The Effect of Nucleus Size on the Cell Dose in Targeted Radionuclide Therapy – A Monte Carlo Study

Abstract

Background: Nowadays, the use of radiopharmaceuticals in medicine is unavoidable. Depending on the distribution of the radiopharmaceutical in the cells, the nucleus absorbed dose changes by the variations in their geometry size. Therefore, this study aims to investigate the S-value by the variation of nucleus size using Geant4 toolkit. **Methods:** Two spherical cells with a variety of nucleus size have been considered as the cancerous cell. Monoenergetic electrons ranging from 5 to 300 keV are distributed uniformly. The S-value for four target-source components (including Nucleus←Cytoplasm, Nucleus←Cell surface, Nucleus←Nucleus, and Nucleus←Nucleus surface) is computed and plotted. Then, the obtained data are compared with analytical Medical Internal Radiation Dose (MIRD) data. **Results:** In Nucleus←Cytoplasm compartment for electrons below 10 keV, obtained S-values show a slight decrease for the nucleus in the radii of around half of the cell radius and then S-values increase with the increase in the nucleus radii. In the S-value of Nucleus←Cell surface, for all electron energy levels, a slight decrease observed with the increase of nucleus radii. For Nucleus←Nucleus and Nucleus←Nucleus surface cases, with an increase in the size of the cell nucleus, a sharp reduction in the S-values is detected. **Conclusion:** It can be concluded that for the beta emitters with low-energy radiation (<40 keV), the S-value is heavily dependent on the nucleus size which may affect the treatment of small tumors. While for the beta emitters with higher-energy radiation (>100 keV), the size of the nucleus is not very noticeable in the induced S-value.

Keywords: *Beta-emitting radiopharmaceutical, Geant4-DNA, nuclear medicine, S-value*

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Introduction

Radiation therapy uses ionizing radiation (e.g; γ, e, α, p,…) to treat cancers by preventing targeted cells from growth and division through DNA damage inside the nucleus.[1] The ultimate challenge of radiotherapy is maximizing damage to tumor cells while minimizing damage to the surrounding healthy cells.[2] Targeted radionuclide therapy (TRT) is a type of systemic treatment of cancers which uses a special radionuclide labeled with specific molecules to deliver radiation to targeted tumor cells.[3] This causes lethal and sublethal damage to cancerous cells. This type of radiotherapy is being used for the treatment of prostate, thyroid, breast, and lung cancers. These organs are formed from the cells with various sizes and shapes. In TRT, selection of radionuclides is very crucial. Historically, beta-emitting radionuclides are mainly used in TRT. In recent years, however, many studies have also been performed using alpha-emitting radionuclides.[4,5] An ideal type of radionuclide for an appropriate therapeutic application depends on many factors such as size, geometry, position, and radiosensitivity of the target organ.[2]

These radioactive atoms have been used for cancer diagnosis and treatment. They are coupled with specific molecules to form radiopharmaceutical drug to explore specific cancerous cells. TRT aims to concentrate radioactive material in a specific organ and cause to ablate targeted organs or cells with little effect on the closely healthy parts.

Internal dosimetry of radionuclides is based on the S-value, defined analytically by the

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committee on Medical Internal Radiation Dose (MIRD).[6] As mentioned in many previous literature,[1,6,7] in internal dosimetry of a radionuclide drug or agent, the absorbed dose in a target organ from source (D (T←S)) is expressed as follows:

$$D\ (T{\leftarrow}S) = \tilde{A}\ S\ (T{\leftarrow}S) \tag{1}$$

Where $\tilde{A}$ is the time-integrated activity in the source region (S) and S (T←S) is the absorbed dose per unit cumulated activity in a specific organ (Gy/Bq. s). Regardless of the cumulated activity, the S-value formula consists of two terms $(\dfrac{E}{M_{target}})$. E and M represent the deposited energy of the incident particle and the mass, respectively, where the energy is deposited. As Cole stated, the range of electrons (R) in the water equivalent matter is related to electron energy (E_e) as $R = 0.0431(E_e + 0.367)^{1.77} - 0.007$.[8]

Therefore, in cell dosimetry, the energy of the particle, size, shape, and distance plays key roles in the S-value calculation.

