

## Study on the Dose Enhancement of Gold Nanoparticles When Exposed to Clinical Electron, Proton, and Alpha Particle Beams by Means of Geant4

### Abstract

**Background:** Various factors effecting deposited energy and dose enhancement ratio (DER) in the simplified model of cell caused by the interaction of a cluster of gold nanoparticles (GNPs) with electron beams were assessed, and the results were compared with other sources through Geant4 Monte Carlo simulation toolkit. **Method:** The effect of added GNPs on the DNA strand breaks level, irradiated to electron, proton, and alpha beams, is assessed. **Results:** Presence of GNPs in the cell makes DER value more pronounced for low-energy photons rather than electron beam. Moreover, the results of DER values did not show any significant increase in absorbed dose in the presence of GNP for proton and alpha beam. Moreover, the results of DNA break with GNPs for proton and alpha beam were negligible. It is demonstrated that as the sizes of the GNPs increase, the DER is enlarged until a certain size for 40 keV photons, while there is no striking change for 50 keV electron beam when the size of the GNPs changes. The results indicate that although energy deposited in the cell for electron beam is more than low-energy photon, DER values are low compared to photon. **Conclusion:** Larger GNPs do not show any preference over smaller ones when irradiated through electron beams. It is proved that GNPs do not significantly increase single-strand breaks (SSBs) and double-strand breaks during electron irradiation, while there exists a direct relationship between SSB and energy.

**Keywords:** Dose enhancement, Geant4, gold nanoparticles, ionizing radiation, strand break

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### Introduction

Cancer and its treatment are vital issues worldwide.<sup>[1]</sup> Radiotherapy (RT) plays a major role in cancer treatment by killing cancer cells and controlling tumors.<sup>[2]</sup> The goal of RT is not limited to introduce lethal dose inside the tumor, but it is also to protect the surrounding normal tissues from potential harms.<sup>[3]</sup> Nevertheless, the limitation of this effort is the resistance of tumor cells to radiation.<sup>[4]</sup> To increase the radio-sensitization of tumor cells, the internalization of high atomic number nanoparticles was proposed. The cross-sections of ionizing radiation interaction are significantly higher for these materials rather than liquid water. Consequently, the absorbed dose is increased and the performance of radiation therapies is enhanced in tumor tissues,<sup>[5]</sup> but this idea has some restrictions such as cancer cell targeting and

toxicity.<sup>[6]</sup> Due to their particular features, gold nanoparticles (GNPs) are of interest in RT since they can easily penetrate into tumor cells because of their small size. The nonrelatively toxic nature of GNPs is the reason for its common use.<sup>[5,6]</sup> Moreover, photoelectric absorption in the presence of high Z materials increases with photon energy; especially at keV energy range, it leads to an increased dose. Stoppage and scattering of electrons in the tissues loaded with GNPs are more than those in cells without GNPs. The interaction between proton radiation and gold generates much localized secondary radiation and low-energy delta ray electrons because of a high cross-section of gold.<sup>[7,8]</sup> Despite the energy and source, there are some important factors that affect dose enhancement and cellular uptake. Some of these features such as size, concentration, and distribution of NPs are dependent on NPs' geometry.<sup>[9]</sup> To date, several simulation geometries have been applied to define simulation sets. They

