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Review

Recent progress in Monte Carlo simulation on gold nanoparticle radiosensitization

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Abstract: Gold nanoparticles (GNPs) are proven effective heavy-atom radiosensitizers to produce imaging contrast and dose enhancement in radiotherapy. To understand the physical and biological effect of adding GNPs to the tumour cells, Monte Carlo simulation based on particle tracking and transport, is employed to predict the dosimetry in the cellular and DNA scale. In this review, we first explore the recent advances in Monte Carlo simulation on GNP radiosensitisation. The development of particle tracking algorithm for very low energy electron in the simulation is discussed, followed by some results regarding the prediction of dose enhancement (microscopic and macroscopic). We then review different Monte Carlo cell models with GNPs in the simulation, the biological effect resulting from DNA damage, and the effects of increasing imaging contrast in the tumour cell due to photoelectric enhancement. Moreover, we explain and look at different studies and results on GNP-enhanced radiotherapy using gamma rays (brachytherapy), megavoltage photon, kilovoltage photon, electron and proton beams.

Keywords: gold nanoparticle; Monte Carlo simulation; radiotherapy; dose enhancement; imaging contrast enhancement

1. Introduction

Radiotherapy is currently used in about 50% of cancer treatments and relies on direct energy deposition into the tumour [1–3]. This energy deposition causes different DNA damages such as double-strand break, which terminates the reproduction ability of the cancer cell [4–8]. Therefore the

tumour is controlled by the therapeutic radiation beam. In radiotherapy, the aim is to produce a conformal dose distribution covering the tumour/target, while sparing the surrounding normal tissues/organs at the same time [9–11]. It is found that heavy-atom radiosensitizers such as gold nanoparticles (GNPs) can increase the imaging contrast as well as the dose at the tumour/target [12–21]. The imaging contrast enhancement can increase the accuracy of the radiation beam targeting, while the dose enhancement can increase the dose absorption in the tumour tissue leading to more cancer cell killing. The rationale behind increasing tumour radiosensitivity regarding GNP addition is that the compositional atomic number of the tumour cell is increased with the GNP uptaken by the cell. This results in a photoelectric effect enhancement, when the target is irradiated by the kilovoltage photon beam [22–24]. The increase of photoelectric electrons improves the imaging contrast between the tumour cell and surrounding normal cells. The photoelectric electrons also increase the energy deposition in the tumour cell to produce a higher cancer control.

Radiation treatment outcome has been improved by adding GNPs in the tumour using the preclinical model. Hainfeld et al. [25] added GNPs of 1.9 nm diameter to the mice bearing the mammary cancer cells. They found that the addition of GNPs highly increased the survival rate of the mice by 86%, compared to only 20% with the irradiation alone and 0% with the GNP addition alone. Hainfeld et al. [26] then performed another preclinical study on using GNPs to treat the radioresistant brain squamous carcinoma. They found that by varying the radiation beam energy, dose fractionation and radiation dosimetry, adding GNPs could increase the treatment outcome of such aggressive squamous cell carcinoma. Since then, many groups started to investigate the role of GNPs in the biological and dosimetric effect in radiotherapy [27–32], and how do the above effects vary with different physical and geometrical parameters of GNP such as the particle size, shape, concentration and distribution [33–37]. To study how the physical and biological effect of GNP addition in the tumour cell ultimately optimizes its therapeutic outcome, computer simulation on the GNP radiosensitization is needed.

Monte Carlo simulation can be used to investigate the physical and biological effect for the GNP addition in radiotherapy. Monte Carlo methods are a broad class of computational algorithms that rely on repeated random sampling to obtain numerical results [38–40]. They are often used in physical, biological and mathematical problems and are most useful when it is difficult or impossible to use other mathematical methods. Since Monte Carlo simulation involves a long computing time, high-performance computing technologies such as cloud computing, parallel processing and GPU processing are used to solve this problem [41,42]. For example, in parallel processing, the processing speed can be improved by using more computing processor/node in Monte Carlo simulation. The dependence of computing time on the number of nodes in Monte Carlo simulation was studied by Chow et al. [43]. Different number of compute nodes from 1 to 50 were used in the Monte Carlo simulation with the computing time recorded. It is found that though applying more number of nodes could reduce the computing time in the simulation, the efficiency of computing time reduction decreased when the number of nodes was increased from 10–50. The optimized number of compute nodes was equal to 6–8 in the simulation and a further increase of node number could not gain a bigger reduction of computing time as expected. This is probably due to the law of diminishing return that extra time would be needed to integrate all Monte Carlo results from the nodes together [44]. The more the number of nodes, the longer the time for dose integration.

