ORIGINAL ARTICLE

A Monte Carlo Study on Dose Enhancement in the Presence of Nanoparticles by Photon Source: A Comparison between Various Concentration and Material of Nanoparticles

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Abstract

Purpose: Recently, the application of high atomic number nanoparticles is suggested in the field of radiotherapy to improve physical dose enhancement and hence treatment efficiency. Several factors such as concentration and material of nanoparticles and energy of beam define the amount of dose enhancement in the target in the presence of nanoparticles.

Materials and Methods: In this approach, a spherical cell was simulated through the Geant4 Monte Carlo toolkit which contained a nucleus and nanoparticles distributed through the cell. To investigate the effect of the concentration of nanoparticles on the deposited dose, it ranged from 3 mg/g to 30 mg/g for different materials like gold, silver, gadolinium, and platinum. Also, various mono-energetic photon beams included low and high energy sources were applied.

Results: The results proved that as the concentration increased, the Dose Enhancement Factor (DEF) enlarged. Overall, almost for all energy and material that were used in this study, the maximum of DEF values occurred in the concentration of 30 mg/g. Moreover, lower energy sources presented higher DEF compared to other sources. The results indicated that the highest amount of DEF transpired for 35 keV photon beams equal to 14.67. Also, the K-edge energy of each material affects DEF values.

Conclusion: To obtain a better outcome in the use of nanoparticles in combination with radiotherapy, a higher concentration of nanoparticles and low-energy photons should be considered to optimize the DEF and thus the treatment ratio.

Keywords: Dose Enhancement; Geant4; Nanoparticles; Photon Beams; Concentration.

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1. Introduction

Nowadays, cancer is a leading cause of human death worldwide [1]. To fight against this disease substantial attempts should be made [2]. Radiotherapy is one of the most famous methods to control tumor cells [3, 4]. The most challenge for radiation therapy is that the therapeutic doses damage normal cells surrounding the tumor and thereby can reduce the effectiveness of this method [1, 4, 5]. Recently, the use of nanoparticles for improving the efficiency of radiotherapy has drawn attention. This effort can increase the effectiveness of dose delivery to the cancer cells, which results in increasing tumor control and also minimizing surrounding normal tissue damage [6-9]. Also, nanoparticles can easily penetrate into cancer cells due to their physicochemical properties [2, 10]. The cross-section of radiation interactions increased in the presence of high atomic number nanoparticles, which produce more secondary electrons and intensify dose in the target. The physical interactions between irradiation and matter based on the energy of photon include photoelectric effect, Compton scattering, and pair production [4, 11]. In calculation studies, the dose enhancement factor is defined as the ratio of the absorbed dose in the target when it is loaded with nanoparticles to the dose without them. It has shown that DEF varies according to some nanoparticles features such as the type of materials, diameter of nanoparticles, concentration, and incident energy of the irradiation [3, 9, 11]. Previous studies have examined the dose enhancement of high Z material like gold (Au), gadolinium (Gd), silver (Ag), and platinum (Pt) in the tumor [11-14]. Here, we applied the Geant4 Monte Carlo toolkit to simulate a more realistic geometry of the cell and define nanoparticles in a 3D space in the cell. Then we evaluated DEFs for different material types, including Au, Gd, Ag, and Pt at various concentrations for different photon energies. Finally, the results were compared with each other to identify the best nanoparticle candidate and photon irradiation conditions which represented a higher dose enhancement effect. It will help to probe optimum conditions to transition to clinical use.

2. Materials and Methods

In this original article, to calculate the effects of high-Z materials on dose enhancement, the Monte Carlo simulation Geant4 toolkit (version 10.2) was applied. Geant4 is an open-source and general-purpose Monte Carlo toolkit implemented for the simulation of the radiation passage through matter [15, 16]. It was initiated by the European Organization for Nuclear Research (CERN) and utilized in vast domains like the simulation of different Large Hadron Collider (LHC) experiments, space science, and medical physics [16-18]. There are broad selections of the physical process, which are described by specific C++ "process classes" to compute and analyze the physical interactions [15-17].