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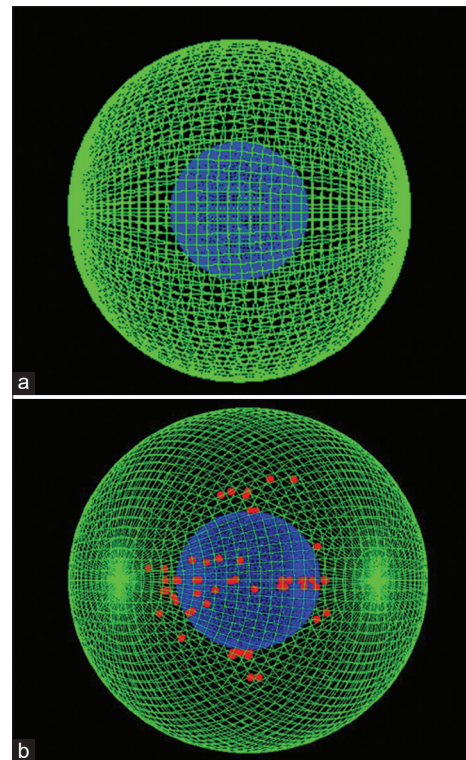
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include assessment of the effect of a NP with different geometries on energy deposition in different media as follows: single spherical GNP in water phantom,<sup>[5,10]</sup> approximately uniform distribution of GNPs with a specific weight fraction throughout the ICRU tissue,<sup>[11]</sup> and homogeneous distribution of NPs through the tumor using MCNPX code.<sup>[12]</sup> Some studies confirm that NPs are absorbed and become accumulated in the cells through endocytosis. They form clusters of GNPs in the cytoplasm, and their distribution in different parts of the cell cannot be uniform.<sup>[13]</sup> Up to now, dose enhancement has been examined for simplified geometries subject to macroscopic conditions; on the contrary, the relationship between dose enhancement and multiple GNPs is not completely identified.<sup>[14]</sup> Finally, some researchers have concluded that dose enhancement is a function of the size of the NPs.<sup>[10,15]</sup> The results obtained from simulation studies indicate that irradiation of big-sized GNPs with proton and photon beams increases the dose in the tumor. Nevertheless, it is proved that a saturation effect occurred on the DER when the NP shell was too thick.<sup>[16]</sup> This newly proposed model is to assess the optimum features of GNPs structure parameters such as the size. Here, the impact of different irradiation sources including photon, electron, proton, and alpha with different energies on the absorbed dose in the target is assessed. Damaging DNA means stopping the growth of cancerous cell or cell kill.<sup>[17,18]</sup> It is assumed that DNA is hurt through single-strand break (SSB), double-strand break (DSB), and base damage due to ionizing radiation in the cellular DNA.<sup>[2,18]</sup> In this study, the amount of SSBs and DSBs in the presence of GNPs in the irradiated cells with electron beams is calculated using the Geant4-DNA toolkit.

## Materials and Methods

### Simulation geometry and setup

The Geant4 Monte Carlo simulation toolkit is applied here because of its extended functionality in dosimetry, microdosimetry, and nanodosimetry, in radiobiological experiments irradiated with photons, electrons, protons, and alpha particles.<sup>[19]</sup> By selecting the Livermore physics list, modeling the physical interactions within the target volume is accomplished because it is capable of simulating the dose distribution in the cells for beam energy values down to 250 eV.<sup>[20]</sup> Since this hit does not hold true for microdosimetric track structures, no prediction on DNA strand breaks is possible.<sup>[3,21]</sup> In the Geant4-DNA process, the details of interactions of particles through a liquid-water medium are simulated to assess the cellular damages.<sup>[3,4]</sup> In this study, the Livermore and Geant4-DNA physics were used to compute the energy deposition in different regions of cell model. Since Geant4-DNA physics and Geant4 electromagnetic physics apply the same software design, this combination is possible.<sup>[5]</sup> The modeled cell consists of a spherical cytoplasm with a radius of 5  $\mu\text{m}$  and a



**Figure 1: Schematic diagram of the geometry of the Monte Carlo simulation: (a) 2  $\mu\text{m}$  spherical nucleus (blue) at the center of the spherical cytoplasm with diameter of 5  $\mu\text{m}$  (green). (b) Nanoparticles (red) with concentration of 10 mg/g distributed randomly in vicinity of nucleus**

nucleus with a radius of 2  $\mu\text{m}$  placed at the center of the cytoplasm based on Byrne *et al.*'s study<sup>[22]</sup> [Figure 1a]. The liquid water is considered a cytoplasm and nucleus material, which is a more realistic estimation of the biological matter.<sup>[5,18]</sup> Confocal images obtained from cell population in the experimental studies clarify that NPs are generally placed around the cell nucleus but do not enter it.<sup>[7,16]</sup> Therefore, they were arranged in an orderly manner in the cytoplasm in the vicinity of the nucleus [Figure 1b]. The investigated concentration is about 10 mg/g in the cell. To calculate the number of NPs in the cytoplasm at a given concentration, the volume and density of GNPs and the cells are used:<sup>[23]</sup>

$$N_{NP} = C \frac{\rho_C}{\rho_{NP}} \left( \frac{r_C}{r_{NP}} \right)^3 \quad (1)$$

Where  $r_C$  and  $\rho_C$  are the radius and density of the cell, respectively. In addition,  $C$  is a given concentration and  $r_{NP}$  and  $\rho_{NP}$  are the radius and density of NPs, respectively.

