ORIGINAL ARTICLE

Internal Dosimetry in Patients Undergoing Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-[DOTA0-Tyr3] Octerotate: A Single-Center Experience

Elahe Mahmoudi [1], Mahasti Amoui [2], Mohammad Reza Deevband [1*], Elahe Pirayesh [2], Mohammad Reza Asgari [1], Mahdi Ghorbani [1*]

[1] *Biomedical Engineering and Medical Physics Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2] *Nuclear Medicine Department, Shohada-e-Tajrish Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

*Corresponding Authors: Mohammad Reza Deevband, Mahdi Ghorbani
Email: mdeevband@sbmu.ac.ir, mhdghorbani@gmail.com

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Abstract

Purpose: Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-DOTATATE (^{177} Lu DOTA-TATE therapy is a form of PRRT which targets Somatostatin Receptors (SSR). It is a form of targeted drug delivery, which is applicable to treat neuroendocrine tumors. PRRT applications are continuously expanding in most departments of nuclear medicine in Iran, but the best of all, no one has studied the mean doses of organs of the patients. This research aims to specify the absorbed dose to patients for the treatment of neuroendocrine tumors using imaging with ^{177}Lu-[DOTA0-Tyr3] octerotate.

Materials and Methods: Whole body planar scintigraphy images were collected for 10 patients, which are used as the basis for the personalized patient dosimetry calculations. The patients had a mean age of 53.5 ± 12 years (ranging from 36 to 70 years) and imaging data were collected at roughly 0 to 2 hours, 4 to 6 hours, 18 to 24 hours, and 36 to 48 hours after the injection of 6401± 628.4 MBq (range of 5500 MBq-7400 MBq) of ^{177}Lu-[DOTA0-Tyr^3] octerotate. Models of time-activity were established for different organs. Finally, using absorbed dose formulation and IDIAC-Dosage software, the mean absorbed dose in the organs was determined.

Results: Mean calculated dose in the kidney and liver were obtained as 0.30-0.82 mGy/ MBq, and 1.05-2.11 mGy/MBq, respectively.

Conclusion: Based on the results, PRRT therapy is a safe method for the treatment of castration-resistant neuroendocrine cancer patients in terms of patient dose. Large inter-individual differences in organ dose were discovered, highlighting the importance of patient-specific dosimetry and treatment planning in the treatment with ^{177}Lu-DOTATATE.

Keywords: Individualized Dosimetry; ^{177}Lu-DOTA0; Tyr3-Octreotate; Neuroendocrine Tumors; Organ at Risk.

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1. Introduction

The development of traditional methods for the treatment of cancer such as surgery, external radiotherapy, chemotherapy, and biotherapy has led to the successful treatment of many cancer patients. Unfortunately, some therapies fail due to the spread of cancer to multiple locations in the body [1]. In metastatic neurological tumors, the use of therapeutic interventions and stimulant options is limited [2].

The most abundant sites of these endocrine cells are the gastrointestinal tract at 70% and the Broncho pulmonary system at 25%, followed by the skin, adrenal glands, thyroid, and genitals [3]. ^{177}Lu-DOTA0, Tyr3-octreotate is a promising treatment for neuroendocrine tumors. This peptide receptor radionuclide PRRT of treatment is based on targeting somatostatin receptors expressed by NETs with peptide chelate, which is DOTATATE (^{177}Lu DOTA-TATE) therapy that is a form of peptide receptor radionuclide therapy (PRRT) which targets somatostatin receptors (SSR). It is a form of targeted drug delivery) [4-6]. The treatment outcome is better when a high dose is delivered to the tumor tissue while it is lower in the organs at risk. The dose-limiting organ for PRRT therapy is the kidney. For this reason, the cumulative absorbed dose to the kidney acts as a crucial indicator to manage further cycles of therapy [4-6].

