

Monte Carlo simulation of the RBE of I-131 radiation using DNA damage as biomarker

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Abstract In general, a weighting factor of one is applied for low linear energy transfer radiations. However, several studies indicate that relative biological effectiveness (RBE) of low energy photons and electrons is greater than one. The aim of this current study was calculating the RBE of I-131 radiation relative to Co-60 gamma photons in 100 μ m spheroid cells using Monte Carlo (MC) simulations. These calculations were compared to experimentally measured results. MCNPX2.6 was used to simulate the I-131 and Co-60 irradiation setups and calculate the secondary electron spectra at energies higher than 1 keV with varying oxygen concentrations. The electron spectra at energies lower than 1 keV were obtained by extrapolation (down to 10 eV). The calculated electron spectra were input into the MCDS micro-dosimetric Monte Carlo code to calculate the DSB induction and related RBE. The calculated RBE of I-131 radiation relative to Co-60 photons, as the reference radiation recommended by the International Commission on Radiation Protection (ICRP), was 1.06, 1.03 and 1.02 for oxygen concentrations of 0, 5 and 100%, respectively. Results of MC simulations indicate the RBE of I-131 is greater than one. This finding, despite a 10% discrepancy with the findings of the previous in vitro study of one of the authors of this paper, reemphasizes that I-131 radiation induces more severe biological damage than current ICRP recommendations.

Keywords Double-strand DNA breaks · Monte Carlo method · Radiation · Relative biological effectiveness · I-131

Introduction

Relative biological effectiveness (RBE) is a key concept in radiobiology to assess biological effects of different radiations and their relevant qualities in radiation protection. This quantity is measured as the ratio of a dose of reference radiation to a dose of test radiation to produce the same biological endpoint [1]. Several parameters of the test radiation such as dose, dose rate and linear energy transfer (LET) are included in this comprehensive analysis to determine toxicity of a specific radiation.

Low-energy radiations are of particular importance as they are more potent than high energy radiations to cause the damage in biological context [2]. The International Commission on Radiation Protection (ICRP) has recommended that a RBE of one be used for all low-energy light particles such as photons and electrons [3]. This assumes that these types of radiations have the same effectiveness when interacting with biological tissues. There is growing evidence in the literature that indicates various low-energy electrons and photons may induce more severe biological damage in living cells per unit absorbed dose than currently assumed [2]. These observations support the fact that an RBE of greater than one should be assigned for these types of radiation [4]. Exact knowledge of the RBE of a specific radiation allows for appropriate application of that radiation in a clinical environment but also can provide useful information in risk assessment of radiation toxicities for health physics applications.

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I-131, with low-energy beta particles and gamma photons, is a common radioisotope used in nuclear medicine. Since its introduction in 1993 [5], I-131 has been successfully used for controlling hyperthyroidism, thyroid glands and thyroid cancers. Radioiodine therapy is the most common procedure performed in therapeutic nuclear medicine [6]. Furthermore, treatment of central nervous system (CNS) tumors using I-131 has been associated with promising therapeutic [7–9]. Due to the therapeutic value of I-131 and its extensive application in medicine, the study of the RBE of I-131 radiation can provide pivotal information about the radiobiology of this radioisotope which may be useful to establish improved protocols in medical applications.

In terms of radiation protection, I-131 is one of the main components emitted in nuclear accidents [10]. It can be easily absorbed in the thyroid, irradiate the thyroid gland and lead to serious complications such as cancer. As it is reported that exposure to I-131 in childhood can increase incidence of thyroid cancer [11], quantification of the RBE of this radioisotope can also be useful in risk assessment and adoption of appropriate preventive measures and regulations.

Determination of RBE is conventionally done experimentally, but as an alternative, it can also be estimated using Monte Carlo (MC) methods [12–14]. In the past decades, MC methods have been widely used to simulate ionizing radiation in biological environment, enhancing our knowledge about the mechanisms involved in induction of biological damage [15–17]. This method can provide information about the interaction of radiation with tissue in both macroscopic and microscopic levels, resulting in detailed particle transport kinematic at discrete interaction sites.

