Development of modern approach to absorbed dose assessment in radionuclide therapy, based on Monte Carlo method simulation of patient scintigraphy

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Development of modern approach to absorbed dose assessment in radionuclide therapy, based on Monte Carlo method simulation of patient scintigraphy

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Abstract. One of the most difficult problems of modern radionuclide therapy (RNT) is control of the absorbed dose in pathological volume. This research presents new approach based on estimation of radiopharmaceutical (RP) accumulated activity value in tumor volume, based on planar scintigraphic images of the patient and calculated radiation transport using Monte Carlo method, including absorption and scattering in biological tissues of the patient, and elements of gamma camera itself. In our research, to obtain the data, we performed modeling scintigraphy of the vial with administered to the patient activity of RP in gamma camera, the vial was placed at the certain distance from the collimator, and the similar study was performed in identical geometry, with the same values of activity of radiopharmaceuticals in the pathological target in the body of the patient. For correct calculation results, adapted Fisher-Snyder human phantom was simulated in MCNP program. In the context of our technique, calculations were performed for different sizes of pathological targets and various tumors deeps inside patient’s body, using radiopharmaceuticals based on a mixed β-γ-radiating (¹³¹I, ¹⁷⁷Lu), and clear β-emitting (⁸⁹Sr, ⁹⁰Y) therapeutic radionuclides. Presented method can be used for adequate implementing in clinical practice estimation of absorbed doses in the regions of interest on the basis of planar scintigraphy of the patient with sufficient accuracy.

1. Introduction.
Application of internal radiation sources in radionuclide therapy attributes very special features to the methodologies of radiological control of absorbed doses. Direct measurement of absorbed dose value in tumor volume is extremely difficult because of the necessity of invasive intervention and the complexity of implementation of the procedure per se in routine clinical practice. At the same time, available reference data on the distribution of radiopharmaceutical (RP) in bodies of small laboratory animals, upon which the values of absorbed dose within the region of interest is directly dependent, do not reach satisfactory levels of correlation with respective indicators for human body [1]. Increased probability of radiation induced complications in normal tissues is the limiting factor both in RNT and in the external beam therapy imposing restrictions on the value of RP activity introduced in the body. Values of absorbed doses in the pathological targets and in normal tissues is extremely important for
ensuring the required therapeutic doses in tumor under the condition of maintaining tolerant levels of irradiation of not affected areas.

Value of absorbed dose within the region of interest is directly dependent on the value of RP activity accumulated in tumor. Modern methods for accumulated activity measurement in the body include the following methodologies [2]:
- Measurement of count rates in region of interest using clinical radiometer;
- Producing planar images using gamma camera;
- Application of SPECT- and PET-tomography;
- Evaluation of activity in blood and urine samples.

For a long time and even nowadays obtaining planar images using gamma camera is the most convenient and easy to use method for quantitative assessment of RP activity accumulated in the region of interest in patient’s body at different time moments. Relative simplicity of the measurement procedure, acceptable costs and low time consuming assured gamma cameras to be “workhorses” of clinical departments of radionuclide therapy.

Nevertheless, certain aspects associated with the specific design of gamma camera and method used for images obtaining must be taken into consideration in order to achieve required level of accuracy of activity estimation according to the data from obtained images. In particular, it is necessary to introduce corrections on the absorption of radiation, radiation scattering in the patient’s body and in the elements of the gamma camera system and on the possibility of photon penetration through collimator septum walls. These and some other specific features impose restrictions on the energy and space resolution of the gamma camera. In particular, in radionuclide therapy radiation dose rate during early stages after RP introduction in the patient’s body can be sufficiently high which may lead to the loss of counts in the camera and to potential possibility of errors in the identification of the position where the photon is generated. On the other hand, low dose rate is the cause of high levels of statistical uncertainties and noises in the images [3].

Spatial resolution of planar images depends, first of all, on the characteristics of the scintillator and the configuration of collimators of gamma camera. Design features of the collimator also play important role in the determination of geometrical sensitivity of the system. Parallel hole collimators are often used in clinical practices and proved themselves in the most positive way for the estimation of activity accumulated in the patient’s body. Compared to other types of collimators (convergent, divergent and pinhole) parallel hole collimators ensure the smallest geometrical distortion of the obtained information and demonstrate relative independence of sensitivity of the image producing system on the source-to-collimator distance within the limits of certain area. Thus, determination of the calibration factor for the selected collimator configuration becomes a routine procedure.

At the same time the processes of radiation absorption along the source-to-collimator distance which is dependent on the RP distribution and on the specific constitution of the patient’s body cannot be left un-noticed and, therefore, the value of the calibration factor in the given geometry becomes the value specific for each separate study and introduction of correction of absorption of radiation is strictly necessary.

