OEDIPE : A Personalised Internal Dosimetric Tool Associating Voxel-Based Phantoms with Monte Carlo Calculation for Nuclear Medicine

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Abstract. In nuclear medicine and particularly in internal radiotherapy, one of the major challenges is to determine the dose for each patient. Current internal dosimetric estimations are based on the Medical Internal Radiation Dose (MIRD) formalism and use standard mathematical models. These standard models are often far from a given patient morphology and do not allow to perform patient-specific dosimetry. Therefore, the Laboratory of Internal Dose Assessment of IRSN has developed an innovative software named OEDIPE, French acronym for “tool for personalised internal dose assessment”, in collaboration with the French institute of health and medical research of Nantes (U892). This software is a user-friendly graphical interface that takes into account specific patient parameters. Indeed, it allows the creation of voxel phantoms based on the patient anatomical image and directly prepares the MCNPX input file suitable for dose calculations. Radionuclides can be distributed at the organ and voxel scale, using cumulated activities based on tomographic images. Absorbed dose calculation can also be performed at these scales, in allowing notably the visualisation of superimposed isodose curves and anatomical images. It could also take into account the temporal distribution of radiopharmaceuticals within the body. OEDIPE has already been validated by comparison either with others codes and with experimental data. The study presented here is a first approach in internal radiotherapy. It deals with a personalised dose calculation carried out for the treatment of hepatocellular carcinoma. Thus, as a result of its flexibility in accommodating complex geometry, the method developed not only represents a diagnostic tool, but also opens up exciting new possibilities such as the optimisation of protocols, in nuclear medicine and in particular in targeted radiotherapy.

KEYWORDS: internal dosimetry; personalised dose; Monte Carlo; voxel phantoms; nuclear medicine.

1. Introduction

In the field of nuclear medicine, the dosimetric studies are essential. On the first hand, in radiological protection, they allow the evaluation of the risk associated with the contamination of the different healthy tissues and to take appropriate medical decisions. On the other hand, in radiotherapy, they can allow the optimisation of the standard treatment in assessing accurate dose values, specific to each patient.

Currently, the dose calculations are based on the Medical Internal Radiation Dose (MIRD) formalism and on the use of mathematical phantoms [1]. However, these phantoms are more or less representative of the human anatomy. It is therefore all the more important to go further in the realisation of studies more realistic and more personalised.

To meet these needs, tools using Monte Carlo computing techniques associated with numerical phantoms are very powerful since they offer the possibility to simulate faithfully and precisely a given situation for dose calculations. Therefore, the OEDIPE software was developed. The originality of the tool is its possibility to reconstruct personalised numerical phantoms issued from medical images, to generate automatically the Monte Carlo input file modelling the studied situation and to visualise easily the results obtained by the calculation.

To validate the software, previous studies comparing OEDIPE with other codes were realised and they have shown very satisfying results:

(i) comparison via OEDIPE of the MCNPX code with the EGS4 [2] Monte Carlo code for an identical geometry corresponding to a realistic case of treatment of medullary thyroid cancer [3];

(ii) comparison via OEDIPE of the MCNPX code with the GSF [4] Monte Carlo code [5];

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(iii) comparison of the OEDIPE interface with the SCMS software developed by Yoriyaz [6] and based on the MCNP4B Monte Carlo code [7], similar to the MCNPX code [5];
(iv) comparison of the OEDIPE interface with the MIRDOSE3 [8] software [9].

An other validation was realised by comparing simulated results using OEDIPE to experimental measurements obtained with thermoluminescent dosimeters threads [10]. To that aim, a radioactive sphere simulating a tumour was placed in the liver of the Liqui-Phil\textsuperscript{TM} phantom, which is a physical phantom representing a human thorax. The liver and the sphere were filled by \textsuperscript{131}I with activities of 78.5 and 256 MBq respectively, simulating a fixation of the radiopharmaceutical more important in the tumour. Three thermoluminescent dosimeters threads were placed here and there of the tumoral sphere. The experiment was then modelled using OEDIPE : the voxelised phantom was created from CT images of the Liqui-Phil\textsuperscript{TM} phantom, the sources were defined and the simulations were done by MCNPX. The comparison of the simulated mean absorbed doses and the mean doses values measured by the three dosimeters threads shows close results, the ratio measured on simulated being between 0.93 and 1.1.

