BioImpacts, **2013**, 3(1), 29-35
doi: 10.5681/bi.2013.002
http://bi.tbzmed.ac.ir/

Effect of Photon Beam Energy, Gold Nanoparticle Size and Concentration on the Dose Enhancement in Radiation Therapy

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ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 03 Sep 2012
Revised: 14 Oct 2012
Accepted: 27 Oct 2012
ePublished: 19 Dec 2012

Keywords:
Gold Nanoparticle
Monte Carlo Method
Dose Enhancement Factor
Radiation Therapy

ABSTRACT

Introduction: Gold nanoparticles have been used as radiation dose enhancing materials in recent investigations. In the current study, dose enhancement effect of gold nanoparticles on tumor cells was evaluated using Monte Carlo (MC) simulation. ***Methods:*** We used MCNPX code for MC modeling in the current study. A water phantom and a tumor region with a size of 1×1×1 cm^3 loaded with gold nanoparticles were simulated. The macroscopic dose enhancement factor was calculated for gold nanoparticles with sizes of 30, 50, and 100 nm. Also, we simulated different photon beams including mono-energetic beams (50-120 keV), a Cobalt-60 beam, 6 & 18 MV photon beams of a conventional linear accelerator. ***Results:*** We found a dose enhancement factor (DEF) of from 1.4 to 3.7 for monoenergetic kilovoltage beams, while the DEFs for megavoltage beams were negligible and less than 3% for all GNP sizes and concentrations. The optimum energy for higher DEF was found to be the 90 keV monoenergetic beam. The effect of GNP size was not considerable, but the GNP concentration had a substantial impact on achieved DEF in GNP-based radiation therapy. ***Conclusion:*** The results were in close agreement with some previous studies considering the effect of photon energy and GNP concentration on observed DEF. Application of GNP-based radiation therapy using kilovoltage beams is recommended.

Introduction

Application of gold nanoparticle (GNP) in dose enhancement in radiation therapy has been studied in the last decade. Although several studies have shown the effect of high atomic number materials used in radiology such as iodinated contrast media on the dose enhancement, development of nano-scaled material with higher penetrability into cells as well as cell nucleus increased scientists' interests in applying these materials in radiation therapy.[1,2] Gold nanoparticles have shown a chemical and biological inertness in cell cultures and animal studies.[3,4] A pioneering study by Hainfeld on mice bearing subcutaneous EMT-6 mammary carcinomas showed a significantly longer survival of one-year for in mice treated with gold nanoparticles and radiation therapy.[5] Additionally, several animal studies have shown better survival in groups treated with GNP and radiation.[3,6-8] Most studies have related the better survival of animals or higher tumor cell control to the dose enhancement occurred as the result of higher photoelectric absorption in gold atoms. On the other hand, a study by Geng *et al*. on ovarian cancer and their treatment with Thio-glucose bound GNPs revealed no significant radiobiologic differences between 90 kVp and 6 MV photon beams. Several Monte Carlo (MC) studies have been performed to explain macroscopic and microscopic levels of events responsible for the biological outcomes.[9-15] In another MC study by Lechman *et al*. it was found that the energy deposited by photoelectrons is the main contribution to radiosensitization; GNP size and its cellular localization are less relevant. While an MC study by GEANT code showed that GNPs with larger diameters contributing more dose to the surrounding tissue.[16] The differences among the results of aforementioned studies indicate that more investigations are needed to converge the current results into a common conclusion.

In the current study, we modeled the photon dose absorption in the presence of GNPs inside a tumor with MCNPX code. We used lower energies to study the effect of photoelectric absorption on deposited energy around GNPs. Moreover, conventional photon energies

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including Co-60, 6 and 18 MV photon beams were simulated where the photoelectric process is irrelevant. The effect of GNP concentration, size and photon energy on macroscopic dose enhancement was investigated.

Materials and methods

The MCNPX MC code (version 2.6.0) was used for dose calculations in the current study. To score dose distribution, a cubic water phantom with dimensions of 20×20×20 cm^3 was simulated. A cubic tumor with dimensions of 1×1×1 cm^3 was simulated at a depth of 2 cm for megavoltage beams and at a surface for kilovoltage beams inside the water phantom. Different diameters of GNPs including 30, 50, and 100 nm were simulated. Also, in this study, the effect of concentrations on dose enhancement was studied. Two different concentrations of gold nanoparticles including 7 and 18 mg Au/g inside the tumor were considered.