The most widely used planar scintigraphy method in vivo for measuring the value of activity within the region of interest as well as for introduction of correction of the absorption of radiation in the patient’s body became the method of obtaining two conjugated opposite scintillation camera images of the patient’s body [4]. Such methodology ensures sufficient accuracy of evaluation of measurements for geometrically well separated sources of activity with insignificant activities of surrounding tissues. The main advantage of this method is the absence of the need to obtain information on the depth of positioning of the region of interest inside the patient’s body which significantly simplifies the procedure of obtaining the required data.

The methodology in question assumes obtaining two opposing (usually the anterior and posterior view) planar images of the whole patient’s body or of the selected region of interest. For point source located at depth \( d \) in the medium with absorption factor \( \mu \) the gamma camera count rates obtained for the anterior \( C_A \) and posterior \( C_P \) images, respectively, are equal to
\[ C_A = C_0 e^{-\mu d}, \]  

(1)

and

\[ C_p = C_0 e^{-\mu(L-d)}, \]  

(2)

where \( L \) is the thickness of the patient for the particular section; \( C_0 \) is the detector count rate in the absence of absorption of radiation in tissues of the patient’s body when detector head is positioned directly above the patient’s body and after its rotation by 180°. The geometrical mean value calculated according to the following relation:

\[ (C_A \cdot C_p)^{1/2} = (C_0^2 e^{-\mu L})^{1/2} \]  

(3)

appears to be independent on the depth of positioning of the region of interest in the patient’s body. Thus, the value of accumulated activity is equal taking into account the system’s sensitivity \( C \) measured in the air to

\[ A = C_0 / K = (C_A \cdot C_p)^{1/2} / (C \cdot e^{-\mu L/2}) \]  

(4)

Absorption factor applied in the methodology is a weighted sum of absorption factors for all tissues of the body along the direction of projection of the image.

Subsequent calculations of activity accumulated within the region of interest using the described methodology require correction caused by radiation scattering along the source–to-detector path which implies the need to implement additional measurements and calculations.

However, application of this methodology in clinical practices results in the accumulation of uncertainties in the determination of the value of absorbed activities associated with the following factors:

– Significant simplification of mathematical description of the processes of radiation transfer along the source-to-detector path which may lead to the underestimation or overestimation of absorption and scattering factors in different tissues;

– Application of described methodology is limited by the cases of centers of RP accumulation located at significant geometrical distances from each other which appears to be rather the exclusion than the rule in the clinical practice;

– Absence of the contribution in the detector readings of results of penetration of high-energy photons through the collimator septum walls.

Moreover, application of the discussed methodology requires implementation of additional radiological measurements for correct estimation of absorption and scattering factors, as well as additional irradiation of the patient by external radiation source for estimating the effective value of attenuation factor in the region of interest.

All these factors complicate the procedure for accurate estimation of the value of accumulated activity of RP in tumor gives the stimulus for searching for the alternative methodology of tumor dose control in radionuclide therapy. Methodology of simulation of radiation transfer by Monte-Carlo method which deservedly becomes more and more popular in RNT allows discussing the possibility of significant enhancement of accuracy of estimation of activity in the patient’s body [5 – 8].

Application of Monte-Carlo method in RNT for calculation of absorbed doses within the tumor and in organs at risk, as well as for estimation of radiation absorption and scattering in the body tissues found its reflection in a number of foreign and indigenous studies [9 – 15].

The purpose of the present study is to develop clinical method for estimation of RP activity accumulated in the region of interest on the basis of simulation by Monte-Carlo method of processes of radiation transfer in the system for obtaining planar scintigraphic images of the patient’s body using gamma camera.
2. Materials and methods.
Therapeutic effect and tumor control assessment in the process of implementation of radionuclide therapy and the probability of development of complications in healthy tissues presupposes the need to accurately determine the doses absorbed in the regions of interest. However, significant dispersion in the values of RP accumulation in the affected organs and in the unaffected structures of the patient’s body associated with individual features of RP dynamics and patient’s metabolism rate serves as the indisputable proof of the need of implementation of individual control of tumor doses after administration of RNT treatment course [16 – 19]. It has to be noted that in connection with specifics features of RNT treatment, significant variability of biokinetic mechanisms of RP accumulation, distribution and washout from the body, as well as with specific features of implementation of radiological measurement procedures, determination of the value of absorbed dose in the region of interest to one order of magnitude is accepted as sufficiently good result, while estimation of uncertainty up to several tens percent is the maximum achievable result during the contemporary phase of RNT development [4].

The layout of determination of the value of accumulated RP activity in the patient’s tumor site suggested in the present paper implies successive implementation of the following three steps.

1. Scintigraphic images are obtained of the vial containing already known activity of the radiopharmaceutical \( A_0 \) placed at the fixed source-to-collimator distance, following which estimation of the detector count rate \( k_0 \) within the specified region of interest of the vial image is undertaken.

