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ARTICLE

OEDIPE, a software for personalized Monte Carlo dosimetry and treatment planning optimization in nuclear medicine: absorbed dose and biologically effective dose considerations

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Abstract – For targeted radionuclide therapies, treatment planning usually consists of the administration of standard activities without accounting for the patient-specific activity distribution, pharmacokinetics and dosimetry to organs at risk. The OEDIPE software is a user-friendly interface which has an automation level suitable for performing personalized Monte Carlo 3D dosimetry for diagnostic and therapeutic radionuclide administrations. Mean absorbed doses to regions of interest (ROIs), isodose curves superimposed on a personalized anatomical model of the patient and dose-volume histograms can be extracted from the absorbed dose 3D distribution. Moreover, to account for the differences in radiosensitivity between tumoral and healthy tissues, additional functionalities have been implemented to calculate the 3D distribution of the biologically effective dose (BED), mean BEDs to ROIs, isoBED curves and BED-volume histograms along with the Equivalent Uniform Biologically Effective Dose (EUD) to ROIs. Finally, optimization tools are available for treatment planning optimization using either the absorbed dose or BED distributions. These tools enable one to calculate the maximal injectable activity which meets tolerance criteria to organs at risk for a chosen fractionation protocol. This paper describes the functionalities available in the latest version of the OEDIPE software to perform personalized Monte Carlo dosimetry and treatment planning optimization in targeted radionuclide therapies.

Keywords: OEDIPE / nuclear medicine / dosimetry / radiobiology / treatment planning

1 Introduction

For decades, targeted radionuclide therapies mostly consisted of the use of ^{131}I for thyroid pathologies. Recently, new radiopharmaceuticals have been introduced in clinics to treat different types of cancer (EANM, 2013). Their design relies on specific vectors, such as peptide receptors, hormones or antibodies, and radionuclides, selected depending on their linear energy transfer, relative biological effectiveness and chemical properties. Associated clinical trials are designed on the same model as those conducted for chemotherapy (Glatting *et al.*, 2013). Standard amounts of activities are administered and increased progressively to test for possible limiting toxicity. The recommended administered activity is derived from these mean outcomes and eventually adjusted depending on patient-specific parameters, such as the patient's weight.

Because of the substantial uptake of ^{131}I by the thyroid gland, this methodology has led to the high efficacy of treatments for thyroid pathologies with low or no toxicity. However, the targeting of tumor cells by new radiopharmaceuticals is much more complex, and their distribution and biokinetics are potentially highly patient-specific (EANM, 2013). Because biological effects, both in terms of response and toxicity, are primarily dependent on absorbed doses delivered to tissues rather than on the administered activity (EANM, 2013), highly personalized techniques estimating absorbed doses delivered to healthy tissues are crucial. These estimations solely can ensure that healthy tissue irradiation will not lead to unacceptable toxicity, and enable treatment planning optimization by the calculation of the maximal activity that could be administered to each specific patient. This concept was specifically highlighted in the 2013/59/EURATOM directive from the Council of the European Union (CEU, 2013). Furthermore, beyond treatment planning optimization, an accurate knowledge of absorbed doses delivered to targeted and non-targeted tissues is essential to establish dose-effect relationships in terms of efficacy and toxicity.

Over the years, different methods have been developed for dosimetry in nuclear medicine. According to the MIRD formalism (Bolch *et al.*, 2009), absorbed doses are determined

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from the cumulated activity and S-factors, which are dependent on the geometry (standard or patient-specific) and radiotracer properties (radionuclide, physical and biological half-lives, residence times). Basic methods consist of the use of standard S-factors considering homogeneous activity distributions in each region of interest (ROI). These methods are thus limited as they do not account for the patient-specific anatomy, tumoral lesions specificities and activity distribution heterogeneity.

