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Technical notes

A Monte Carlo approach to small-scale dosimetry of solid tumour microvasculature for nuclear medicine therapies with ^{223}Ra-, ^{131}I-, ^{177}Lu- and ^{111}In-labelled radiopharmaceuticals

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ABSTRACT

The small-scale dosimetry of radionuclides in solid-tumours is directly related to the intra-tumoral distribution of the administered radiopharmaceutical, which is affected by its egress from the vasculature and dispersion within the tumour. The aim of the present study was to evaluate the combined dosimetric effects of radiopharmaceutical distribution and range of the emitted radiation in a model of tumour microvasculature.

We developed a computational model of solid-tumour microenvironment around a blood capillary vessel, and we simulated the transport of radiation emitted by ^{223}Ra, ^{111}In, ^{131}I and ^{177}Lu using the GEANT4 Monte Carlo. For each nuclide, several models of radiopharmaceutical dispersion throughout the capillary vessel were considered.

Radial dose profiles around the capillary vessel, the Initial Radioactivity (IR) necessary to deposit 100 Gy of dose at the edge of the viable tumour-cell region, the Endothelial Cell Mean Dose (ECMD) and the Tumour Edge Mean Dose (TEMD), i.e. the mean dose imparted at the 250-μm layer of tissue, were computed. The results for beta and Auger emitters demonstrate that the photon dose is about three to four orders of magnitude lower than that deposited by electrons. For ^{223}Ra, the beta emissions of its progeny deliver a dose about three orders of magnitude lower than that delivered by the alpha emissions.

Such results may help to characterize the dose inhomogeneities in solid tumour therapies with radiopharmaceuticals, taking into account the interplay between drug distribution from vasculature and range of ionizing radiations.

Introduction

In the framework of internal radionuclide therapies, small-scale dosimetry and microdosimetric approaches to the tumour structure are fundamental to foresee the therapeutic effects attainable. The biokinetics of therapeutic radiopharmaceuticals follow different pathways, depending upon the route of administration, the molecular targeting mechanism, and the physio-pathologic conditions of the patient, affecting the uptake in normal tissues and tumour.

An administered radiopharmaceutical is distributed systemically by blood flow and microscopically by diffusion and/or other mechanisms of egress from capillaries, as affected by its molecular weight, charge or polarity (if any), and surface topography and by the distribution and accessibility of its molecular target.

Any ensuing radiation damage is thus determined by the microscopic biodistribution of the radiopharmaceutical and by the range and ionization density or linear energy transfer (LET) of its emitted radiations. Since several radionuclides are of common use in nuclear medicine therapies, exploiting beta, Auger or alpha emissions, and a variety of molecules is available as carriers with different targeting pathways, a systematic study of the small-scale

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dosimetry of therapeutic radiopharmaceuticals in and around the tumour microvasculature is therefore necessary.

Several approaches have been proposed in the past years, mainly dealing with alpha-particle therapies. In particular, a microdosimetric model of tumour microvasculature was introduced by Humm concerning radioimmunotherapies with ^{211}At [1]. More recently, Huang et al. [2] presented a Monte Carlo study of the effectiveness of Tumour Anti-Vascular Alpha Therapies (TAVAT), in which the doses delivered to the endothelial cell (EC) elements have been evaluated.

A more general approach to the small-scale dosimetry of tumour microenvironment and angiogenesis was developed by Zhu et al. [3], in which a model of capillaries in a pathologic tissue was assumed, and two alpha emitters (^{211}At and ^{213}Bi) and six beta emitters (^{32}P, ^{33}P, ^{67}Cu, ^{90}Y, ^{131}I, ^{188}Re) were investigated.

The aim of the current study was to extend this model to other, frequently used therapeutic radionuclides, the alpha emitter ^{223}Ra, the beta-emitters ^{131}I and ^{177}Lu, and the Auger electron-emitter ^{111}In.

Our analysis, relying on a specifically developed GEANT4 [4] Monte Carlo code, allowed us to quantify the contributions to the radiation dose of each emitted radiation around the capillary vessel for several models of radionuclide distribution encountered in different therapies: radio-embolization procedures, anti-angiogenic radiopharmaceuticals, and other models involving extra-vascular distribution.

Materials and methods

We developed a Monte Carlo simulation in GEANT4, release 10.0.p02, a simulation toolkit originally developed for high energy physics, and now widely applied also in the field of medical radiation physics [5,6]. In particular, the code developed for this study was derived from others previously validated for microdosimetric evaluations of dose enhancement in external beam radiotherapy [7] and for radionuclide dosimetry purposes [8].

The present simulation was aimed to evaluate the dose distribution around a 1-mm-long capillary embedded in soft tissue.