The study presented here is the first application realised using OEDIPE in targeted radiotherapy. The personalised dose calculations realised at the organ and at the voxel level were achieved in collaboration with the regional center of fight against cancer of Rennes (France) and was dedicated to the treatment of the hepatocellular carcinoma.

2. Materials and methods

2.1 The OEDIPE software

OEDIPE, French acronym for “tool for internal personalised dose assessment”, is a user-friendly graphical interface developed in IDL\textsuperscript{®} language. This software associates the specific anatomical data of the considered persons (morphology, composition and density of the tissues) issued from Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) images to the Monte Carlo code MCNPX. The general principle of OEDIPE is presented in figure 1.

**Figure 1:** The OEDIPE software principle: 1 Input of the data required for the simulation (phantom, source(s), detector(s)), 2 Automatic creation of the MCNPX input file, 3 MCNPX calculation, 4 Treatment of the relevant data of the MCNPX output file, 5 Visualisation of the results (absorbed dose or energy spectrum)
For the dose assessment, the different features of the software are defined according to the following step:

- Importation of data obtained from the CT or MRI images of the patient and automatic creation of the corresponding voxelised phantom, in which are defined the organs and their densities. The segmentation (i.e. organ’s delineation) can be performed either using OEDIPE or using external tools such as Isogray™, the outlines being then possibly imported into the software;
- Definition of the sources (type of sources, type of radionuclides, activity);
- Automatic creation of the MCNPX input file;
- Process of the MCNPX output file providing mean doses to the organs or the doses at the voxel level, the isodoses being superimposed to the anatomical images.

The source repartition can be considered in OEDIPE either as punctual or as homogeneously distributed over one or various organs. The user can also choose an inhomogeneous source repartition at the voxel level with the use of cumulated activity matrix issued from Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) images. Since recently, it is also possible to attribute the distribution of activity of the radiopharmaceuticals over the time in the different organs derived from the biokinetic models of ICRP Publication 53 and 80 [11, 12].

MCNPX (MCNP eXtended) is a multi-particle, all-energy (keV-TeV) Monte Carlo general purpose transport code from Los Alamos National Laboratory [13]. The latest improvements of the code enable a more efficient particle tracking in voxels. Phantom geometry was defined using the repeated structural feature of the code [14].

2.2 The personalised dose assessment for the treatment of the hepatocellular carcinoma

2.2.1 Clinical data

The hepatocellular carcinoma is a quite frequent cancer. It is at the fifth rank with about 437000 new cases per year in the world and its incidence is increasing in several countries, mainly due to the increase of the chronic hepatitis C. Moreover, the prognosis of this cancer is poor, the ratio mortality/incidence being around 1, which means that once the diagnostic is done, the majority of the patients will die in the year [15]. Three types of treatments are considered: the resection, the transplantation and the percutaneous destruction. The evidence of interest of these treatments is week [16]. The transplantation can be curative but the contraindications (age, physiological state) and the shortage of transplant limit the indications. Because of the increase of the waiting period before transplantation, during which tumors are likely to extend, a “waiting” treatment is needed. One treatment proposed to limit the tumoral progression is the hepatic intra-arterial injection of lipiodol labelled with iodine.

2.2.2 Lipiodol characteristics

The lipiodol is the vector for iodine 131. The radiopharmaceutical resulting for the labelling by iodine 131 is named Lipiocis™ (Cis Bio International). The particularity of the lipiodol is that it follows the arterial flux, is distributed mainly in the tumoral formations and stay there during a long period (several months). This is explained by the fact that the hepatocellular carcinoma is a hypervascularised tumour. The intra-arterial injection of Lipiocis™ is thus a treatment of targeted radiotherapy by locoregional application.