Two groups of photon beams were used in the current study. For the first group, monoenergetic beams from 50-120 kVp, was used to investigate the photoelectric absorption effect on dose enhancement. This energy range can be found in photon spectra of orthovoltage beams. The second group consisted of three commonly used photon beams in radiation therapy including 60Co, 6 and 18 MV photon beams of Varian 2100 CD linac. For MC modeling of tumor irradiation, simple beam model was used according to previous studies.[17-19] A point photon source with energy spectra of 6 and 18 MV photon beams were defined in MCNPX input file. The water phantom and GNP-loaded tumor were irradiated at a source to a surface distance of 100 cm for megavoltage beams. For monoenergetic beams, the source to a surface distance of 50 cm was used.

In order to simulate the spherical gold nanoparticles with different concentrations inside the tumor uniformly, the lattice property of MCNPX code was employed. Fig. 1 shows the dose scoring phantom. Three levels of lattice definition were used. The first level was cells with a size of 2×2×2 mm^3 inside a tumor. The second level was the cells (micrometer size) with dimensions of 0.001×0.001×0.001 mm^3 which filled the first level cells uniformly. And the third level was a spherical GNP that filled each micrometer size cells inside the tumor. The first and second level cells were filled with water. A number of second level cells were selected to create the desired concentration in terms of 7 and 18mg of GNP per gram of water. The medium around the cubic tumor region was filled with water without GNP. With such an MC model, it was possible to change the concentration of GNPs by changing the number of second level cells.

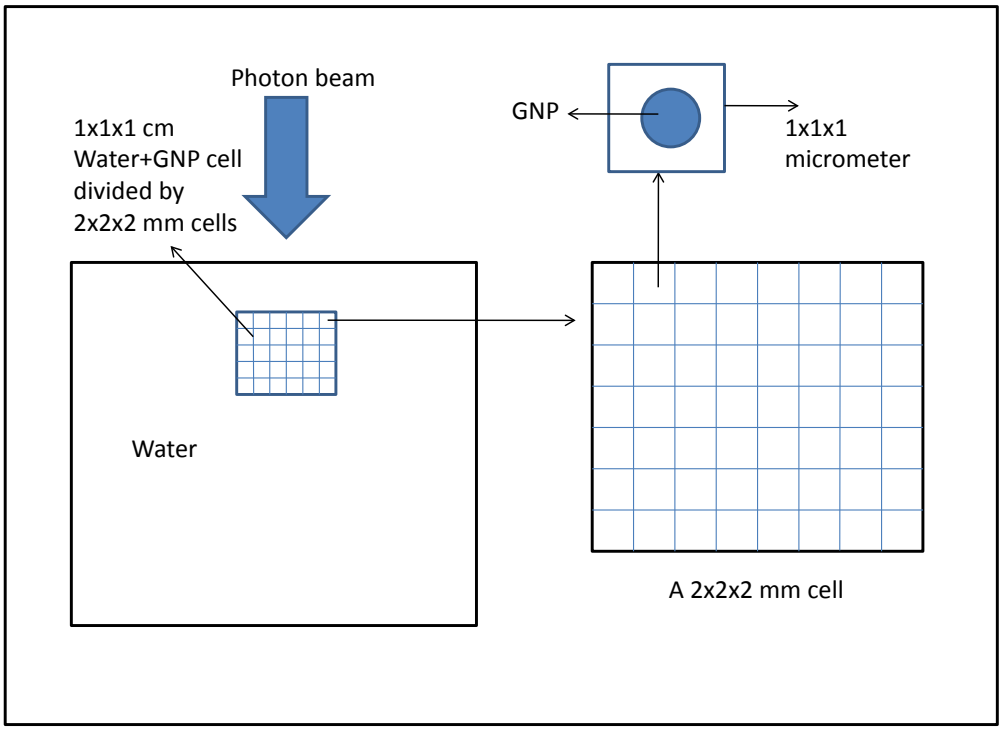

Fig.1. The schematic representation of simulated geometry by MCNPX code.

The size of GNP can also be changed by altering GNP size in the third level. The dose deposition was scored by a F6 tally inside the first level cells with a volume of 8 mm^3. In other words, spatial dose resolution was 2 mm in all directions inside the tumor. The F6 tally scores deposited energy inside a cell in terms of MeV/g. No photon and electron energy cutoff was used and the default cutoff energy of 1 keV was applied for each photon history. The statistical uncertainty of results was less than 1.5% for all dose scoring cells.