In previous work of one of the authors of the current paper, an experimental study of the RBE of I-131 radiation relative to Co-60 gamma rays showed the RBE of I-131 was 1.16 [18]. In the present study, the RBE of I-131 radiation relative to Co-60 gamma rays was calculated in 100 micrometer spheroid cells using MC simulations. These results were then compared with the measured data obtained from the previous in vitro study [16] to further the investigation of I-131 dosimetry. The results of MC simulations can provide insight into the underlying physics of the RBE increase and also allow simulation of more complex and clinically relevant conditions such as the effect of oxygenation level on DNA damage.

Materials and methods

Monte Carlo simulations

Two MC codes were paired in this work, MCNPX v.2.6 [19] and fast Monte Carlo damage simulation (MCDS)

[21–23]. To determine RBE, the electron spectra were first calculated for both I-131 and Co-60 in MCNPX. These spectra were then entered into MCDS where the DNA damage is simulated with the result being the number of induced double strand breaks (DSB) per base pair.

MCNPX was chosen to calculate the electron spectra since multiple particle source definitions can be used allowing simulations for both Co-60 and I-131 simultaneously. Photon and electron energy cutoffs were set to the minimum value of 1 keV to include delta rays. The calculated spectra were differential in energy and collected using track length tally (F4) in MCNPX. In tally type 4, the weight of each electron in the spectrum is proportional to its track length in the cell. It should be noted that the weight of each energy bin in the spectrum is proportional to total track length of that particles that had the energy between minimum and maximum boundaries of the bin [20].

Calculations show that slowing down spectra for electron sources (energies >20 keV) and photon sources (e.g. Co-60) have similar behavior at energies lower than 1 keV [21–23]. Using this fact, spectra values at energies lower than 1 keV were obtained using the Vassiliev method [23] (Eq. 1). Calculated spectra at energies lower than 1 keV were merged with spectra at energies higher than 1 keV by using continuity of the spectra.

Energy distribution of each beta emission mode was obtained by using the Fermi theory of the beta decay via:

$$N(E) = C(E^2 + 2Em_e c^2)^{1/2} (Q_i - E)^2 (E + m_e c^2) \quad (1)$$

E and $m_e c^2$ are the kinetic and rest energy of the emitted electron. Q_i is the maximum energy of each mode. In the Eq. 1, C is constant and was determined for each mode via equation:

$$C_i = 1 / \int_0^{Q_i} (E^2 + 2Em_e c^2)^{1/2} (Q_i - E)^2 (E + m_e c^2) dE \quad (2)$$

The probability of the energy, E , was calculated via equation:

$$P(E) = \sum_{i=1}^3 w_i C_i (E^2 + 2Em_e c^2)^{1/2} (Q_i - E)^2 (E + m_e c^2) \quad (3)$$

In Eq. 3, w_i and Q_i are the relative intensity and maximum energy of i_{th} beta emission mode respectively. As these equations are obtained from quantum theory, the uncertainty is negligible.

Calculated electron spectra for energies higher than 25 eV were input into the MCDS code to calculate the DSB induction per Gray per gigabase pair ($Gy^{-1} Gbp^{-1}$). Rather than modeling the transport of the high energy electrons as is done in MCNPX, MCDS uses the

Fig. 1 Geometry of the I-131 MC simulations

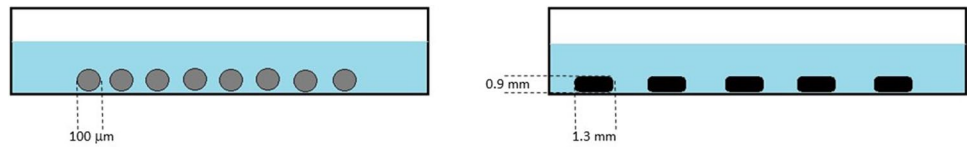


Table 1 Gamma photons and their relative intensities

Energy (MeV)	0.723	0.637	0.364	0.284	0.080	0.030
Intensity	0.018	0.073	0.812	0.061	0.026	0.039

