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Review

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Estimation of the Biological Effectiveness of Auger Electron-Emitting Radiopharmaceuticals for Targeted Radiotherapy

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ABSTRACT

Relative biological effectiveness (RBE) plays an important role in relating physical dose to cell-killing biological dose. The calculation of the RBE is an important basic task in realization of radionuclide therapy using ^{64}Cu. In this study, the method of calculating the RBE of emitted particles from ^{64}Cu is presented using Monte Carlo simulation. U-87 MG cell model is designed to perform Monte Carlo simulation. The Geant4 simulation tool kit was used to simulate the secondary particles for transport into media. The specific energy in the cell nucleus and the domain was estimated. The Microdosimetric Kinetic model (MK model) is used to estimate RBE. The method presented in this study may be helpful to estimate biological dose in treatment with ^{64}Cu.

Key Words: Biological effectiveness, Auger electron, ^{64}Cu, Microdosimetric kinetic model, Geant4

Introduction

Radiopharmaceuticals, a combination of biologically active molecules and radioisotopes, have revolutionized the field of diagnostic imaging and targeted therapies. They provide non-invasive insight into molecular processes at the cellular level, making them invaluable in diagnostic procedures such as PET, SPECT and scintigraphy for early detection of diseases. Beyond diagnostics, radiopharmaceuticals are an integral part of targeted radionuclide therapy, enhancing treatment efficacy while minimizing damage to healthy tissue.

^{64}Cu is used in positron emission tomography (PET) imaging, notable for its extended half-life of 12.7 hours. Its utility spans diverse applications, including hypoxia imaging utilizing ^{64}Cu ATSM, and more recently, it has been employed for therapeutic purposes (1, 2). ^{64}Cu is a well-known Auger electron emitter used in targeted radionuclide therapy. Within the realms of medical physics and radiobiology, radionuclides that emit Auger electrons are highly valued for their application in targeted radiotherapy, particularly in the management of metastatic cancers. The emitted electrons have inherently limited travel distances, usually spanning only a few

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micrometers, which facilitates the concentrated delivery of a high dose directly to diminutive tumor sites.

The treatment using the other ionization radiation is also based on X-ray radiotherapy prescription dose by considering the different biological effects compared to conventional therapeutic X-ray (3). The development of an effective method for calculating relative biological effectiveness (RBE) is fundamental step for the therapeutic use of radiopharmaceuticals. The microdosimetric kinetic (MK) model is a theoretical framework used in carbon ion therapy to predict the biological effectiveness of ionizing radiation at the cellular level. The MK model links microdosimetric measurements, such as the specific energy deposited at cellular or sub-cellular levels, with radiobiological outcomes, thus calculates RBE by considering the energy distribution within microscopic volumes, providing a more accurate assessment of the potential damage to DNA and cell structures (4, 5).

The goal of the study was to establish a calculation method for the RBE of ^{64}Cu therapy. Glioma is a type of malignant tumor that is highly radioresistant and difficult to treat, so it was thought to be a good clinical target of radionuclide therapy using ^{64}Cu. In this study, we selected glioma cells, U-87 MG, and show how to estimate the RBE of emitted particles from ^{64}Cu using Monte Carlo simulation combined with the MK model.

Material and Method

1. Monte Carlo Simulation

A Monte Carlo simulation approach is employed to estimate the cell survival parameter. The simulation modeling of ^{64}Cu is a sophisticated process that involves the detailed representation of the source geometry and physics. The simulation of radionuclide decay and the subsequent pattern of energy deposition was carried out using the Geant4 Monte Carlo toolkit (version 11.3.0), while the Geant4-DNA package was used to improve calculation accuracy in low energy electromagnetic interaction region (6, 7). The atomic relaxation model was employed to incorporate the process of Auger emission. ^{64}Cu emits the secondary particles such as photons and Auger electrons and interacts synergistically with U-87