A proper database of cellular S-value for different ionizing particles and specially for spherical cells with various sizes has analytically been driven by MIRD.[6] Besides the mentioned analytical method, Monte Carlo (MC) approaches also can be used to calculate the deposited energy in the matter. This approach relies on repeated random sampling to collect numerical results. MC is applied to solve any quandary having a probabilistic description in physics and mathematics.[9-11] MC methods apply for studying particle transportation in biological media for decades.[12] Today, MC track structure codes can calculate the detailed description of particle transport in mater (event by event). Geant4-DNA package has used in many previous studies to calculate the S-value in different aspects, including geometries,[7] particles,[13] and physics.[14] Its results show a good agreement with other MC codes and analytical method.

A living organ consists of numerous cells with different sizes, shapes, and activities.[15] The cell as the basic structure of living organisms consists of cytoplasm, and it contains many biomolecules such as proteins and nucleic acids.[16] The nucleus was the first subcellular structure observed in the cell and is very vital for cell life.[17] The cells and its nucleus are known to be either spherical or ellipsoidal.[15] In the cancerous colon, a wide range of cells and nucleus with different sizes and shapes are available. Cell dosimetry is very important task in TRT. In many cellular dosimetry pieces of research, the cell is usually considered to be two spherical and concentric shells with a specific radius size. These fill with water as a representative of the biological matter. Typical human cells and nuclei size vary from 6 to 20 µm for the cell and vary between 4 and 18 µm for the nucleus.[6] The nucleus is the most important target in a cell when facing with ionizing radiation. Sufficient dose can cause unrepaired DNA damages and ultimately lead to the death of cancerous cells. As mentioned above, colon cancer consists of a considerable number of the cell which has different size. Hence, it is very crucial to understand the role of cell and its nucleus size in the microscale dosimetry.

In most previous studies about cellular dosimetry, the effect of the nucleus size has been assessed employing the most commonly electron emitter radiopharmaceuticals in nuclear medicine which contain electrons with different energies and weighting factors and simulation codes.[18-20] However, the effect of electron energy has not been specifically addressed. In other words, the effect of the energy will not specially be provided by applying the electron emitter radionuclides with wide energy spectrum. Therefore, in the present work, monoenergetic electron sources are chosen between 5 keV and 300 keV because of the β-emitter radionuclides which mostly emit electron within these ranges of energies. The variation of S-value was calculated for a symmetric cell with different nucleus size and electrons with different energy. The cell radius was kept constant (5 µm and 10 µm), whereas the radius of the nucleus was varied over a wide range.

Materials and Methods

Monte Carlo code selection

In medical physics, MC track structure codes are commonly employed to produce random numbers for presenting the stochastic characteristic of physical interactions of particles, while transporting in biological matter. These codes are very useful tools used for understanding the physical mechanism of deposited energy in these materials.[21,22]

The Geant4-DNA as part of the Geant4 toolkit (10-p04) is widely employed for simulating event-by-event interaction (particle-water), for low-energy electrons (down to 7.4 eV) in liquid water as a equivalent of human cell materials.[23] Geant4-DNA is an open-source code which is available for microdosimetry.[13] S-values are computed by MC simulations of electron tracks in the cell as it suggested in Geant4-DNA expansion.[7] The physical model provided in G4EmDNA physics was selected for electron–water interactions.

General simulation setting

Two distinct spherical cells with 5 µm and 10 µm radii are created to describe the applied S-value variations by the nucleus size. S-values were simulated for each cell with variety of nucleus sizes (2.5–9 µm). Four significant target-source combinations were used: nucleus←cytoplasm, nucleus←cell surface, nucleus←nucleus, and nucleus←nucleus surface. The source histories contain 50,000 monoenergetic electrons which were uniformlydistributed.