The depth doses per initial photon along the beam central axis were tallied in the presence of GNPs for different concentrations and sizes. The results were divided by no GNP case. By this way, macroscopic dose enhancement factor (MDEF) was calculated for all cases considering different energies, concentrations, and GNP sizes.

Results

Fig. 2, 3 and 4 show calculated DEFs with depth of 30, 50 and 100 nm GNPs and two concentrations of 7 and 18 mg/g. As it is seen, DEF values for kilovoltage beams are considerably varied with beam energy and concentration. However, the DEF for all energies and GNP sizes does not vary with depth. Additionally, there are slight fluctuations in calculated DEF with depth, which are related to the uncertainties in MC results.
Fig. 2 shows the DEF inside the GNP loaded region and surrounding water for GNPs with the diameter of 30 nm for different kVp energies. It can be seen that two different concentrations of 7 and 18 mg/g have been used. The results show that the highest DEF is for 90 keV photon beam and the 50 keV is placed in the second order. Also, there is no DEF in the water beyond the tumor region.

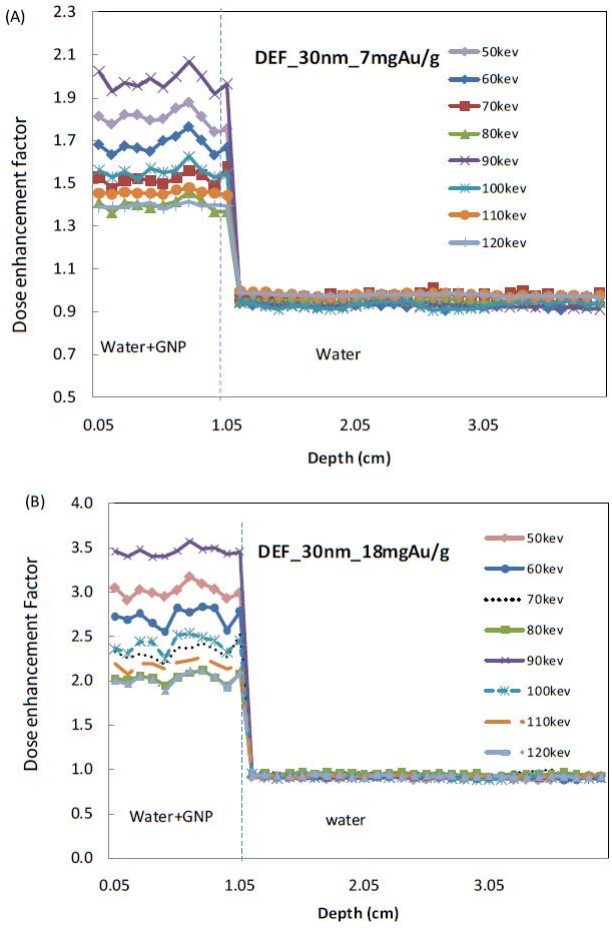

Fig. 2. The calculated dose enhancement factors for 30 nm gold nanoparticles inside tumor region with two concentrations (A) 7mg Au/g (B) 18 mg Au/g.

