Influence of concentration, nanoparticle size, beam energy, and material on dose enhancement in radiation therapy

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ABSTRACT

The purpose of this study was to analyse the effects of the type, concentration, and nanoparticle diameter of dose enhancement materials on the dose enhancement of low- and high-energy megavoltage (MV) X-rays acquired from a medical linear accelerator using Monte Carlo simulation. Monte Carlo simulation was performed with the Monte Carlo N-Particle Transport (MCNPX) code, using the energy spectrum of the linear accelerator and a mathematical Snyder head phantom. A 5-cm-diameter virtual tumour was defined in the centre of the phantom. Gold, gadolinium, iodine and iron oxide were used as dose enhancement materials. Varying concentrations (7, 18 and 30 mg/g) of nanoparticles of different diameters (25, 50, 75, 100 and 125 nm) were applied, and the dose enhancement was comparatively evaluated for 4, 6, 10 and 15 MV X-rays, and a 60Co source. Higher dose enhancement factors (DEFs) were observed when the incident energy was low. Moreover, the dose enhancement effects were greatest with gold nanoparticles, followed by gadolinium, iodine, and iron oxide nanoparticles; the DEFs were 1.011–1.047 (gold), 1.005–1.030 (gadolinium), 1.002–1.028 (iodine) and 1.002–1.014 (iron oxide). The dose enhancement effects increased with increasing nanoparticle diameter and concentration. However, the concentration of the material had a greater impact than the diameter of the nanoparticles. As the concentration and diameter of nanoparticles increased, the DEF also increased. The 4 and 6 MV X-rays demonstrated higher dose enhancement compared with the 10 and 15 MV X-rays.

KEYWORDS: Monte Carlo simulation, dose enhancement, nanoparticles

INTRODUCTION

In radiotherapy, it is important to increase the therapeutic ratio (TR) through an increase in the tumour control probability (TCP) and through maintenance of sufficiently low normal tissue complication probability (NTCP) [1, 2]. The development of radiotherapy technologies, including intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc radiotherapy (VMAT), has improved the TR [3]. Various strategies, including the application of hyperthermia, concurrent chemoradiation therapy, and radiation dose enhancement, have also been considered to improve the TR [4–6]. In dose enhancement, materials with a high atomic number and electron density are loaded into the tumour volume to increase the cross-section of radiation interactions with these materials, which increases the locally absorbed energy [7–9]. These physical interactions can be explained using the photoelectric effect, Compton scattering, and pair production; increases in secondary electrons generated from these interactions can contribute to dose enhancement [10]. Numerous in vivo and in vitro studies as well as Monte Carlo simulations have been used for several years to investigate the effects of dose enhancement. Previous studies have reported the use of gold (Au), gadolinium (Gd) and iodine (I) in dose enhancement [11–13]. Recently, the use of iron oxide (Fe₃O₄), which shows superior performance as a contrast medium in...
superparamagnetic magnetic resonance imaging (MRI), has also been used for dose enhancement. In addition, there have been reports on its usage as a drug carrier and radiosensitizer in radiotherapy, because it displays excellent biocompatibility and target directivity [14, 15]. With 6-MV X-rays and Au nanoparticles, Hainfeld has reported a 1.17-fold dose enhancement [10]. Bahreyni has reported a dose enhancement of >5% with a brachytherapy source and 30 mg/ml of Gd [16].

In consideration of the absorption within tissues and enhanced permeability and retention (EPR), nanoparticles with diameters of <400 nm have been used for studying dose enhancement [17]. Although the effects of dose enhancement have been shown to vary according to the type of materials, diameter of the nanoparticles, material concentration, and incident energy of the irradiation [18], very few studies have directly compared the impact of dose enhancement with respect to these various factors. Furthermore, most previous studies have reported on dose enhancement of monoenergetic beams and low-energy X-rays. In other words, comparative evaluation of the effects of various materials, nanoparticle diameters, material concentrations, and incident energies on dose enhancement by applying low- and high-energy megavoltage (MV) X-rays generated by a medical linear accelerator.

**MATERIALS AND METHODS**

Monte Carlo modelling

Monte Carlo code simulation, which is based on random number sampling, is capable of representing 3D particle transport in various materials and sources [19]. The Monte Carlo N-Particle Transport Code (MCNPX, ver. 2.5.0, USA), developed at Los Alamos National Laboratory (LANL, USA), was used for the simulations in this study. We used the mathematical Snyder head phantom, which was produced by Snyder et al. The mathematical Snyder head phantom is based on three ellipses composed of the brain parenchyma, skull and scalp.