The cell is irradiated by a planar source with dimensions of 6  $\mu\text{m} \times 6 \mu\text{m}$ . The source is originated on 6  $\mu\text{m}$  from the left-hand side of the cell along the  $z$  axis. In order not to prevent the effect of the source-related parameters on the results, the source characteristics of different types of radiation were kept constant, and only the energy and type of radiation were changed during simulation.

The number of primary projectiles used in each simulation was  $10^7$ . The dose was calculated in both nucleus and cytoplasm. The dose enhancement ratio (DER) is the ratio of absorbed dose in the cytoplasm or nucleus with and without the presence of GNPs:

$$\text{DER} = \frac{\text{Absorbed dose with GNPs}}{\text{Absorbed dose without GNPs}} \quad (2)$$

### Influence of beam energy and sources

To deliver an appropriate amount of dose to the target volume in cancer therapy, particle beams such as protons and alpha particles are applied in the clinical trial.<sup>[13]</sup> In many studies, the effects of the combination of these sources such as proton,<sup>[5,7,15]</sup> electron,<sup>[24,25]</sup> and alpha particle<sup>[13]</sup> with NP are assessed, which admit the advantages of these methods in RT and improve treatment. The effectiveness of GNPs' presence in cell killing for low and high Linear Energy Transfer (LET) radiations is observed in an *in vitro* study, where the production of hydroxyl radical increases in the medium.<sup>[2]</sup>

The effect of different energies and sources on dose absorbed in the cytoplasm and nucleus in our geometry is calculated by choosing proton and alpha irradiation with different megavoltage energies and photon and electron beam, mainly for keV energies.

### Effect of gold nanoparticle size

The 50 keV electron beam and 40 keV photon irradiations were selected to record the correlation between energy deposition and NP size. For the same concentration of GNPs, the NP size is within 20–150 nm range. The effect of GNP size was investigated only for electron and photon. The reason is that our main goal was to assess the effect of GNPs size under electron irradiation. In addition, the computation time for calculating dose by the used geometry is too long.

### Effect of gold nanoparticles on DNA single-strand breaks and double-strand breaks

WholeNuclearDNA example in GEANT4-DNA provides the development of detailed DNA and cellular geometries through its DetectorConstruction class.<sup>[26]</sup> For this purpose, in this part of our study, GNPs are added into the Geant4-DNA extension to assess the effects of different GNPs sizes and electron beams with different energies on SSBs and DSBs, in comparison to the same simulation conditions in the absence of GNPs. A DSB is assumed when two SSBs are placed in opposite strands, and the distance between them is less than or equal to 10 base pairs.<sup>[27,28]</sup>

## Results

### Effect of energies and sources

#### Proton radiation

The amounts of DER in the nucleus and cytoplasm in the presence or absence of GNPs during exposure to proton are

summarized in Figure 2. The DER is more pronounced for nucleus than the cytoplasm is, and this finding indicates that DER is almost constant in both cases. There is no significant effect on the nucleus, and the DER is about 1 in this region. For the cytoplasm, the volume of DER is below 1. The obtained results show that there is a slightly higher DER in the nucleus than in the cytoplasm. The reason is that low-energy electrons have a short range and deposit their energy in relatively close distance from NPs. It is demonstrated that interaction of the proton or secondary electron with high Z material produced more low-energy electrons in proton therapy, which induced additional direct and indirect damages to cells.<sup>[5]</sup> It is observed that a small increase in secondary electrons is obtained with a range of proton energies (1–250 MeV) compared to photons.<sup>[7]</sup> Previous studies confirmed that their energy is deposited near NPs.<sup>[29]</sup> It is revealed that Auger and secondary electrons significantly contribute to dose enhancement caused by proton irradiation, but only at short distances (<100 nm).<sup>[30]</sup>

#### Alpha irradiation

The DER data, as a function of alpha energy in both areas, are illustrated in Figure 3. Mono-energy alpha particles with energies from 0.3 to 10 MeV were selected. The DER in the cytoplasm remains almost constant for all energies. As for the nucleus case, DER volume is below 1–2 MeV, and then, it reaches a plateau around 1 for higher energies.