Nowadays, thanks to 3D medical imaging advances and increasing computational power, CT or MRI data can be used to model the patient's anatomy using patient-specific voxel phantoms. Moreover, the patient-specific activity distribution can be described from single-photon emission computed tomography (SPECT) or positron emission tomography (PET) data which enable one to account for its heterogeneity. Finally, the pharmacokinetics can be accounted for using either a kinetic model with parameters obtained from blood, urine or feces sampling or a biokinetic model established from serial emission data. The introduction of more accurate methods for dosimetry, such as dose kernel methods or direct Monte Carlo calculations (Bolch *et al.*, 1999; Sgouros *et al.*, 2004; Petitguillaume *et al.*, 2014), has followed from these technological advances. Additionally, to improve tumor control while preserving healthy tissues, the notion of Biological Effective Dose (BED) (Dale, 1985) was introduced to establish fractionation strategies in external beam radiation therapies (EBRT). These radiobiological considerations, which enable one to take advantage of the differences in radiosensitivities and repair time constants between tumoral and healthy tissues, have been shown to be of interest to increase treatment efficacy while keeping a constant incidence and severity of toxicity (RCR, 2006). Recently, growing interest has been shown in radiobiological aspects involved in targeted radionuclide therapies (Sgouros *et al.*, 2004; Cremonesi *et al.*, 2008) because of their potential added value in improving the risk-to-benefit balance. Furthermore, the notion of Equivalent Uniform Biologically Effective Dose (EUD) (O'Donoghue, 1999) was introduced as a useful quantity to compare heterogeneous absorbed dose distributions with a homogeneous distribution that would have the same biological effects. The EUD can thus be used to assess the levels of potential toxicity and tumor control related to a given absorbed dose distribution (Wu *et al.*, 2002) using, for example, the normal tissue complication probability (NTCP) and tumor control probability (TCP) models.

However, up to now, all these advanced techniques and concepts have been, in the majority, only used for research-oriented projects. The development of the OEDIPE software, a French acronym for "tool for personalized internal dose assessment", was carried out to both pursue research projects and provide a user-friendly dosimetry and treatment planning tool for nuclear medicine clinical applications. OEDIPE development was initiated at the French Institute for Radiation Protection and Nuclear Safety (IRSN) for *in vivo* measurement calibration and internal contamination dosimetry using direct Monte Carlo calculations (Franck *et al.*, 2001; de Carlan *et al.*, 2003). It was then continued to perform dosimetry for nuclear medicine applications from patient-specific voxelized geometry and estimated cumulated activity distribution (Chiavassa *et al.*, 2006). Recently, OEDIPE was further developed to automatically derive the 3D activity distribution from emission images registered on the patient-specific geometry. Additional tools were also implemented to provide the maximal injectable activity (MIA) that could be administered to the patient according to tolerance criteria for organs at risk (OARs), either for mean absorbed doses, dose-volume fractions or maximal absorbed doses (Petitguillaume *et al.*, 2014). Finally, an additional module was developed to calculate the 3D distribution of the BED and EUD to ROIs. A specific optimization tool was also implemented to calculate the MIA for fractionated protocols. The aim of this article is to present the functionalities which are available in this latest version of OEDIPE.

2 Materials and methods

OEDIPE is a user-friendly graphical user interface (GUI), developed in Interactive Data Language (ITT Visual Information Solutions, Boulder, Colorado). Figure 1 describes the general principle of the 3D personalized Monte Carlo dosimetry method. First, ROI outlines, drawn on the patient anatomical images, and registered emission (SPECT or PET) data are directly imported into OEDIPE to define the patient's anatomy and cumulated activity distribution, respectively. These data are then used in OEDIPE, along with radionuclide properties, to generate the input file for the MCNPX Monte Carlo transport code. OEDIPE is finally used to process the MCNPX output file. Specific features of the OEDIPE software are further described in the following paragraphs of this section.

