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Original Article

Radiation dosimetry of ^{89}Zr labeled antibody estimated using the MIRD method and MCNP code

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ABSTRACT

One important issue in using radiopharmaceuticals as therapeutic and imaging agents is predicting different organ absorbed dose following their injection. The present study aims at extrapolating dosimetry estimates to a female phantom from the animal data of ^{89}Zr radionuclide accumulation using the Sparks-Idogan relationship. The absorbed dose of ^{89}Zr radionuclide in different organs of the human body was calculated based on its distribution data in mice using both MIRD method and the MCNP simulation code. In this study, breasts, liver, heart wall, stomach, kidneys, lungs and spleen were considered as source and target organs. The highest and the lowest absorbed doses were respectively delivered to the liver (4.00E-02 and 3.43E-02 mGy/MBq) and the stomach (1.83E-03 and 1.66E-03 mGy/MBq). Moreover, there was a good agreement between the results obtained from both MIRD and MCNP methods. Therefore, according to the dosimetry results, [^{89}Zr] DFO-CR011-PET/CT seems to be a suitable for diagnostic imaging of the breast anomalies for CDX-011 targeting gpNMB in patients with TNBC in the future.

1. Introduction

Breast cancer is a prevalent malignancy among women worldwide. In this regard, triple negative breast cancer (TNBC) accounts for about 15% of all breast cancers. The cancerous cells in TNBC have no estrogen, progesterone receptors and also can not provide too much HER2 protein. TNBC cells differ from other types of breast cancer cells in which they can proliferate and spread quicker, limited treatment efficiency, and a more difficult to diagnose. Glycoprotein non-metastatic B (gpNMB) is one of the most commonly protein coding genes overexpressed in the TNBC patients and it is associated with the increase of metastatic cells [1,2].

In majority of normal cells, gpNMB is expressed intracellularly, allowing greater selectivity for targeting malignant cells through its extracellular domain. Moreover, higher amount of gpNMB expression in TNBC is found to be related with the worse metastasis-free survival and overall survival (OS) which makes it an attractive target for treatment with antibody drug conjugate, glembatumumab vedotin (CDX-011) [3]. In this connection, Yardley et al. (2015) reported that the increasing level of gpNMB expression associated with higher response rates to CDX-011 [4].

There is a growing consensus that [^{89}Zr]DFO-CR011 can be an appropriate diagnostic imaging agent for CDX-011 targeting gpNMB in patients with TNBC [4,5]. In this regard, preclinical studies reported the direct relationship between the level of gpNMB expression and the effectiveness of gpNMB-targeted therapy using CDX-011 [6,7].

The sensitivity of PET in conjunction with the properties of ^{89}Zr can provide the high-resolution images and quantitative value to track the distribution of the antibody into its clearance from the bloodstream [8]. Consequently, [^{89}Zr]DFO-CR01 might be a non-invasive and sensitive tool to evaluate the gpNMB expression in clinical trials. In this regard, dosimetry measurements are of great importance for ^{89}Zr-DFO-CR011 to support clinical translation and radiation safety. The present study aims at estimating the absorbed dose in human body according to the ID/g% data obtained from the biological distribution of ^{89}Zr-DFO-CR011 in mice model. Absorbed dose in human body was estimated using the MIRD (Medical Internal Radiation Dose) method and MCNP5 (Mont Carlo Neutron particle) code in adult female phantom.

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2. Materials and methods

At the first step, the accumulation activity %ID/g (Fig. 1) was calculated using the data of mice model reported by Marquez-Nostra et al. (2017) [9].

The time-integrated activity was then calculated using Equation (1):

$$\tilde{A}(r_S.T_D) = \int_0^{T_D} \tilde{A}(r_S.t)dt \quad (1)$$

$\tilde{A}(r_S.T_D)$ shows the time-integrated activity of each organ at time t (time after injecting the radiopharmaceutical). Time-diagram of time-integrated activity in the organs was plotted. The area under the diagram was also calculated [10,11]. Using the Sparks-Idogan relationship, the activity accumulates from the rat body to the human [12]:

$$\tilde{A}_{humanorgan} = \tilde{A}_{animalorgan} \times \frac{Organmass_{human}/Bodymass_{human}}{Organmass_{animal}/Bodymass_{animal}} \quad (2)$$

The mean absorbed dose in the target organ was calculated by the MIRD method:

$$D(r_T.T_D) = \Sigma_{rS}\tilde{A}(r_S.T_D)\, S(r_T \longleftarrow r_S) \quad (3)$$

$\tilde{A}(r_S.T_D)$ is the time-integrated activity (or total number of nuclear transformations) in source tissue r_S over dose-integration period T_D .

Factor S is the mean absorbed dose in the target organ (r_T) in the source organ time-integrated activity (r_S)) [10].

The absorbed dose proportional to the energy per unit mass can be calculated using equation (4):

$$D \propto k\frac{\tilde{A}}{m}E \rightarrow D = k\frac{\tilde{A}}{m}E \quad (4)$$

Fig. 2 demonstrates the MIRD ORNL-Female phantom. The absorbed dose was performed by the MCNP5 simulation code. In this study, the MIRD-ORNL-Female and TALLY-*F8 phantoms were used to calculate the cumulative activity as the absorbed dose for each organ [13].