In this review, we explain and discuss the recent progress of particle transport and interaction in Monte Carlo simulation, followed by an exploration of some Monte Carlo results regarding dose and

imaging contrast enhancement for GNP addition. Recent studies of biological and imaging contrast effect on GNP addition based on different cell models are reviewed. Finally, we discuss some recent advancements of GNP-enhanced radiotherapy using different types of radiation beams such as gamma rays, photon, electron and proton.

2. Monte Carlo simulation

2.1. Particle interaction and transport

Monte Carlo simulation for nanodosimetry is different from macrodosimetry that secondary electrons have to be tracked down to a very low energy range (~10 eV) in the cellular or DNA medium [19–22,45–47]. Moreover, some particle interactions such as Auger process, which is not significant in macrodosimetry, has to be implemented properly in the nanometer level [48,49]. Unlike in the classical definition of dose which is a function of energy and mass, nanodosimetry focuses on particle track structures in the DNA scale. Since nanodosimetry is necessary to account for the particle track structure resulting in DNA damage to predict the radiobiological effect, the metrology requires a significant reduction of the target volume.

To perform Monte Carlo simulation in biomedical nanotheranostics, Montenegro et al. [50] modified the general purpose Geant4 Monte Carlo code to consider the resonant atomic and molecular transitions of heavy nanoparticles irradiated by monoenergetic X-ray. Their Monte Carlo model considering Auger decays resulted in an enhancement of energy deposition in the GNP layer, and they concluded that their model employing the resonant theranostics methodology could be used to predict energy deposition of tumour enclosed with heavy-atom nanoparticles. He et al. [51] determined the self-consistent coordination-averaged energies for gold atoms based on the energy properties of bulk gold. They performed Monte Carlo simulation on gold films according to the energy barrier determined by the microscopic reversibility principle, and found that the energy barrier was about 0.2 eV for atomic diffusion of gold on the (111) surface undergone a late transition state.

To predict the energy deposition and dose enhancement for GNP addition, a geometric model considering various complex combinations of length scales (heterogeneous multiscale) in a phantom was developed based on the EGSnrc-based Monte Carlo code [52]. By comparing with the published data, Martinov et al. [53] demonstrated that their heterogeneous multiscale model could ensure an accurate prediction for both macroscopic and microscopic effects due to GNP addition. As it is well known that Monte Carlo simulation for macroscopic dosimetry is based on condensed-history models for electron energies larger than few hundred electron volts, these models are not suitable for nanodosimetry, since event-by-event particle tracking was demanded in gold down to 10 eV. Sakata et al. [54] used the Genat4-DNA Monte Carlo code, which was an extension of the Geant4 simulation toolkit, to study the particle track structure for GNPs. The code included discrete physics model for electron transport in gold with full atomic de-excitation cascade. Sakata et al. [54] compared the new physics models with the Geant4 Penelope and Livermore condensed-history models [55] and found that in the submicron sized volumes, only the new physics model could predict the high backscattering that should be present around the GNP in that scale. They therefore concluded the new model was good at particle transport simulation in GNP compared with the condensed-history models of Genat4. He et al. [56] used the Geant4-DNA code to predict the DNA damage due to the dose enhancement of using GNPs in radiotherapy. By constructing a single GNP

very close to the DNA molecule, He et al. [56] found that there was a strong dependency of the dose enhancement on the GNP size, distance to the DNA and photon beam energy.

