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Research article

Gold nanoparticle DNA damage in radiotherapy: A Monte Carlo study

Chun He [1] and James C.L. Chow [2,3,*]

[1] Division of Engineering Science, University of Toronto, Toronto, ON, M5S 1A4 Canada
[2] Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON M5G 2M9 Canada
[3] Department of Radiation Oncology, University of Toronto, Toronto, ON, M5T 1P5 Canada

*** Correspondence:** Email: james.chow@rmp.uhn.on.ca; Tel: 416-946-4501; Fax: 416-946-6566.

Abstract: This study investigated the DNA damage due to the dose enhancement of using gold nanoparticles (GNPs) as a radiation sensitizer in radiotherapy. Nanodosimetry of a photon irradiated GNP was performed with Monte Carlo simulations using Geant4-DNA (ver. 10.2) in the nanometer scale. In the simulation model, GNP spheres (with diameters of 30, 50, and 100 nm) and a DNA model were placed in a water cube (1 μm^3). The GNPs were irradiated by photon beams with varying energies (50, 100, and 150 keV), which produced secondary electrons, enhancing the dose to the DNA. To investigate the dose enhancement effect at the DNA level, energy deposition to the DNA with and without the GNP were determined in simulations for calculation of the dose enhancement ratio (DER). The distance between the GNP and the DNA molecule was varied to determine its effect on the DER. Monte Carlo results were collected for three variables; GNP size, distances between the GNP and DNA molecule, and the photon beam energy. The DER was found to increase with the size of GNP and decrease with the distance between the GNP and DNA molecule. The largest DER was found to be 3.7 when a GNP (100 nm diameter) was irradiated by a 150 keV photon beam set at 30 nm from the DNA molecule. We conclude that there is significant dependency of the DER on GNP size, distance to the DNA and photon energy and have simulated those relationships.

Keywords: gold nanoparticle; DNA; Monte Carlo simulation; dose enhancement; radiotherapy

1. Introduction

Radiotherapy is commonly employed option in cancer treatment which uses ionizing radiation. The therapy is used to control cancer/tumor cells by delivering a specific radiation dose in order to

cause lethal genetic damage within tumor cells [1–3]. One challenge in radiotherapy is that the radiation not only damages the targeted cancer cells but also surrounding normal cells resulting in various side effects such as skin irritation, nausea, fatigue, and secondary cancers [4]. Delivered dose to the tumor must be weighted against the predicted dose to healthy structures, defining limits for the treatment prescription. In order to minimize the damage of normal cells surrounding the tumor cells, research into radiation sensitization, which is capable of increasing the tumor cell susceptibility to radiation, receives significant attention [5,6]. In radiotherapy, radiation sensitizers can be used to enhance the therapeutic ratio of treatment. As the sensitizer can also enhance the image contrast of the tumor, the accuracy of radiation beam targeting is also improved [7–10].

Gold nanoparticles (GNPs) have been proposed as an effective radiation sensitizer [11–14] and there are multiple properties of GNPs that make it an ideal material for radio-sensitization. First, GNPs have ability to enhance the radiation effect to a large surrounding area that does not require the NPs to be delivered to all tumor cells [15]. Second, GNPs are known to have low systemic clearance allowing the NPs enough time to be absorbed by the tumor. GNPs are also well absorbed into the circulatory system and thus can easily permeate the tumor and along with the low systemic clearance results in an enhanced permeation and retention effect [16]. Moreover, it is easy to vary the size and shape of GNPs so one can achieve optimum delivery and effects based on the tumor size and location [17]. GNPs are inert and highly biocompatible. Therefore, it is safe for patients who use GNP as a radiation sensitizer. Gold is also chosen due to its large atomic number (compared to a tumor or water), which leads to a larger photoelectric cross section, increased secondary electron production and thus a higher dose enhancement than many other materials [7,10]. Regulla et al. studied the dose enhancement effects of metallic gold surfaces irradiated by photon beams [18]. It was verified through experiments that enhancement of up to a factor of 100 was found in polymethylmethacrylate situated close to the metallic gold foil.

GNP addition to tumors was studied in the preclinical stage of radiotherapy. Herold et al. showed that 1% of GNPs contained in a solution can increase average doses by 42–43% for 200 kVp photon beams [19]. They reported that injecting GNPs with sizes of 1.5–3.0 μm to the mice could have dose enhancement effects on tumors. In another work, Hainfeld et al. reported that with injection of GNPs into tumors in mice increased their one-year survival rate to 86% compared to 20% without injection of GNPs [20]. Hainfeld et al. also did an intravenous injection of GNPs into mice with squamous cell carcinoma and compared the results of irradiating mice with and without GNPs. They found that tumors in the mice with GNPs during irradiation shrunk much faster than without GNPs, and 9 of 10 mice had no visible tumors within one month [21]. For estimation of the dose enhancement effect due to GNP addition, Cho conducted Monte Carlo simulations on modalities of the 140 kVp, 4 and 6 MV photon beams, and 192-Ir gamma rays [22]. Cho's simulation results showed that a dose enhancement of larger than 10% could be achieved with low-energy photon beams and 192-Ir gamma rays. On the other hand, high-energy photon beams (4 and 6 MV) did not see a significant dose enhancements using GNPs. Cho's simulation, however, was estimated macroscopically over the tumor volume, and suggested further simulation was necessary to investigate GNP as a radiation sensitizer in the micrometer (or nanometer) scale.

