

BIOKINETIC AND DOSIMETRY OF ^{90}Y -DOTATOC THERAPY FOR NEUROENDOCRINE TUMOURS

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ABSTRACT. Biokinetic model is a mathematical model which describes the behavior of the ^{90}Y in human body during the treatment of neuroendocrine tumours. This paper presents calculation of absorbed doses in human organs in biokinetic model ^{90}Y for DOTATOC therapy. For this purpose, the human body is represented by five compartments: blood, kidneys, urinary bladder, tumour and liver. The input file was developed and designed to calculate absorbed doses in human organs, when compartments, as kidneys, liver and tumour, are sources of ^{90}Y . For this purpose, computer software MCNP5/X was used. To solve the system of equations obtained from the model, one data must be taken from the measurements of ^{90}Y in blood or urine. Results obtained, showed that highest absorbed dose is in tumour, compared to other organs in human body.

Key words: ^{90}Y , DOTATOC THERAPY, neuroendocrine tumours, biokinetic model, MCNP5/X software.

INTRODUCTION

^{90}Y -DOTATOC ([Y-DOTA0, Tyr3]-octreotide) is successfully used during last 15 years for the treatment of neuroendocrine tumours that are inoperable, or metastatic (ZAKNUN et al., 2013, CREMONESI *et al.*, 2010). These tumours often have no symptoms and are discovered only when metastases occur. These tumours increased from 1.09 to 5.25 cases per 100 000 inhabitants per year in the period from 1994 to 2009 (SINGH *et al.*, 2017).

^{90}Y -DOTATOC in Peptide Receptor Radionuclide Therapy (PRRT) is used to treat the patient with neuroendocrine tumours (NET), as this kind of peptide provides quick concentration of radionuclide to tumour tissue, while the rest activity is excreted through the kidneys and bladder. Certain amount of radioactivity is accumulated in kidney which can cause the significant damages and reducing the kidney function (BARONE *et al.*, 2005; OTTE *et al.*, 1999). Due to this fact, there is a tendency to optimize the treatments by development of the personalized dosimetry in order to achieve the largest doses in tumour with smaller as possible dose in kidneys (BODEI *et al.*, 2015; HINDORF *et al.*, 2009).

The aim of this study was to calculate absorbed doses in organs and tumour tissue (YORIYAZ *et al.*, 2001). This was based on the available methods for the measurement of ^{90}Y -DOTATOC distribution in the organs of the human body and on the solution of mathematical model which determines transfer coefficients for critical organs.

MATERIALS AND METHODS

Application procedure and blood and urine sampling

As the results of biokinetic model, totally 11 equations and 12 unknown integration constants were obtained. Such system cannot be solved and one additional information is needed. This data is provided from the measurements of ^{90}Y –DOTATOC in blood or urine.

Measurements were performed on 10 patients which were treated by this therapy in Clinical Centre Kragujevac (MATOVIC, 2012). Patients received activity of ^{90}Y –DOTATOC between 2.7 and 5.4 GBq. Blood was sampled at the moment when the application of radiopharmaceutical was terminated, and later at each hour during first 6 hours and after in intervals of 6 h up to 72 h after application of the radiopharmaceutical. Urine was also collected and measured 72 h after application. Activities in urine and blood samples were measured in liquid scintillation counter RACKBETA, LKB-Wallac. Counter was calibrated with the known samples of ^{90}Y , and it is found that efficiency to ^{90}Y is 90.2%.

Details of the computational model

Radiation dose in different organs from beta radiation emitted by ^{90}Y –DOTATOC located in the kidneys were calculated for human ORNL phantom (KRSTIC and NIKEZIC, 2007). For this purpose, MCNP5/X software (X-TEAM, 2003), which performs simulation of transport of neutrons, photons and electron in different materials and geometries, was used. In this paper simulation of transport of electrons is performed in the adult male ORNL phantom.