2.2. Dose enhancement

Comparing Monte Carlo results with and without GNP addition in a homogeneous or heterogeneous medium, dose enhancement could be predicted as per different physical and geometrical parameters of GNPs. Cho [57] carried out Monte Carlo studies using the EGS-based Monte Carlo code based on preclinical results from Hainfeld et al. [25] to determine the dose enhancement for GNP addition in water. Cho tried to vary the polyenergetic photon beams (140 kVp, 4 and 6 MV) and GNP concentration in water using a macroscopic approach. He found that the dose enhancement with GNP irradiated by the 140 kVp photon beam was at least a factor of 2 for gold concentration equal to 7 mg-Au/g-water. For the 4 and 6 MV photon beams, the dose enhancement was only 1% and 7% with the same concentration. Cho also found that dose enhancement increased with gold concentration when the photon beam energy was constant. Zhang et al. [58], instead of using a macroscopic gold-water mixture model as suggested by Cho [57], they used a water phantom model containing 10^{13} GNPs per cm^3 of water. Considering solid GNPs in water, they found that the dose enhancement was up to 60% when the phantom was irradiated by an Ir-192 brachytherapy source. They also found that the gold-water mixture model overestimated the dose enhancement up to 16%. Leung et al. [59], trying to avoid the complex distribution pattern of GNPs in water, considered irradiation of a single GNP using kilovoltage and megavoltage polyenergetic photon beams. Their Monte Carlo results using the Geant4 code showed that the presence of GNP could result in a secondary electron production increased by 10- to 2000-fold compared to an absence of a GNP. They found that majority of energy deposition of the irradiation was outside the GNP but self-absorbed by the nanoparticle, and they concluded that the irradiation of GNP at lower photon energies was more efficient for cancer cell killing. Apart from the EGS- and Geant4-based Monte Carlo code, Hwang et al. [60] used the MCNPX Monte Carlo code to predict the effects of nanoparticle size, concentration, beam energy and material on the dose enhancement in radiotherapy. They found that the nanoparticle concentration had a bigger impact than its size, and the 4 and 6 MV photon beams showed a higher dose enhancement than the 10 and 15 MV beams.

3. Biological and physical effect in cell

3.1. Cell model

To study the biological and physical effect on GNPs added to the cell, different cell models were developed in Monte Carlo simulation. Douglass et al. [61] constructed cell models containing a single GNP randomly positioned in the cytoplasm and a layer of gold (300 nm) enclosed the nucleus of the cell. When the cell was irradiated by an 80 kVp photon beam, they found that the dose enhancement ratio of the GNP depended on the amount of gold and the position of the gold cluster within the cell. Focusing on the positional effect of the GNP in the cell, Zygmanski et al. [62] used the Geant4 code to investigate the simulation geometry of the GNP with varying source-to-GNP distance, beam size, and GNP size. They found that the dose enhancement ratio is very sensitive to the simulation geometry and the relation between the enhancement ratio of a cluster of GNPs and a

single GNP is nonlinear. This demonstrated that parameters such as the number of nanoparticles per cell and distance between the GNP and target would be important to determine the biological effectiveness associated with GNP. Cai et al. [63] modelled human breast cancer cell as a single cell, as monolayer and a cluster with different GNP sizes positioned in the extracellular space, on the cell surface, in the cytoplasm or the nucleus of the cell. They compared their simulated dose enhancement factors with the clonogenic survival of MDA-MB-361 human breast cancer cells with GNP addition and irradiation. Through comparison with experimental data, Cai et al. [63] concluded that their cell model could predict dose enhancement of GNPs for various experimental conditions. Moreover, they found that the GNP position in the cell, beam energy and the number of GNP affected the dose enhancement in the cell. These results agreed with other works [22,33,36,58,59]. To study the biological responses of DNA strand breaks due to the irradiated GNP in the cell, Xie et al. [64] constructed a cell model with detailed DNA structure in the nucleus for Monte Carlo simulation using the PARTRAC code. Their simulation results showed that the presence of GNP produced notable energy deposition enhancement, mainly contributed by the Auger electrons, within a few micrometer from the GNP surface. However, the DNA strand break enhancement was found smaller because of the DNA distribution inside the nucleus (enhancement factor = 1–1.5). Xie et al. [64] concluded that GNP was a good radiosensitizer in radiotherapy. However, other biological effects such as the DNA repair process and cell survival should be followed in order to provide more accurate prediction of enhancement in cancer cell kill.