To avoid the side effects of ^{177}Lu-DOTA0, Tyr3-octreotate and determine the tolerance dose to each organ, more advanced knowledge is needed about the biological distribution of the radionuclide and toxic factors, biokinetics and ^{177}Lu-DOTA0, Tyr3-octreotate dosimetry data. Accurate dosimetry calculations are time-consuming [7, 8].

Previous studies' findings show that the absorbed dose to the organs varies from the kidney, liver, spleen, bladder, and whole body. The IDIAC-DOSE is a new software for internal dose assessment by computer and it uses MIRD's (Medical internal dosimetry) established phantom-based metrology for dosimetry objectives [9].

In a study, absorbed doses for various organs were calculated from the images using a combination of linear approximation, exponential fitting, and target-specific S-value in accordance with the MIRD scheme by Said *et al.* [10]. In that study, six patients who had a history of prostate cancer and radiographic evidence of metastatic disease had PRRT treatment with ^{177}Lu-DOTA-Tyr3-octreotate were evaluated [10].

The average absorbed dose was estimated using OLINDA/EXM software. As a result, large variability in absorbed dose was observed among different organs. Kidneys received the highest dose of radiation. To the best of our knowledge, there are presently no announced data on the absorbed dose calculated by the IDIAC-DOSE software (an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms) for systemic therapy using ^{177}Lu-DOTATATE. There is a need for a simple, quick, and accurate computing approach that could be applied in clinics for this investigation. This study aims to use the IDIAC-DOSE program to estimate the absorbed dose to the critical and non-target organs during the first rotation of ^{177}Lu-DOTATATE therapy in patients with neuroendocrine tumors.

2. Materials and Methods

Administration of ^{177}Lu-octreotate was pleasingly accepted without any severe side effects. Absorbed doses in a single cycle were measured using the absorbed dose formula and the IDIAC-DOSE software. For the successful search, four timelines were used.

Between September 2019 and September 2020, a total of 10 consecutive patients with the mean age of 53.5 ± 12 years (range: 36 to 70 years) with metastatic somatostatin receptor-expressing neuroendocrine tumors received one cycle of PRRT treated with ^{177}Lu-DOTA-Tyr3 octreotate administered at a mean activity of 6401.0 ± 628.4 per cycle. This experimental study was conducted in the Nuclear Medicine Department of Shohada-e-Tajrish Hospital in Tehran. The criteria for the selection of the patients to enter the study were: patients with somatostatin-positive tumors and no prior treatment with PRRT. Lesions included pancreatic endocrine tumors, gastrointestinal carcinoid tumors, and pulmonary carcinoid tumors. The demographic characteristics of the patients are presented in Table 1.

Table 1. Characteristics of the patients in the present study

Number of the patient	Sex	Age (year)	Body mass index (kg/cm^2)	Activity (MBq)	Site of metastasis
1	Male	70	24	5920	Liver
2	Female	45	21	6290	Liver, lymph node
3	Male	50	23	5550	Liver
4	Male	62	24	7400	Skeletal, Lymph node
5	Male	35	25	5550	Liver,lymphnode,abdomen
6	Male	55	24	5920	Liver, abdomen
7	Female	70	25	5550	Liver
8	Female	48	23	5550	Skeletal, liver
9	Male	60	28	7400	Skeletal, liver
10	Female	40	24	7400	Liver, lymph node
Mean ± standard deviation		53.50 ±12.00	24.01±1.79	6253.00 ± 826.40	