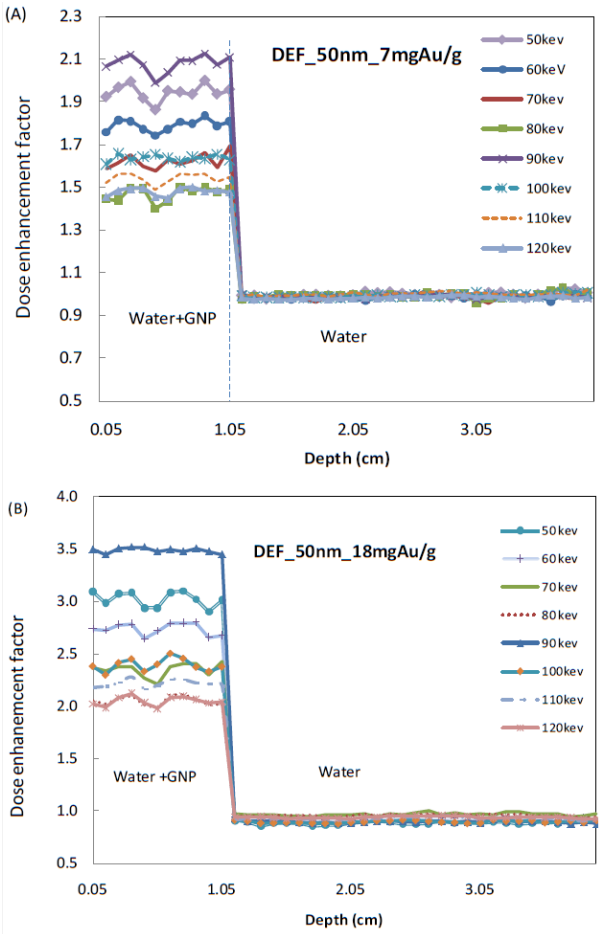

Fig. 3. The calculated dose enhancement factors for 50 nm gold nanoparticles inside tumor region with two concentrations (A) 7mg Au/g (B) 18 mg Au/g.

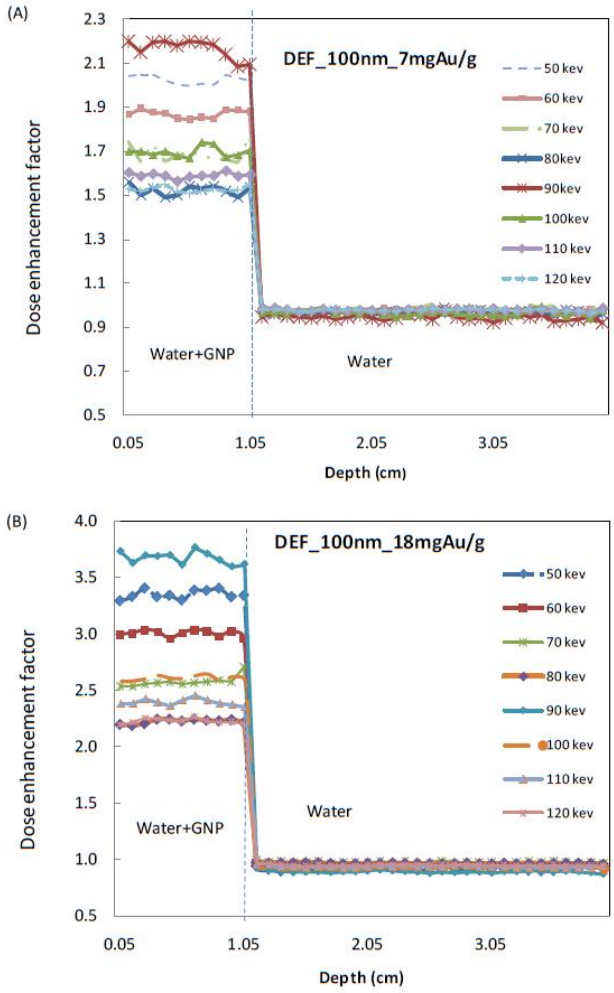

Fig. 4. The calculated dose enhancement factors for 100 nm gold nanoparticles inside tumor region with two concentrations (A) 7mg Au/g (B) 18 mg Au/g.

In Fig. 3, the DEF was depicted versus depth for the GNPs with the diameter of 50 nm in two concentrations. Moreover, in Fig. 4, like two previous figures, the DEF was depicted versus depth for GNPs with the diameter of 100 nm. The same pattern of DEF versus depth is seen for all energies and GNP sizes. The effect of concentration in all GNP sizes is pronounced in Fig. 2, 3 and 4. More detailed information on DEF variations with GNP size, concentration, and photon energy is tabulated in Table 1.