3.2. Physical and biological effect

Physical effect of imaging contrast in the target can be improved by adding GNP to the tumour so as to change the scattering and absorption properties between the cancer and normal tissue. Using Monte Carlo model, Lin et al. [65] proved that by controlling the optical characteristics of nanoshells in tissue, GNP could be used as an effective contrast agent for optical diagnostics of diseased tissue. Zagaynova et al. [66] performed a small-animal experiment by adding nanoshells to the rabbit skin. They found that there was an increase in the intensity of optical coherence tomography signal in the superficial skin parts. Monte Carlo results from their skin models also demonstrated GNP effect similar to that obtained in the experimental part of the study, which supporting contrast enhancement for GNP addition [67]. Arifler [68] used Monte Carlo simulation to determine the nanoparticle-induced changes in reflectance signals in epithelial tissues with GNP addition. Arifler [68] found that the contrast profile was sensitive to the GNP labelling scheme, optical sensor geometry and wavelength, and concluded that with an optimization of the above parameters, GNP contrast agent could improve the diagnostic potential of optical measurements. To study the X-ray fluorescence signal enhancement for GNP, Manohar et al. [69] developed a Monte Carlo model for a cone-beam X-ray fluorescence computed tomography setup using the MCNP code. The model was verified by measurement based on scatter photon spectra using the 105-kVp cone-beam X-ray filtered by 1 mm of lead or 0.9 mm of tin. From the calculated X-ray fluorescence/scatter spectra data, Manohar et al. [69] concluded their simulation model could help in developing benchtop X-ray fluorescence computed tomography system for preclinical molecular imaging using GNPs. In addition, the imaging contrast enhancement of kilovoltage beam generated by a computed tomography was studied by Albayedh et al. [70] using Monte Carlo simulation. By varying the nanoparticle concentration, beam energy and nanoparticle type, they found that the computed tomography imaging contrast could be improved by adding GNP

to the target and considering high GNP concentration and low photon beam energy.

A Monte Carlo-based GNP radiosensitization model was developed by Lechtman et al. [71] to predict the increased radiobiological effectiveness in GNP-enhanced radiotherapy. The model considered different cell lines, beam energies, GNP sizes, positions and concentrations in the cell, and was verified by experimental cell survival data. On the other hand, Amato et al. [72] studied the anti-angiogenic effect on tumour capillary vessels in GNP-enhanced radiotherapy using Monte Carlo simulation. Using the 150 kV photon beams, the antiangiogenic and cytotoxic effect of GNP addition were investigated by evaluating the GNP diffused out of the tumour vessels. Amato et al. [72] found that the radical dose enhancement factor was related to the GNP concentration, and concluded that the GNP-based radiosensitizer was useful in producing anti-angiogenic and cytotoxic dose enhancement effects. The GNP-induced vasculature damage effect in radiotherapy was also investigated by Lin et al. [73] using Monte Carlo simulation (TOPAS code). They studied this radiosensitizing effect using different kinds of beam, namely, proton, megavoltage photon and kilovoltage photon. By considering the GNP size, beam energy and GNP blood concentration in the vessel, Lin et al. [73] concluded that the addition of GNP had potential to produce vasculature damage through high dose spikes caused by the presence of GNP. This effect would be more significant if GNPs were actively accumulated at the tumour vasculature walls as the nanoparticles could cause very high local dose escalation to the blood vessel disrupting its functionality in the tumour.

4. GNP-enhanced radiotherapy

4.1. Photon beam

Kakade et al. [74] suggested using the polymer gel dosimeter to measure the dose enhancement in GNP-enhanced radiotherapy. The PAGAT gel mixed with different concentrations of GNPs was verified by Monte Carlo simulation using the EGSnrc code. For the 6 and 15 MV photon beams, they found that there was no significant dose enhancement in the GNP-added gel. Therefore, Kakade et al. [74] concluded that the polymer gel dosimetry was a suitable method of dose estimation and verification for clinical implementation of GNP-enhanced radiotherapy. Zabihzadeh et al. [75] carried out a study on the distribution of GNP in radiotherapy using the kilovoltage photon beams (35, 55, 75 and 95 keV). Using the MCNP-4C Monte Carlo code, they found that the 55 keV photons had the highest dose enhancement factor compared to other energies. Moreover, they found that the heterogeneous model was better than the homogeneous for the dose enhancement study, because it was closer to the real distribution of GNPs in the tumour. Brivio et al. [76] used Monte Carlo simulation to evaluate the potential benefit of using GNPs to treat the neovascular age-related macular degeneration with stereotactic radiosurgery. The GNPs were accumulated at the bottom of the macula irradiated by the 100 kVp X-ray. Keeping in mind the need to spare the optic nerve, retina and other surrounding healthy tissues, a dose enhancement of 1.97 could be achieved by using the 20 nm diameter GNP. Moreover, they found that the prescribed dose could be reduced by half to the macular endothelial cells, when using GNPs in the treatment. The radiation dose enhancement in skin therapy was studied by Zheng et al. [77] using Monte Carlo simulation. By comparing various types of nanoparticles made of gold, platinum, iodine, silver and iron oxide, they found that GNP produced the highest dose enhancement in skin therapy using the kilovoltage photon beams. They also found that the dose enhancement depended on the

nanoparticle type, concentration, skin target thickness and beam energy.