The standard low-energy Livermore electromagnetic physics list was used. The transport and interactions of the secondary particles with nearby water atoms were then simulated using the Geant4-DNA extension physics list. In the current simulation, a spherical cell with a radius of 5 µm and a nucleus with a radius of 2 µm, which is located at the center of the cell, were modeled (Figure 1). In dose enhancement calculations, a liquid water equivalent tissue, which is a much more realistic approximation of biological matter, was used as the base material in the cell [15, 17, 19-21]. So in this effort, water has defined the material of the cell.

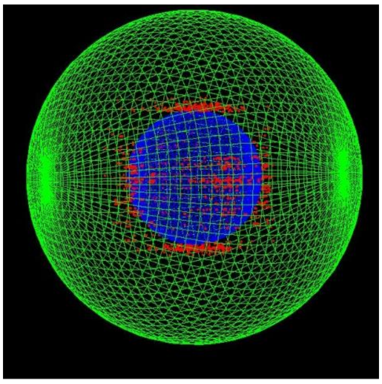

Figure 1. Schematic representation of the geometry of the cell (green) used in Monte Carlo simulation. The nucleus (blue) placed at the center of the cell and nanoparticles (red) distributed in the cell

In this case, different concentrations of 50 nm nanoparticles, in the form of nanospheres with nanometers scale, were uniformly distributed throughout the cell but they did not enter into the nucleus. This size was chosen because it confirmed that 50 nm nanoparticles present the highest cellular uptake into the cells [22]. To calculate the number of nanoparticles at given nanoparticle concentrations, the volume and density of nanoparticles and those of the cell were considered as below [5] (Equation 1):

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

Where r_C and ρ_C are the radius and density of the cell, respectively. Moreover, C is a given concentration in milligram per gram (mg/g) and r_{NP} and ρ_{NP} are the radius and density of nanoparticles, respectively.

In this effort, the nanoparticle concentrations ranged from 3-30 mg/g and various materials like ^{79}Au, ^{78}Pt, ^{64}Gd, and ^{47}Ag were tested as nanoparticle materials. Water nanoparticles of the same size were also simulated for comparison. Mono-energetic photon beams originate in a planar source located 6 micrometers away from the center of the nucleus' cell that was simulated in this study (center of the blue sphere in Figure 1). Low-energy photons include 35, 75, and 95 keV and also high-energy photons (6 MV photons) were used to assess the effect of various incident beam energies. The total number of histories for each simulation was set at 2×10^7 to decrease the simulation error under 5%. The volume of the nucleus was defined as scoring volume to measure the energy deposition in it as our target.

In the first step, the dose enhancement was studied to vary the material of nanoparticles with respect to nanoparticle concentration. Secondary, to compare radiation quality effects on dose enhancement, Monte Carlo simulation of dose enhancement in the nucleus was performed.

To evaluate the effects of dose enhancement based on the type and concentration of materials and incident energy, DEF in the target was defined as (Equation 2):

$$\text{DEF}=\frac{\text{Deposited dose with nanoparticles (Gy)}}{\text{Deposited dose without nanoparticles (Gy)}} \quad (2)$$

For each concentration, DEF was assumed by calculating the ratio between the dose (Gy) results at the nucleus with or without nanoparticles.

3. Results

In the current study, the influence of two different factors was evaluated on the DEF values. The first factor is the photon beam energy, which is investigated by choosing four different photon sources, including low- and high-energy photon beams and the second factor is the nanoparticles concentration in the cell.

Table 1 shows the calculated DEF values obtained by Geant4 simulations for the different concentrations of nanoparticles in which the cell was irradiated by the 35 keV photon source. As can be seen, the calculated DEF value increased as the nanoparticles concentration went higher for all cases and reached its maximum value of 14.67 at a concentration of 30 mg/g for Ag nanoparticles. The highest and lowest values of DEF belonged to Ag and Gd nanoparticles, respectively.