2. Therapeutic activity \( A_0 \) is introduced in the patient’s body, after a certain period of time specific for each RP type and characteristics the period of maximum RP accumulation in the tumor scintigraphic examination of the patient is performed. Estimation of the detector count rate \( k_{tum} \) in the region where the tumor is located and the value of tissue background \( k_{bg} \) in the close enough vicinity to the tumor is performed using the tools for contouring the region of interest on the obtained planar image provided using the software imbedded in the scintigraphic equipment.

3. Value of accumulated activity in the affected tumor is determined according to the following formula:

\[
A = A_0 \cdot \frac{(k_{tum} - k_{bg})/(k_0 \cdot p)}{p},
\]

(5)

Where \( p \) is the correction factor calculated using Monte-Carlo method for specific clinical case for the geometry used in obtaining scintigraphic images which is identical to the conditions of measurement of activity in the vial and in the patient’s body.

The obtained correction factor allows taking into account the combination of corrections on the radiation absorption and scattering in biological tissues of the patient, in the air gap between the patient’s skin surface and the gamma camera collimator, as well as in the collimator of the imaging system per se taking into account penetration of high-energy photons through the collimator septum walls.

Fischer-Snyder phantom parameters of which correspond to the sizes of adult human body was simulated for calculating the above factor in the MCNP code [20]. Different target volumes, with different sizes approximated with spheres with radii varying from 1 cm to 5 cm were located inside the phantom’s body at different depths.

Also model of the system for obtaining scintigraphic images including gamma camera (NaI crystal detector) and parallel hole collimator in which walls of apertures are made of tungsten and have hexagonal shape was developed for performing calculations using the MCNP code. The number of apertures, their lengths and cross-section geometrical characteristics were selected in according to the type and the energy distribution of radiation emitted by radionuclide in the respective RP. Parameters of gamma camera collimators used for simulation and calculations using the MCNP code, are presented in Table 1.
Table 1. Parameters of gamma camera collimators manufactured by Siemens.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Medium energies</th>
<th>High energies</th>
<th>Super high energies</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{67}$Ga</td>
<td>$^{131}$I</td>
<td>$^{18}$F</td>
<td></td>
</tr>
<tr>
<td>Aperture shape</td>
<td>Hex</td>
<td>Hex</td>
<td>Hex</td>
</tr>
<tr>
<td>Number of apertures ($\times1000$)</td>
<td>14</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Aperture length, mm</td>
<td>40.64</td>
<td>59.7</td>
<td>50.5</td>
</tr>
<tr>
<td>Membrane thickness, mm</td>
<td>1.14</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Aperture diameter, mm</td>
<td>2.94</td>
<td>4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Figure 1. Layout for the determination of gamma camera count rate in the measurements of vial containing activity $A_0$.

Figure 2. Layout for the determination of gamma camera count rate during scintigraphic study of the tumor located inside the patient’s body and containing activity $A_0$.

Geometry of the experiment simulated in the calculations coincides with the conditions for obtaining planar scintigraphic images using gamma camera. Layout for the determination of the gamma camera count rate in the measurements of 5-ml vial containing activity $A_0$ administered to the patient is presented in Figure 1. Such model of the experiment corresponds to the realistic clinical situation. Planar images of the vial are obtained when the detector is in position above and below.

Figure 2 demonstrates the model of scintigraphic examination of the patients with RP introduced in the body. It is important to note that the value of activity of the radiopharmaceutical modeled in the
target of pathology is equal to the value of $A_0$ originally contained in the vial. Thus, the required factor taking into account corrections on the radiation absorption and scattering along the whole source-to-detector path is determined in the experiment under modeling from the following relation:

$$p = \frac{k_{mc}^{\text{amp}}}{k_{mc}^{\text{tum}}}$$  \hspace{1cm} (6)

In this relation $k_{mc}^{\text{amp}}$ is the gamma camera count rate for simulation by the Monte-Carlo method of the process of obtaining planar images of the vial containing activity $A_0$; $k_{mc}^{\text{tum}}$ is the count rate for the modeled scintigraphic study of the phantom of human body with respective sizes of the tumor and depth of its position. Position of the gamma camera during measurement corresponds to realistic clinical situation when in accordance with settings of the equipment the distance between the patient’s body surface and the collimator of the system for obtaining the image is fixed to be equal to 3 cm.

3. Results and discussion.
Measurement of correction factor $p$ according to the described methodology was implemented for RP on the basis of both mixed $\beta$-$\gamma$-emitters $^{131}\text{I}$ and $^{177}\text{Lu}$ and pure $\beta$-emitters $^{90}\text{Y}$ and $^{89}\text{Sr}$ for which bremsstrahlung emission generated in the patient’s body was registered.

