Absorbed Dose Estimation of $^{177}$Lu-DOTATOC in Adenocarcinoma Breast Cancer Bearing Mice

S. Zolghadri, M. Mousavi-Daramoroudi, H. Yousefnia, F. Abbasi-Davani

Abstract—In this study, the absorbed dose of human organs after injection of $^{177}$Lu-DOTATOC was studied based on the biodistribution of the complex in adenocarcinoma breast cancer bearing mice. For this purpose, the biodistribution of the radiolabeled complex was studied and compartmental modeling was applied to calculate the absorbed dose with high precision. As expected, $^{177}$Lu-DOTATOC illustrated a notable specific uptake in tumor and pancreas, organs with high level of somatostatin receptor on their surface and the effectiveness of the radio-conjugate for targeting of the breast adenocarcinoma tumors was indicated. The elicited results of modeling were the exponential equations, and those targeting of the breast adenocarcinoma tumors was indicated. 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solution was measured by γ-ray spectroscopy on an HPGe detector basing on the major photons of $^{177}$Lu. The radiochemical purity of the solution using ITLC method was performed on the above-prepared quality control mixture. For this purpose, 5 μl of the solution was spotted on Whatman No. 3 paper and developed in two solvent systems [A: 10 mmol.L$^{-1}$ diethylene triamine pentaacetic acid (DTPA) at pH=5 and B: 10% ammonium acetate:methanol (1:1)].

$^{177}$Lu-DOTATOC was prepared according to the previously reported literature [15]. 115 μg/μl DOTATOC was added to the vial containing 7 mCi of $^{177}$LuCl$_3$, while the pH of the mixture was set to 4 utilizing 0.4 M sodium acetate. The reaction mixture was heated in 90 °C water bath for 30 min. The radiochemical purity of the mixture was then surveyed by ITLC method.

### B. Biodistribution of $^{177}$Lu-DOTATOC in Mice Bearing Breast Adenocarcinoma Tumors

A bolus of $^{177}$Lu-DOTATOC (100 μL, 3.7MBq) was injected via the tail vein in mice and animals were euthanized at 2, 4, 24, 48, 72, and 168 h by CO$_2$ asphyxiation.

For pharmacokinetics studies, samples of blood and tissues (heart, kidneys, spleen, stomach, intestine, lung, liver, skin, bladder, bone, muscle, thyroid, adrenal and pancreas) of interest were excised, weighted, and counted for radioactivity in a p-type coaxial HPGe detector. Data were calculated as percent injected dose per gram tissue (%ID/g) with the aid of suitable standards of the injected dose.

### C. Biodistribution Modeling of $^{177}$Lu-DOTATOC

A biodistribution model can anticipate the time course of radioactivity concentration in a tissue region from knowledge of the local physiological variables and the input function (%ID/g of tissues). Compartmental modeling is the most commonly used method for eliciting the behavior of the radiopharmaceutical absorption, mathematically [16]. Estimation of the absorbed dose data will be more accurate if the data points of the activity–time curve increase. This model is a substitute way to the direct calculation of cumulated activity. In subsequent, the biodistribution modeling will be benefiting for molecular imaging and in vivo dosimetry.

In this part of work, using ANACOMPTM software, the equations derived from time dependent model of all the tissues were obtained. In fact, these equations produce numerous points (or % ID/g data) on the time–activity curves of each tissue, which it increases the acceleration of absorbed dose calculations as well as high accuracy.

### D. Dosimetric Calculations

The calculated mean value of the percentage injected activity per gram of tissue (%IA/g) for the organs in mice was extrapolated to uptake in organs of a 73-kg adult, using the following formula:

\[
\frac{\%IA}{\text{organ}_{\text{human}}} = \frac{\%IA}{\text{organ}_{\text{mouse}}} \times m_{\text{human organ}} \times \frac{M_{\text{human}}}{M_{\text{mouse}}}
\]

where m is the organ mass and M is the total body weight $\frac{\%IA}{kg}$.

