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

M. Hadisi¹, N. Vosoughi¹, H. Yousefnia^{2*}, A. Bahrami-Samani², S. Zolghadri², R. Bagheri²

¹Department of Energy Engineering, Sharif University of Technology, Tehran, Iran ²Radiation Application Research School, Nuclear Science and Technology Research Institute (NSTRI), Tehran, Iran

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*Corresponding author: Hassan Yousefnia, Ph.D., E-mail: hyousefnia@aeoi.org.ir

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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 ⁶⁸Ga-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 ¹⁷⁷Lu, ¹³¹I, ⁹⁰Y and ¹⁶¹Tb for therapeutic purposes has been reported ⁽¹⁰⁻¹¹⁾. While the clinical trials of some of these radiolabeled compounds, such as ¹⁷⁷Lu- PSMA- R2, ¹⁷⁷Lu- PSMA I&T, and ¹⁷⁷Lu- CTT-1403, are in process ⁽¹²⁾, Phase III VISION study of ¹⁷⁷Lu-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

ABSTRACT

Background: PSMA is known as a suitable marker for imaging and targeted therapy of malignant tumors, especially prostate cancer. While; ¹⁷⁷Lu-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 ¹⁸⁸Re, 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 ¹⁸⁸Re-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 ¹⁸⁸Re-HYNIC-PSMA can be considered a safe compound for the treatment of PSMA expressing tumors.

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 ¹⁷⁷Lu, ⁹⁰Y, ⁴⁷Sc, and ²²⁵Ac 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, ¹⁸⁸Re with superior physical features ($E_{\beta max}$ =2.12 MeV, $E\gamma$ =155 keV (15.1%), $t_{1/2}$ =17.005 h) can be easily provided from the ¹⁸⁸W/¹⁸⁸Re generator with a high specific activity. It can constitute kinetically inert metal complexes with peptides in various oxidation states, unlike the Y³⁺, Lu³⁺, and the other lanthanides ⁽¹⁸⁾.

Although, the particular physical characteristics of ¹⁸⁸Re and promising clinical outcomes of the diagnostic and therapeutic radiolabeled PSMA agent, preparation of ¹⁸⁸Re radiolabeled compounds of PSMA has not been reported until now, whereas different peptides, mainly somatostatin analogues, have been labeled with ¹⁸⁸Re ^(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 ¹⁸⁸Re-labeled PSMA and to estimate the human organ absorbed dose of this new therapeutic agent based on human data.

MATERIALS AND METHODS

¹⁸⁸W/¹⁸⁸Re 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 for analytical high-performance liquid used 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 ¹⁸⁸Re 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 ¹⁸⁸Re-HYNIC-PSMA

Elution and quality control of the washing product was accomplished like in the former published literature ⁰. For the radiolabeling purposes, 30 μ g 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⁺ReO₄⁻ and while the pH was justified to 4-4.5, the reaction mixture was stirred and heated up to 95°C 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 ¹⁸⁸Re-HYNIC-PSMA in Wistar rats

 100μ L 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 ¹⁸⁸Re-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).

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

$$D = \tilde{A} \times DF \tag{3}$$

Wherever \tilde{A} 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 ¹⁸⁸Re-HYNIC-TOC was studied in five rats, and the values were represented as mean \pm standard deviation (mean \pm 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 ¹⁸⁸Re-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 ¹⁸⁸Re-HYNIC-PSMA from HPLC column was observed after approximately 9 min, while free rhenium was eluted only 1 min after injection.



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 ¹⁸⁸Re-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 ¹⁸⁸Re-HYNIC-PSMA injection are exhibited in table 1.

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Target ergans	Equivalent	Target	Equivalent				
Target Organs	dose (Gy/GBq)	organs	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				

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

^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 ¹⁷⁷Lu. ¹⁷⁷Lu with physical characteristics excellent 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). ¹⁸⁸Re with a tissue penetration range of 11mm and through ¹⁸⁸W/¹⁸⁸Re availability generator is particularly attractive for medium, and large-sized tumors and regarding its similar chemical properties with 99mTc, 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 ¹⁸⁸Re-HYNIC-PSMA was considered as a novel therapeutic complex. However, regarding the higher energy of ¹⁸⁸Re beta particles in contrast to ¹⁷⁷Lu 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 ¹⁸⁸Re-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 ¹⁷⁷Lu-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 ⁹⁰Y-labeled PSMA was also investigated in patients who did not receive sufficient response to several cycles of [¹⁷⁷Lu] Lu-PSMA-617 treatment ⁽³¹⁾. The values obtained in these studies

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 ¹⁷⁷Lu/⁹⁰Y/¹⁸⁸Re-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 ¹⁸⁸Re-PSMA-617 injection is much lesser than ⁹⁰Y-PSMA-617 and is comparable to the values of ¹⁷⁷Lu-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

critica	organs	[Gy/	′GBq].
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	¹⁷⁷ Lu-	¹⁷⁷ Lu-	¹⁷⁷ Lu-	⁹⁰ Y-	¹⁸⁸ Re-
	PSMA-617	PSMA-617	PSMA-617	PSMA-617	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

¹⁸⁸Re-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 ¹⁸⁸Re-HYNIC-PSMA injection is comparable with the ¹⁷⁷Lu-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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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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