Table 2 Beta particles maximum energies and relative intensities

Maximum energy (MeV)	0.248	0.334	0.606
Intensity	0.021	0.074	0.893

incident electron energy weighted by the electron spectra to compute DSB induction [24, 25]. With this method, the potential “double counting” of delta rays from the two separate MC codes is avoided. MCDS parameters were tuned following the method used by Semenenko, et al. to obtain minimum difference with measurements and track structure simulations [25]. MCDS uses typical mammalian cell for DNA damage calculations including oxygen and chemical fixation [26].

Benchmark simulations

To benchmark the MC simulations, a Theraton cobalt therapy unit was simulated in MCNPX to obtain a percent depth dose (PDD) curve in a simulated water tank. The Theraton cobalt therapy unit was simulated exactly including all shield components, Co-60 source and moveable jaws. The overall simulated uncertainty was 0.5% for one standard deviation. The calculated PDD was then compared with measured data in the same geometry as the simulation.

RBE simulations

The MC simulations of I-131 included both emitted photons and electrons. Table 1 shows photons and their relative intensities that were included in the simulations. Table 2 shows the electrons and their relative intensities that were transported in MC simulations. Electron spectra were calculated in spheroid water cells with thickness of 100 micrometers in a T-25 flask filled with I-131 solution, as shown in Fig. 1. Water was chosen as the cell medium due to the limitations of modelling the cytoplasm and nucleus in MCNPX. For Co-60, the same T-25 flask with the 100 micrometer spheroids was simulated at a SSD of 70 cm from the Co-60 source with a 12×12 cm²

field size. This MC geometrical set-up chosen because it is similar to previous experimental measurements.

MCDS version 3.008 was used for the DNA damage calculations. This code uses four adjustable parameters for DNA damage calculations [26, 27]:

- δ_{sb} Number of strand breaks Gy⁻¹ cell⁻¹
- f Base damage to strand break ratio
- n_{min} Minimum number of undamaged base pairs between neighboring elementary damages
- n_{seg} Number of base pairs in the DNA segment

Three of these parameters (δ_{sb} , n_{min} , f) are independent of particle type and energy but n_{seg} is not. For electrons, n_{seg} is computed as

$$n_{seg} = 149200 - \frac{123600x}{x + 267} \text{ base pairs}$$

$$\text{Where } x = \left[1 - \frac{1}{1 + \frac{T}{m_0c^2}} \right]^{-1} \tag{4}$$

In this equation, T and m_0c^2 are kinetic energy and rest mass of the electron, respectively [27]. MCDS parameters are tuned to obtain the minimum difference with measurements and track structure simulations ($\delta_{sb} = 217 \text{ Gy}^{-1} \text{ Gbp}^{-1}$, $n_{min} = 9 \text{ bp}$, f=3) [27, 28]. This code uses typical mammalian cell for DNA damage calculations with including oxygen and chemical fixation [29].

To match the experimental setup, glioblastoma cells were simulated. The minimum allowed kinetic energy for DNA damage calculations by MCDS is 25 eV [26]. DNA damage lesions were calculated under fully aerobic (100% O₂) and anoxic (0% O₂) conditions. The RBE of I-131 radiation relative to Co-60 gamma rays was then determined by normalizing to the number of DSB for Co-60 via Eq. 5:

$$RBE_x = \frac{DSB_{I-131}}{DSB_{Co60}} \tag{5}$$

Results

Benchmark simulations

The benchmark test in MCNPX showed good agreement between the measured and calculated PDD. It can be seen from Fig. 2 that the measurement and simulation are within 1% of each other, falling inside the accepted level [30], validating our model.