Leung et al. and Chow et al. used Geant4 Monte Carlo code to simulate the interaction of GNPs with photons and electrons [23–25]. They calculated the effective range, deflection angle, dose deposition, and interaction processes of secondary electrons produced by radiation. Their simulation results showed that with GNPs, secondary electron production increased by a factor of 10 to 2000

compared to radiation without GNPs. This was particularly pronounced for low-energy (50–250 kVp) photon beams that had a significantly higher production of secondary electrons. However, Leung et al. did not consider the interaction between the GNPs and DNA at the nanometer scale [23]. To perform Monte Carlo simulations for nanodosimetry, Monte Carlo code such as the Geant4-DNA should be used in this case as it can simulate the physical processes of low-energy particle interactions used for modeling DNA damage induced by ionizing radiation [26].

In this study, the effect of DNA damage due to the dose enhancement of GNP addition was studied using a Monte Carlo simulation. In order to understand variations of dose enhancement using GNPs as a radiation sensitizer, the simulation examined different sizes of GNP, distances between the GNP and the DNA, and photon beam energies. Moreover, the dosimetric impact of coating the GNP surface for protective purpose was investigated by Monte Carlo simulation. With simulation results of various irradiation setups, the most effective configuration for GNPs as a radiation sensitizer can be predicted at the nanometer scale.

2. Materials and Method

2.1. Simulation geometry

A spherical GNP was centered inside a cube of water with dimensions of $1 \times 1 \times 1$ μm^3. A DNA molecule was placed on the right-hand side of the GNP at distances of 30, 80 and 130 nm as shown in Figure 1. The GNP was irradiated by photon beams with energies equal to 50, 100, 150 and 200 keV. The photon source was 200 nm from the left-hand side of the GNP along the horizontal axis, and the diameter of the photon field was twice that of the diameter of the GNP. The central beam axis was set to the center of the GNP. Three GNP sizes (diameters of 30, 50 and 100 nm) were used for the Monte Carlo geometry [23–25]. In the simulation, secondary electrons produced by the photon-irradiated GNP deposited energy upon reaching the DNA molecule. The energy accumulated in the DNA was then estimated and used to calculate the dose enhancement ratio (DER). In order to predict the secondary electron production in water without the GNP, the simulation was repeated using the same geometry except the material of the NP was changed from gold to water.

2.2. Monte Carlo simulation

The energy deposition in the DNA due to the irradiated GNP was predicted by Monte Carlo simulation using the Geant4-DNA code (ver. 10.2) [27]. Geant4 is a Monte Carlo software toolkit developed by CERN that provides a set of physical processes for the transport and interaction of particles with matter [28,29]. The software can construct the environment of the irradiated GNP attached to the DNA in water, and set the DNA as a dose scorer to calculate the total energy deposition. Geant4 requires users to have CMake3.3 or higher to run the code, C++ Compiler and Standard Library supporting C++ 11 Standard for programming [30]. Geant4-DNA provides a virtual machine containing CentOS Linux, the latest version of Geant4 (ver. 10.2), visualization tools, analysis tools, and other utilities. VMware workstation 12.1.0 was used for running the virtual machine. The code was run on a virtual machine because the machine has all the pre-installed software that needed by Geant4 and made the entire process closely follow the documentation provided for Geant4. Moreover, the instructions given by CERN recommend running on the Linux

operating system (OS).