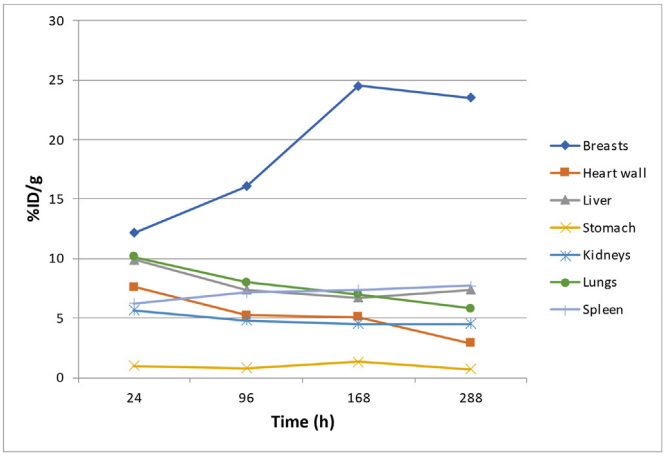

Fig. 1. Biodistribution of ^{89}Zr-DFO-CR011 in different time points (Mean values represent percent injected dose per gram (%ID/g)).

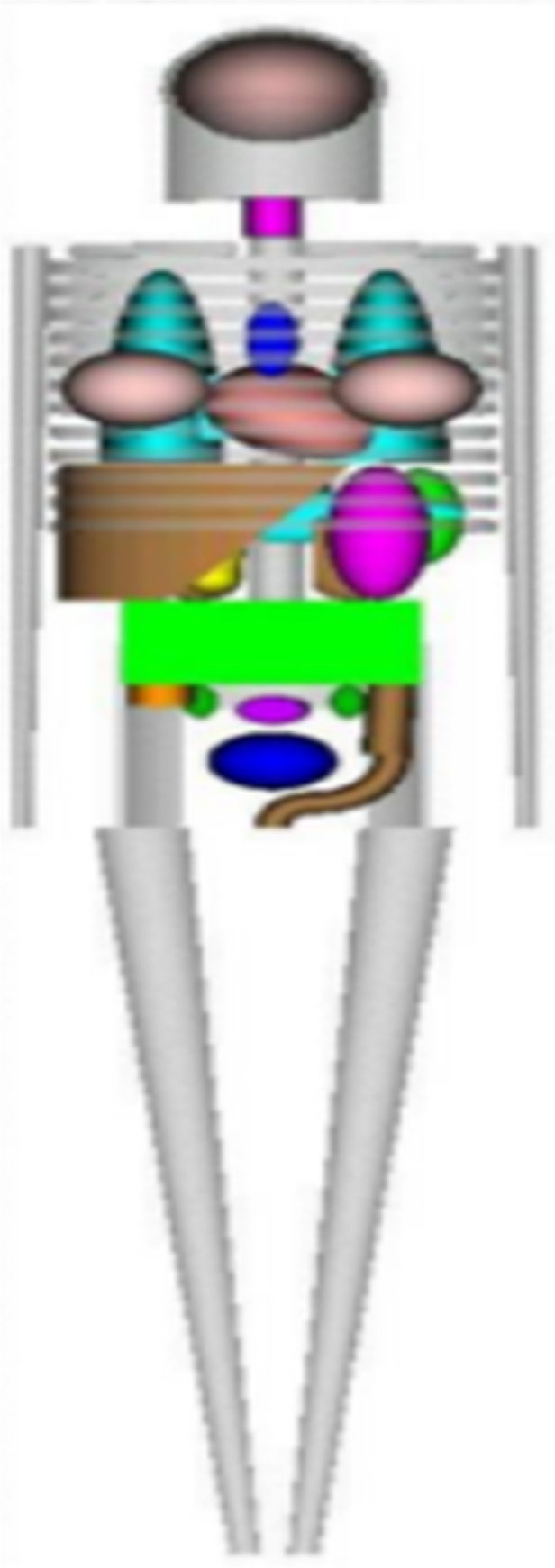

Fig. 2. MIRD ORNL-FEMALE phantom.

Table 1
The Absorbed dose of different organs of the human body obtained using the MIRD method analysis and the MCNP5 simulation code.

Target Organ	Absorbed Dose by MIRD method (mGy/MBq)	Absorbed Dose by MCNP code (mGy/MBq)
Breasts	6.24E-03	6.66E-03
Heart wall	1.18E-02	1.60E-02
Liver	4.00E-02	3.43E-02
Stomach	1.83E-03	1.66E-03
Kidneys	2.44E-02	2.86E-02
Lungs	6.51E-03	4.78E-03
Spleen	8.16E-03	3.10E-03

3. Results and discussion

The present study simulated the injection of 1MBq ^{89}Zr radionuclide using MIRD method and MCNP code to determine the absorbed dose in different human organs (Breasts, Heart wall, Liver, Lungs, Kidneys, Spleen, and Stomach). The ^{89}Zr radionuclide accumulation activity was also calculated using the tumor mice data (Fig. 1). Table 1 shows the comparison of absorbed dose between the MIRD method analysis and the MCNP simulation code. According to the results, the liver absorbed the highest amount of dose with 4.00E-02 and 3.43E-02 mGy/MBq. Moreover, the kidneys and the heart wall came respectively at the second and third ranks.