#### Electron beam

Comparison of DER in the target with or without GNPs when exposed to electron beams with energies within 50 keV to 15 MeV range is assessed [Figure 4]. It is observed that DER volume is below 1 for low-energy electron, and then, it is increased to around 1 in the nucleus for higher energies. Applying GNPs has no advantages in DER in the cytoplasm; hence, the DER volumes in the cytoplasm are below 1 at all energies. The efficiency of GNPs is assumed to be failing when an electron beam is used.

Electrons interact with matter via inelastic collisions with atoms and molecules and radiative interactions. Inelastic collisions result in excitations and ionizations, resulting

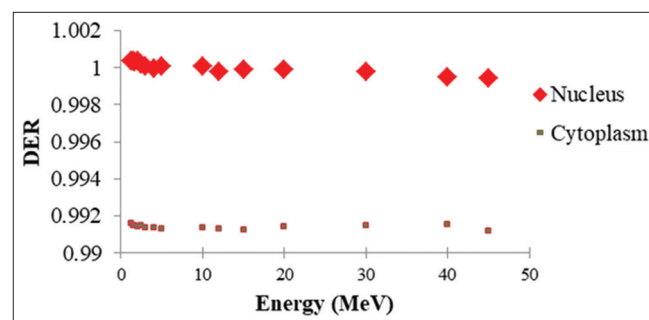


Figure 2: Dose enhancement ratio in the cytoplasm and nucleus when gold nanoparticles are irradiated with protons with different energies

in secondary electrons.<sup>[31]</sup> The interactions between high-energy electron beam and matter are carried out by processes such as ionization or radiative losses. The probability of electron radiative losses increases in the presence of high Z NPs, which produced photon inside the target. The energy lost to radiative losses is spread farther before it is absorbed.<sup>[32]</sup>

*Photon beams*

In Figure 5, the y axis is the DER determined based on photon energies, the x axis. Results show the DER in the nucleus versus cytoplasm. Here, a general trend of an increase in DER volumes at low energy is evident. It is noted that the magnitude of higher DER volumes is about 5 for the cytoplasm and about 8 for the nucleus both at 30 keV. The DER is approximately 1 for high-energy photons

and follows a similar trend in both areas. According to the energy of the photon beam, several interactions such as Compton scattering and photoelectric effects can occur between photon beam and materials.<sup>[33]</sup> The photoelectric effect is dominated at lower energies and reaches a maximum, which relies on the material under consideration. Due to the photoelectric effect, photoelectrons and Auger electrons are created.<sup>[33]</sup> The cross-section of the photoelectric effect and high Z materials was high; therefore, GNPs enhanced the dose in the target.<sup>[3,10,23]</sup> It is revealed that two peaks corresponding to K and M edge energies exist in high Z materials such as gold and bismuth. At higher photon energies, Compton scattering occurs, which is independent of Z.<sup>[33]</sup> It is proved that the absorbed dose in the nucleus and nucleolus is higher than that in other regions because they are in the vicinity of GNPs.<sup>[3]</sup>