2.1 Geometry definition

Patient-specific voxel phantoms can be created from the patient CT or MRI data using OEDIPE. To create these phantoms, the first method consists of direct segmentation based on thresholds defined in Hounsfield unit values. Otherwise, ROI outlines, generated using external software, can be imported in RTSTRUCT format (Isogray®, Hermes®, Pinnacle®, Integrated Registration®, etc.), .aql format (Aquilab®) or Dosigray format (Dosigray®). Once generated, the voxel phantom is displayed on the phantom viewer interface, presented in Figure 2. This phantom can then be modified using several tools, such as air removal, resizing or fusion of ROIs. Finally, specific materials, defined in terms of density and elemental compositions, can be attributed to each ROI from a database which can be modified by the user.

2.2 Radioactive source definition

Nuclear decay data are directly available in OEDIPE using a database containing 246 radionuclides described in ICRP publication 38 (ICRP, 1993). The radioactive source is then defined either as homogeneous sources located in specific ROIs or as a heterogeneous 3D distribution. For homogeneous sources, the definition of a source only requires one to specify the ROI where it is located, the radionuclide and its cumulated activity, expressed in terms of cumulated disintegrations

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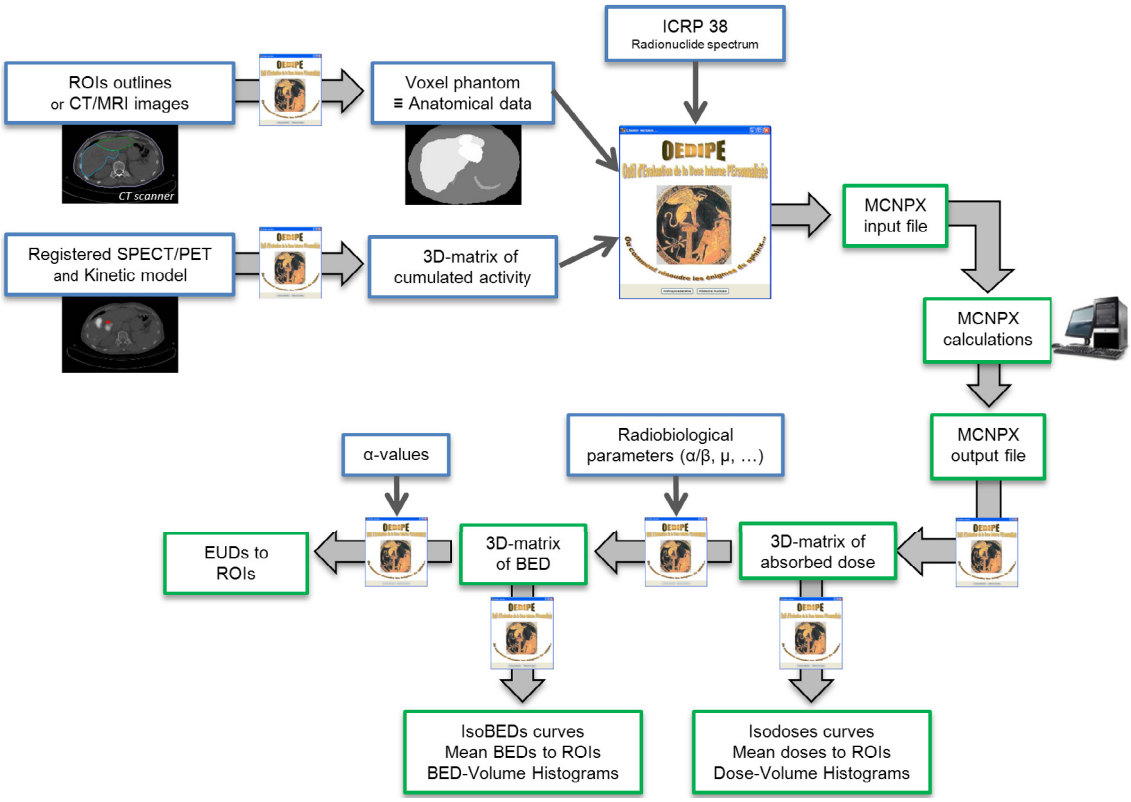

Fig. 1. General principle of 3D personalized Monte Carlo dosimetry using OEDIPE software.