Electron uniformly distribution

In the S-value calculations, the electron decays are considered to be uniformly distributed within the source geometry. For generating primary, events in the source volume include cell surface, nucleus surface, and cytoplasm; the rejection mode[24] was applied and random point was generated on the spherical cell or nucleus with radii using the following steps.[25] First of all, random number U was selected from U (−1, 1) as follows:

$$A = \sqrt{1-(2U-1)^2} \qquad (2)$$

The none can calculate the Cartesian coordinate (x, y, z) for the electron location as follows:

$$\begin{cases} x = R.A\sin(2\pi.U) \\ y = R.A\cos(2\pi.U) \\ z = (2U-1) \end{cases} \qquad (3)$$

Data analysis

Kolmogorov–Smirnov (K-S) or specifically Lilliefors test is used to confirm the normal distribution of the calculated data with MC simulation.[26,27] In this work, the normality of data is tested with the K-S test (critical value = 0.05), and the uncertainty corresponding to 1 σ was examined for obtained results. We validated our model against the available data which has obtained from general purpose codes for 10 keV to 1 MeV incident electron energies (*t*-test and $P \leq 0.05$).[6,7,14] Then, the obtained data were compared with analytical MIRD data.[7,14]

Results

The calculation of electron energy deposition has been carried out by Geant4-DNA in liquid water as a surrogate of the cell material. Monoenergetic electrons were uniformly distributed in the cytoplasm or on the cell surface for two spherical cell geometries with different nuclei sizes. For validation of the obtained Geant4-DNA data, some selected geometry for different components are chosen, and their results are compared with MIRD data and then the percentage difference is plotted in Figure 1.

The S-values (Nucleus←Cytoplasm, Nucleus←Cell surface, Nucleus←Nucleus, and Nucleus←Nucleus surface) are plotted as a function of nucleus radii for two cell geometries (radii 5 μm and 10 μm) in Figures 2-5. The uncertainty corresponding to 1 σ which has not shown in figure was below 2% for all results.Geant4-DNA data in comparison with MIRD analytical model generally indicate that in the S (N←Cy) compartment of the cell and nucleus with radius of 5 μm and 3 μm and for electron energy 5 keV, 20 keV, 50 keV, 100 keV, and 300 keV, the absolute maximum deviations are about 16% for 300 keV electrons and the absolute minimum deviation is 1% for 20 keV [Figure 1a]; furthermore, in S (N←Cs) compartment of the cell and nucleus with radius of 5 μm and 3 μm, the absolute maximum deviation is <13% for

5 keV and the absolute minimum deviation is 2% for 300 keV electrons [Figure 1b], and also in S (N←Ns) compartment of nucleus with radius of 4 μm, the absolute maximum deviation is less than 11% for 100 keV electron and the absolute minimum deviation is more than 8% for 5 keV electron [Figure 1c], In addition, in S (N←N) compartment of nucleus with radius of 5 μm, the absolute maximum deviation is <8% for 50 keV electron and the absolute minimum deviation is more than 1% for 300 keV electron [Figure 1d]; this deviation could be associated to the electron penetration and inclusion of the gamma photons in the Geant4 calculation, which were neglected by MIRD analytical data.[7,14] This comparison shows that the obtained data are in good agreement (*t*-test and $P = 0.05$) with the MIRD data.

In our MC simulation, the S-value (N←Cs) was negligible for the small cell (Rc = 5 μm) and nucleus size below 4 μm and low-energy electrons (<5 keV) which is due to the penetration range smaller than 1 μm. This issue is also occurred for the cell with radii of 10, for electron energy 5, 8, and 10 keV for the nucleus radii below 9, 8, and 7 μm, respectively. These values are not included in Figure 3a and b.