**Effect of nanoparticle size on absorbed dose**

The deposited energy of GNP in the nucleus of different sizes exposed to 50 keV electrons and 40 keV photons in the nucleus is tabulated in Table 1. The total dose for exposure by 50 keV electron beams is higher than that of the 40 keV photons. The reason is that the dose deposition patterns arising from photon and ion interaction with biomaterials are different.<sup>[34]</sup> The average absorbed dose is about 3158 Gy when electron beams are applied. The dose values are almost uniform in all different GNP sizes. In addition, there are no striking changes in absorbed dose in the nucleus with or without GNPs in electron case. Changes in DER volumes with respect to GNPs size in the nucleus for electron beams and photon irradiations are tabulated in Table 1. It is observed that DER for electron beams is negligible. The maximum value of DER for 20 nm GNPs, in this case, is approximately 1.008. In addition, the size affects DER when exposed to 40 keV photons. The DER volumes increase as GNPs sizes increase up to GNPs, with 80 nm diameter. It is proved that the probability of secondary electrons generation gets higher as the GNPs diameter is increased.<sup>[10]</sup> It is understood from the data in Table 1 that as NP diameters increase, the DER starts to decline due to self-absorption effect, which prevents secondary electrons from escaping from NPs to their outer surface.<sup>[16]</sup>

As observed in Table 2, the dose increased in the presence of GNPs for photon irradiation, something that does not hold true for electron beams. As the size of GNPs increased, the dose in the cytoplasm fluctuated and slowly increased up to GNPs with the size of 100 nm and then decreased for photon beams; however, the numerical volume of dose with or without GNPs is almost the same for all GNPs sizes in the case of electron beams. The results of this assessment on DER, as a function of the size of NPs for the selected monoenergetic photon source of 40 keV and 50 keV electron beam irradiation, are tabulated

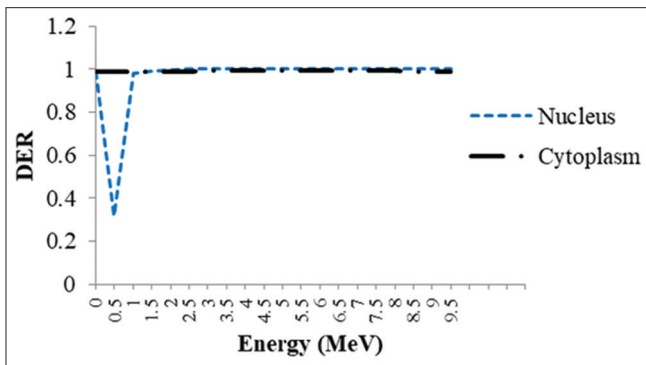


Figure 3: Comparison of dose enhancement ratio in the cytoplasm and nucleus with or without gold nanoparticles when exposed to alpha particles with different energies

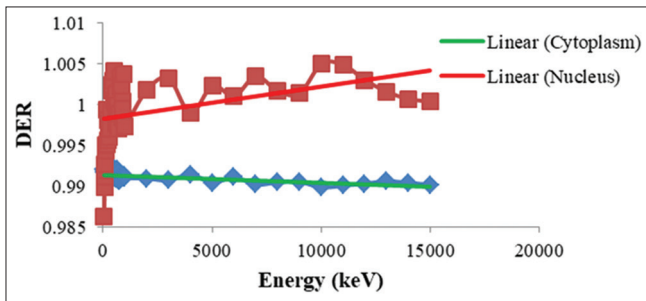


Figure 4: Dose enhancement ratio in the cytoplasm and nucleus as a function of electron energy in the presence or absence of gold nanoparticles

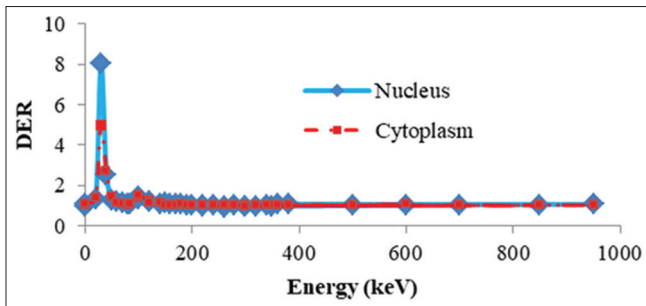


Figure 5: Summary of dose enhancement ratios in the target when irradiated with photon beams

**Table 1: Deposited energy and dose enhancement factor in the nucleus with or without gold nanoparticles for 20 nm to 150 nm gold nanoparticles of concentration 10 mg/g for 40 keV photon irradiation and 50 keV electron beam**