### Table 1. The ICRU 46 material specifications for brain parenchyma, skull and scalp

| Atom | Mass number | Fraction | Atom | Mass number | Fraction | Atom | Mass number | Fraction |
|------|-------------|----------|------|-------------|----------|------|-------------|----------|
| H    | 1           | 0.107    | H    | 1           | 0.050    | H    | 1           | 0.100    |
| C    | NOE         | 0.145    | C    | NOE         | 0.212    | C    | NOE         | 0.204    |
| N    | 14          | 0.022    | N    | 14          | 0.040    | N    | 14          | 0.043    |
| O    | 16          | 0.712    | O    | 16          | 0.435    | O    | 16          | 0.645    |
| Na   | 23          | 0.002    | Na   | 23          | 0.001    | Na   | 23          | 0.002    |
| P    | 31          | 0.004    | Mg   | NOE         | 0.002    | P    | 31          | 0.001    |
| S    | NOE         | 0.002    | P    | 31          | 0.081    | S    | NOE         | 0.002    |
| Cl   | NOE         | 0.003    | S    | NOE         | 0.003    | Cl   | NOE         | 0.003    |
| K    | NOE         | 0.003    | Ca   | NOE         | 0.176    | K    | NOE         | 0.001    |

NOE = naturally occurring element.
Results
The DEFs were analysed through changes in the absorbed energy with changes in depth within the phantom, and through the DEF in the tumour volume. Figure 2 shows changes in the absorbed energy with depth observed at a concentration of 30 mg/g of 125-nm-diameter nanoparticles. The dose enhancement varied depending on the type of material and incident energy. When the incident energy was lower, the dose enhancement was higher. Further, higher dose enhancement was observed with Au, followed by Gd, I and Fe$_2$O$_3$. In addition, due to the effects of dose enhancement within the tumour volume, the influence of the photons was reduced, which subsequently led to decreased dose at the back of the tumour volume. Figure 3 shows changes in the DEF based on the nanoparticle diameter and incident energy at a concentration of 18 mg/g. Larger diameter nanoparticles resulted in a higher DEF as follows: 1.044 (4 MV), 1.040 (6 MV), 1.030 (10 MV), 1.023 (15 MV) and 1.032 ($^{60}$Co). Thus, when the incident energy was lower, higher DEFs were observed. Fe$_2$O$_3$ showed the following results: 1.021 (4 MV), 1.017 (6 MV), 1.007 (10 MV), 1.004 (15 MV) and 1.009 ($^{60}$Co). Fe$_2$O$_3$ nanoparticles showed dose enhancement that was 2–3% lower than that of Au. Furthermore, changes in dose enhancement were confirmed according to the incident energy of the dose enhancement materials, and the dependence of the dose enhancement on material changes was more pronounced at lower incident energies.

Figures 4 shows changes in the DEF with respect to changes in the concentration of the dose enhancement materials using 100-nm nanoparticles; significant increases in the DEF were observed at higher concentrations of dose enhancement materials. Moreover, at a concentration of 30 mg/g, Au nanoparticles showed the following results: 1.044 (4 MV), 1.040 (6 MV), 1.030 (10 MV), 1.023 (15 MV) and 1.032 ($^{60}$Co). Au nanoparticles showed dose enhancement that was 2–3% lower than that of Au. Furthermore, changes in dose enhancement were confirmed according to the incident energy of the dose enhancement materials, and the dependence of the dose enhancement on material changes was more pronounced at lower incident energies.

Tables 2 and 3 show DEFs of Au, Gd, I and Fe$_2$O$_3$ with respect to the incident energy, diameter of nanoparticles and concentration within the tumour volume. In all materials, when the concentration and diameter of the nanoparticles increased, increases in the DEF were observed. However, when the incident energy was lower,
Fig. 3. Dose enhancement factor of the nanoparticle diameter for 18 mg/g of (a) gold, (b) gadolinium, (c) iodine and (d) iron oxide (Fe₂O₃) dose enhancement materials.

Fig. 4. Dose enhancement factor of the dose enhancement material for various concentrations (mg/g) of 100-nm-diameter nanoparticles with (a) 4 MV, (b) 6 MV, (c) 10 MV, (d) 15 MV and (e) 60Co sources.
Table 2. The average values of the dose enhancement factor inside the tumour for various nanoparticle diameters and concentrations of gold and gadolinium