In this regard, Laforest et al. (2016) calculated an absorbed dose of different organs in women with HER2-Positive Breast Cancer using several radionuclides such as ^{64}Cu, ^{68}Ga and ^{89}Zr. They reported ^{89}Zr as the most favorable radionuclide for Monoclonal Anti Bodies (MAB) imaging. They found that the liver absorbs the highest amount of dose with 1.63 mGy/MBq whereas the brain receives the lowest dose with 0.39 mGy/MBq [14]. Reinier Hernandez et al. (2009) used ^{89}Zr-Df-ALT for PET imaging in pancreatic cancer. They observed the highest radiolabeled uptake in the liver with increasing radionuclide concentration from 10 mg to 50 mg [8]. In 2011, Shanehsazzadeh et al. measured the absorbed dose of ^{67}Ga-cDTPA-GnRH at time intervals (0.25, 0.5, 1, 2, 4, 24, and 48 h post injections) using the MIRD method. The biodistribution of ^{67}Ga-cDTPA-GnRH in rats showed high absorption in the breast and low absorption in the muscle and blood. The results of the present study showed that the highest absorbed dose was delivered to the liver with 4.00E-02 and 3.43E-02mGy/MBq, while the lowest absorbed dose was delivered to the stomach with 1.83E-03 and 1.66E-03mGy/MBq [15]. Naserpour et al. (2021) estimated the absorbed dose of ^{99m}Tc-MAA in the human phantom using the MIRD and MCNP methods based on the animal biodistribution data. They found that the highest amount of dose was absorbed in the lungs (MIRD: 6.8E-2 mGy/MBq, MCNP: 6.32E-2 mGy/MBq). Moreover, there was a good agreement between the results obtained from both the MIRD and MCNP methods for the lungs [16].

The use of ^{89}Zr and ^{124}I labeled with the chemical compound DN30 in PET imaging was investigated, and it was found that compared with ^{124}I, ^{89}Zr had a higher uptake in gastric cancer. ^{89}Zr was also introduced as a long-term effective positron emission for development in the PET imaging systems based on therapeutic anti-c-metBAs [17,18].

As mentioned, the highest absorbed dose was 4.00E-02 and 3.43E-02 mGy/MBq for the liver which was consistent with the patient's clinical data whereas the lowest amount of dose was absorbed in the stomach with 1.83E-03 and 1.66E-03 mGy/MBq. In this regard, Marquez- Marquez-Nostra et al. (2017) similarly extrapolated the human-absorbed dose from the animal data. The difference between Marquez-Nostra et al. and the present study relates to the fact that they used OLINDA/EXM while this study relied on MIRD and MCNP for dosimetry [9]. Nevertheless, similar to the results, Marquez-Nostra et al. results demonstrated that the liver absorbed the maximum amount of dose. The difference between MIRD and MCNP5 code results might be due to the difference between the measurement methods, human and mice tissues geometry in the organs and distribution model of radiopharmaceuticals. MCNP5 simulation can provide dosimetric data with high accuracy, especially in heterogenous tissues; however, it requires a long simulation time to limit its usage in routine clinical applications. On the other hand, MIRD is a rapid and user-friendly method; nevertheless, it suffers from low accuracy, especially in inhomogeneous organs and non-uniform activity distribution. In this regard, the good agreement between the results of the MCNP5 and MIRD methods can confirm the usefulness of MIRD in the clinic.

4. Conclusion

This study estimated the absorbed dose in the human phantom model based on the mice biological data. The results showed that the highest absorbed dose was delivered to the liver with 4.00E-02 and 3.43E-02 mGy/MBq while the stomach received the lowest dose with 1.83E-03 and 1.66E-03 mGy/MBq. In addition, [^{89}Zr] DFO-CR011-PET/CT seems to be suitable for diagnostic imaging of the breast anomalies for CDX-011 targeting gpNMB in patients with TNBC in the future.

Research ethics standards compliance

This research was performed according to the declaration of principles due to human studies. The protocol number of our ethics committee approval is IR.IUMS.FMD.REC.1397.330. Informed consent obtained from patients who participated in clinical investigations in Persian language.

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Guarantor

The scientific guarantor of this publication is Prof. Mahdi Sadeghi.

Statistics and biometry

No complex statistical methods were necessary for this paper.

Informed consent

No informed consent was necessary for this paper.

Ethical approval

Institutional Review Board approval was obtained.

Study subjects or cohorts overlap

No previous study subjects or cohorts used in this study.

Methodology

- prospective
- Diagnostic and prognostic Study
- performed at one institution

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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