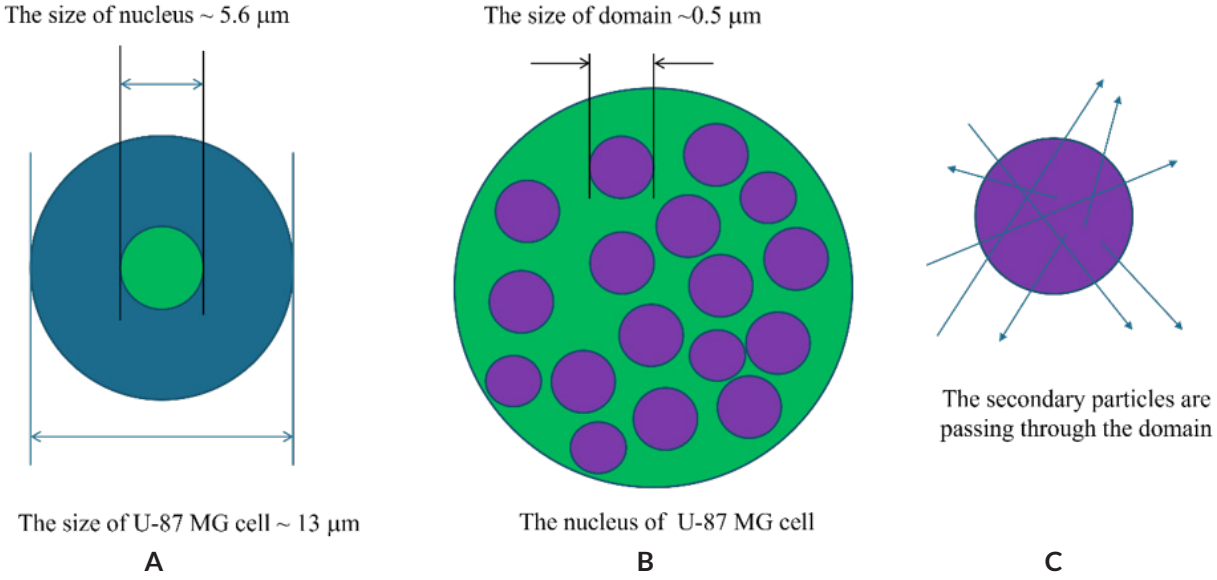

Figure 1. The geometry of the cell nucleus used in the simulation. (A) shows the cell size and its nucleus size. (B) show domain in the cell nucleus. (C) shows the secondary particles that pass through the domain.

MG cell nucleus.

A cube of water 1 mm × 1 mm × 1 mm with a sphere was constructed to simulate the transport of the emitted particles from ^{64}Cu. There are domains in the cell and the energy imparted to the domains is converted into the specific energy depending on the domain size. The nucleus size of the cell is 5.6 μm and it represents the cell nucleus of U-87 MG cell (8). The source modelling assumed that ^{64}Cu was uniformly distributed in the nucleus. Therefore, the entire region of the sphere was considered as the volumetric source of emitted particles from ^{64}Cu. The G4RadioactiveDecay module was used to generate the emitted particles.

Figure 1 shows the geometry used to simulate the calculation of the energy deposition by radionuclides. The inner-sphere volume is considered the U-87 MG cell nucleus while the outer volume represents a cell volume. The NIST materials labeled as 'G4_WATER' was employed to represent liquid water with a density of 1 g/cm³. All simulations were performed in a multi-threaded single workstation powered by Intel® Xeon® CPUs with a total of 48 cores/96 threads on CentOS Linux Stream 8.

2. Biological effect estimation

The biological effect was calculated using the MK model. The MK model is a biophysical model for calculating the biological effect ratio and is a theory developed to predict cell survival. The MK model has been successfully applied to carbon ion therapy and is already adapted in clinic (9).

According to the MK model, the cell surviving rate S is described as below (4, 5),

$$-lnS = (\alpha_0 + \gamma\beta)D + \beta D^2 = \alpha D + \beta D^2 \quad [1]$$

In this equation, each a_0 and β is the cell survival parameters for X-ray. α is the cell survival parameter of the radiation of interest; in this study, the radiation refers to particles emitted from ^{64}Cu. γ is the single event dose mean specific energy in a domain. α_0 represents single track double strand breaking and β represents double track double strand breaking. γ is associated sub-lethal lesions, where the single-track, single-strand breaking is not repaired after irradiation. The floating parameter α is described as follows:

$$\alpha = \frac{1-exp\{(\alpha_0+\beta\gamma)\gamma_n\}}{\gamma_n} \quad [2]$$

In this equation, γ_n is the dose mean specific energy in the nucleus. The micro dosimetric values γ and γ_n are calculated by using the Geant4 simulation.