| Nanoparticle diameter (nm) | Material concentration (mg/g) |   7  |  18  |  30  |  7  |  18  |  30  |  7  |  18  |  30  |  7  |  18  |  30  |  7  |  18  |  30  |
|---------------------------|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gold                      |                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 4 MV                      |                               | 1.033 | 1.040 | 1.047 | 1.029 | 1.036 | 1.044 | 1.026 | 1.035 | 1.040 | 1.023 | 1.033 | 1.036 | 1.021 | 1.029 | 1.035 |
| 6 MV                      |                               | 1.029 | 1.035 | 1.042 | 1.025 | 1.032 | 1.040 | 1.022 | 1.029 | 1.036 | 1.019 | 1.028 | 1.034 | 1.017 | 1.025 | 1.032 |
| 10 MV                     |                               | 1.012 | 1.021 | 1.031 | 1.012 | 1.020 | 1.030 | 1.011 | 1.019 | 1.028 | 1.010 | 1.020 | 1.026 | 1.011 | 1.017 | 1.024 |
| 15 MV                     |                               | 1.010 | 1.016 | 1.024 | 1.008 | 1.016 | 1.023 | 1.007 | 1.015 | 1.021 | 1.007 | 1.015 | 1.021 | 1.007 | 1.012 | 1.020 |
| $^{60}$Co                 |                               | 1.018 | 1.025 | 1.034 | 1.016 | 1.025 | 1.032 | 1.014 | 1.023 | 1.031 | 1.012 | 1.022 | 1.028 | 1.011 | 1.018 | 1.025 |
| Gadolinium                |                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 4 MV                      |                               | 1.026 | 1.030 | 1.030 | 1.022 | 1.025 | 1.027 | 1.020 | 1.023 | 1.023 | 1.017 | 1.022 | 1.021 | 1.016 | 1.017 | 1.019 |
| 6 MV                      |                               | 1.023 | 1.024 | 1.027 | 1.018 | 1.021 | 1.024 | 1.016 | 1.019 | 1.019 | 1.014 | 1.017 | 1.017 | 1.012 | 1.014 | 1.016 |
| 10 MV                     |                               | 1.005 | 1.010 | 1.011 | 1.005 | 1.010 | 1.011 | 1.005 | 1.009 | 1.010 | 1.004 | 1.009 | 1.009 | 1.004 | 1.006 | 1.008 |
| 15 MV                     |                               | 1.003 | 1.006 | 1.007 | 1.003 | 1.005 | 1.007 | 1.002 | 1.004 | 1.006 | 1.001 | 1.004 | 1.006 | 1.001 | 1.000 | 1.004 |
| $^{60}$Co                 |                               | 1.010 | 1.013 | 1.014 | 1.009 | 1.012 | 1.013 | 1.008 | 1.012 | 1.012 | 1.007 | 1.012 | 1.010 | 1.005 | 1.007 | 1.009 |

Table 3. The average values of the dose enhancement factor inside the tumour for various nanoparticle diameters and concentrations of iodine and iron oxide

| Nanoparticle diameter (nm) | Material concentration (mg/g) |   7  |  18  |  30  |  7  |  18  |  30  |  7  |  18  |  30  |  7  |  18  |  30  |  7  |  18  |  30  |
|---------------------------|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Iodine                    |                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 4 MV                      |                               | 1.021 | 1.027 | 1.028 | 1.018 | 1.021 | 1.024 | 1.018 | 1.019 | 1.022 | 1.014 | 1.019 | 1.018 | 1.012 | 1.016 | 1.017 |
| 6 MV                      |                               | 1.017 | 1.023 | 1.024 | 1.015 | 1.019 | 1.020 | 1.014 | 1.016 | 1.019 | 1.010 | 1.015 | 1.015 | 1.009 | 1.012 | 1.013 |
| 10 MV                     |                               | 1.003 | 1.005 | 1.010 | 1.004 | 1.005 | 1.010 | 1.003 | 1.003 | 1.009 | 1.002 | 1.002 | 1.007 | 1.002 | 1.001 | 1.006 |
| 15 MV                     |                               | 1.001 | 1.004 | 1.005 | 1.000 | 1.003 | 1.005 | 1.000 | 1.001 | 1.005 | 1.000 | 1.000 | 1.003 | 1.000 | 1.000 | 1.003 |
| $^{60}$Co                 |                               | 1.006 | 1.011 | 1.013 | 1.007 | 1.010 | 1.012 | 1.006 | 1.007 | 1.010 | 1.004 | 1.006 | 1.009 | 1.002 | 1.003 | 1.007 |
| Iron oxide                |                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 4 MV                      |                               | 1.017 | 1.021 | 1.024 | 1.014 | 1.018 | 1.021 | 1.012 | 1.015 | 1.018 | 1.011 | 1.014 | 1.016 | 1.009 | 1.011 | 1.014 |
| 6 MV                      |                               | 1.012 | 1.018 | 1.020 | 1.012 | 1.015 | 1.017 | 1.009 | 1.012 | 1.015 | 1.006 | 1.010 | 1.013 | 1.005 | 1.007 | 1.010 |
| 10 MV                     |                               | 1.002 | 1.002 | 1.007 | 1.002 | 1.003 | 1.007 | 1.001 | 1.002 | 1.005 | 1.001 | 1.002 | 1.005 | 1.000 | 1.002 | 1.004 |
| 15 MV                     |                               | 1.000 | 1.001 | 1.005 | 1.000 | 1.001 | 1.004 | 1.000 | 1.001 | 1.002 | 1.000 | 1.001 | 1.001 | 1.000 | 1.001 | 1.000 |
| $^{60}$Co                 |                               | 1.004 | 1.006 | 1.011 | 1.004 | 1.005 | 1.009 | 1.003 | 1.004 | 1.007 | 1.002 | 1.003 | 1.006 | 1.002 | 1.002 | 1.005 |
higher DEFs were observed. Based on our results, a relatively high dose enhancement was identified for 4 and 6 MV X-rays. The effects of dose enhancement were highest for 4 MV X-rays, followed by 6 MV, $^{60}$Co, 10 MV and 15 MV. Incident energies of $>$10 MV showed a DEF of $<$1%, i.e. a very small dose enhancement.