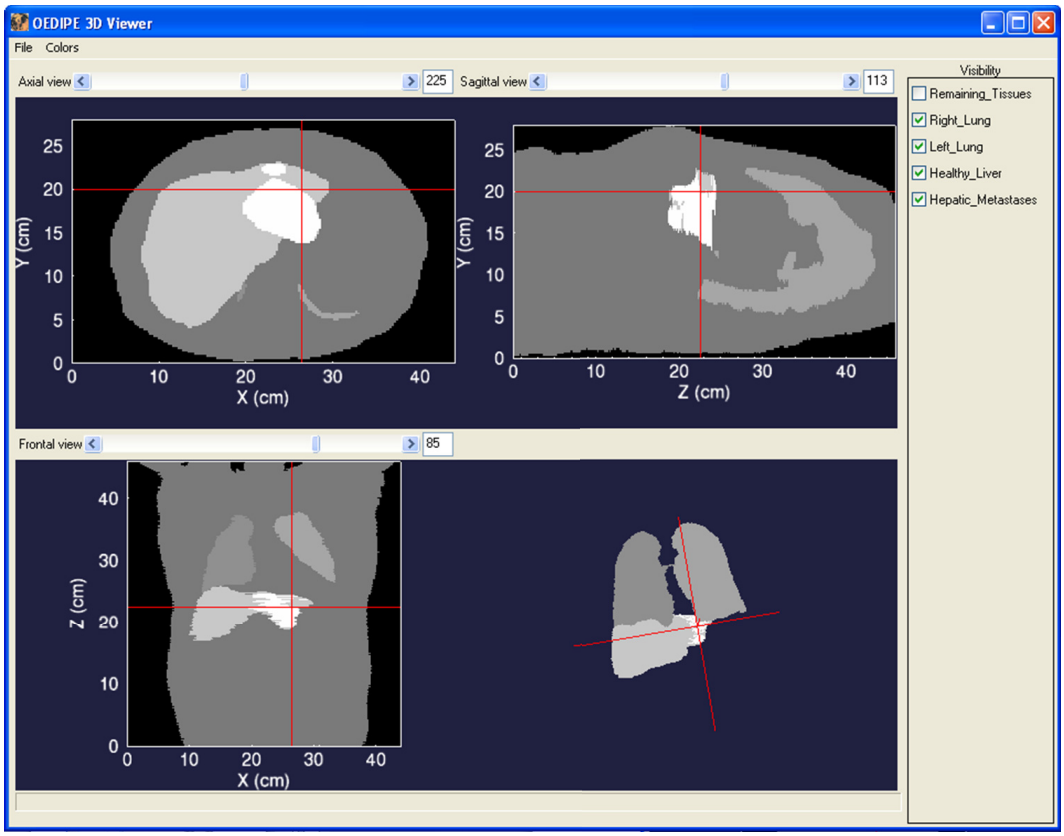

Fig. 2. Phantom viewer interface with control tools for the display of the voxel phantom.