The RBE of 10% survival level is estimated using the following formula:

$$RBE_{10} = \frac{D_{10,X-ray}}{D_{10,64Cu}} = \frac{2\beta D_{10,X-ray}}{\sqrt{\alpha^2+4\beta ln(0.1)}-\alpha} \quad [3]$$

In this equation, $D_{10,64Cu}$ is the dose value from emitted particles from ^{64}Cu at 10% survival level and $D_{10,X\text{-}ray}$ is the corresponding dose to 10% survival level when using 200 kVp X-rays. β is linear quadric model parameter using 200 kVp X-rays (10). From formula above, the RBE_{10} can be calculated based on the MK model and Monte Carlo simulation. The parameters of the MK model, the survival parameters in the case of X-ray of U-87 MG cells, are based on previous studies (11). The domain size was set to be 0.5 μm. The specific energy was calculated by Geant4 Monte Carlo simulation.

Result

Figure 2 shows U-87 MG cell in Geant4 simulation. Figure 2(a) shows the simulation geometry. Green line means cell itself, redline means cell nucleus. The purple sphere inside the redline means domain. The center of the simulation coordinates. A domain is placed in a sphere at the center of the U-87 MG cell nucleus. Each domain was placed 2 μm apart in the x, y, z directions. A total of 13 domains were placed inside the cell nucleus. Figure 2(b) shows a histogram of the location of the emitted particles in three dimensions. The particles

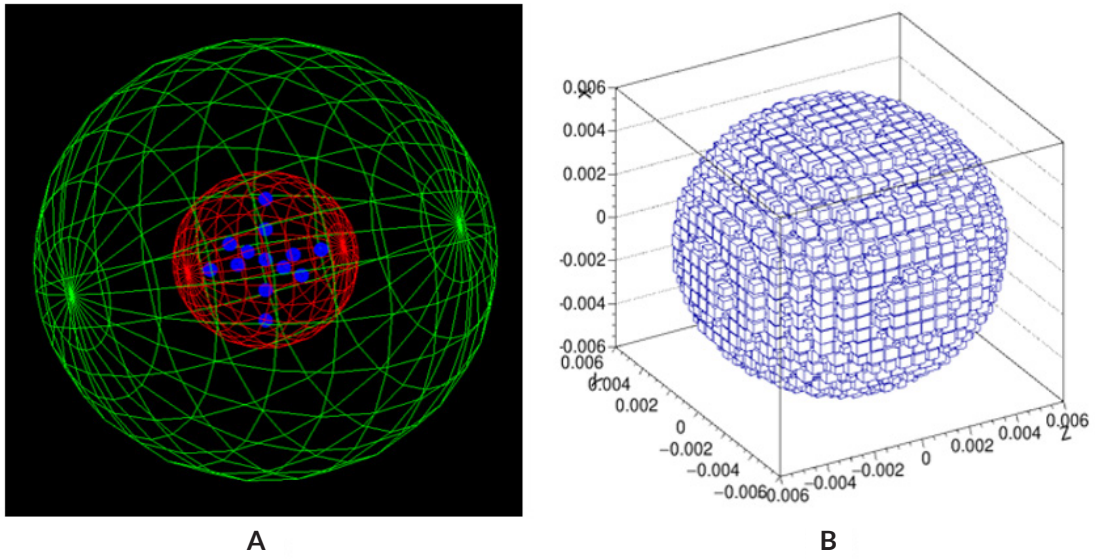

Figure 2. The U-87 MG cell modeling in Geant4 simulation. (A) shows the simulation geometry. Greenline means cell, redline means cell nucleus. The purple sphere inside the redline means domain. (B) shows the point where each particle is generated in three dimensions.