Diameter (nm)	40 keV photons with GNPs (Gy)	40 keV photons without GNPs (Gy)	50 keV electrons with GNPs (Gy)	50 keV electrons without GNPs (Gy)	DER for 40 keV photons	DER for 50 keV electrons
20	0.6359450	0.2505050	3195.28	3169.51	2.54	1.008
30	0.8255320	0.2890980	3173.75	3153.73	2.86	1.006
40	1.0747000	0.4526650	3161.98	3166.48	2.37	0.999
50	0.7823940	0.3458030	3154.2	3169.2	2.26	0.995
60	1.0107000	0.4621790	3159.4	3166.28	2.19	0.998
70	1.2587900	0.5015630	3155.44	3163.29	2.51	0.998
80	1.3470400	0.3076450	3188.13	3172.6	4.38	1.005
90	0.9935180	0.3052460	3147.13	3178.43	3.25	0.990
100	1.1809500	0.4393990	3100.02	3160.62	2.69	0.981
110	0.6742360	0.2957370	3133.83	3178.99	2.28	0.986
120	0.9552360	0.4276540	3097.71	3157.93	2.23	0.981
130	0.9123760	0.4276540	3120.62	3159.51	2.13	0.988
140	0.9362780	0.4256540	3123.75	3158.44	2.20	0.989
150	0.5610050	0.2712870	3196.95	3175.87	2.07	1.007

GNPs – Gold nanoparticles; DER – Dose enhancement ratio

**Table 2: Deposited energy and dose enhancement factor in the cytoplasm as a function of different gold nanoparticle sizes of concentration 10 mg/g for photon irradiation and electron beams**

Diameter (nm)	40 keV photons with GNPs (Gy)	40 keV photons without GNPs (Gy)	50 keV electrons with GNPs (Gy)	50 keV electrons without GNPs (Gy)	DER for 40 keV photons	DER for 50 keV electrons
20	0.355926	0.168631	1590.12	1604.53	2.11	0.991
30	0.376053	0.162872	1591.8	1604.44	2.31	0.992
40	0.468918	0.201622	1589.88	1603.33	2.33	0.992
50	0.467099	0.197434	1591.86	1603.84	2.37	0.993
60	0.560576	0.211319	1590.14	1603.55	2.65	0.992
70	0.555761	0.200836	1588.93	1602.41	2.77	0.992
80	0.489028	0.202779	1588.87	1603.06	2.41	0.991
90	0.542690	0.202499	1589.62	1603.25	2.68	0.991
100	0.587469	0.196782	1589.72	1601.57	2.99	0.993
110	0.513170	0.203760	1590.3	1602.56	2.52	0.992
120	0.532046	0.197985	1587.82	1601.65	2.69	0.991
130	0.443695	0.197452	1589.12	1601.98	2.25	0.992
140	0.504139	0.198165	1587.49	1601.51	2.54	0.990
150	0.375299	0.197215	1587.31	1602.89	1.90	0.991

GNPs – Gold nanoparticles; DER – Dose enhancement ratio

in Table 2. DER values slightly increase and reach a peak at 100 nm for photon beams. The lowest amount of DER is about 1.90 at GNPs with the diameter of 150 nm. There is no significant change when 50 keV electron beams are applied regarding GNPs size. The amount of DER in these conditions is about 0.99.

### Single-strand break and double-strand break

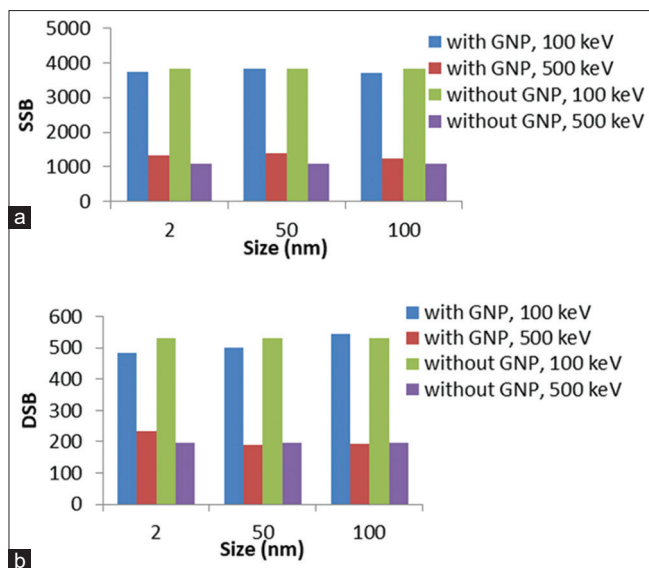
The levels of SSB and DSB damages calculated for different NP sizes through two mono-energetic electron beams are shown in Figure 6. As observed, the breaks do not increase in a significant manner in the presence of GNPs, while higher breaks in both SSB and DSB occur at low energy. The amount of SSBs increased more noticeably in the presence of GNPs for 500 keV electron beams. The level of SSBs increased about 27% when 50 nm GNPs