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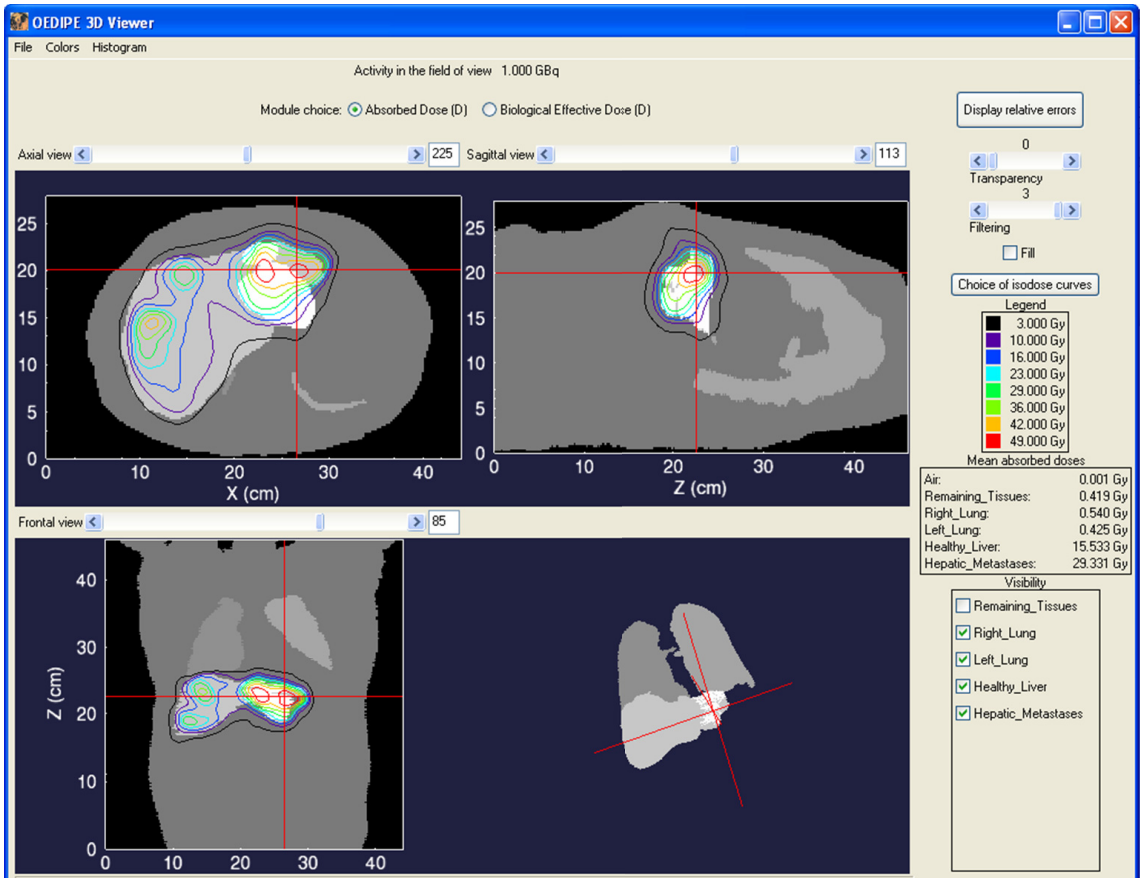

Fig. 3. 3D viewer interface for the display of isodose or isoBED curves superimposed on the voxel phantom.

occurring in the ROI over a given time period. A heterogeneous 3D distribution is defined as a 3D matrix of cumulated activity. Counts in each voxel can be obtained from emission data (SPECT or PET) using two methods. First, emission data can be registered beforehand, with external software, on the anatomical images used to create the patient-specific voxel phantom and then uploaded into OEDIPE in DICOM format. Second, emission data can be registered using OEDIPE's registration module, which has been developed for rigid registration of SPECT/CT or PET/CT data on a CT or MRI scan. The radionuclide and either the activity in the field of view or a conversion factor must then be keyed in to convert counts into cumulated activity over an infinite period of time expressed in terms of cumulated disintegrations occurring in each voxel. Finally, cumulated activities in specific ROIs can be removed depending on the user's intent.

2.3 MCNPX input file generation

After the definition of the geometry and the source distribution, the last parameters that have to be defined are the types of results which are expected from the MCNPX calculations, *i.e.* mean absorbed doses to ROIs or absorbed doses to each voxel, and the total number of histories to simulate. The MCNPX input file is finally generated from the geometry, the source distribution and these last parameters.