In accordance with settings of the system for obtaining planar images using gamma camera applied in the clinical practices, energy range of the registered radiation was set in the code at the level corresponding to 20% deviation upwards and downwards from the most typical line in the spectrum of the investigated radionuclide.

Radius of tumors in the patient’s body examined in the study was approximated by spherical geometry with sizes varying from 1 cm to 5 cm, while the examined depths of tumor localization in the patient’s body changed from the central lateral line of the phantom to its surface with step equal to 1 cm. Indicators of gamma camera count rate used in the calculations of correction factor were normalized to unit activity in the region of interest.

Results of calculations of correction factors for radiation absorption and scattering obtained by the Monte-Carlo method in the geometry corresponding to the problem described in the present paper are shown in Tables 2 – 5.

**Table 2.** Calculated values of the correction factor $p$ for pathological target volumes containing RP on the basis of $^{131}\text{I}$

<table>
<thead>
<tr>
<th>Distance from the central lateral axis of the phantom, cm (target radius 1 cm)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.423</td>
<td>0.532</td>
<td>0.593</td>
<td>0.665</td>
<td>0.732</td>
<td>0.762</td>
<td>0.811</td>
<td>0.832</td>
<td>0.901</td>
<td>0.944</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target radius, cm (distance from the axis 0 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>0.423</td>
</tr>
</tbody>
</table>
### Table 3. Calculated values of the correction factor $p$ for pathological target volumes containing RP on the basis of $^{177}$Lu

<table>
<thead>
<tr>
<th>Distance from the central lateral axis of the phantom, cm (target radius 1 cm)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.216</td>
<td>0.219</td>
<td>0.222</td>
<td>0.228</td>
<td>0.232</td>
<td>0.236</td>
<td>0.243</td>
<td>0.252</td>
<td>0.273</td>
<td>0.294</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target radius, cm (distance from the axis 0 cm)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.216</td>
<td>0.224</td>
<td>0.233</td>
<td>0.239</td>
<td>0.243</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Calculated values of the correction factor $p$ for pathological target volumes containing RP on the basis of $^{90}$Y

<table>
<thead>
<tr>
<th>Distance from the central lateral axis of the phantom, cm (target radius 1 cm)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.010</td>
<td>0.013</td>
<td>0.020</td>
<td>0.023</td>
<td>0.028</td>
<td>0.036</td>
<td>0.041</td>
<td>0.047</td>
<td>0.054</td>
<td>0.074</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target radius, cm (distance from the axis 0 cm)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.010</td>
<td>0.013</td>
<td>0.019</td>
<td>0.024</td>
<td>0.032</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Calculated values of the correction factor $p$ for pathological target volumes containing RP on the basis of $^{89}$Sr

<table>
<thead>
<tr>
<th>Distance from the central lateral axis of the phantom, cm (target radius 1 cm)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.013</td>
<td>0.015</td>
<td>0.017</td>
<td>0.022</td>
<td>0.024</td>
<td>0.027</td>
<td>0.029</td>
<td>0.034</td>
<td>0.037</td>
<td>0.046</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Target radius, cm (distance from the axis 0 cm)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.013</td>
<td>0.019</td>
<td>0.022</td>
<td>0.023</td>
<td>0.026</td>
<td></td>
</tr>
</tbody>
</table>

Characteristic increase of the value of correction factor with increased size of tumor in the phantom body, as well as with its distance to the surface of the body is associated with decreasing thickness of the layer of biological tissue of the phantom absorbing radiation along the source-to-detector path. Reduction of numerical values for RP on the basis of $^{177}$Lu as compared to RP on the basis of $^{131}$I is explained by significantly lower characteristic energy of the spectrum and reduction of photon contribution in percent in the total exposure dose created by radiation emitted by the radionuclide.

Determination of count rate of the gamma camera for the cases of $^{90}$Y and $^{89}$Sr required significant increase of computer processor time expenditures by the code for obtaining statistically reliable
results which is associated with low probability of registration of brehmstrahlung emission generated in the body tissues.

Calculated correction factor allows obtaining information about the accumulated value of RP activity in the region of interest. In this case determination of absorbed doses in tumor and in normal tissues does not cause any difficulties.

The methodology of target doses control in the RNT on the basis of obtaining planar scintigraphic images of the patient and calculation of radiation transfer by Monte-Carlo method suggested in the present study allows determining the value of activity of the radiopharmaceutical accumulated in the tumor and in normal tissues taking into account radiation absorption and scattering in biological tissues of the patient and in the materials of the imaging system.

Values of factors determining corrections on radiation absorption and scattering calculated for RP on the basis of $^{131}$I, $^{177}$Lu, $^{90}$Y, $^{89}$Sr and presented in the paper for defined geometry and different depth of and different sizes of the affected volume, allowing implementing in clinical practice estimation of absorbed doses in the regions of interest on the basis of planar scintigraphy of the patient with sufficient accuracy.

Acknowledgments
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