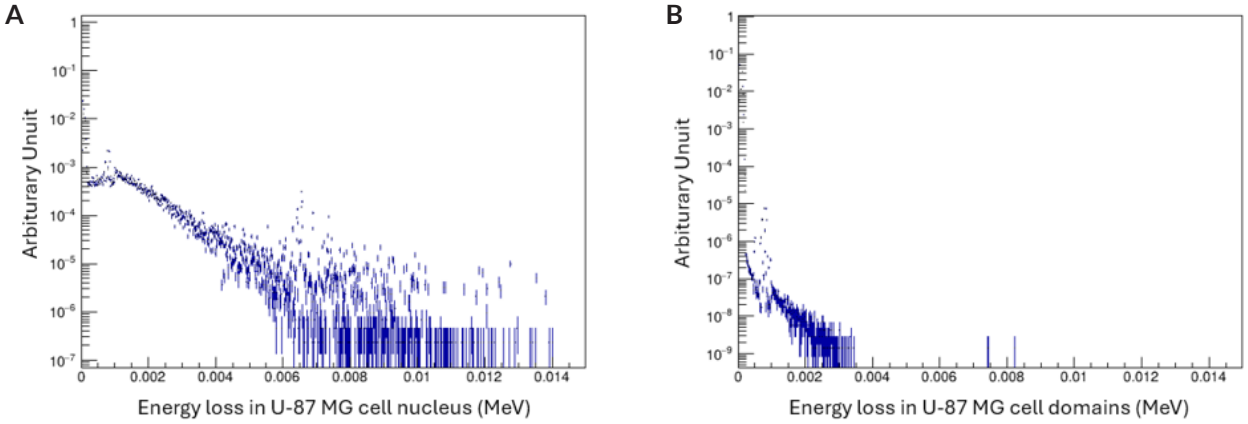

Figure 3. The energy loss of the emitted particles form ^{64}Cu. (a) shows the distribution of energy loss of particles passing through the cell nucleus. (b) shows the distribution of energy loss of particles passing through the domain.

released from ^{64}Cu are evenly distributed in the cell nucleus.

Figure 3 shows the distribution of the energy loss of emitted particles from ^{64}Cu. The energy transferred by the interaction of the secondary borrowers with the cell nucleus causes DNA strand breaks, which is associated with cell death. Therefore, the amount of energy loss is important regardless of the type of particle. The left panel (a) shows the distribution of energy loss of particles passing through the cell nucleus, and the right panel (b) shows the value when passing through the domain. The mean value of energy loss are 217 eV and 35 eV, respectively.

Figure 4 shows the distribution of energy transferred

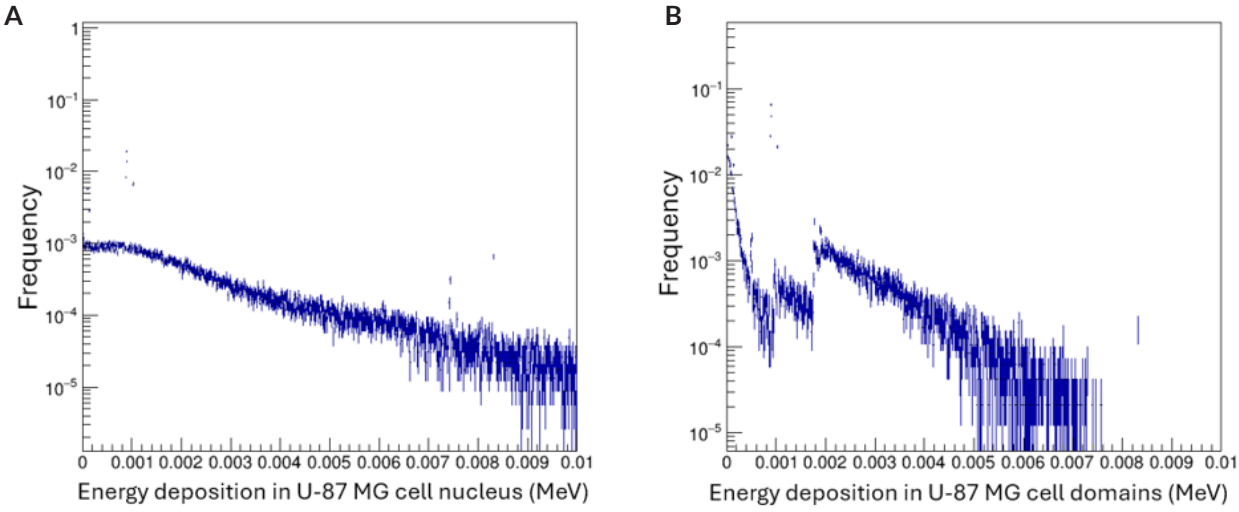

Figure 4. The energy deposition to U-87 MG cell. (A) shows the energy deposition in cell nucleus. (B) shows the energy deposition in the cell domains.