were added, and the level of DSB increased about 20% at 500 keV electron beam. On the contrary, the DSB level is more significant for higher GNPs at 100 keV electron beams. The difference between DSBs in the presence or absence of GNPs is around 14% at 100 nm GNPs.

### Discussion

To assess the benefits of GNPs as a dose enhancer in radiation treatment, several simulations are run. Irradiation by electron beams is explored in various manners.

The results of this study reveal that GNPs in combination with the electron beams have no important outcome in case of physical dose enhancement for all energies [Figure 4], which is smaller than estimations for photons with these energies. A few studies have determined the lowest



**Figure 6: Single-strand break (a) and double-strand break (b) damages induced by two mono-energetic electron beams**

advantages in applying NPs in electron therapy compared to photon therapy. For example, Chow *et al.*<sup>[35]</sup> examined the secondary electron production from a GNP irradiated by monoenergetic 50 keV, 250 keV, 1 MeV, and 4 MeV electron beams using Monte Carlo simulation. They concluded that the yield of secondary electrons of the electron beams in the presence of GNPs is not higher than that of a photon beam. Electron beam has fewer benefits compared to the photon in combination with GNPs. In addition, energy deposition of secondary electrons is higher for lower energy electron beams. Moreover, using Monte Carlo code, Zheng and Chow<sup>[36]</sup> proved that DER values in GNPs application are significantly lower for 4 MeV electron beams compared to photon beams.

There exist disparities within several experimental studies, which signify advantages of consuming GNPs with MeV electron beam. However, simulation studies do not show any effectiveness in dose enhancement in the presence of GNPs; increasing apoptotic signals in tumors may play a prominent role in this combination therapy.<sup>[37]</sup>

Unlike photon therapy, in which the ionization processes run through photoelectric effects, the ionization processes are run directly by particle beams such as the proton and heavy ions.<sup>[13]</sup> The DER is below 1 in the cytoplasm and is around 1 in the nucleus for the proton in this simulation [Figure 2]. The DER is within 0.16–1.001 range and below 1 in the nucleus and cytoplasm for the alpha beams in this simulation [Figure 3]. In a recent study by Saied *et al.*, the mass stopping power of alpha particles in liquid water was investigated. They concluded that the highest values of alpha particle stopping power were around 1 MeV. Therefore, the DER was equal to 1 for our used energies in this study.<sup>[38]</sup>

In a simulation study, local radial dose enhancement for MeV energy proton irradiation in the presence of NPs