4.2. Electron beam

For radiotherapy using electron beams, Chow et al. [78] studied the secondary electron production from a single GNP irradiated by monoenergetic electron beams using Monte Carlo simulation. They found that the mean effective range of the secondary electron increased with an increase of the GNP size and electron beam energy. Moreover, they found that the proportion of energy deposition inside the GNP versus that outside increased with the GNP size. However, an electron source with GNPs was worse than photon source as the secondary electron yield per unit mass of gold was less than water. This result agreed with Zheng et al. [77] when studying the dose enhancement with GNP addition in electron skin therapy. From their Monte Carlo results, Zheng et al. [77] found that electron beams did not produce as high dose enhancement as the kilovoltage photon beams in skin therapy. However, in the cell experiment, Mehrnia et al. [79] determined a dose enhancement of up to 1.62 when the 4 MeV electron beams was used in the breast cancer cells with GNPs. They therefore concluded the 4 MeV electron beams could be applicable for superficial tumour and intra-operative radiation therapy.

4.3. Proton beam

Lin et al. [80] used Monte Carlo simulation to compare the dose enhancements of using megavoltage photon beam, kilovoltage photon beam and proton beam in GNP-enhanced radiotherapy. They found that the predicted dose enhancement with GNP for proton beam could be up to 14, and the dose enhancement was not dependent on the proton energy. They also found that similar amount of energy deposition could be obtained with the GNP interacting with the proton, kVp photon and MV photon within several nanometers from the surface of the GNP. However, secondary electrons produced by the GNP interacting with the kVp photon had the longest range in water compared to the MV photon and proton. They therefore concluded that proton therapy produced significant dose enhancement only if the GNPs were very close to the biological target. Martinez-Rovira et al. [81] also performed Monte Carlo simulation to evaluate the local dose enhancement combining proton therapy and nanoparticles. They found that the local dose enhancement was up to 1.7 when the source was placed on the nanoparticle surface, and for a realistic configuration of simulation model, the local energy deposition was negligible. Martinez-Rovira et al. [81] therefore concluded that the physical effects might only play a minor role in the cell damage, and other effects such as the biological and chemical processes should be responsible for the enhanced radiosensitization observed in experiments. Similar results were obtained by Cho et al. [82] carrying out Monte Carlo simulation on the Auger/secondary electron production from the GNP irradiated by proton. They found out a high dose enhancement of up to 17 in the immediate vicinity (<100 nm) of the gold nanorods. However, the average dose enhancement over the entire vial was minimal. They concluded whereas Auger/secondary electrons production was significant from the GNP/nanorods, it only happened at a short distance smaller than 100 nm from the GNP/nanorods only.

4.4. Brachytherapy

In cancer treatment using the radioactive sources, Bahreyni Toossi et al. [83] compared the tissue dose enhancement between gadolinium nanoparticles and GNPs using Monte Carlo simulation (MCNPX code). Brachytherapy sources of Co-60, Au-198, Ir-192 and Yb-169 were used in the simulation with different concentrations of gadolinium nanoparticles and GNPs. From the Monte Carlo results using a water phantom, they found that GNPs showed higher dose enhancement than gadolinium nanoparticles as a dose enhancer material. Asadi et al. [84] studied the GNP-based brachytherapy enhancement in choroidal melanoma using a Monte Carlo simulation. The I-125 source was used and the simulations based on the MCNP5 code were carried out in a human eye and water phantom. The simulation results showed that the dose at the tumour increased with the GNP concentration inside the target. Therefore, irradiation time could be reduced by adding GNPs prior to the treatment. Asadi et al. [85] then evaluated the normal tissue dosimetry in the human eye using the Pd-103 and I-125 brachytherapy sources, when GNPs were added to the choroidal melanoma. Their Monte Carlo results showed that the I-125 source had a higher dose enhancement than the Pd-103 source. Yan et al. [86] on the other hand, carried out Monte Carlo simulation to study the dosimetric effect in eye radiotherapy using a novel focused kilovoltage X-ray. They compared the full width at half maximum and central axis depth dose of the focused kilovoltage X-ray and an Eyephysics plaque using I-125 seeds. By comparing the dose distribution using simulation, Yan et al. [86] found that the proposed X-ray technique showed advantage in sparing healthy critical organs without sacrificing the tumour control. Moreover, this X-ray beam technique is non-invasive. For other brachytherapy sources, Al-Musywel et al. [87] compared the dose enhancement of Ir-192 and Cs-137 source in GNP-based brachytherapy using Monte Carlo simulation. By varying the GNP concentration, they found that the increase of dose enhancement was more in low-energy photon sources having high GNP concentration up to 30 mg-Ag/g-water. Lai et al. [88] used Monte Carlo simulation to study the dosimetric effect of GNPs conjugated with electron emitting radionuclides (In-111, Lu-177 and Y-90). This labelled GNP depot could improve the dose delivery and uniformity to the target by using a low penetrating electron sources.