MCNP code was used to calculate mean absorbed dose (in MeV/g *per one particle of radiation*) in organs and tissues of the human body (ICRP 1991). Analytical models of the human body were developed in publication (ECKERMAN *et al.*, 1996). All organs of the human body were represented with analytical equations. Each kidney is an ellipsoid cut by a plane, given by the following equation:

$$\left(\frac{x-x_0}{a}\right)^2 + \left(\frac{y-y_0}{b}\right)^2 + \left(\frac{z-z_0}{c}\right)^2 \leq 1 \text{ and } |x| \geq x_1 \quad (1)$$

Parameter x_0 is taken as positive for the left kidney, and negative for the right, the volume is 288 cm^3 for both kidneys; parameters (in *cm*) y_0 and z_0 are 6 and 32.5, respectively. Values (in *cm*) a , b and c are 2.5, 1.5 and 5.5.

The liver (volume is 1830 cm^3) is represented by an elliptical cylinder cut with a plane as follows:

$$\left(\frac{x}{a}\right)^2 + \left(\frac{y}{b}\right)^2 \leq 1$$

$$\frac{x}{x_m} + \frac{y}{y_m} - \frac{z}{z_m} \leq -1, \text{ and } z_1 \leq z \leq z_m \quad (2)$$

Parameters (in *cm*) a and b are 16.50 and 8, respectively. Values (in *cm*) for x_m , y_m , z_m and z_l are: 35, 45 and 43 *cm*, respectively.

The tumour has a spherical shape and is located in the centre of the abdomen, between the kidneys and near the liver and pancreas. The diameter of tumour was 3 *cm*.

According to ORNL, human phantom consists of three types of tissues, skeletal, lung and soft, with different densities and elemental compositions. All equations for organs of ORNL phantom, with other relevant information (chemical compositions, volumes, masses etc), were programmed in input files for MCNP-4B code (KRSTIC and NIKEZIC, 2007). By combining surfaces through Bull algebra, MCNP-4B forms cells representing various organs.

To calculate doses in other organs when the source of radiation is located in the kidneys, liver and tumour, ORNL phantom of human body was used. This model does not give details of human kidneys, liver and tumour. In addition, uniform distribution of activity in these organs is assumed.

The intention was to calculate the mean absorbed dose in all organs of human body from the radioactivity located in the kidneys and liver of ORNL phantom, using MCNP software. The results obtained from MCNP in $MeV \cdot g^{-1}$ per one emitted particle.

Since the kidneys appear in pair, they are presented in MCNP as the union of regions which contain left and right kidney. The number on histories must be increased to ensure low statistical error. As the calculation time in this case would be enormous, calculations were done separately.

For the calculations, a spectrum of electrons emitted by ^{90}Y is needed. Spectrum of beta (β) radiation for ^{90}Y (<http://ie.lbl.gov/education/isotopes.htm>) are presented in Fig. 1. Particle energy was sampled according to yields using random method incorporated in MCNP software. In order to simulate emission of whole spectrum of β^- radiation, large number of histories was created (about 10^8) to ensure uncertainty lower than few percent. As a result of computation, *mean absorbed dose per one particle* of radiation (β) from kidney as a source was obtained for adult male ORNL phantom.