Table 1. Comparison of the calculated DEF values for the different concentrations and materials for 35 keV source

Concentration	DEF			
	Gd	**Pt**	**Ag**	**Au**
3 mg/g	1.28	2.18	3.47	2.23
10 mg/g	1.95	4.52	6.09	4.37
20 mg/g	2.94	6.81	7.86	6.35
30 mg/g	4.34	9.11	14.67	8.31

Table 2 displays the relationship between DEF values and nanoparticles concentration for the 75 keV photon beams as with the previous source. The DEF values exhibited a significant increase in Gd concentrations from 3 to 30 mg/g. The DEF value reached its maximum value of 2.44 at the concentration of 30 mg/g for this case. However, the same general behavior is noticed for other nanoparticles, as concentration rose, DEF values increased at a low rate.

Table 2. Calculated dose enhancement ratio for 3-30 mg/g of Au, Ag, Pt, and Gd nanoparticles inside the cell with 75 keV sources

Concentration	DEF			
	Gd	**Pt**	**Ag**	**Au**
3 mg/g	1.12	1.02	1.04	1.01
10 mg/g	1.37	1.06	1.10	1.08
20 mg/g	1.85	1.13	1.13	1.13
30 mg/g	2.44	1.12	1.29	1.14

Table 3 displays a comparison between the various materials of nanoparticles for the DEF values versus the different nanoparticles concentrations. In general, DEF within the target was higher for gold and platinum nanoparticles than for the other nanoparticles. DEF from gold and platinum nanoparticles were equal to 3.17 and 3.10, respectively, which was higher than silver nanoparticles and gadolinium nanoparticles at 30 mg/g. Moreover, the DEF values increase more notablely with concentration for Au and Pt nanoparticles rather than Gd and Ag nanoparticles which insignificantly enlarged.

Table 3. Dose enhancement factor for different concentrations (mg/g) of nanoparticles with 95 keV sources

Concentration	DEF			
	Gd	**Pt**	**Ag**	**Au**
3 mg/g	1.04	1.26	1.01	1.37
10 mg/g	1.15	1.92	1.03	1.96
20 mg/g	1.18	2.5	1.06	2.7
30 mg/g	1.42	3.1	1.09	3.17

Table 4 illustrates changes in the DEF with differences in the concentration of nanoparticles for 6 MV photons. It demonstrated that DEF values were almost the same with increasing concentration except for the concentration of 30 mg/g. DEF reached a peak at this concentration for Gd and Ag nanoparticles.

Table 4. Comparison between different concentrations of various nanoparticles for the DEF values from 6 MV source

Concentration	DEF			
	Gd	**Pt**	**Ag**	**Au**
3 mg/g	1	1	1	1.02
10 mg/g	1.04	1.01	1	1.02
20 mg/g	1.03	1.02	1	1.02
30 mg/g	1.12	1	1.11	1.02

Figure 2 shows the variation of DEF as a function of nanoparticle concentrations for gold nanoparticles when irradiated by photon beams with different energies. For any given concentration, nanoparticles yield the highest dose enhancement under 35 keV photons which followed by 95 keV photons case. The most enlargements in DEF according to increasing the concentration occurred at the concentration of 10 mg/g for these two cases which were around 95 % and 43 %, respectively. Moreover, DEF was almost the same for all concentrations when irradiated by 75 keV and 6 MV photons.

Figure 3 summarizes dose enhancement factors for four silver (Ag) nanoparticle concentrations irradiated by various photon beams. As can be seen, the dose enhancement factor remains nearly constant with increase in particles concentration from 3-30 mg/g for all energies except 35 keV photon beams. The most significant change in DEF observed for this case transpired at higher concentrations. By increasing the concentration from 20 to 30 mg/g, it rose about 86 percent.