Hematology, liver function, and renal function tests were accomplished 6 weeks before the first treatment, 4 and 6 weeks after each treatment, and at follow-up visits. Due to the need to protect the kidneys [4], an intravenous infusion of mixed aminoacid solution (2.5 % L-lysine and 2.5 L-arginine in 1000 ml) was started half an hour before the radioactive administration at the rate of 250 ml/h and at least for 4 hrs. All patients signed documented informed consent so that their data be published as anonymized. All patients underwent whole-body anterior-posterior planar image acquisitions at 0 - 2 hrs., 4 - 6 hrs., 18 – 20 hrs., and 36 - 48 hrs. after the administration of the first therapy. All measurements were performed with a dual head gamma camera (Symbia Evo Excel Siemens) equipped with a 3.8-inch thick NaI (Tl) crystal. Images were obtained at a scan speed of 16 cm/min and an energy window of 20% for the 113 and 208 keV double peaks (anterior-posterior). A ^{177}Lu source (25 ml, 296 MBq) was positioned as a point source. The same matrix, pixel size, and output settings for the whole body images were used to acquire static images for 300 seconds. The number of counts in a Region Of Interest (ROI) around the source in the images was founded and divided by the scanning time. The system calibration factor for ^{177}Lu was determined in counts per second per MBq (cps/MBq) using the following Equation [11]:

$$Calibration\ factor = \frac{Counts\ per\ second\ (cps)}{Specified\ activity\ (MBq)} \quad (1)$$

The subject data were acquired using both detector heads, resulting in geometric mean whole-body planar images being formed in investigation time, as outlined in the Medical Internal Dosimetry (MIRD) approach. The conjugate view approach is a typical method for quantifying organ activity and radioactive material redistribution over time between various organs. This method is according to the measurement of a source encountered at a certain effective depth (d) in an environment illustrated by an attenuation factor (μ). On subsequent scans, the count rates were determined by drawing ROIs for the liver, spleen, kidneys, and bladder. Close to the ROI, the background count rate was also measured. Then, near each organ and the entire body, small and independent ROIs were drawn. Measurements were made in the anterior view (R_A) and in the posterior view (R_P) which can be described by Equation 2:

$$\sqrt{R_A . R_P} = \sqrt{R_0^2 . e^{-\mu L}} \quad (2)$$

The activity was calculated from the system sensitivity (cps/MBq) in air (C) by Equation 3:

$$A = \frac{R_0}{C} = \frac{\sqrt{R_A . R_B}}{C . e^{-\mu \frac{L}{2}}} \quad (3)$$

The thickness [l] of the source organ can be obtained from Equation 4 as follows:

$$A = \frac{R_0}{C} = \frac{\sqrt{R_A . R_B}}{C . e^{-\mu \frac{l}{2}} . \frac{Sinh(\mu . \frac{l}{2})}{\mu . \frac{l}{2}}} \quad (4)$$

To simplify Equation 4, Equation 5 can be used:

$$F = \frac{\mathrm{Sinh}(\mu \frac{\mathrm{L}}{2})}{\mu . \frac{\mathrm{L}}{2}} \quad (5)$$

F is the attenuation correction factor.

Eventually, activity was measured for various organs at different times, using the following Equation [12]:

$$A = \sqrt{\frac{R_A R_P}{e^{-\mu L}}} \frac{F}{C} \quad (6)$$

Cumulative activities were evaluated at separate institutions utilizing a program in the MATLAB software.

The residence time (h) for each agent was estimated by separating the cumulative activity and the managing activity. Absorbed dose estimations in the present study were performed using the MIRD scheme. The mean absorbed dose for each organ was measured with Equation 7:

$$\bar{D} = \sum_{source} \tilde{A}^{source}_{cummulative} \times S \text{ (source} \leftarrow \text{target)} \quad (7)$$

Where, $\bar{D}$ is the absorbed dose per target, $\tilde{A}^{source}_{cummulative}$ is the cumulative activity per source, and *S*-value is the absorbed dose per cumulative activity for separately paired source-target. The dose value was calculated using the *S*-value factors for ^{177}Lu, obtained from the Radiation Dose Assessment Resource (RADAR) website [13, 14]. Additionally, the ICRP (International Commission Radiological Protection) 89 and MIRD number 5 standard organ sizes were used [15, 16]. Dosimetry was then performed using the IDIAC-DOSE software. A computer program for internal dosimetry, using the IDIAC-DOSE, was developed on the basis of the International Commission on Radiological Protection (ICRP) absorption fractions [9]. All results were represented as mean ± SD (Standard Deviation). Full data assessment was performed using Microsoft Excel Plus 2013 software and MATLAB software 2018 version. The statistical investigation was performed using the SPSS (Statistical Package for the Social Sciences) version 16 software.