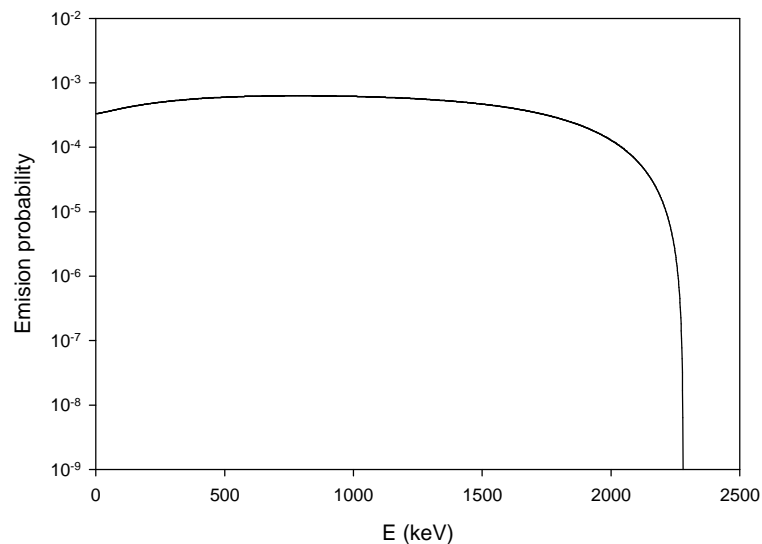


Figure 1. Spectrum of β radiation emitted by ^{90}Y .

RESULTS AND DISCUSSION

MCNP software was applied to calculate the absorbed dose in organs of ORNL phantom in *MeV/g per particle*. Mean absorbed dose per particle of radiation from kidneys, liver and tumour (as sources) in ORNL human phantom presented in Table 1. In the first column are given the human organs, in the second, third and fourth are kidneys, liver, and tumour, respectively.

The table shows that the largest dose in tumour, which is the ultimate goal of this therapy. The values obtained in this work were 39, $2.8 \cdot 10^3$ and $9.06 \cdot 10^6$ *aGy/particle* where the source of radiation is located in the kidneys, liver, and the tumour, respectively. However, the kidneys received large dose, and before the application of this therapy, renal function must be tested. During the therapy to the patient intravenously administered the positively charged amino acids (L-arginine, L-lysine), which serve as the renal protective agents. It is recommended that the dose in the kidneys to limit to 23 Gy (BARONE *et al.*, 2005).

Table1. Results of MCNP5/X calculations for absorbed dose per particle in organs of human body (kidneys, liver and tumour are the sources of irradiation).

Organs	Results of absorbed dose per particle (<i>aGy/particle</i>)		
	kidneys	liver	tumour
skin	1.28	1.03	1.13
<i>liver</i>	8.17	$1.3 \cdot 10^4$	$1.62 \cdot 10^2$
stomach	8.21	13.04	6.00
urinary bladder	1.62	0.21	0.43
gonads	0.16	0.03	0.07
brain	0.014	0.04	0.03
oesophagus	3.75	107	10.26
colon	4.10	1.52	3.28
thyroid	7.48	0.020	1.13
skeleton	3.26	4.81	4.77
<i>kidneys</i>	$1.20 \cdot 10^3$	8.12	$6.77 \cdot 10^2$
pancreas	14.9	54.5	28.90
spleen	18.9	9.17	4.31
thymus	0.509	5.45	1.53
adrenals	16.7	43.5	$6.57 \cdot 10^2$
gall bladder	12.6	11.4	2.73
heart	1.92	40.4	5.83
small intestine	5.80	1.93	0.08
lungs	1.84	12.8	6.07
<i>tumour</i>	39	$2.8 \cdot 10^3$	$9.06 \cdot 10^6$

CONCLUSION

In this work, absorbed dose for ORNL human phantom in tumour and main organs were calculated, when kidneys, liver and tumour are sources of beta-irradiation. The values obtained in this work were 39, $2.8 \cdot 10^3$ and $9.06 \cdot 10^6$ aGy *per one particle*. To estimate the number of particles in organs, it is necessary to develop biokinetic model which describes behavior of radionuclide ^{90}Y in human body. Parameters of such model should be determined based on activity of ^{90}Y measured in urine and blood of patients for evaluation of total dose in individual human body organs. Depending on the size of the tumour, it is possible to estimate whether the applied activity is sufficient for tumour destruction, which is the goal of this therapy.