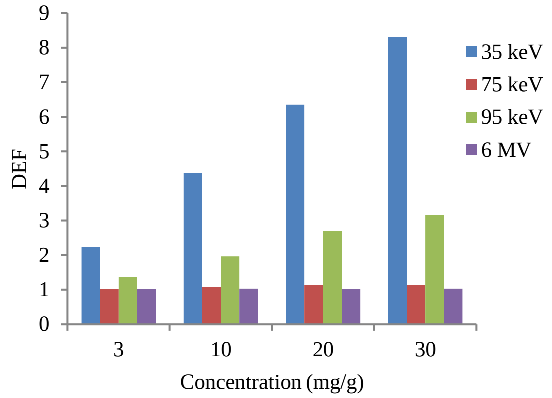

Figure 2. Dose enhancement due to various concentration of Au for different energy

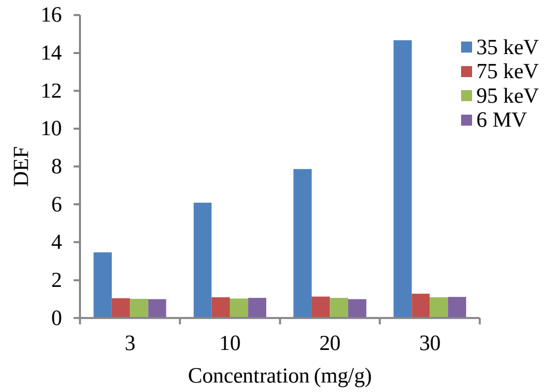

Figure 3. DEF vs. Ag concentrations for 35, 75, 95 keV, and 6 MV beam energy

As shown in Figure 4, for any given concentration of platinum nanoparticles, 35 keV photon beams provide the maximum dose enhancement, while 75 keV and 6 MV photons have slightly lower changes than other sources.

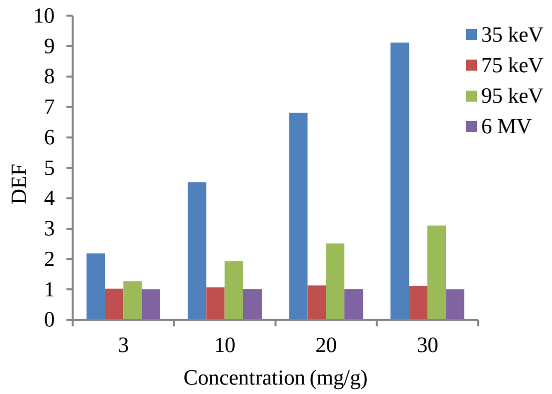

Figure 4. Dose enhancement factor vs. photon energy for four different platinum concentrations

Meanwhile, DEF in 95 keV photons case was verified with changes in concentration amounts.

Figure 5 shows how the cellular dose enhancements depend on the energy of photons at different particle concentrations for gadolinium nanoparticles. The results confirm that for any given nanoparticle concentration, 35 keV photons offer significantly higher dose enhancements. Moreover, 75 keV source is placed at the second stage. Remarkably, when nanoparticles concentration increased to 10 mg/g, the DEF enlarged about 52 % for 35 keV photons.

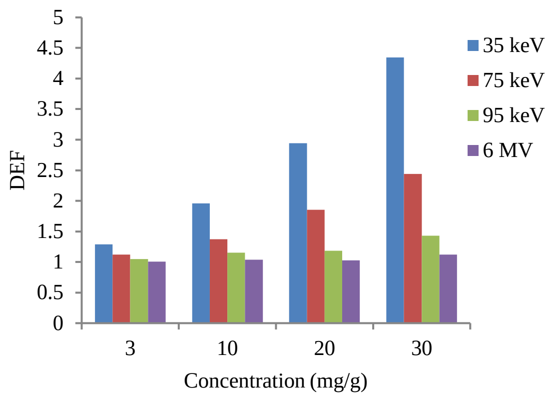

Figure 5. Dose enhancements for Gd nanoparticles with 3-30 mg/g concentration for different sources

4. Discussion

In this study, it can be inferred that DEF is generally increased as the concentration of nanoparticles increased, especially at low-energy photons (Tables 1-4).

Our results are in agreement with the other simulation studies. For instance, Zheng *et al.* [3] reported the following Monte Carlo simulation that gold nanoparticles increase the dose to a higher level of between 5.2 and 6.3 when irradiated by kV photon compared to the electron beam.