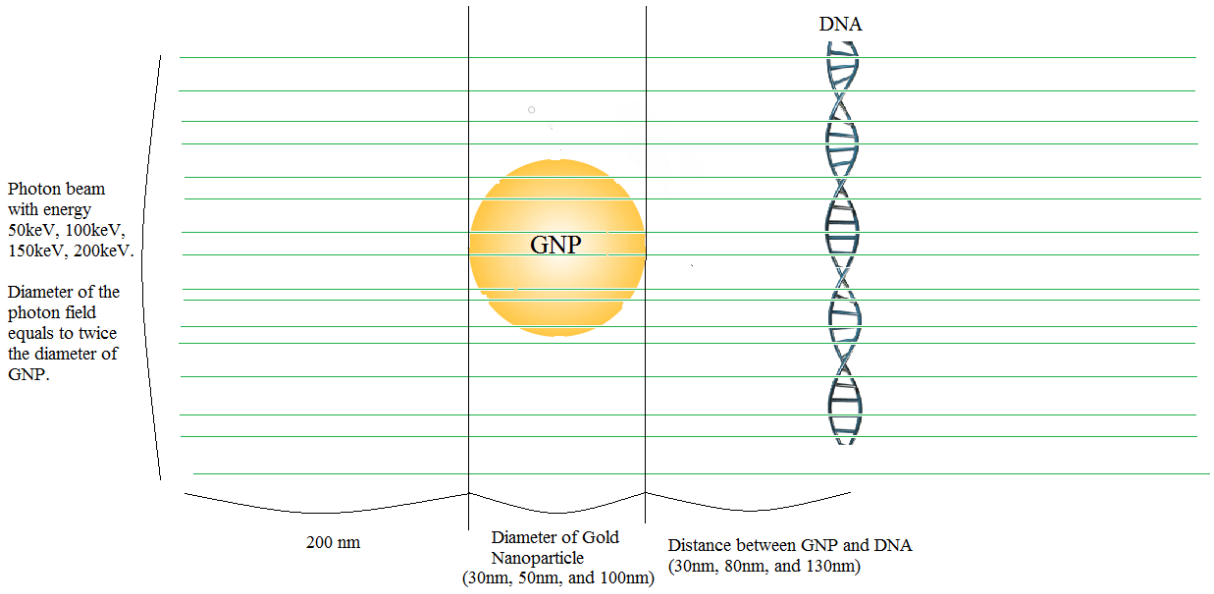

Figure 1. Schematic diagram showing the geometry of the Monte Carlo simulation.

2.3. GNP coating

Since NPs are in the nanometer scale and possess a high surface-to-volume ratio, it is extremely reactive in a medium. In order to stabilize the NP in water or in a solvent, a coating is needed as a protective layer [31,32]. Generally, citrate or polymers such as polyethylene glycol (PEG) or polyvinyl alcohol (PVA) are used as the coating material for the GNP [33,34]. Although the coating layer is very thin (1–6 nm) and mainly made of low atomic number elements such as carbon, oxygen and hydrogen, there is concern that the coating would affect the secondary electron production during irradiation. In this study, we examined the impact of the coating layer on the dose enhancement of GNPs. Dose enhancements of the GNP with and without coating were compared in different sizes of GNP and photon beam energies. Three coatings, namely citrate ($C_6H_8O_7$), PEG ($C_{2n}H_{4n+2}O_{n+1}$) and PVA $(C_2H_4O)_n$ were used.

2.4. Dose enhancement ratio

The enhancement of energy deposition leading to DNA damage due to the addition of GNPs can be determined using the DER defined as:

$$DER = \frac{Dose\ in\ the\ DNA\ with\ GNP\ addition}{Dose\ in\ the\ DNA\ without\ GNP\ addition} \quad (1)$$

To calculate the dose to the DNA without GNP addition, the material of the NP was changed from gold to water, which mimicked the absorption of tumor mass (we assumed water equivalence). It is seen in Equation (1) that if there is general dose enhancement from the presence NPs, the DER should be larger than one [35].

3. Results and Discussion

3.1. Effect of GNP coating

Table 1 shows the average DER of GNPs of different sizes (diameters of 30, 50 and 100 nm) irradiated by 50, 100, 150 and 200 keV photon beams for the various coatings. It is seen that the addition of coating on the GNPs did not affect the dose enhancement compared to the GNPs without coating. The unchanged DER showed that the effect of the polymer coating on secondary electron production from the GNPs was insignificant. This may be due to the small interaction cross-sections of the carbon, hydrogen and oxygen atoms having relative small atomic numbers. Therefore, the energy deposition in the DNA was likely unaffected by the GNP coatings.

Table 1. Average DER with the GNP coating using different materials.

Photon beam energy (keV)	No coating	Citrate	PEG	PVA
50	2.4	2.4	2.4	2.4
100	2.7	2.7	2.7	2.7
150	2.8	2.8	2.8	2.8
200	2.8	2.8	2.8	2.8

Tables 2–5 show the DER for 50, 100, 150 and 200 keV photon beams, different sizes of GNPs and distances between the GNP and DNA.

Table 2. Average DER of the 50 keV photon beams with different sizes of GNP, and distances between the GNP and DNA.

DER		Distance (nm)		
		30	80	130
Size in diameter (nm)	30	2.3	2.2	2.2
	50	2.4	2.3	2.3
	100	2.9	2.7	2.6

Table 3. Average DER of the 100 keV photon beams with different sizes of GNP, and distances between the GNP and DNA.