5. Conclusion

Monte Carlo simulation is a powerful tool to predict energy deposition in GNP-enhanced radiotherapy. Based on a simulation model containing a radiation source and target with GNP in a bulk tumor or cellular medium, the energy produced by the secondary electrons from the GNP and irradiated volume can accurately be determined as per various parameters such as the GNP size, shape, distribution, concentration, beam energy and the distance between the source and target. Monte Carlo results such as dose enhancement with GNP addition can help to further predict the biological effect related to the cancer cell killing such as the DNA damage. The simulated results help us to gain deeper insight of physical and biological interactions in GNP, which is very useful for the development of next generation heavy-atom radiosensitizer in cancer therapy [89].

6. Future challenges and perspectives

With the recent progress of Monte Carlo simulation on GNP radiosensitization (Table 1), more

accurate Monte Carlo predictions can be achieved by building and improving the particle physics algorithm in the nanometer scale. However, after more than 10 years of study, such intensive research on GNP still has not proceeded to clinical use. This is partially because at present, simulation requires developing a thorough physics model that allows event-by-event electron tracking in gold down to 10 eV, and verifications using the cell or small-animal survival data are limited. In addition, as the concept of nanodosimetry for GNP was new, it took time for people to accept when they considered the classical definition of dose in macrodosimetry which is quite different.

Table 1. Recent advancements of Monte Carol simulations on GNP.

Monte Carlo Studies	Advancements	References
Particle interaction and transport	Auger process in Monte Carlo simulation	48, 49, 50
	Development and verification of the Geant4-DNA code	45, 46, 47, 48, 54, 55, 56
Dose enhancement	Dose enhancement ratio in clinical radiation beams calculated by the EGS, Geant4 and MCNPX code.	8, 57, 58, 59, 60, 70, 77
Cell model	GNP randomly distributed in the cell with different beam types, beam energies and GNP sizes.	61, 62, 63
	DNA structure in the nucleus of a cell.	64
Single GNP	GNP irradiated by photon beams.	54, 56, 59
	GNP irradiated by electron beams.	78
Physical and biological effect	GNP as an imaging contrast	31, 65, 66, 67, 68, 69, 70
	Radiobiological effectiveness and anti-angiogenic effect	13, 27, 28, 35, 49, 71, 72, 73
GNP-enhanced radiotherapy	Photon beams	25, 26, 75, 76, 77
	Electron beams	77, 78, 79
	Proton beams	24, 80, 81, 82
	Gamma rays (brachytherapy)	83, 84, 85, 86, 87, 88

For GNP irradiated by ionizing radiations, more work should be carried out on kilovoltage photon beams as they produce the highest dose enhancement compared to megavoltage photon beams. However, for charged particles such as electrons and protons, there is no substantial evidence of a real advantage when GNPs are added to the tumour.

Moreover, it is expected that more work about the biological effect of cancer cell kill, such as the DNA double-strand break linked to the physical effect from the simulation, can be carried out. Since low-energy electrons can induce complex DNA damage [90], more Monte Carlo studies on how GNP enhances clustered DNA damage are needed. A thorough and comprehensive nanodosimetric Monte Carlo model should be developed for the advancement of GNP radiosensitizer for clinical and diagnosis application.

Conflict of interest

The author declares no conflict of interest.

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