The extrapolated values (%IA) in human organs at 4, 24, 72 and 168 h were fitted with the exponential equations of compartmental model and the equations were integrated to obtain the number of disintegrations in the source organs. The integrals (MBq.s) for all organs were evaluated and used for the dosimetry evaluation.

For instance, below formulation is related to accumulated activity in blood of mice:

\[
\hat{A} = \int_0^{168} A(t) \, dt
\]

where $\hat{A}$ and $A(t)$ is:

\[
\hat{A} = \sum_{i=1}^m n_i \phi_i \frac{1}{m}
\]

\[
A(t) = \int_0^t \frac{\%ID}{g} \, dt
\]

where the product $n_i \phi_i$ is the average energy per decay (0.147 MeV), $\phi_i$ is the absorbed fraction in the target, $m$ is the mass of the target region (kg), and $k$ is some proportionality constant ($\frac{mGy.kg}{MBq.s.MeV}$), and $A(t)$ is the activity of each organ at the time t.

In this method the uptake per organ is extrapolated one-to-one from mouse to human. The extrapolated human source organ residence times were used as input in the OLINDA/EXM dosimetry software to calculate the absorbed doses per administered activity in humans [18].

### III. RESULTS AND DISCUSSIONS

#### A. Preparation and Quality Control of $^{177}$Lu-DOTATOC

$^{177}$Lu was prepared with the specific activity of 2.6-3 GBq.mg$^{-1}$ and radiochemical purity of 98%. Photons of 112 and 208 keV energy was observed while counting the samples on an HPGe. Thin layer chromatography showed the radiochemical purity of greater than 99% for $^{177}$Lu-DOTATOC.

#### B. Biodistribution of $^{177}$Lu-DOTATOC in Mice Bearing Breast Adenocarcinoma Tumors

After intravenous administration of $^{177}$Lu-DOTATOC, it was highly accumulated in the tumors in 24 h p.i. (1.123 %ID/g), and approximately 63% of it was retained in 168 h p.i. (0.71 %ID/g). Radioactivity in the kidney reached a maximum level of 4.252 %ID/g at 4 h. After the kidneys as excretory organs, radioactivity was maintained at higher levels.
in the tumor (1.094 to 1.123 %ID/g) and in the pancreas (0.599 to 0.752 %ID/g) before 24 h and then gradually decreased. Radioactivity in the liver was maintained at higher levels (0.424 %ID/g) before 4 h and gradually decreased with time. Low levels of radioactivity distribution were found in the skin, muscle, and spleen. While tumor uptake decreases slightly with time, tumor to blood and tumor to muscle activity ratio reach to the maximum amounts in 168 h post injection, that it is an important option for planning of the treatment and even imaging.

For better conclusion and ensure of acceptable positioning of complex, the accumulation of $^{177}\text{Lu-DOTATOC}$ species in main organs of normal rats [15] and tumoral mice is compared in Fig. 1.

As it can be seen in this figure, in both states, the complex is washed out from the circulation immediately, while the initiate uptake in tumoral mice is so less than other state. Kidney excretion as the main excretion route can be observed for both species that occur due to the water solubility for $^{177}\text{Lu-DOTATOC}$, but its uptake in tumoral mice is higher than normal rats. A major difference in liver uptake is observed for both of them. Albeit, the major differences in spleen and liver uptake are observed for the two states but that is to say $^{177}\text{Lu-DOTATOC}$ has almost no significant and alarming spleen and liver accumulation.

Also, the radiolabeled compound has higher accumulation in tumoral term rather than normal term in pancreas as sstr-positive tissues at all times after injection. Thus, it goes without saying that adenocarcinoma tumor with high expression of sstr, has authority to accumulating of the complex more than other organs.

C. Biodistribution Modeling of $^{177}\text{Lu-DOTATOC}$

The compartmental model was used to produce a mathematical description of the complex behavior in each organ and elicitation of exponential equation in order to obtain integrated data of accumulated activity and finally their utilization of them for dosimetry. The following equations (Table I) and figures (Fig. 2) of modelling were obtained for each organ. In each case, t=0 corresponds to the time of injection.

