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Abstract

The GATE 6.1 Monte Carlo simulation platform based on the GEANT4 toolkit is in constant improvement for dosimetric calculations. Here, we explore its use for calculating internal absorbed dose distribution in mice for the treatment of malignant melanoma after injection of a new specific radiopharmaceutical labeled with iodine 131. We estimate the dosimetric accuracy of GATE 6.1, by calculating first S values and by comparing them and absorbed doses to organswith EGSnrc for a digital mouse phantom and a CT scan based mouse phantom.

1. Introduction

GATE 6.1 [Jan et al 2004, Jan et al 2011] is a Monte Carlo simulation platform which makes use of GEANT4 version 9.4 [Agostinelli et al 1993, GEANT4 2010]. Through a user-friendly interface without the complexity of GEANT4, GATE offers now a diversity of tools dedicated to radiotherapy: geometry and source modeling, time dependence management, use of recent GEANT4 models and processes. Nevertheless, GATE hasn't been used widespread for nuclear medicine therapy but much more in the field of small animal nuclear medicine imaging and quantification. In a previous paper, we have validated GATE making use of GEANT4 version 9.4 Standard Electromagnetic Physics Package for the production of accurate dose distributions using monoenergetic electrons from 50 keV to 20 MeV in agreement with EGSnrc or MCNP4C [Maigne et al 2011]. Here, we explore its use for targeted radiotherapy using ^{131}I by computing S values on digital and CT scan based mouse phantoms and comparing our results to EGSnrc simulations. Then, these results were applied in a preclinical study involving a new radiolabeled melanin-localizing benzamide, named ICF01012, selected to treat the malignant melanoma [Chezal et al 2008]. ^{131}I-labeled ICF01012 may be effective for therapeutic targeting of melanin-positive melanoma. Before testing this radiopharmaceutical on human, we performed a dosimetric study in mice using the MIRD methodology [Loevinger et al 1991]. S values computed with GATE were combined with pharmacokinetics extracted from [^{125}I]-ICF01012 biodistribution [Chezal et al 2008, Bonnet Duquennoy et al 2009].

2. Materials and Methods

2.1. Monte Carlo codes

2.1.1. GATE

The present work was performed with version 6.1 of the GATE generic Monte Carlo platform. This version of GATE makes use of GEANT4 version 9.4. The GEANT4 Standard Electromagnetic Physics Package which describes electron and photon interactions between 990 eV and 100 TeV, was used in all simulations, taking into account electron impact ionisation, multiple scattering, and bremsstrahlung generation. We implemented these physics processes (Physics List) according to the ElectroMagnetic Physics List Standard option 3which is designed by the GEANT4 collaboration for applications requiring higher accuracy for electrons, hadrons and ions tracking without magnetic fields. The production threshold was set to 2 µm for electrons, positrons and photons.

2.1.2. EGSnrc

Simulations were performed using the EGSnrc C++ class library egspp [Kawrakow et al 2009]. We applied the PRESTA II electron-step algorithm and the EXACT boundary crossing algorithm. The electron and the photon tracking cuts, respectively ECUT and PCUT, were set to 521 keV and 10 keV. Statistical uncertainties were always kept under 2%.

2.2. Monte Carlo simulations set up

2.2.1. Digital mouse phantom

The phantom was the MOBY whole-body mouse representing a 33g, normal 16-week-old male C57BL6 mouse [Segars et al 2004]. The phantom was realized as a three-dimensional, rectangular array of 128×128×450 cubic voxels of 0.25×0.25×0.25 mm^3. It was enhanced by the addition of a spherical structure of 10 mm in diameter representing the melanoma tumor, located on the right side of the mouse and by the addition of two spherical structure of 3.4 mm for both eyes. Densities of four materials were defined : soft tissue (1.0 $g.cm^{-3}$), lung (0.3 $g.cm^{-3}$), bone (1.92 $g.cm^{-3}$) and air (1.25 $mg.cm^{-3}$). Mass of organs of interest were chosen as reported in Table 1.