2.4 Voxel absorbed doses

At the end of the Monte Carlo simulations, the MCNPX output file is processed using OEDIPE to get either mean absorbed doses to ROIs or absorbed doses on the voxel scale. By default, these results are related to the cumulated activity over an infinite period of time for the specified activity in the field of view. If absorbed doses on the voxel scale have been extracted, a 3D viewer interface, presented in Figure 3, is generated to display isodose curves superimposed on the voxel phantom along with mean absorbed doses to ROIs. Furthermore, control tools enable one to choose the number and values of isodose curves and to adjust their smoothing, filling or transparency level.

2.5 Voxel biologically effective doses (BEDs)

On the 3D viewer, the user can select the radiobiological module. For the time being, BEDs on the voxel scale can be calculated in the case of a protracted irradiation with a decaying source in the absence of washout; the source decay is thus only related to the isotope radioactive decay. When switching to this module, the user will be allowed to set, for each ROI, tissue-specific radiobiological parameters, such as the α/β ratio and the sub-lethal damage repair period (T_p). The 3D distribution of BEDs can then be calculated from the absorbed dose

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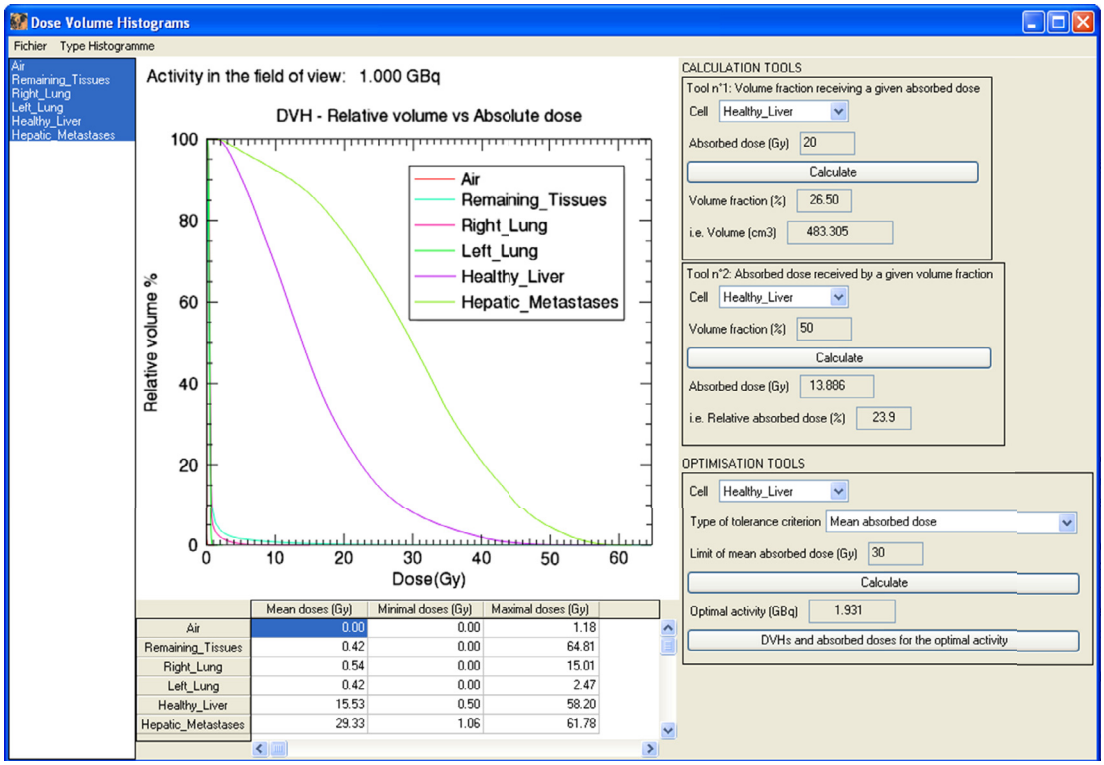

Fig. 4. Histogram viewer interface with optimization tools for the display of DVHs and BVHs.