In Table 1, average DEFs over the tumor volume were shown for different energies, concentrations and GNP sizes. As it can be seen, with an increase in the concentration of gold nanoparticles, the DEFs are raised in the tumor region for all energies and GNP sizes. The highest values of the average DEFs were 3.5- 3.7 for 90 keV beam with 18 mgAu/g concentration for 30, 50 and 100 nm GNPs. According to the results, the dose enhancement values for the monoenergetic low energy beams were meaningfully higher than megavoltage beams, because the photoelectric absorption coefficients of gold at K- (80.7 keV) and L- (11.9 - 14.4 keV) were high. It means that photoelectric interaction happens in low energy photons and its highest probability occurs where the energy of hitting photon is slightly higher than the binding energy of electrons in K- and L shells. As it was expected from basic radiation physics, in our study, the photoelectric interaction and its peak photon absorption happened for k-shell electrons with 80.7 keV binding energy and monoenergetic photons with 90 keV. Then, with increasing the photon energy from 90 to the higher energies, the photoelectric interaction probability was reduced. The second highest DEF is seen in 50 keV photons, as their main interactions occur with L-shell electrons. For other energies higher than 50 keV and lower than 90, the observed DEFs are less than DEF of 50 keV because the rate of photoelectric interaction is decreased with an increase in photon energy beyond the L-shell binding energy.

Table 1. The average dose enhancement over tumor volume for different beams, GNP sizes and concentrations

Beam Energy	30 nm		50 nm		100 nm	
	Concentration (mg/g)					
	7	18	7	18	7	18
50 keV	1.8	3.0	1.9	3.0	2.0	3.3
60 keV	1.7	2.7	1.8	2.7	1.9	3.0
70 keV	1.5	2.3	1.6	2.4	1.7	2.6
80 keV	1.4	2.0	1.5	2.1	1.5	2.3
90 keV	2.0	3.5	2.1	3.5	2.1	3.7
100 keV	1.5	2.4	1.6	2.4	1.7	2.6
110 keV	1.4	2.2	1.5	2.2	1.6	2.4
120 keV	1.3	2.0	1.5	2.1	1.5	2.2
^{60}Co	1.02	1.03	1.01	1.02	1.01	1.02
6 MeV	1.01	1.01	1.01	1.01	1 .01	1.01
18 MeV	1.01	1.01	1.02	1.01	1 .02	1.01

Discussion

To find the optimum energy for GNP-based radiation therapy, as it can be seen from Table 1, the first preferred energy could be 90 keV and the second energy could be the 50 keV with lower DEF. However, it should be mentioned that there are several low energy brachytherapy sources including radioactive and X-ray sources that can be employed for GNP-based radiation therapy. Additionally, there is a possibility of using orthovoltage units with maximum energy of 300 kVp (maximum photon fluence happens at 1/3 Emax) and proper filter in order to produce the required photon spectrum for external radiation therapy.

The DEF for 7 mg/g concentration varies between 1.4 and 2.1 for all GNP sizes and kilovoltage beams, while

the range of variation is between 2 and 3.7 for 18 mg/g concentration.

In other words, increasing the concentration by 2.5 folds results in a 2 times approximate higher DEF inside the tumor region. However, comparing the DEFs tabulated in Table 1 reveals that DEF shows the slight increase along with GNP size and in some cases the effect on DEF is negligible. It means that the effect of GNP concentrations on dose enhancement is very pronounced, compared to GNP size. Considering the concentration effect, it can be stated that increasing the concentration of GNP results in the increase of the number of GNPs and consequently the number of gold atoms. It accordingly causes more photoelectric interactions between photons and gold atoms. However, about the negligible effect of GNP size on DEF, as far as we know, according to a previous study, the range of photoelectrons created from a GNP is ranged approximately between 3 micron and 1 mm which is more than the particle size and the self-absorption of GNPs can be ignored.[16] So the number of photoelectrons that delivers the dose to the surrounding tissue is proportional to the number of gold atoms in the pathway of photon beam rather than to the size of the GNP.

Moreover, our results were consistent with a nanodosimetric study by Lechman *et al*. who showed that GNP size (1.9,5,30,100 nm) is not an influencing factor on the number of photoelectric absorption in nanodosimetric scale around GNPs for the photon energies above the k-edge of gold atom.[20] However, they did not report any DEF for the studied photon beams. Also, the relation between the observed number of produced photoelectrons and the macroscopic quantity like DEF was not explained.

A recent study by Leung *et al*. also investigated the microscopic consequences of irradiating a single GNP sphere with GEANT code.[21] In their study, the effect of GNP with sizes of 2, 50 and 100 nm on the number of secondary electron production was investigated. The results showed that GNPs with a larger diameter delivered more doses to tumor volume and lower photon energies were recommended for efficient cell killing.[16] It is worth mentioning that in the study by Leung *et al*. no DEF was proposed for the studied energy beams. They studied the effect of GNP in secondary electron production for different photon beams without explaining how their results in nanodosimetric scale relates to the reported DEF in previous studies. There is another point that should be noticed; the observed difference between our study and Lueng *et al*. may come from the different Monte Carlo codes used in two studies. It means that two MC codes of GEANT and MCNP use different algorithms for electron transporting in the presence of GNPs.