DER		Distance (nm)		
		30	80	130
Size in diameter (nm)	30	2.7	2.6	2.4
	50	2.7	2.6	2.5
	100	3.1	3.0	2.8

Table 4. Average DER of the 150 keV photon beams with different sizes of GNP, and distances between the GNP and DNA.

DER		Distance (nm)		
		30	80	130
Size in diameter (nm)	30	2.2	2.2	2.2
	50	2.8	2.8	2.7
	100	3.7	3.5	3.2

Table 5. Average DER of the 200 keV photon beams with different sizes of GNP, and distances between the GNP and DNA.

DER		Distance (nm)		
		30	80	130
Size in diameter (nm)	30	2.5	2.3	2.2
	50	2.7	2.7	2.6
	100	3.5	3.4	3.3

3.2. Dependence of the size of GNP on DER

In Tables 2–5, it is seen that the DER increased with the size of the GNP. This shows that a larger GNP generates more secondary electrons than a smaller one. This GNP size effect was most significant for the 150 keV photon beams, where the DER was increased by 68%, 59% and 45% when the distances between the GNP and DNA were equal to 30, 80 and 130 nm, respectively. When the photon beam energy was less than or equal to 50 keV, the DER was only increased by 26%, 23% and 18%, for distances of 30, 80 and 130 nm, respectively. These results agreed well with our previous work focusing on the secondary electron production and particle interaction [23,35]. In addition, it should be noted that the DER calculated in this study was only based on the energy deposited within the DNA. It was independent of the energy deposition which was self-absorbed by the GNP [23]. It can be seen from Tables 2–5 that the DER of the DNA increased from about 2.2 to 3.7 when the diameter of the GNP increased from 30–100 nm using photon beam energies of 50–200 keV. This shows that a larger GNP can lead to larger energy deposition and thus damage to the DNA.

3.3. Dependence of the distance between the GNP and DNA on DER

In a preclinical GNP-enhanced radiotherapy study, GNPs were delivered to the tumor of mice by injection. The uptake of GNPs is based on a natural mechanism due to the vascularization of tumors and increased permeability within the tumor vasculature because of angiogenesis [36,37]. When the GNPs are taken up by the tumor cell, some of the GNPs move inside the cell nucleus and are therefore very close to the DNA. In this study, the distance between the GNP and DNA was changed to affect the transport of secondary electrons produced from the photon-irradiated GNP. In Tables 2–5, the DER of the DNA was found only slightly increased when the distance between the GNP and DNA decreased from 130 to 30 nm. For photon beam energy of 100 keV, the DER of DNA only increased from 8% to 13% as shown in Table 3. Since the uptaken GNPs could be transported to any position inside the tumor cell nucleus, it is seen that the closer the GNP is to the DNA, the larger

the dose enhancement and thus DNA damage [23]. This is because the short distance between the GNP and DNA makes the interaction of secondary electrons from the GNP more probable, causing additional double-strand breaks [38].

3.4. Dependence of the photon beam energy on DER

When a material of a high atomic number is introduced into a medum such as water, it is well-known that dose enhancement can be achieved by irradiating the material with kV photon beams. This dose enhancement effect is due to the large increase in photoelectric cross-section of for photon beams in the kV energy range [7]. Compared to MV photon beams, Leung et al. found that the interaction ratio of kV photon beams (50–250 kVp) from irradiated GNPs were approximately 2000–300, while for higher beam energies (MV) the ratio was approximately 10 [23]. Unlike MV photon beams, which have an adequate penetrative power to treat deep-seated tumor in patient, kV photon beams are used to treat superfical lesions, and are currently used in orthovoltage and intraoperative radiotherapy [39,40].

In Tables 2–5, it is seen that there is no significant variation between the photon beam energy and DER in the kV photon beam range of 50–200 keV. The DER of DNA varied between 2.2 and 3.7 in that energy range with different sizes of GNP and distances between the GNP and DNA. Moreover, our Monte Carlo results are closer to the observed experimental radiosensitizations [41] when compared to the predicted dose enhancements based on the GNP concentration, source energy and mass energy attenuation coefficient [42].

4. Conclusion

Dose enhancement in the DNA due to GNP addition was determined at the nanometer scale using kV photon beams. It was found that kV photon beams can be enhanced by GNPs by factors of 2.2–3.7 compared to photon beams with no GNPs. From the Monte Carlo results, the largest DER was found for the 100 nm diameter GNP located 30 nm from the DNA molecule, and irradiated by a 150 keV photon beam. It is concluded that the dose enhancement of the DNA varied with the size of the GNP, distance between the GNP and DNA, and slightly varied with the photon beam energy. Future work will include photon beam energy in megavoltage range.

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Conflict of Interest

The authors have no potential conflict of interests on financial or commercial matters associated with this study.

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