distribution using either equation 1 or 2 (Dale, 1985) depending on whether the user wants to define a specific duration of irradiation T or to consider an infinite treatment time, *i.e.* as long as the activity is present in the body. If the duration T is at least ten-fold the radioactive decay half-life, equation (1) can be approximated with equation (2). In these equations, D is the voxel absorbed dose in Gy, λ is the radioactive decay constant in s^{-1}, μ is the repair constant in s^{-1} defined as $\mu = \ln(2)/T_p$, α is the radiosensitivity per unit dose in Gy^{-1}, β is the radiosensitivity per unit square dose in Gy^{-2} and T is the treatment time in s.

$$BED_T = D \times \left[1 + \frac{2D\lambda^2}{\mu - \lambda}\left(\frac{\beta}{\alpha}\right) \times \frac{\frac{1}{2\lambda}\left[1 - e^{-2\lambda T}\right] - \frac{1}{\mu+\lambda}\left[1 - e^{-T(\mu+\lambda)}\right]}{1 - e^{-\lambda T}} \right] \quad (1)$$

$$BED_\infty = D \times \left[1 + \frac{D\lambda}{\mu + \lambda}\left(\frac{\beta}{\alpha}\right) \right]. \quad (2)$$

The 3D viewer (Fig. 3) is then updated to display isoBED curves superimposed on the voxel phantom along with mean BEDs to ROIs.

2.6 Dose- and BED-Volume Histograms

Cumulative dose-volume histograms (DVHs) or BED-volume histograms (BVHs) can be obtained depending on whether absorbed doses or BEDs are displayed on the 3D viewer. These histograms, along with mean, minimum and maximum absorbed doses or BEDs to ROIs, are displayed on the histogram viewer interface, presented in Figure 4. The user can select the ROIs for which plots will be displayed and whether absolute or relative quantities should be plotted. Plot formats can be modified by the user before being saved as pictures using standard file formats. A text file containing the mean, minimum and maximum values of absorbed doses or BEDs to ROIs can also be exported.

2.7 Equivalent Uniform Biologically Effective Dose (EUD)

The EUD can be calculated from the BVH viewer interface. The EUD is calculated using equation (3) (O'Donoghue, 1999), where α is the radiosensitivity per unit dose in Gy^{-1}, Ψ is the BED distribution and $P(\Psi)$ is the probability density function of the BED. α-values for each ROI are set by the user and differential BVHs, calculated from the cumulative BVHs, are normalized to get the probability density function $P(\Psi)$. The EUD is finally calculated for each ROI.

$$EUD = -\frac{1}{\alpha}\ln\left(\int_0^\infty P(\Psi)\, e^{-\alpha\Psi} d\Psi\right). \quad (3)$$

2.8 Treatment planning optimization tools

OEDIPE can be used for treatment planning optimization using tools available from the histogram viewer (Fig. 4) for both the absorbed dose (D) and BED modules. Specific tools

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enable one to calculate either the volume fraction of a ROI receiving a given dose (D or BED) or the dose received by a given ROI fraction. Optimization tools can be used to calculate the MIA that meets a tolerance criterion for a ROI. For both modules, the tolerance criterion can be defined on the mean dose, on the volume fraction receiving a given dose or on the maximal dose; an example is presented in Figure 4 for the calculation of the MIA related to a mean absorbed dose to healthy liver which should not exceed 30 Gy. Tolerance criteria defined on the volume fraction will be of interest for organs with a "parallel" architecture, such as the liver or lungs, whereas those defined on the maximal dose will be of interest for organs with a "serial" structure, such as the spinal cord (SFRO, 2007). For the radiobiological module, as the BED is not proportional to the injected activity, a dichotomy algorithm is used which stops when the tolerance criterion is met with an error inferior to the accepted error keyed in by the user. Furthermore, to study fractionation protocols, an additional option was developed to calculate the MIA for a tolerance criterion and a fractionation protocol defined as a number of fractions and the distribution of the total activity among these fractions. The user can then either choose a protocol with time delays between fractions of at least ten-fold the radioactive decay half-life or define specific time delays. In the second case, the BED distribution is calculated using equation (1) for each fraction and considering both the residual activity from the previous fractions and the additional activity of the new fraction. However, for the irradiation delivered after the last administered fraction, the BED distribution is calculated using equation (2). Once the MIA has been calculated, DVHs and BVHs can be obtained and displayed, along with mean, minimum and maximum absorbed doses and BEDs, for this optimal activity and the specified fractionation protocol. Finally, EUDs can also be calculated; the total EUD for fractionated protocols being equal to the sum of EUDs delivered by each individual fraction.