In particular, we simulated a cylindrical vessel having 10-μm inner radius and 10-μm-thick wall, composed by the standard NIST material [4] "G4_SKIN_ICRP" (density 1.09 g cm^{-3}), filled by blood represented by the material "G4_BLOOD_ICRP" (density 1.06 g cm^{-3}), and surrounded by a set of 23 co-axial cylindrical layers made of "G4_TISSUE_SOFT_ICRP" (density 1.03 g cm^{-3}), 10-μm-thick each. In view of the maximum distribution range of

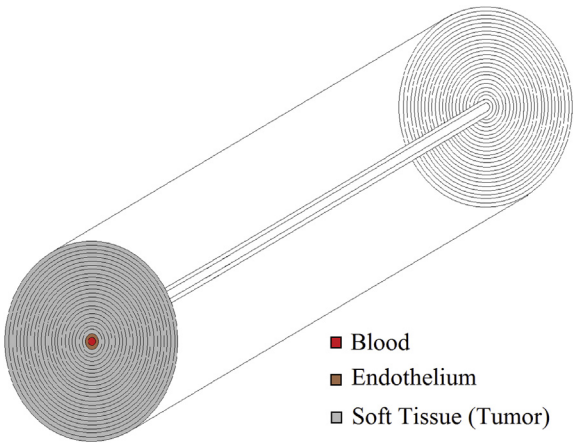

Figure 1. Geometrical lay-out of the simulation.

Table 1
Nuclear properties of the simulated radionuclides. Only the main emissions are listed; the full decay data are available in Ref. [10]. The column $E_{e\text{-}mono}$ lists the energies of the main monoenergetic (Auger or conversion) electrons.

Radionuclide	$T_{1/2}$	E_α (MeV)	$<E_\beta>$ (keV)	$E_{e\text{-}mono}$ (keV)	E_γ (keV)
^{223}Ra	11.43 d	5.7	–	See Ref. [10]	Neglected
^{219}Rn	3.96 s	6.8	–		
^{215}Po	1.78E−3 s	7.4	–		
^{211}Pb	2.16E+3 s	–	450		
^{211}Bi	3.63E+3 s	6.5 (99.7%)	176 (0.3%)		
^{211}Po	0.52 s	7.4	–		
^{207}Tl	2.86E+2 s	–	496		
^{131}I	8.02 d	–	181.5	3.4 45.6	364
^{177}Lu	6.71 d	–	132.9	6.2 47.6 101.7	113 208
^{111}In	2.80 d	–	–	2.72 19.3	171 245

oxygen and nutrients from a capillary vessel [9], we assumed a viable tumour edge located at 250 μm of radial distance from the capillary axis. In Fig. 1 a schematic view of the simulated regions is shown.

We considered four radionuclides among those used in nuclear medicine therapies: the alpha emitter ^{223}Ra together with its daughters, the Auger-gamma emitter ^{111}In, and the two beta-gamma emitters ^{131}I and ^{177}Lu. The decay modes with respective energies, taken from Ref. [10], are summarized in Table 1.

In the framework of the GEANT4 simulation code, we compared the three physics models for electromagnetic interactions, namely, the Standard e.m. physics model, and the ones based on Livermore data and Penelope parameterizations [4]. A range cut of 0.5 μm was adopted for all tracked particles, in order to obtain proper spatial accuracy in the energy deposition, consistent with the sizes of the simulated geometry. We tracked 10^7 primary events of ^{111}In, ^{131}I and ^{177}Lu decays, while $5\cdot10^5$ ^{223}Ra decays were chosen, so that the statistical uncertainties associated with the presented results are below 1%, a value lower than the uncertainties on the parameterizations of the experimental cross-sections employed by GEANT4 in the energy range explored in our study [11,12].

Since, at state of the art, the extra-vascular distribution of each radiopharmaceutical is not known exactly, we assumed several configurations of radionuclide radial distribution across the various layers (blood, EC and tissue layers), as reported in Table 2. These assumptions are based on the different realities that may be encountered in the clinics. For example, configuration A (blood only) can represent a radio-embolization procedure; configuration B (EC only) can represent an anti-angiogenic radiopharmaceutical; configuration C results from a mixed effect of the previous configurations; configurations D-G represent other models of extra-vascular distributions.

Energy deposition per primary event was scored for each layer and represented as a function of the radial distance from the

Table 2
Radial distribution configurations of the radionuclides used.

Configuration#	Regions	Range (μm)
A	Blood	0–10
B	Endothelial cells	10–20
C	Blood + E.C.	0–20
D	E.C. + Tumour	10–50
E	E.C. + Tumour	10–100
F	E.C. + Tumour	10–150
G	E.C. + Tumour	10–200

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