2.2.2. CT scan based phantom

CT scans of C57BL6 mouse were obtained using an Explore CT 120 MicroCT of General Electrics. A modified Feldkamp's filtered back-projection algorithm was used to reconstruct a 3D volume with 875×875×1041 voxels at an isotropic voxel size of 98.85 µm. We chose CT images 12 hours after injection of [^{131}I]-ICF01012. The ISOgray treatment planning systems was then used to contour organs of interest in the reconstructed CT mouse volume. Tumor, eyes, bones, lung, kidneys, liver and thyroid were contoured. We applied the same densities and atomic compositions for organs as chosen for the MOBY phantom. The mass of organs of interest are listed in Table 1.

Table 1 : Masses of organs of the mouse phantoms considered.

Organs	**Mass MOBY phantom (g)**	**Mass CT scan phantom (g)**
Melanoma	0.20	0.28
Thyroid	0.0005	0.0003
Eyes	0.015	0.014
Liver	0.59	0.58
Kidneys	0.30	0.18
Lungs	0.15	0.12

2.2.3. S values computations

^{131}I decay was simulated by isotropically emitting electrons and photons in organs according to the ^{131}I electron energy spectrum and gamma rays[1]. A total of 25.10^6 particles per organ were simulated to produce dose distributions and compute S values for each organ in the phantom. The statistical relative uncertainty was below 0.2%.

2.3. Quantification of the biodistribution

The goal of the quantification of the distribution is to estimate the cumulated activity of [^{131}I]-ICF01012 for each organ in order to compute absorbed. In this study, the cumulated activity was extracted from [^{125}I]-ICF01012 pharmacokinetics.

2.3.1. Data acquisition of iodine labeled benzamide

^{125}I-labeled ICF01012 radiopharmaceutical biodistribution was tested on ten male black mice C57BL6 of approximately 24 grams (Iffa-Creed, France) bearing melanoma tumors without metastases. The quantification of the activity expressed in kBq/g was carried out using a detector-imaging AMBIS 4000 (Scanalytics, CSPI, San Diego, CA). Seventeen days before administration of the [^{125}I]-ICF01012, melanoma cells were introduced by subcutaneous injection on the side of each mouse. Radiopharmaceutical activity was 1.7 MBq. Two mice were euthanized at 1 hour, 6 hour, 24 hour, 5 days, and 8 days after intravenous administration of [^{125}I]-ICF01012. Sagittal sections of 40 µm were used for measurements of the activity in the following organs from 2 to 20 slices: tumor, eyes, liver, lungs, kidneys and thyroid.

2.3.2. Effective periods and cumulated activity calculations

From [^{125}I]-ICF01012 biodistributions, we determined the initial activity of the radiopharmaceutical by a mono-exponential fit. The effective period of [^{131}I]-ICF01012 was calculated by taking into account the same biological period as [^{125}I]-ICF01012. Then, the cumulated activity of [^{131}I]-ICF01012 was computed for a therapeutic activity of 37 MBq. Table 2 shows the quantities determined for different organs.

Table 2 : ^{131}I biological period (h), ^{131}I effective period (h), ^{125}I initial activity (Bq/kg) and ^{131}I cumulative activity (Bq.s/kg) for melanoma, thyroid, eyes, liver, kidneys and lungs.

Organs	**^{131}I biological period (h)**	**^{131}I effective period (h)**	**^{125}I initial activity (Bq/kg)**	**^{131}I cumulative activity (Bq.s/kg)**
Melanoma	150.6	84.5	$3.61x10^8$	$3.44x10^{15}$
Thyroid	101.9	66.6	$7.49x10^8$	$5.63x10^{15}$
Eyes	273.2	112.9	$4.24x10^8$	$5.40x10^{15}$
Liver	7.6	7.6	$1.77x10^8$	$1.52x10^{14}$
Kidneys	5.1	5.1	$2.12x10^8$	$1.19x10^{14}$
Lungs	4.4	4.4	$1.25x10^8$	$6.19x10^{13}$

3. Results and discussion

3.1. Comparisons of S values

[1] Evaluated Nuclear Structure Data File : http://www.nndc.bnl.gov/useroutput/131i_mird.html

For a given radionuclide, S values depend strongly on the dimension, shape, mass and location of the organs. Table 3 shows the S values computed with GATE 6.1 and EGSnrc. The differences between GATE 6.1 and EGSnrc don't exceed 1.5% except for thyroid and eyes. For small organs, the ranges of emitted electrons are not negligible compared to the dimensions of the organs and the tracking of the particles becomes crucial. The differences observed between the MOBY phantom and the CT scan based phantom are not representative except for thryoid and eyes.