D. Dosimetric Calculations

The organ radiation absorbed doses for the administration of $^{177}\text{Lu-DOTATOC}$ to humans, as determined using compartmental modelling data from the residence times in mice, are shown in Table II.
Fig. 2 Temporal behavior of biodistribution of $^{177}$Lu-DOTATOC in mice organs

**TABLE I**

<table>
<thead>
<tr>
<th>Target</th>
<th>Estimated dose (mSv/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.000659</td>
</tr>
<tr>
<td>Brain</td>
<td>0.000347</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.000228</td>
</tr>
<tr>
<td>GB Wall</td>
<td>0.000518</td>
</tr>
<tr>
<td>LLI Wall</td>
<td>0.032473</td>
</tr>
<tr>
<td>Small Int</td>
<td></td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.00443</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.039803</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.020837</td>
</tr>
<tr>
<td>Bone</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
</tr>
</tbody>
</table>

Dosimetry was analyzed by the OLINDA/EXM software. Extrapolated radiation dose for a 73-kg male adult. GB: Gallbladder Wall; LLI, lower large intestine; Int: Intestine and content; ULI, upper large intestine, UB Wall: Urinary Bladder Wall.

**TABLE II**

**MATHEMATICAL RELATIONSHIPS DERIVED FROM BIODISTRIBUTION MODELING OF $^{177}$Lu-DOTATOC**

\[
\begin{align*}
\text{Blood:} & \quad f_1 = 0.593e^{-0.07055t} + 1.001e^{-0.02047t} + 0.2801e^{-0.64086t} + 0.173e^{-0.09260t} + 0.07991e^{-0.04855t} - 1.18e^{-0.03629t} + 0.0313e^{-0.0594t} \\
& \quad f_2 = -1.088e^{-0.03233t} - 1.001e^{-0.02032t} - 0.3391e^{-1.0321t} + 0.2145e^{-0.01226t} + 0.363e^{-0.6094t} + 0.8404e^{-0.3956t} \\
\text{Liver:} & \quad f_3 = -1.01e^{-0.03604t} + 0.622e^{-0.07756t} + 0.04146e^{-0.31471t} - 0.2766e^{-0.1753t} + 0.1017e^{-0.54371t} + 0.8331e^{-0.02010t} - 0.06458e^{-0.75088t} \\
& \quad f_4 = -1.01e^{-0.03604t} + 0.622e^{-0.07756t} + 0.04146e^{-0.31471t} - 0.2766e^{-0.1753t} + 0.1017e^{-0.54371t} + 0.8331e^{-0.02010t} - 0.06458e^{-0.75088t} \\
\text{Heart:} & \quad f_5 = 1.614e^{-0.05001t} + 0.03848e^{-0.01403t} + 0.07462e^{-0.00599t} - 0.2356e^{-0.09071t} \\
& \quad f_6 = 1.323e^{-0.0089t} - 0.3186e^{-0.0144t} - 0.3158e^{-0.0046} - 0.3814e^{-0.0093} \\
\text{Tumor:} & \quad f_7 = -1.31e^{-0.35355t} + 0.4578e^{-0.61387t} + 0.2319e^{-0.004966t} + 0.5195e^{-0.01860t} + 0.4017e^{-0.34284t} + 0.2713e^{-0.0441t} + 1.16e^{-0.2287t} \\
& \quad f_8 = 0.3199e^{-0.31477t} + 1.325e^{-0.01866t} + 0.1506e^{-0.77711t} + 0.404e^{-0.31332t} + 0.7947e^{-0.1585t} \\
\end{align*}
\]
IV. CONCLUSION

$^{177}$Lu-DOTATOC is a promising potential candidate for targeted therapeutic radiopharmaceutical for treatment of sstr-expressing tumors specially breast adenocarcinoma tumors. Also, it was shown that the compartmental model may be an approach for estimation of the human absorbed dose beneficially after i.v. administration of $^{177}$Lu-DOTATOC with the time integrated data from the equations of modelling. The dosimetric calculations delivered the safe and appropriate dose for therapy of SSTR-positive tumors although further biological studies in other appropriate animals are still needed.

REFERENCES