- About 75% of the injected Lipiocis™ stay at the hepatic level; the rest being found at the pulmonary level. The retention outside these two areas is minimal [17].
- At the hepatic level, the fixation ratio tumour/liver is variable according to patients, mostly superior to 5. This ratio increase over the time, the clearance at the liver level being relatively slow.
- The parameters stay stable after a second injection, showing the absence of saturation of the fixation and therefore allow considering repeated injections.

The injected activity is the same for each patients whatever the size of the tumour and the number of injections (between two and five) are: 2,2 GBq (60 mCi). This leads in some patients to a sub-dosage
in the tumour, that doesn’t allow an efficient treatment. Moreover, pneumopathies appears in 2% of
the patients, 50% being lethal, what could be due to an over-dosage in the lungs.

2.2.3 Quantification protocol

A single photon emission computed tomography (SPECT) imaging session was realised for two
patients, 7 days after the injection (J_7) of Lipiocis™. The acquisitions were achieved with a Millenium
VG camera (commercialised by GEMC) option Hawkeye. The projections were acquired during
the session and saved in a 128*128 matrix, the field of view including the liver and the lungs. These
projections were then reconstructed to obtain the image in 3 dimensions. Moreover, a CT scan was
realised.

The region of interest corresponding to the source regions (tumour, healthy liver, left and right lungs)
were visually assessed on the SPECT images corrected from the attenuation and the diffusion. The
activity of these regions is determined from the number of detected events, corrected from the dead
time and a sensibility factor obtained experimentally using an elliptical physical phantom. The
activities present at the time of injection (J_0) were calculated following the equation:

\[ A_0 = A_T \exp(\ln(2)t/T_{eff}) \]

where \( A_0 \) and \( A_T \) are the activities (MBq) calculated in the source regions at \( J_0 \) and \( J_7 \) respectively, \( t \) is
the delay between the injection and the acquisition of the images (7 days) and \( T_{eff} \) is the effective
period of the tracer for the considered organ (days).

The effective periods used were taken from the literature [17, 18]:
- 4.7 days for the tumoral liver;
- 3.8 days for the healthy liver;
- 4.85 days for the lungs.

The cumulated activities during the time of irradiation were calculated following the equation:

\[ \tilde{A} = \int_0^\infty A_n(t)dt = A_0 \int_0^\infty \exp(-\ln(2)t/T_{eff})dt = A_0 T_{eff}/\ln 2 \]

2.2.4 Voxelized phantom creation

The phantom geometries were realised from the CT images using OEDIPE. The matrixes of
128*128*128 voxels of 4.42 mm³ initially obtained were reduced in eliminating automatically the
unneeded air voxels. The reduced matrixes were then of 102*58*90 and 102*55*90 voxels for the
patient 1 and 2 respectively. The air, the lungs, the bone and the soft tissues were automatically
segmented while the liver and the tumour were manually segmented. The left and right lungs were
manually separated. The densities and compositions were associated to the different tissues using the
data issued from the ICRU report 44 [19].

2.2.4 Dose calculation

For each simulation, all the emissions of the iodine 131 were simulated (electrons, \( \beta \) et \( \gamma \)) from the
data of the ICRP 38 [20]. As a first step, the mean absorbed doses were calculated in the organs and
tissues (tumour, liver, left and right lungs, soft tissues and bone) for the two patients with a statistical
uncertainty less than 2%. To that aim, 100000 particles were simulated. As a second step, to calculate
the spatial distributions of doses at the voxel level, 100 million of particles were simulated.

3. Results

The cumulated activities calculated for two patients were quite different (Table 1). The specificity of
the targeting was notably better for the patient 1 than for the patient 2. The patient 2 had a fixation
abnormally high in the left lung due to a malformation of the hepatic artery.
Table 1: Cumulated activities (MBq.s) determined in the tumour, the healthy liver and the lungs of two patients using SPECT images.