Discussion

The cellular S-value as a microdosimetry parameter is necessary for dosimetry of the beta and Auger emitter radiopharmaceutical which is used in radioimmunotherapy and nuclear medicine imaging. The S-value strongly depends on the size of the cancerous cell and the subcellular distribution of the radioactivity.[6]

Several studies have been done to investigate the S-value in a specific cell using Geant4-DNA extension and other MC codes,[1,3,7,13] but most of them have focused on the S-value variation against the kind of decayed particles and delivered energy from the source to the target or models validation. In all of these studies, the reference is obtained data from MIRD as earlier analytical model.[6] In this work, we have tried to study the possible relationship between the S-value and the nucleus size as the main aim in the cell for the range of the electron energy.

The obtained results about the effect of nucleus size on the S-value showed that in the S (N←Cy) compartment, for the cell-5 μm and low monoenergetic electrons (<10 keV) [Figure 2a], the estimated penetration depth for the electron, as Cole stated, was much smaller than the distance of the cell membrane from the nucleus.[8] With an increase in the radius of the nucleus, the S-value showed an increment trend. While for higher energy (≥10 keV), the decrement trend was observed [Figure 2a]. Cai *et al*. reported a decreasing trend in S-value with increasing nuclei radius from 5 to 10 μm, which can be due to the different sources of radiation.[18] They used different
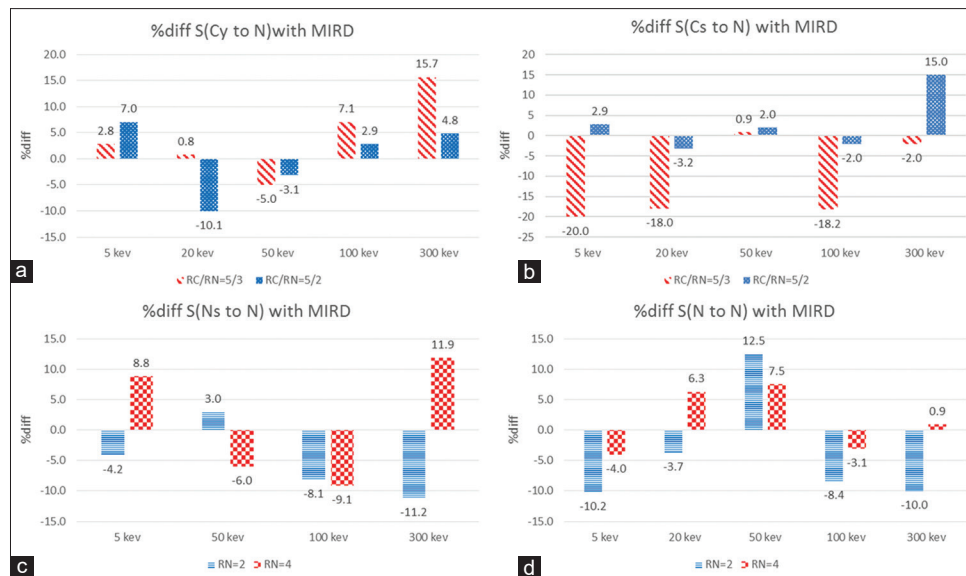
Figure 1: The S-value percentage difference between MIRD and Geant4-DNA data in this study in some selected geometries and compartments(a-d)

simulation code (MCNP) to transport electrons emitted from ^{111}In, so the difference between our results and the stated study at low energies is expected. Decreasing trend was observed for bigger cells [Figure 2b] and 50 keV electrons (with a range of about 40 μm). The observed rising trend in the S-value of 5 μm cell radii with the nucleus radii from 3.5 to 4 μm resulting from low-energy electrons (e. g., 5 and 8 keV), is due to the increase in the energy deposition. However, in the large cell (10 μm) and for low-energy electrons, at first, with the increase in the nucleus radii, the S-value decreases but then increases for the nucleus radii more than 7 μm. It can be concluded that at the beginning of the increase in the nucleus, its mass overcomes the deposited energy, and then energy deposition shows more growth ($\Delta E \gg \Delta M$). The maximum difference between the low and high levels of the S-value observed for low-energy electrons (5 keV) which reach 197% and 234% for cell 5 and 10 μm, respectively. For much more energetic electrons, the variations of the S-value are between 20% and 50% for small cell (5 μm) and reach 60%–70% for the larger ones (10 μm). As a consequence, the absorbed dose in the cells with the large ratio of Rc/Rn (large cell-small nuclei) is different from the cells with the small ratio of Rc/Rn for low-energy electrons.