MCNPX simulations

Figure 3a shows the calculated electron energy spectra for the Co-60 and I-131 experimental setups for energies higher than 10 eV. The calculated spectra uncertainty was less than 0.14% for all energy bins. The extrapolated spectra uncertainty was less than 0.1%. Each spectrum is normalized to have an area under the curve equal to 1.0. It can be seen from this figure that electron spectrum for I-131 in the low energy region is higher than the electron spectrum for Co-60 source. The incorporation of vibrational excitations causes the slight increase in the electron spectra at approximately 100 eV [23]. Thus one step can be seen at 100 eV in these spectra. Figure 3b shows the calculated electron energy spectra for the Co-60 and I-131 for energies higher than 1 keV for better representation of the two spectra differences.

RBE simulations

Table 3 shows the calculated DSBs and related RBEs under anoxic (0% O₂), normoxic (5% O₂) and fully aerobic (100% O₂) conditions. The uncertainty of calculations was

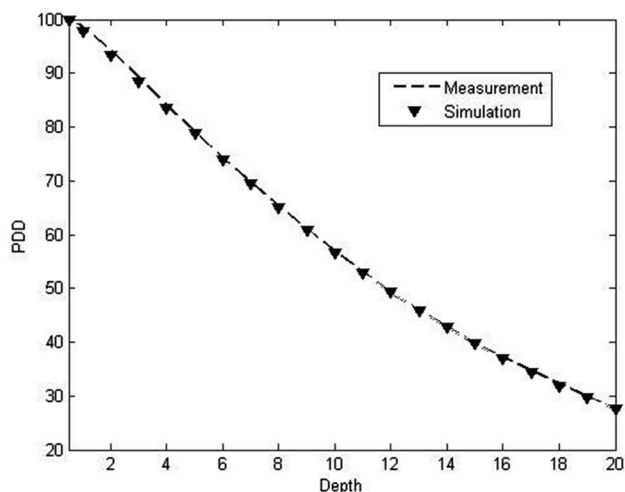


Fig. 2 Results of the PDD benchmarking simulation for the Co-60 Theratron. Note the agreement is within 1%

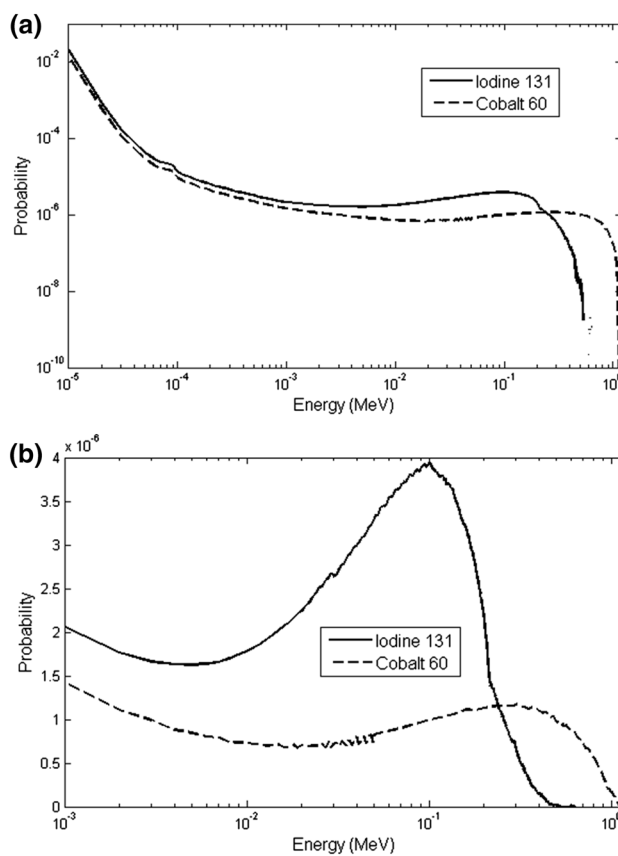


Fig. 3 Spectra for Co-60 and I-131 for energies greater than 10 eV (a) and greater than 1 keV for better representation of the two spectra differences (b)

less than 0.3% for all conditions. Table 3 also shows that DSB of I-131 and Co-60 for fully aerobic conditions and normoxic conditions are almost three times higher than for anoxic conditions.