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References:

- [1] BARONE, R., BORSON-CHAZOT, F., VALKEMA, R., WALRAND, S., CHAUVIN, F., GOGOU, L., KVOLS, L.K., KRENNING, E.P., JAMAR, F., PAUWELS, S. (2005): Patient-Specific Dosimetry in Predicting Renal Toxicity with ^{90}Y -DOTATOC: Relevance of Kidney Volume and Dose Rate in Finding a Dose-Effect Relationship. *J. Nucl. Med.* **46**: 99S-106S.
- [2] BODEI, L., KIDD, M., PAGANELLI, G., GRANA, C.M., DROZDOV, I., LEPENSKY, C., KWEKKEBOOM, D.J., BAUM, R.P., KRENNING, E.P., MODLIN, I.M. (2015): Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur. J. Nucl. Med. Mol. Imaging* **42**: 5-19.
- [3] CREMONESI, M., FERRARI, M., ZOBOLI, S., CHINOL, M., STABIN, M. G., ORSI, F., MAECKE, R.H., JERMAN, E., ROBERTSON, C., FIORENZA, M., TOSI, G., PAGANELLI, G. (2000): Biokinetics and dosimetry in patients administered with ^{111}In -DOTA-Tyr³-Octreotide: implications for internal radiotherapy with ^{90}Y -DOTATOC. *Nucl. Med. Commun.* **21**: 568-569.
- [4] ECKERMAN, K.F., CRISTY, M., RYMAN, J.C. (1996): *The ORNL Mathematical Phantom Series*. Oak Ridge National Laboratory Report. Oak Ridge, TN, USA. Updated 08 April 2009. <http://ordose.ornl.gov/resources/Mird.pdf>
- [5] HINDORF, C., CHITTENDEN, S., CAUSER, L., LEWINGTON, V.J., MÄCKE, H.R. (2007): Flux G D. Dosimetry For ^{90}Y -DOTATOC Therapies in Patients with Neuroendocrine Tumours. *Cancer Biother. Radio.* **22**: 130-135.
- [6] KRSTIC, D., NIKEZIC, D. (2007): Input files with ORNL-mathematical phantoms of the human body for MCNP-4B. *Com. Phys. Commun.* **176**: 33-37.
- [7] MATOVIC, M. (2012): Peptide receptor radionuclide therapy of neuroendocrine tumours:

Case series. *Arch. Oncol.* **20**: 143-148.

- [8] OTTE, A., HERMANN, R., HEPPELER, A., BEHE, M., JERMANN, E., POWELL, P., MAECKE, H.R., MULLER J. (1999): Yttrium-90. DOTATOC: first clinical results. *Eur. J. Nucl. Med.* **26**: 1439-1447.
- [9] SINGH, S., GRANBERG, D., WOLIN, E., WARNER, R., SISSONS, M., KOLAROVA, T., GLODSTEIN, G., PAVEL, M., OBERG, K., LEYDEN, J. (2017): Patient-Reported Burden of a Neuroendocrine Tumor (NET) Diagnosis: Results From the First Global Survey of Patients With NETs, *J.G.O.* **3**: 43-53.
- [10] Table of Radioactive Isotopes. <http://nucleardata.nuclear.lu.se/toi/perchart.htm>
- [11] X-5 MONTE CARLO TEAM. (2003): MCNP—a General Monte Carlo N-Particle Transport Code, Version 5 Vol. I: Overview and Theory. Los Alamos, NM: Los Alamos National Laboratory; LA- UR- 03- 1987
- [12] YORIYAZ, H., STABIN, G.M., SANTOS, A. (2001): Monte Carlo MCNP-4B-based absorbed dose distribution estimates for patient-specific dosimetry, *J. Nucl. Med.* **42**: 662-669.
- [13] ZAKNUN, J.J., BODEI, L., MUELLER-BRAND, J., PAVEL, M.E., BAUM, R.P., HÖRSCH, D., O'DORISIO, M.S., O'DORISIO, T.M., HOWE, J.R., CREMONESI, M., KWEKKEBOOM, D.J. (2013): The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur. J. Nucl. Med. Mol. Imaging* **40**: 800-816.