3. Results

Figure 1 illustrates the renal pharmaceutical activity curve for the patients and undoubtedly displays the difference clearance rate per patient, which again shows the importance of dosage in the form of per patient.

Figure 2 shows the curves for the liver as can be noticed from the early uptake curves. From the results, resident times and absorbed dose per MBq for all

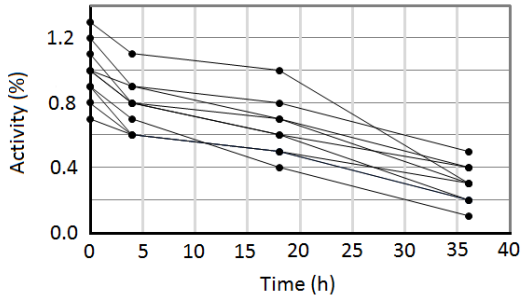

Figure 1. Renal absorption percentage of activity curve versus time (after administration) curve

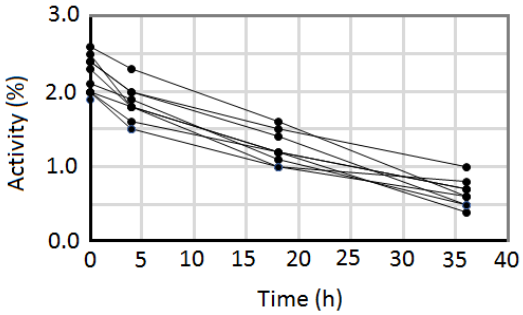

Figure 2. Liver absorption percentage of activity curve versus time after administration

organs were recorded using IDIAC-DOSE software for dose in terms of mGy/MBq (Table 2). The mean absorbed doses were 1.64 ± 0.06 mGy/MBq for the liver and 1.36 ± 0.04 mGy/MBq for the spleen. The calculated mean absorbed doses were 0.18 ± 0.004 mGy/MBq for the bladder, 0.60 ± 0.17 mGy/MBq for the kidneys, and 0.08 ± 0.02 mGy/MBq for the whole body.

The dosimetry results for all patients obtained from the absorbed dose formalism are reported in Table 2. The calculated mean absorbed doses were 0.46 ± 0.09 mGy/MBq for the kidneys, 1.53 ± 0.05 mGy/MBq for

Table 2. Mean absorbed dose per organ per administered activity (mGy/MBq) obtained by the absorbed dose IDIAC-DOSE software and formulism for different organs

Organ	Absorbed dose calculated using MIRD formula (mGy/MBq)	Absorbed calculated using IDIAC-DOSE (mGy/MBq)
Whole body	0.08 ± 0.02	0.06 ± 0.04
Kidneys	0.60 ± 0.17	0.46 ± 0.09
Spleen	1.36 ± 0.04	1.20 ± 0.00
Liver	1.64 ± 0.06	1.53 ± 0.05
Bladder	0.18 ± 0.00	0.13 ± 0.00

the liver, 1.20 ± 0.05 mGy/MBq for the spleen, 0.13 ± 0.00 mGy/MBq for the bladder, and 0.06 ± 0.04 mGy/MBq for the whole body.

The differences between absorbed doses obtained for the organs using the absorbed dose in the IDIAC-DOSE software method and MIRD formulism are shown in Figure 3. Comparison of mean absorbed doses in the organs obtained by the MIRD formulism (gray column) and the IDIAC-DOSE software (black columns) show variations in the results.

