of HYNIC with DOTA leads to the reduction in renal affinity [14]. In the recent research on ^{99m}Tc-HYNIC-PSMA, it is recognized as an engaged radiopharmaceutical for SPECT/CT imaging of PSMA$^+$ prostate cancer [16]. This radiolabeled compound indicated a lesser effective absorbed dose as well as a higher tumor-to-background ratio at 2h post-injection compared to the other similar PSMA tracers, including ^{99m}Tc-MIP-1404 and ^{99m}Tc-MIP-1405 [17].

Among the therapeutic radionuclides, ^{188}Re with superior physical features ($E_{\beta max}$=2.12 MeV, Eγ=155 keV (15.1%), $t_{1/2}$=17.005 h) can be easily provided from the ^{188}W/^{188}Re generator with a high specific activity. It can constitute kinetically inert metal complexes with peptides in various oxidation states, unlike the Y^{3+}, Lu^{3+}, and the other lanthanides [18].

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Although, the particular physical characteristics of ^{188}Re and promising clinical outcomes of the diagnostic and therapeutic radiolabeled PSMA agent, preparation of ^{188}Re radiolabeled compounds of PSMA has not been reported until now, whereas different peptides, mainly somatostatin analogues, have been labeled with ^{188}Re [19, 20]. On the other hand, absorbed dose estimation can help to evaluate the maximum amount of injection activity and is recognized as preliminary step in the development of new radiopharmaceuticals. This study aimed to prepare ^{188}Re-labeled PSMA and to estimate the human organ absorbed dose of this new therapeutic agent based on human data.

MATERIALS AND METHODS

^{188}W/^{188}Re generator and HYNIC- PSMA were provided from Pars Isotope Co. (Tehran, Iran). All other chemicals were purchased from Sigma Aldrich Co. (Germany). Silena high purity germanium (HPGe) detector and a bio scan AR-2000 radio TLC (Bioscan, Europe Ltd CO., France) were employed for radionuclidic and radiochemical purity evaluation. A JASCO 880-PU intelligent pump (Ohio, USA) was used for analytical high-performance liquid chromatography (HPLC). Animal studies were implemented relevant to the United Kingdom Biological Council's Guidelines. The Wistar 18-week male rats weighing 180-220 g (n=5) kept at routine day/night light program and under standard rodent diet pellets, were purchased from the Pasteur Institute of Iran. The approval of the NSTRI Ethical Committee was obtained for conducting this research. The human dose factor of ^{188}Re radionuclide was extracted from OLINDA/EXM version 1.0 software. The experiments were repeated five times while the obtained data was compared by Student *t*-test.

Preparation and quality control of ^{188}Re-HYNIC-PSMA

Elution and quality control of the washing product was accomplished like in the former published literature [0]. For the radiolabeling purposes, 30 µg of HYNIC-PSMA (1 mg/mL in ultra-pure water), 45 mg of tricine (in phosphate buffer, pH=7.2), and 15 mg of EDDA (in 0.1 N NaOH) were added to the vial comprising 5 mCi of $Na^{+}ReO_4^{-}$ and while the pH was justified to 4-4.5, the reaction mixture was stirred and heated up to 95ºC for 30 min.

HPLC and ITLC methods were utilized for the investigation of radiochemical purity. ITLC was performed on Whatman No. 1 paper using 0.1 M ammonium acetate/methanol (1: 1) solution. The mobile phase of A: Ultrapure water-TFA 1% (V/V) and B: Acetonitrile were applied to assess the purity by the HPLC method.

Biological evaluation of ^{188}Re-HYNIC-PSMA in Wistar rats

100µL of the radiolabeled compound was injected into the rats via their tail vein, and its biodistribution was studied up to 24 h. The injected dose per gram (% ID/g) for each organ was achieved after the activity measurement using the p-type coaxial HPGe detector.

Compartmental modeling and equivalent absorbed dose estimation

The absorbed dose of ^{188}Re-HYNIC-PSMA in human organs was determined according to the rats' biodistribution data. The non-decay corrected %ID/g was plotted versus time using ANACOMP software for compartmental modeling. The cumulated activity for each organ was specified by calculating the area under the curve. The relative organ mass extrapolation was applied to determine the accumulated activity in human organs according to equation 2 and in similarity to the previously reported literature [22, 23].

$$\tilde{A}_{Human\ organ} = \tilde{A}_{Animal\ organ} \times \frac{Organ\ mass_{human}/Body\ mass_{human}}{Organ\ mass_{animal}/Body\ mass_{animal}} \quad (2)$$

The absorbed dose was computed by the RADAR method according to equation 3:

$$D = \tilde{A} \times DF \quad (3)$$

Wherever Ã is the accumulated activity, and DF represents the absorbed dose (mGy) per unit of activity and time (MBq.s). In this study, the values of DFs were taken from OLINDA/EXM software [24].