The most important source-target compartment in clinical purpose is the N←Cs compartment (the cell membrane usually absorbs radiopharmaceutical drug). In this compartment and for all level of energies, a monotonic decrement was observed in the S-value as the size of the cell nucleus increased. The penetration range for low-energy electrons (<5 keV) is smaller than 1 μm, and hence no S-value data are calculated for the cell with the radius of 5 μm and nucleus sizes below 4 μm [Figure 3a]. The maximum and minimum differences between the

observed S-values were seen for 5keV electrons and 20 keVelectrons, respectively.

In the N←N and N←N-surface compartment and for all level of energies, a monotonic reduction in the S-value observed as the size of the cell nucleus increased. The variations of S-values sharply decrease for the nucleus between 1 μm and 4 μm for a cell with radius 5 μm as Cai *et al*. pointed out for nucleus radius from 2 to 4 μm.[18] Moreover, for the small ratio of Rc/Rn, the variety of S-value is negligible in comparison to the changes in the nucleus radius [Figures 4 and 5].

Moradi *et al*. have reported the highest difference in the S-value between various radionuclides when radioactive source was localized in the nucleus, and there was not considerable difference in the nucleus dose when radionuclides were localized in cytoplasm and over the cell membrane.[19]

In a large colon of cancerous cells along with a large variety in the target region (most commonly nucleus), it must be considered the variety of nucleus size for eradicating cancerous cells. In some cases, the change in the nucleus size induces a large variation in the deposited energies to the nucleus. However, it can be concluded that the induced S-value in the cell depends on both the size of the nucleus and the energy of ionizing particles. Most beta emitters, being used in medicine, often emit electrons in energies >100 keV. Therefore, the effects of nucleus size on the S-value are negligible for these radio drugs. On the other hand, for the low-energy beta emitters (<40 keV) such as [58]Co, [103 m]Rh, [119]Sb, 161Ho, and [189 m]Os which may be applicable in the radiation treatment of small tumors, the nucleus size can play a key role.[28]
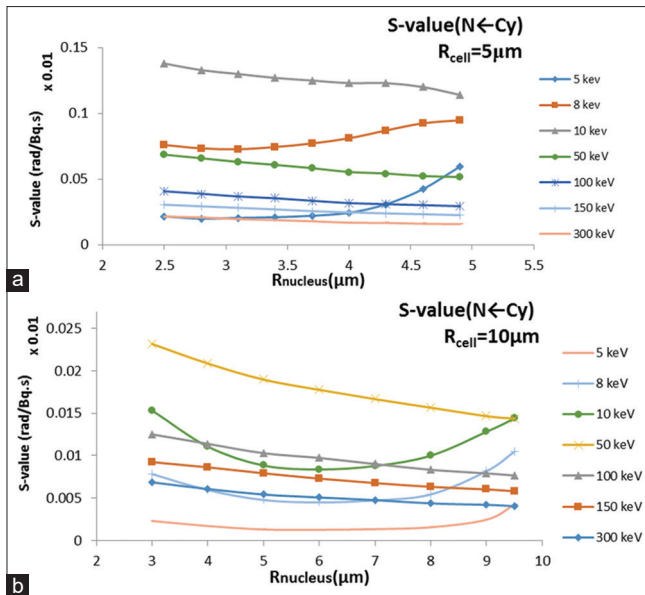
Figure 2: The absorbed dose per unit cumulated activity, S-value (N←Cy) calculated for electron with various energies (5–300 keV) for cells with (a) radius of 5 with nucleus radii 2.5, 2.8, 3.1, 3.4, 3.7, 4, 4.3, 4.6, 4.9 μm and (b) radius of 10 μm with nucleus radii 3, 4, 5, 6, 7, 8, 9, 9.5 μm
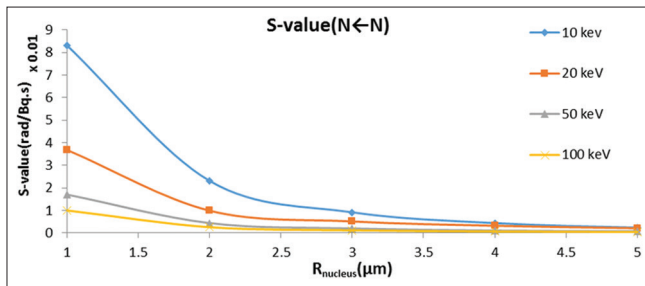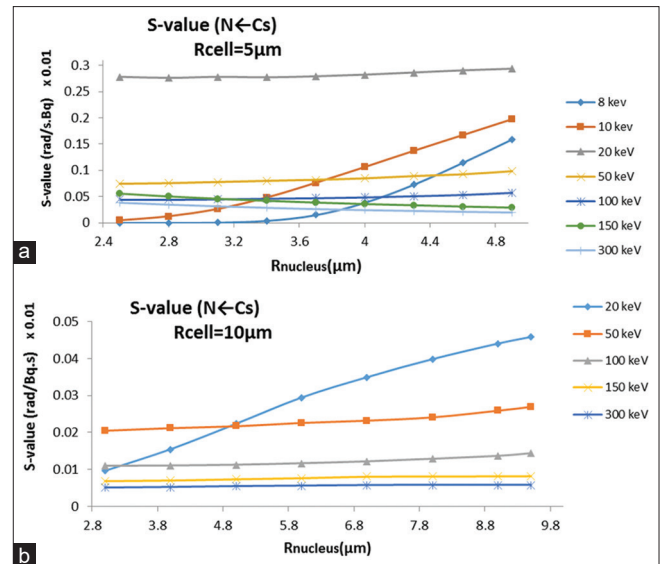