**DISCUSSION**

Due to the high atomic numbers of dose enhancement materials, differences occur between the mass attenuation coefficients and the cross-section within the medium, resulting in dose enhancement [29]. Photons in the kiloelectronvolt (keV) energy spectrum [lower than the megaelectronvolt (MeV) energies considered here] showed a high DEF. This enhancement occurs because the interaction arising from the difference in the atomic numbers of dose enhancement materials increases the cross-section of the photoelectric effects relatively more than that of Compton scattering [17, 30]. However, photons in energy spectrums higher than MeV energies are more likely to respond to Compton scattering than photoelectric effects, because the cross-section of Compton scattering has a lower dependence on the atomic number of materials [31]. Mesbah et al. reported the following Monte Carlo simulation results: a DEF of 1.01 was observed for 6 MeV photons, and DEFs of $\geq$3.0 were shown for keV energy X-rays, thus supporting this hypothesis for the effects of the energy spectrum. In particular, when the incident energy is close to the binding energy of the K-shell with a high cross-section of photoelectric effects, high DEFs are observed [32].

When the dose enhancement within the tumour volume was compared with changes in the incident energy, higher DEFs were observed according to the following decreasing order: 4 MV, 6 MV, $^{60}$Co, 10 MV and 15 MV. The $^{60}$Co source emits $\gamma$-rays with an average energy of 1.25 MeV; thus, the above observed outcomes were due to differences in the average energy between the $^{60}$Co source and MV X-rays.

Although Fe$_3$O$_4$ has received attention as the next-generation contrast medium for MRI because of its excellent biocompatibility, stability inside the body, target directivity, and high enhancement [14], the use of Fe$_3$O$_4$ in studies on dose enhancement materials has been limited. In the in vitro study conducted by Khoei et al., using 6-MV X-rays, a dose enhancement of $>$10% was reported [33]. However, the present study observed a dose enhancement of 1.0–2.4%. This discrepancy seems to be a result of the difference between in vitro methods and the Monte Carlo simulation, and further studies are required on Fe$_3$O$_4$.

In external radiation therapy, a high acceleration voltage of $>$15 MV, rather than a low acceleration voltage, is preferred for better sparing of the healthy tissue surrounding a target volume. It is believed that the higher dose enhancement factors achieved at low energies would create such an effect.

This study showed that higher DEFs were observed with increasing concentration of dose enhancement materials and with increasing nanoparticle diameters. A previous study, using Au nanoparticles, also reported increases in the DEF associated with increases in the concentration and diameter of nanoparticles [31]. However, the concentration and diameter of nanoparticles also have an effect on toxicity [34]. Furthermore, the diameter of the nanoparticles influences the absorption in tissues as well as the EPR; thus, in vitro experimental results are required (at least for the corresponding in vivo experimental results) on dose enhancement that considers the DEF, toxicity, and tissue absorption [17].

**CONCLUSIONS**

Based on the Monte Carlo simulation, the dose enhancement of MV X-rays generated from a medical linear accelerator resulting from the use of Au, Gd, I and Fe$_3$O$_4$ nanoparticles was compared and analysed.

High-energy MV X-rays, which have a polychromatic energy spectrum, are most commonly used in radiotherapy. This study analysed the dose enhancement for high-energy MV X-rays and the energy spectra generated from a medical linear accelerator in a phantom. Therefore, this study has a significant meaning for clinical radiotherapy applications.

The dose enhancement differed significantly according to the incident energy, material concentration, and the diameter of the nanoparticles. The 4 and 6 MV X-rays showed a relatively high DEF compared with the 10 and 15 MV X-rays. The 10 and 15 MV X-rays improved the dose enhancement only by 1–2%.

Furthermore, as the concentration and diameter of the nanoparticles increased, the DEF in the tumour volume also increased; this result suggests that a higher radiation dose would be delivered to the tumour volume, which would further contribute to improvements in the TR. The results of this study will provide useful data for future in vitro and in vivo studies.

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**CONFLICT OF INTEREST**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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