Statistical analysis

The biodistribution of ^{188}Re-HYNIC-TOC was studied in five rats, and the values were represented as mean ± standard deviation (mean ± SD). The data were contrasted with Student's *t*-test. P values of <0.05 were regarded statistically significant.

RESULTS

Preparation and quality control of ^{188}Re-HYNIC-PSMA

The ITLC and HPLC chromatograms illustrated a radiochemical purity of higher than 99% (figure 1). ITLC chromatogram indicated the migration of the radiolabeled compound to the upper parts of the paper (R_f = 0.7). Elution of ^{188}Re-HYNIC-PSMA from HPLC column was observed after approximately 9 min, while free rhenium was eluted only 1 min after injection.

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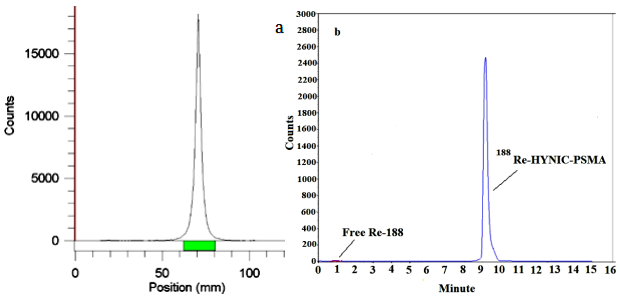

Figure 1. a) ITLC chromatogram of 188Re-HYNIC- PSMA using Whatman No. 1 paper and 0.1 M ammonium acetate / methanol (1: 1) as the stationary and mobile phase, respectively. **b)** HPLC chromatogram of 188Re-HYNIC- PSMA using A: Ultrapure water-TFA 1% (V/V) and B: Acetonitrile as the mobile phase with the gradient-elution of : 0–3 min, A: 100%, B: 0%; 3–10 min, A: 50%, B: 50%; 10–15 min, A: 0%, B: 100%, the flow rate of 1.5 mL/min and the injection volume of 20 µL.

Biodistribution studies of ^{188}Re-HYNIC-PSMA in rats

The non-decay corrected percentages of activity versus time for each organ resultant from ANACOMP software are indicated in figure 2.

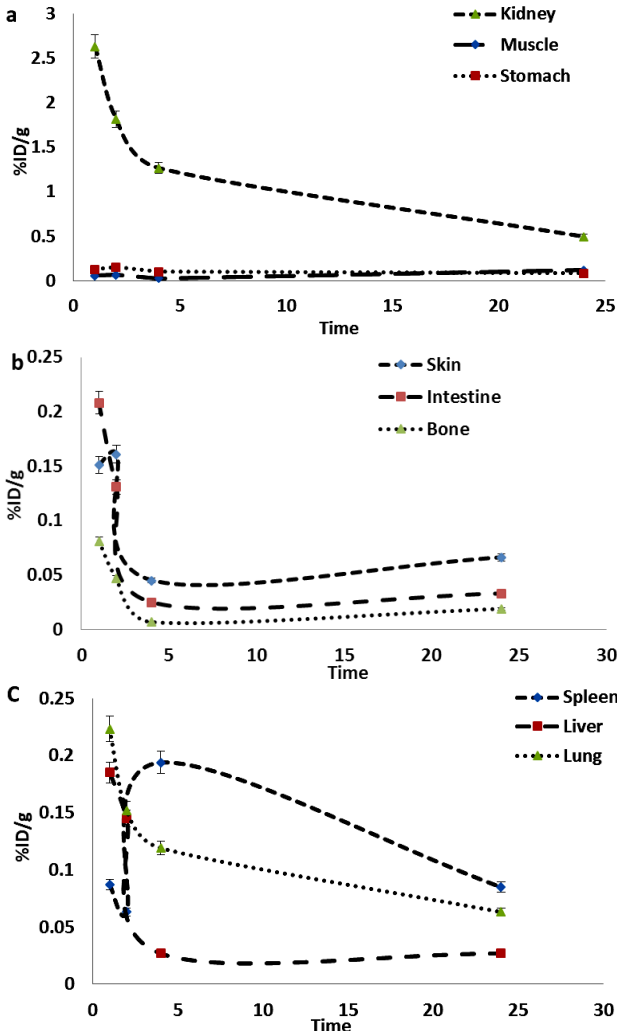

Figure 2. Non-decay corrected percentages of activity per gram (%ID/g) versus time for **a)** kidney, muscle and stomach, **b)** skin, intestine and bone, **c)** spleen, liver and lung after 188Re-HYNIC-PSMA injection.