3 Results and discussion

In nuclear medicine, OEDIPE has been used for both diagnostic and therapeutic applications. Up to now, the main purpose of the studies conducted was either dosimetry or treatment planning optimization. In terms of dosimetry, absorbed doses delivered by commonly used diagnostic radiopharmaceuticals for the latest ICRP reference computational phantoms (Hadid *et al.*, 2013) were calculated using OEDIPE. A personalized Monte Carlo dosimetry was then performed for knee treatments with ^{90}Y-synovectomy (O'Doherty *et al.*, 2014). The results were used to evaluate the performance of other methods, such as OLINDA and dose-kernel techniques, for these treatments. Furthermore, OEDIPE was used to study the potential of personalized Monte Carlo dosimetry for treatment planning optimization in selective internal radiation therapies (SIRT) (Petitguillaume *et al.*, 2014). In this specific context, predictive dosimetry was performed from ^{99m}Tc-MAA evaluations and used to calculate the MIA with different tolerance criteria on OARs. In particular, the availability of a tridimensional distribution of absorbed doses allowed considering tolerance criteria defined on DVHs; these criteria being of interest to take advantage of the parallel characteristics of the OARs, *i.e.* the lungs and nontumoral liver in SIRT. Considering the computational time, the automation of several steps in OEDIPE and the time delay between the ^{99m}Tc-MAA evaluation and the ^{90}Y-microsphere treatment, the discussed methodology would be compatible with the specific treatment workflow and thus applicable in clinical routine for treatment planning in SIRT. Furthermore, the potential added value of personalized Monte Carlo dosimetry integrating the evaluation step and treatment planning optimization in targeted radionuclide therapy was confirmed.

The OEDIPE radiobiological module will be of interest to establish BED-effect relationships with pertinent values of radiobiological parameters from clinical outcomes in targeted radionuclide therapies. Moreover, both treatment planning optimization and treatment evaluation in targeted radionuclide therapies will be achievable using OEDIPE. In terms of treatment planning optimization, the availability of the BED distribution and the associated EUD will enable one to calculate the MIA according to BED-based tolerance criteria. In such a way, it will also be possible to compare potential biological effects resulting from different therapeutic options, such as EBRT, brachytherapy or other fractionation protocols.

4 Conclusion

The OEDIPE software is a user-friendly interface with an automation level suitable for personalized Monte Carlo dosimetry for nuclear medicine applications in clinics. For targeted radionuclide therapies, this advanced dosimetry can be used for both treatment planning and treatment efficacy evaluation. Specific tools are available to define the anatomy and the activity distribution for direct Monte Carlo calculations of the absorbed dose distribution. A new module has been implemented to calculate the biologically effective dose (BED) distribution and the equivalent uniform biologically effective doses (EUDs) to ROIs. Optimization tools are available, as a help for treatment planning optimization, to calculate the maximal injectable activity that could be administered to the patient while still meeting tolerance criteria on organs at risk (OARs). These tools can be used to design fractionation protocols and evaluate them in terms of the mean BED and EUD to OARs and tumoral lesions. Further improvements are ongoing to automatically model the patient-specific biokinetics from serial emission data.

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