Discussion

In this study, a MC method was used to calculate the RBE of a common low-energy source that is commonly used in therapeutic nuclear medicine. MCNPX was used to calculate secondary electron spectra for I-131 and Co-60. The calculated electron spectra were input into the MCDS code

Table 3 Calculated DSBs Gy⁻¹ Gbp⁻¹ and corresponding RBEs in irradiated cells under the anoxic (0% O₂) normoxic (5% O₂) and fully aerobic (100% O₂) conditions

Oxygen concentration	0%	5%	100%
Calculated DSB for irradiation with ¹³¹ I	3.3	8.0	8.7
Calculated DSB for irradiation with ⁶⁰ Co	3.1	7.8	8.5
RBE	1.06	1.03	1.02

to calculate the DSB induction per Gray per gigabase pair ($\text{Gy}^{-1} \text{Gbp}^{-1}$). According to the results of the Monte Carlo simulations, the calculated RBE of I-131 radiation relative to Co-60 gamma photons was determined to be in the range of 1.02 to 1.06, with respect to the concentration of oxygen.

Comparing the result of the current simulation with that of previous experimental measurements ($\text{RBE} = 1.16$), there is an about 10% discrepancy between findings of these two studies [16]. This observed difference most likely stems from uncertainties introduced by simplifying the MC simulations combined with uncertainties in the experiments themselves. In terms of the MC simulations, our assumption was that the cells were composed completely of water since modelling the individual components of the cytoplasm was impossible in MCNPX and MCDS. To mitigate the effect of this assumption, the uncertainties in the MC simulations were minimized. As stated in the results, the uncertainty in the MCNP code was well within the accepted 1% uncertainty for the calculated the spectra and the benchmark simulation [28]. The uncertainty was also less than 0.5% for the MCDS simulations and we believe that the low uncertainty in the MC simulations counteracts the uncertainty introduced by the assumption that the cell was composed entirely of water.

To address the experimental uncertainty is on the order of 5%, we attempted to match our simulated geometry to the experimental setup but limitations in cell modelling in both MC codes presented problems. By reducing overall uncertainty as described above, we attempted to mitigate these differences in the simulations. Additionally, there were differences in the biological endpoints used to assess RBE. In the experiment, a comet assay was used to assess DNA damage based on the change in tail moment [16]. It is impossible to simulate a comet assay in MCDS so the number of double strand breaks per Gbp was chosen as the closest biological endpoint. Despite these limitations, it is evident from both studies that the RBE of I-131 radiation is greater than unity, which reemphasizes that RBE of low-energy I-131 radiation, should be elevated.

Assuming this to be the case, some revisions seem to be necessary to assess the quality of I-131 radiation. The elevated value of the RBE of I-131 radiation means that a specific activity of I-131 may induce more biological damage than was previously thought to have with the RBE of 1. The ICRP acknowledges that photons and electrons have RBE of greater than one, but still recommends a weighting factor of 1 for all these light particles [31]. The reason of this decision is mainly because of the fact that the uncertainty of the RBE of photons and electrons may be covered by the uncertainty of risk coefficient for cancer [4]. Thus, it seems to be appropriate to adopt RBE of 1 for light particles for radiation protection purposes. However, in risk assessment of the radiation the calculations and values need to

be as accurate as possible. Since RBE is a key quantity to derive the radiation weighting factor, it is necessary to consider exact values of RBE to accurately determine effective and equivalent dose [4]. The new RBE of I-131 radiation ($\text{RBE} > 1$) means that a specific activity of this isotope can produce more damage in living tissues than it was thought before.

From the data obtained here, it is also obvious that by increasing the oxygen concentration in the environment of spheroid cells, RBE decreases which is in agreement with study performed by Stewart et al. [26]. This finding shows that in oxygenated environment, the repairing mechanism of the damaged DNA increases, leading to lower toxicity of the I-131 radiation and consequently lower RBE of the radiation.

Conclusion

MC simulation revealed that RBE of I-131, in spite of official recommendations by the ICRP, is greater than unity which is in agreement with a previous experimental study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval is not required because of the type of the study that was a simulation not practical study on human or animal.

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