Compartmental modeling and absorbed dose estimation

The equivalent and effective absorbed dose of human organs after ^{188}Re-HYNIC-PSMA injection are exhibited in table 1.

Table 1. The absorbed dose of human organs after ^{188}Re-HYNIC-PSMA injection.

Target organs	Equivalent dose (Gy/GBq)	Target organs	Equivalent dose (Gv/GBq)
Bladder Wall	0.46±0.03	Liver	0.12±0.01
Bone	0.02±0.00	Lungs	0.19±0.02
Stomach Wall	0.02±0.00	Red Marrow	0.07±0.00
Small Intestine	0.03±0.00	Muscle	0.03±0.00
ULI[a] Wall	0.02±0.00	Skin	0.03±0.00
LLI[b] Wall	0.02±0.00	Spleen	0.24±0.02
Kidneys	0.69±0.08	Total Body	0.08±0.00

[a] ULI: upper large intestine; [b] LLI: lower large intestine,

DISCUSSION

While various therapeutic radiolabeled compounds for binding to PSMA have been reported, they are mainly prepared based on ^{177}Lu. ^{177}Lu with excellent physical characteristics and easily production with high specific activity, is considered a good candidate for radionuclide therapy; however it is much recommended for the small-sized tumor considering the short range of its beta particles [25, 26]. ^{188}Re with a tissue penetration range of 11mm and availability through ^{188}W/^{188}Re generator is particularly attractive for medium, and large-sized tumors and regarding its similar chemical properties with ^{99m}Tc, these radionuclides can be regarded as theranostic pair [27].

In this study, while ^{99m}Tc –HYNIC-PSMA has been utilized recently for imaging of patients with prostate cancers and indicated better pharmacokinetics compared to the previous radiolabeled compounds of ^{99m}Tc-PSMA, preparation of ^{188}Re-HYNIC-PSMA was considered as a novel therapeutic complex. However, regarding the higher energy of ^{188}Re beta particles in contrast to ^{177}Lu and the considerable kidney uptake of PSMA radiopharmaceuticals [28, 29], the safety of this new radiolabeled compound should be examined by estimating the absorbed dose of human organs.

The absorbed dose of ^{188}Re-HYNIC-PSMA was calculated according to the biodistribution data in rats. Although, this extrapolation may result in the amounts less or more than the actual values, it is known as the first step in the safety assessment and determination of injectable activity in humans [30]. While ^{177}Lu-labeled PSMA ligands were known as the promising agents for treating patients with mCRPC, several types of research were performed examining the absorbed dose in the patients. Recently, the absorbed dose of ^{90}Y-labeled PSMA was also investigated in patients who did not receive sufficient response to several cycles of [^{177}Lu] Lu-PSMA-617 treatment [31]. The values obtained in these studies

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for the critical organs are given in table 2.

As seen in table 2, the kidney should be considered as the dose-limiting organ in the treatment of prostate cancers with ^{177}Lu/^{90}Y/^{188}Re-PSMA-617 radiopharmaceuticals. A small amount was perceived in the liver compared to the kidney as the second organ receiving the highest dose. The absorbed dose of critical organs after ^{188}Re-PSMA-617 injection is much lesser than ^{90}Y-PSMA-617 and is comparable to the values of ^{177}Lu-PSMA-617.

Table 2. The absorbed dose of human organs after injection of ^{177}Lu-PSMA-617, ^{90}Y-PSMA-617, and ^{188}Re-PSMA-617 in the critical organs [Gy/GBq].

	^{177}Lu-PSMA-617	^{177}Lu-PSMA-617	^{177}Lu-PSMA-617	^{90}Y-PSMA-617	^{188}Re-PSMA-617
kidney	0.52	0.54	0.63	2.1	0.69
liver	0.08	0.10	-	-	0.12
Red marrow	0.04	-	0.03	0.19	0.07
reference	(32)	(33)	(35)	(35)	This study

CONCLUSION

^{188}Re-HYNIC-PSMA indicated rapid removal from blood and high aggregation in the kidney. The highest absorbed dose was observed in the kidney and bladder wall. The amount of absorbed dose after ^{188}Re-HYNIC-PSMA injection is comparable with the ^{177}Lu-PSMA-617. Therefore, it can be regarded as a safe compound from the radiation protection point of view and can be remarked as an alternative treating patients with larger tumor lesions.

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***Conflicts of interests*:** There is no conflicts of interests.

***Ethical consideration*:** The approval of NSTRI Ethical Committee was obtained for conducting this research.

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***Author contribution*:** All of the authors contribute in designing the experiments, collecting the data and analysis as well as writing the paper.

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