<table>
<thead>
<tr>
<th>Sources organs</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>$3.64 \times 10^8$</td>
<td>$2.83 \times 10^8$</td>
</tr>
<tr>
<td>Healthy liver</td>
<td>$5.40 \times 10^7$</td>
<td>$3.83 \times 10^8$</td>
</tr>
<tr>
<td>Right lung</td>
<td>$2.54 \times 10^7$</td>
<td>$8.71 \times 10^7$</td>
</tr>
<tr>
<td>Left lung</td>
<td>$1.27 \times 10^7$</td>
<td>$2.06 \times 10^8$</td>
</tr>
<tr>
<td>Total cumulated activity</td>
<td>$9.42 \times 10^8$</td>
<td>$9.58 \times 10^8$</td>
</tr>
</tbody>
</table>

Table 2 shows the results obtained for the mean absorbed doses calculated for the two patients. A significant variation is found between the absorbed doses in the left and right lungs of the patients. Thus, the patient 2 presents an absorbed dose of 18.8 Gy in the left lung. This value is relatively high and comes close to the dose limit in the lungs fixed for an external irradiation (20 Gy).

Table 2: Mean absorbed doses (Gy) in different target organs of the two patients calculated using OEDIPE.

<table>
<thead>
<tr>
<th>Organs/Tissues</th>
<th>Patient 1 (Gy)</th>
<th>Patient 2 (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>0.56</td>
<td>0.93</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>0.62</td>
<td>0.69</td>
</tr>
<tr>
<td>Right lung</td>
<td>2.89</td>
<td>7.80</td>
</tr>
<tr>
<td>Left lung</td>
<td>1.49</td>
<td>18.80</td>
</tr>
<tr>
<td>Liver</td>
<td>18.97</td>
<td>11.36</td>
</tr>
<tr>
<td>Tumour</td>
<td>476.55</td>
<td>461.78</td>
</tr>
</tbody>
</table>

The doses to the organs being an insufficient information since it is a mean dose, that it does not allow to detect the area of over- or sub-dosage and to link the dose to the effects of the treatment, the doses to the voxel level were also determined for the two patients. The results are presented as isodoses superimposed to the segmented anatomical images of the patient 1 and 2 (figures 2 and 3). The personalised dosimetry at this scale allows to obtain spatial dose distribution into the organs and tissues and bring more information.

Figure 2: Spatial dose distribution with isodoses superimposed to the segmented anatomical images of the patient 1
4. Conclusion

The OEDIPE software was validated either by comparisons with other codes (EGS4, GSF) or softwares (MIRDOSE3, SCMS) either by comparisons with experimental data. These studies have demonstrated the advantages and the potential of the tool in nuclear medicine. Bolstered by these results, the first application in targeted radiotherapy presented in this article was achieved. It has enabled to establish concretely the protocol to be adopted and how the results can be processed. This application has also underlined the interest of the personalisation of the dose assessment. Finally, in achieving for an important number of patients a personalised dose calculation at the voxel level, enough relevant data could be collected, in order to establish a link between the dose and the effects of the treatment.

Nevertheless, a limited point can be highlighted through this example. Indeed, to obtain accurate cumulated activities during the irradiation period and therefore effective periods specific to the patient, an important number of SPECT/CT images should be realised. However, for practical reasons and the health status of patients, it is often difficult to have more than three or four imaging sessions. Thus, a compromise could be found in using, in addition, the biokinetics of the radiopharmaceuticals issued from the ICRP Publication 53 and 80 [11, 12], recently integrated into OEDIPE.

For all these aspects, OEDIPE provides an attractive and powerful alternative to calculate accurate and personalised doses to patients. Moreover, this methodology can be used to address a wide range of issues relevant to the dose calculation optimisation, particularly for radiological protection and internal radiotherapy.

REFERENCES