From radiation therapy point of view, the more practical quantity that could be used in the radiation therapy of cancer patients is calculated or measured DEF resulted from GNPs inside the tumor. Although microscopic or nanodosimetric studies are attempting to explain the differences between observed macroscopic DEF and results coming from radiobiologic studies. As in the most of simulation studies, no DEF was found for megavoltage energies used in conventional radiation therapy. But there are some radiobiologic studies that reported the significant cell killing of megavoltage energies in the presence of GNPs.

Our results were in close agreement with the study by Cho *et al*. who used BEAMnrc/DOSXYZnrc for external beams calculations. They found DEF having a factor of at least 2 for 140 kVp x-ray with 7mg Au/g tumor assuming no gold outside the tumor. Also, a DEF of 1.007 for a conventional 6 MV photon beam was reported.[9]

For megavoltage cases, the tumor was located at 2 cm in depth, DEFs were calculated and the results were shown in Table 1. There was a slight increase of less than 3%, in absorbed dose inside the tumor region in the presence of GNP. It can indeed be explained that most interactions of high energy photons with atoms occur by Compton Effect which is not dependent on atomic number. Thus, dose enhancement cannot happen due to the Compton interactions of photons with gold atoms. But in low energy photons where the photoelectric interaction is a major way of photon interaction with atoms, the complete photon absorption occurs with higher probability in energies slightly more than k- and L-edges energies. In the study by Jones *et al*., the microscopic dose enhancement around Gold nanoparticles was calculated for low energies (less than 100 KeV) and a 6 MV beam.[11] Their results showed that for the low energy beams, the secondary electron fluence within a GNP-loaded tumor was increased by as much as two orders of magnitude, leading a 2-fold increase in electron energy deposition over radial distances up to 10 micrometers. They did not find considerable microscopic dose enhancement for the 6 MV photon beam. Another MC study of beam energy consideration for GNP-based radiotherapy reported a regular 110 kVp bremsstrahlung spectrum as an optimum energy for higher DEF achievement.[22]

Reviewing biological results on the cell killing effect of different photon energies with GNPs reveals very different consequences compared to DEF scoring MC studies.[13,14,23-26] For example, a study by Geng *et al*. on radiation therapy with thio-glucose bound gold nanoparticles showed that cell proliferation inhibition caused by GNPs in ovarian cancer cells did not differ significantly from the photon beam energy and the

proliferation inhibition of 31% and 27% were reported for 90 kVp and 6 MV photons, respectively.[27] However, reasons behind the observed differences between biological and physical studies are beyond the scope of current study and has been mentioned by a previous review article.[28] Lastly, a recent study has proposed an explanation for the difference seen between physical DEF of megavoltage beams and their biological effects on GNP-based radiation therapy.[14]

From the point of translational medicine, the authors believe that the current study on application of gold nanoparticles demonstrates a great potential to improve the outcome of cancer patients' treatment with an increase in the tumor control probability and a decrease in normal tissue complications. Because with the presence of GNPs inside the tumor and having a DEF of around 3, the required dose for eradicating cancerous cells can lower considerably, and consequently the normal tissue around the tumor will receive radiation of almost three times less than of conventional radiotherapy. Finally, it should be noticed that there are many obstacles such as efficient targeting of GNPs for cancerous cells and low penetration of kVp beams that should be tackled before its clinical applications. It means we need methods to accumulate the GNPs inside the cancerous cells up to 18 mg/g for having a DEF of around 3. On the other hand, special kilovoltage units should be designed to provide photon beams with required features needed for a GNP-based radiation therapy.

Conclusion

The results showed significant dose enhancement for the kilovoltage photon beams used in the current study. We found no meaningful dose enhancement for megavoltage beams in our study. There was a direct and significant relationship between GNP concentrations and DEF for kilovoltage photon beams. Additionally, the GNP size showed a slight effect on the calculated DEF in current study.

Competing interests

The authors declare no competing interests.

Acknowledgment

The authors would like to thank the research vice-chancellorship of Tabriz University of Medical Sciences for their financial support of this project.

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