to the cell nucleus and domains by the emitted particles from ^{64}Cu. For the cell nucleus, the mean energy deposition is evenly spread. In case for domains, the energy deposition is populated below 7 keV. The mean value of energy deposition are 107 eV and 21 eV, respectively.

The critical energy deposition values associated with cell survival using the MK model are the dose-weighted average of the specific energy by a single energy deposition event in a region and the specific energy by a single energy deposition event in a nucleus. The two values obtained through Monte Carlo simulation are 97.4 nGy and 27.4 nGy, respectively, and the cell survival parameter α and the biological effect are calculated by applying the MK model using formula (2) and (3). The α value is 0.18 Gy^{-1} and the RBE of 10% survival level of U-87 MG is 1.3.

Discussion

^{64}Cu is a versatile radionuclide that has garnered significant attention for its application in radiopharmaceutical therapy. With a half-life of 12.7 hours, ^{64}Cu can be used for both diagnostic imaging through positron emission tomography (PET) and therapeutic purposes due to its beta-emitting properties. ^{64}Cu, Auger electron emitter, can make concentrated energy deposition over short distances. This property enhances cell killing, making it effective for targeted radionuclide therapy (TRT). Additionally, ^{64}Cu can be a good candidate for radiotherapy because it preferentially accumulates in hypoxic tumor sites where large dose delivery is required.

Recent studies have utilized Geant4 to estimate the biological effects of ^{64}Cu radiopharmaceuticals, focusing on the absorbed dose of emitted particles and their relative biological effectiveness (12, 13). From the results of the simulation and previous biological experiments, the RBE of ^{64}Cu emitted particles on CHO wild-type cells was found to be significantly higher than X-ray and almost equivalent to that irradiated with Carbon ions with a linear energy transfer (LET) of 70 keV/μm. However, the RBE can vary depending on the inherent radiosensitivity of the cells.

In the MK model the specific energy is directly related to the radiation dose. The specific energy in domains reflects the localized energy deposition by ionizing radiation, which contributes to the overall absorbed

dose and thus determines the biological effectiveness. In other words, the MK model assumes that there is a region associated with apoptosis called the domain. The calculation method in this study could have significant clinical benefits in radionuclide therapy by improving the accuracy of predicting the biological effectiveness of radiation treatments. This method links microdosimetric measurements, such as energy deposited at the cellular or subcellular level, to radiobiological outcomes, thereby improving treatment efficacy and reducing potential side effects. However, the domain of MK model is different from the DNA double helix structure that is associated with actual apoptosis. In a recent study, the DNA double helix structure was implemented in the same simulation package and the simulation results for alpha particles with high LET were consistent with the results of existing cell experiments (14). Therefore, validation at the level of the DNA double helix structure will provide a more realistic interpretation of the results of this study (15).

One of the biggest advantages of using the MK model is a clinically validated model that has been adapted for carbon ion therapy and is still being refined. The proposed method in this study is a Monte Carlo simulation method based on the MK model. While Monte Carlo simulation provides unparalleled accuracy at the whole-cell level, the significant hardware requirements and computational time needed to generate a realistic model at the human DNA level pose a significant challenge. This study aims to explore efficient strategies to overcome these limitations and thereby increase the applicability of Monte Carlo simulations in biological research. Therefore, the proposed MK model-based RBE calculation method is expected to be applied in clinical practice and used effectively.

Conclusion

In this study the biological effect of ^{64}Cu radiopharmaceuticals has been calculated using MK model combined with Monte Carlo simulation. The RBE of ^{64}Cu for U-87 MG cell was estimated to be higher than that of X-rays. The suggested method can be seamlessly integrated into treatment regimens that utilize conventional X-ray based radiotherapy. This will be an important step in creating a detailed simulation model to determine the RBE for radiopharmaceutical radiotherapy.

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