increased by a factor up to 2.<sup>[39]</sup> The dose was calculated in near distance from the center of the NP as the local enhancement only exists at nanometer distances away from the NP and the source is located between the inner NP sphere and the outer water sphere to get the pure effect of proton irradiation on the NP. In the present study, the simulation setup is different from the work. The source was placed out of the cell, which is in the farther distance from NPs. However, it is demonstrated in simulation studies that microscopic dose enhancement is achieved by proton point source, but a minor role of physical effects is suggested for more realistic source configurations in increasing damage.<sup>[30]</sup> The data here clarify that like previous studies,<sup>[3,10]</sup> dose enhancement is higher in kilovoltage energies than in high-energy photons [Figure 5]. The results here imply that the highest DER occurs at 30 keV equal to about 5 and 8 for cytoplasm and nucleus, respectively [Figure 5]. These results are in agreement with those obtained in the study carried out by Cai *et al.*<sup>[40]</sup> It is deduced that nuclear dose enhancement factor (NDEF) strongly depends on photon energies with peaks at 15, 30/40, and 90 keV. NDEF reaches a peak around 30–40 keV and shows a shoulder at 90 keV when GNPs are in the extracellular space, on the cell surface, or in the cytoplasm. It is proved in a study<sup>[41]</sup> that an increase in distance between GNPs and target makes the dose fall in a rapid manner. Here, it is found that DER is approximately more significant in the nucleus for all sources [Figures 2-5], and this fact is proved when GNPs are situated in the close vicinity of the nucleus, therefore, the deposited energy is higher in this region. When the photon energy reaches a certain amount, the photoelectric effect is most pronounced depending on the kind of applied materials. There are two peaks in higher Z materials such as gold corresponding to the K and M edge energies.<sup>[42]</sup> It is proved in our work that the DER in the nucleus and cytoplasm for photon beams is greater for energy equal to 30 keV [Figure 5]. Moreover, there is another minor peak in DER between 90 and 100 keV. It is shown that in this proposed geometry model, DER in the nucleus enlarged with increasing in NP size until limited size at 40 keV photons beams [Table 1]. These results are in agreement with earlier analytical findings, which indicate that it is a consequence of raising the secondary electron production and particle interaction.<sup>[10,43]</sup> However, for larger GNPs, DER starts to decline [Table 1] corresponding to self-absorbed effect. He *et al.*<sup>[43]</sup> proved that the DER increases with GNP size within 30–100 nm range, especially for 150 keV photon beams. They also mentioned that their results are independent of the energy deposition self-absorbed by the GNP. Moreover, it is essential to note that cellular uptake and biological parameters depend on the selection of GNPs size, which should be considered in experimental efforts.<sup>[44]</sup>

A similar assessment for 50 keV electron beam is run in this study. No significant correlation is found between DER and GNP diameters [Tables 1 and 2]. The maximum

value of DER in the nucleus is 1.008 for 20 nm GNPs. The deposited energy in both nucleus and cytoplasm for electron beams has a significantly higher value than that in any photon case [Tables 1 and 2]. A simulation study indicates that 2 nm GNP, which is the smallest one in that study, is most effective in the energy deposition in the target. It is also concluded that as GNP size increased and electron beam energy decreased, the energy self-absorption of the secondary electron was enlarged.<sup>[35]</sup>

The formation of DSB contributes to DNA damage.<sup>[24]</sup> For this reason, several studies have assessed SSB and DSB levels in electron therapy. For instance, it is proved that the combination of nanogold and nanosilver with electron beam increased the formation of DSBs in the cell line.<sup>[45]</sup> On the contrary, GNPs do not increase DSBs when X-rays are applied.<sup>[24]</sup> According to Figure 6, SSBs are higher when GNPs are consumed for 100 keV electron beam. This disparity between different studies may imply that not only the physical dose but also complex biological processes are involved in the cell death as a consequence of the combination of nanoparticles and irradiation.<sup>[41]</sup>

## Conclusions

The deposited energy and DER are determined through Geant4 toolkit for several conditions including combination of GNPs with various sources such as proton, alpha, electron, and photon at different ranges. Some other parameters of simulations including GNP size are modified, and their results were discussed. The effect of GNPs on DNA breaks is assessed. In general, the difference in breaks with or without GNPs is not significant. It is found that DER for electron beam insignificantly changed with an increase in GNPs size. Through the simulation here, it is revealed that DER is greater for low-energy photons in comparison to other incident beams. The largest volume of DER of photons is about 8 and 5 folds in the nucleus and cytoplasm when GNPs are consumed, and the same is around 1 and below 1 for electron beams in the cellular regions, respectively. It is concluded that GNPs in combination with electron beam are less efficient compared to the other incident beam, specifically at low-energy photons. Further studies should be run to determine optimum energy for incident electron and other appropriate conditions where GNPs and RT are combined to be consumed in clinical practices. The simulation results in this study could be of use in understanding parameters involved in improving RT by consuming nanoparticle agents.

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## Conflicts of interest

There are no conflicts of interest.

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