Table 3 : ^{131}I S values for the MOBY phantom and the CT scan based phantom computed with GATE 6.1 and EGSnrc.

Organs	**S value MOBY phantom ($Gy.Bq^{-1}.s^{-1}$)**		**S value CT scan phantom ($Gy.Bq^{-1}.s^{-1}$)**	
	GATE 6.1	**EGSnrc**	**GATE 6.1**	**EGSnrc**
Melanoma	$1.42x10^{-10}$	$1.42x10^{-10}$	$9.97x10^{-11}$	$1.01x10^{-10}$
Thyroid	$2.54x10^{-08}$	$2.61x10^{-08}$	$4.01x10^{-08}$	$4.15x10^{-08}$
Eyes	$1.41x10^{-09}$	$1.45x10^{-09}$	$1.55x10^{-09}$	$1.59x10^{-09}$
Liver	$5.58x10^{-11}$	$5.63x10^{-11}$	$5.57x10^{-11}$	$5.61x10^{-11}$
Kidneys	$8.45x10^{-11}$	$8.49x10^{-11}$	$1.45x10^{-10}$	$1.43x10^{-10}$
Lungs	$1.32x10^{-10}$	$1.34x10^{-10}$	$1.62x10^{-10}$	$1.67x10^{-10}$

3.2. Comparisons between digital and CT scan based dosimetries

The absorbed dose computed from S values and cumulated activity computed from measurements are presented in Figure 1. For clinical purposes, this information is mandatory to establish the relationship between the injected activity of [^{131}I]-ICF01012 and the inhibition of tumoral growth and metastases spread observed for mice.

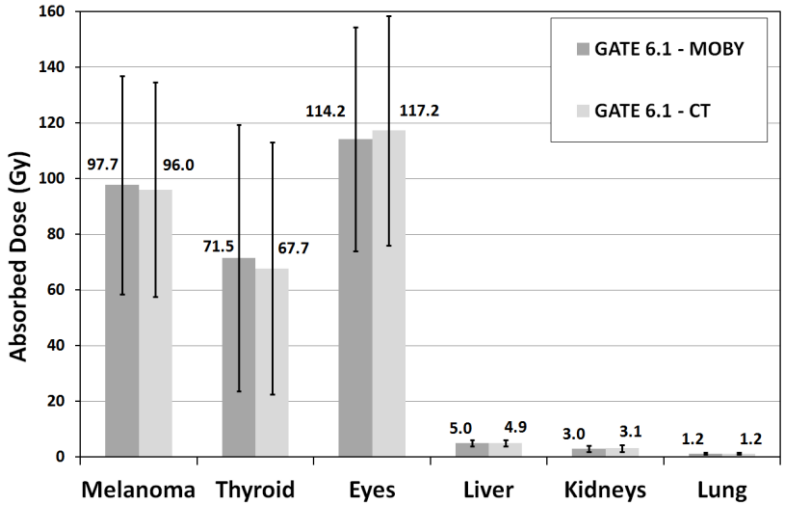

Figure 1 : Comparisons of absorbed dose to organs for the MOBY phantom and the CT scan based phantom, [^{131}I]-ICF01012.

4. Conclusion

In a previous publication, we have validated GATE/GEANT4 for the transport of monoenergetic electrons between 50 keV and 20 MeV. Here, we have shown that in a preclinical context GATE 6.1 (making use of the Standard Electromagnetic Package of GEANT4 9.4) is suitable for targeted radiotherapy application involving ^{131}I beta emitter. GATE provides not only convivial tools but gives access to the versatility of GEANT4 physics. In a near future, it will be possible to extend the physics

range at a lower scale by using GEANT4-DNA models and processes allowing the tracking of charged particles at the nanometer scale.

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