Figure 3: The absorbed dose per unit cumulated activity, S-value (N←Cs) calculated for electron with various energies (20–300 keV) for cells with (a) radius of 5 with nucleus radii 2.5, 2.8, 3.1, 3.4, 3.7, 4, 4.3, 4.6, 4.9 μm and (b) radius of 10 μm with nucleus radii 3, 4, 5, 6, 7, 8, 9, 9.5 μm
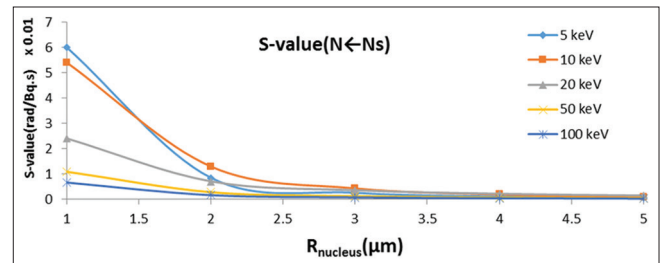

Figure 4: The absorbed dose per unit cumulated activity, S-value from nucleus to nucleus (N←N) calculated for electrons with various energies (10–100 keV) for cell nucleus with radii of 1–5 μm

Figure 5: The absorbed dose per unit cumulated activity, S-value from nucleus surface to nucleus calculated for electrons with various energies (5–100 keV) for cell nucleus with radii of 1–5 μm

Conclusion

Geant4-DNA extension was used to calculate how dose deposition in a biological cell affected by variation in the nucleus size and source location. It is observed that various compartments of S-value change differently in the cell with different size nucleus for different electron energies. In any therapeutic protocol in TRT, it must be noted that the variety of the cell nucleus size in addition to the type of radioactive agent plays an important role in the treatment of the cancerous cells.

Conflicts of interest

There are no conflicts of interest.

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