In another study, Zabihzadeh *et al.* [23] have shown that 55 keV beam energy represented a good result for combining photon beam and gold nanoparticles. Also, a linear relation was observed between DEF and the concentration of gold nanoparticles.

On the other hand, Mousavi *et al.* [24] have indicated the improvement in mice treatment with MV photons when cells contain GNPs. This discrepancy seems to be a result of the difference between in vivo methods and the Monte Carlo simulation.

Moreover, recent studies indicated that there is a direct relationship between atomic number and photoelectric cross-section (Z^3) [1]. Additionally, as concentration increases the effective atomic number of the medium would enlarge which exceeds the local dose. Also, other studies proved that the DEF values are proportional to nanoparticles concentration [2, 25].

In the simulation study done by Hwang *et al.* [11], using MCNPX code, they reported that there is a direct relationship between the concentration of nanoparticles and DEF. Moreover, the lower incident energy results in higher dose enhancement factors.

The atomic numbers of Gold, platinum, gadolinium, and silver are 79, 78, 64, and 47, respectively. It should be noticed that based on the irradiation energy, various materials will produce different secondary electrons. It is as a result of different absorption cross-sections [12]. Also, it is more important to take into account the toxic effects of nanoparticles that are in close relation with concentration. It is considered as a factor to limit utilizing of higher concentration [11, 23, 26, 27]. Furthermore, the kind of nanoparticles material is important to achieve the highest amount of DEF in some cases. As can be seen in Table 1, Ag nanoparticles reached a peak of 14.67 at 35 keV photon beams which is the highest level among all materials. Also, gadolinium is most notable among other materials under 75 keV photon beams, as shown in Table 2. In addition, for the 95 keV photon source, Au and platinum nanoparticles have the maximum amounts (Table 3). It proved that the most significant dose enhancements obtained when photon energy is close to the binding energy of the K-edge [11, 20]. The K-edge energies of silver, gadolinium, gold, and platinum are 25.5, 50.2, 80.7, and 78.3 keV, respectively.

Bahreyni *et al.* [12] have performed a study based on Monte Carlo code to compare dose enhancement by gold and gadolinium nanoparticles with various concentrations for brachytherapy sources. They have reported higher efficiency of gold compared to gadolinium.

The discrepancy between the dose enhancements in various studies can be related to the fact that the difference in geometry, energy, and other aspects of simulation would represent different results.

In this study, we calculated and assume the physical aspects of using nanoparticles in radiation fields. It should be considered that one of the important limitations of using nanoparticles in radiation therapy is the toxicity of normal tissues. Therefore, it would be necessary to investigate the biological effects of nanoparticles in real radiotherapy.

In summary, the relationship between the concentration and energy for each type of nanoparticles, including Au, Ag, Pt, and Gd presented in Figures 2-5. It inferred that 35 keV photons offered more DEF values for all energies and materials. DEF peaked at 8.3, 4.34, 9.11, and 14.67 at the concentration of 30 mg/g for Au, Gd, Pt, and Ag nanoparticles, respectively. Moreover, by increasing concentration, the most changes in DEF values occurred for 35 keV photon beams not for higher energies. Previous studies suggest that the energy of photon beams is an important parameter for the evaluation of DEF. In low-energy photon beams; the photoelectric effect is the dominant interaction which is inversely related to energy. So, lower energy results in higher DEF values [12].

5. Conclusion

Geant4 Monte Carlo toolkit was utilized to perform a comparative study between nanoparticles features and the energy of source. Nanoparticles with different concentrations between 3 to 30 mg/g distributed through the spherical cell. Dose enhancement factor in the nucleus, which is centered in the cell, was calculated for different material and energy. In this approach, it concluded that dose enhancement depends on incident energy and the type of material. The dose enhancement was higher when the incident energy was lower. Also, the DEF increased for higher nanoparticles concentrations for low energy photon beams. On the other hand, for all concentrations and material, the calculated DEF values obtained from the 35 keV source are higher than other sources. The obtained data from this study should be followed by experimental studies to investigate other biological factors which influence treatment.

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