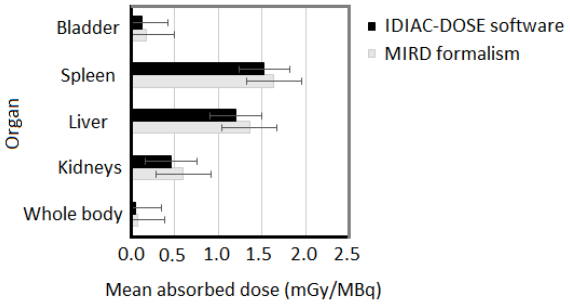

Figure 3. Mean absorbed dose (mGy/MBq) obtained from IDIAC-DOSE software and MIRD formulism for different organs

A comparison of the results of this study with different organ dosimetry studies on ^{177}Lu-DOTATATE is presented in Table 3.

4. Discussion

After the time integral measurement of activity in the individual organs, the calculation of the absorbed dose was performed using the IDIAC-DOSE software which integrates the S-value element.

One of the qualifications of the IDIAC-DOSE software is to specify the absorbed dose per organ due to the dose of electrons and photons. The managed therapy must therefore benefit from a margin of safety. Because they did not examine patient-specific changes in body shape and size are observed, activity levels in source organs are uniform.

Visceral doses vary considerably between patients, increasing the total absorbed activity in organs at risk and target tissues which may lead to overexposure to the patient. The reasons for these deviations may be the effect of the bio distribution of various

Table 3. Comparison of the results of the organ dose which is reported in different studies on ^{177}Lu-DOTATATE

	Baka *et al.* [17]	Said *et al.* [10]	Sandström [1]	Current study (Formalism)	Current study (IDIAC-DOSE software)
Number of patients	9	6	30	10	10
Activity administered	7.4 GBq	7.4 GBq	7.4 GBq	6253 ± 826.4 MBq	6253 ± 826.4 MBq
Imaging time point	30 min, 24 h,72 h, 96 h	30 min, 4 h, 24 h, 48 h, 72 h	24 h, 96 h, and 168 h	0-2 h, 4-6 h, 18-24 h and 36-48 h	0-2 h, 4-6 h, 18-24 h and 36-48 h
Scintigraphic method	Planar images	Planar images	Planar, SPECT/CT images	Planar images	Planar images
dosimetry method	MIRD	OLINDA-EXM MIRD	OLINDA/EXM MIRD	MIRD	IDIAC-DOSE
Absorbed dose in kidneys	0.23 mGy/MBq	0.64 ± 0.41 Gy/GBq	Right: 4.69 Gy Left: 4.39 Gy	0.60 ± 0.17 mGy/MBq	0.46 ± 0.09 mGy/MBq
Absorbed dose in liver	2.22 mGy/MBq	0.76 ± 0.32 Gy/GBq	2.80 Gy	1.64 ± 0.06 mGy/MBq	1.53 ± 0.05 mGy/MBq
Absorbed dose for spleen	1.64 mGy/MBq	1.23 ± 0.59 Gy/GBq	5.35 Gy	1.36 ± 0.04 mGy/MBq	1.20 ± 0.005 mGy/MBq
Absorbed dose for bladder	No	0.17 ± 0.11 Gy/GBq	No	0.18 ± 0.004 mGy/MBq	0.13 ± 0.005 mGy/MBq
Absorbed dose for whole body	No	No	No	0.08 ± 0.02 mGy/MBq	0.06 ± 0.04 mGy/MBq

radiopharmaceuticals in different patients, the amount of radioactivity absorbed in different organs, and the speed of excretion of the radiopharmaceutical from the body. Another reason for this variation is related to the performance of radiopharmaceuticals in various patients due to the severity of the disease. Generally, radiation doses to organs are within acceptable limits. However, there is considerable individual variation, meaning that patient dosimetry is important.

The mean absorbed dose in total body, renal, liver, and bladder reported in the present study were roughly comparable to those reported previously by Baka *et al.* [17], Said *et al.* [10], and Sandestrom [1] (Table 3). The contrast between the results of the different studies is mainly due to differences in imaging techniques, duration of image acquisition, and the type of software and methods used. Explaining the circumstances, it can be mentioned that dose estimation should be based on two-Dimensional (2D) or three-Dimensional (3D) planar gamma camera images. Furthermore, additional regular measurements lead to a better real determination of the integrated radioactivity over time, signifying a MORE precise integral dose.

Ultimately, the software and methods used have a significant impact on the accuracy of the calculation of absorbed doses in each organ. The accuracy of the determined inner dose relies on the accumulated activity in the organs; therefore, it is important to choose precisely and easily without disrupting the load on the nuclear medicine environment. The method suggested in the study is a simplistic method that can be easily conducted in every polyclinic. The calculation of the absorbed dose using the MIRD formulism is time-consuming but easy.

The use of the IDIAC-DOSE software greatly reduces the calculation error, but the method based on the formula of absorbed dose improves the accuracy of the renal absorbed dose calculation, compared with the calculation by the IDIAC-DOSE software, by which the dose received by the organs (left kidney, right kidney) can be determined individually. Differences in organ size may affect the estimated absorbed dose. Studies have shown that there can be significant differences between different patient anatomies and phantoms, therefore, the accuracy of the estimated dose can be affected. Accurate organ volumes can be obtained using high spatial resolution imaging modalities, such as CT (computed tomography) or MRI (magnetic resonance imaging). Estimating absorbed dose utilizing standard organ dimensions or patient-specific organ dimensions can result in a wide variety of changes in the amount of absorbed dose. In expansion, the ROI area per organ in the image may vary from the patient's position in the camera. Accomplishing 3D imaging with SPECT/CT (single-photon emission computerized tomography) and PET/CT (positron emission tomography) dosimetry methods or hybrid methods can enhance the accuracy of the absorbed dose estimation for separate organs. Likened to SPECT/CT or PET/CT, planar scintigraphy stays the simplest and least time-consuming proceeding for whole-body imaging in terms of the asset time, calibration, and recovery element quantification. An additional factor that altered the analysis in this organ overlap, such as high intestinal absorption or lesion overlap, and it could influence the obtained the results. Many investigations have shown that planar image dosimetry tends to overestimate the dose for organs and that newer modalities such as PET tend to offer a dose that is less than one percent. Slightly compared to the dosimetry method, it is still acceptable to have a planar dosimeter. Personalized internal dosimetry includes a large number of estimations and procedures when performed, and it is important to note that each person reacts differently to the same stimuli in the body. The results of the study show how dose-limiting organs can be assessed and precautions taken to decrease the risk of radiation effects. Planar conjugate imaging is a promising beginning to comprehend internal dose calculation. In Iran, this method of dose estimation for patients being treated with ^{177}Lu is relatively new; therefore, it will be useful for physicists to familiarize themselves with it. This method with individual dosimetry and also towards SPECT dosimetry will reduce the number of tests and the time period in which dosimetry can be performed.

Considering the small number of patients referred to the treatment center in this study and the time-consuming and expensive nature of the dosimetry operation, it is suggested that this study be conducted in a number of different treatment centers with a larger number of patients to increase the precision of the obtained results.

5. Conclusion

In this study, the absorbed dose of different organs was investigated in patients with endocrine cancer who

were treated with ^{177}Lu-DOTATATE. Based on the obtained results, organs such as the kidney showed lower levels of absorption of ^{177}Lu-DOTA-Tyr 3octreotate and therefore the highest absorbed dose, while the liver and spleen had the highest level of absorption and the absorbed dose was relatively lower. PRRT therapy is a safe method for the treatment of castration-resistant prostate cancer patients in terms of patient dose. Large inter-individual differences in organ dose were discovered, highlighting the importance of patient-specific dosimetry and treatment planning in treatment with ^{177}Lu-DOTATATE. Knowing this information can help to treat patients with endocrine tumors, therefore, knowing the absorbed dose in each organ helps the physician to take the necessary measures to protect the organs that absorb a large dose.

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