Nanoparticle Location and Material-Dependent Dose Enhancement in X-ray Radiation Therapy

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ABSTRACT: Nanoparticles of high atomic number (Z) materials can act as radiosensitizers to enhance radiation dose delivered to tumors. An analytical approach is used to calculate dose enhancements to tumor endothelial cells and their nuclei for a series of nanoparticles (bismuth, gold and platinum) located at different sections relative to nuclei by considering contributions from both photoelectrons and Auger electrons. The ratio of the dose delivered to cells with and without the nanoparticles is known as the dose enhancement factor (DEF). DEFs depend on material composition, size, and location of nanoparticles with respect to the cell and the nucleus. Energy of irradiating X-ray beam affects X-ray absorption by nanoparticles and plays an important role in dose enhancements. For diagnostic X-ray sources, bismuth nanoparticles provide higher dose enhancements than gold and platinum nanoparticles for a given nanoparticle size, concentration and location. The highest DEFs are achieved for nanoparticles located closest to the nucleus, where energy depositions from short-range Auger electrons are maximum. With nanoparticles ranging in diameter between 2 and 400 nm, the dose enhancement increases with decrease in particle size. The results are useful in finding optimized conditions for nanoparticle-enhanced X-ray radiation therapy of cancer.

1. INTRODUCTION

Radiotherapy aims to maximize radiation dose delivered to tumors with minimum damage to surrounding healthy tissues. The promising ability of gold nanoparticles as effective radiosensitizers for localized tumor dose enhancements has been extensively explored due to high X-ray absorption cross-section of gold compared with biological tissues. 1−8 Previous experiments with mice have shown significant increase in dose delivered to tissue volumes in the presence of gold nanoparticles. 9 Monte Carlo simulations have been performed extensively to investigate various parameters such as photon energy, particle size, concentration, and location that govern radiosensitizing properties of gold nanoparticles. 10−14 A recent study also shows how geometry of nanoparticles affects X-ray dose enhancement. 15 Other theoretical studies reveal that targeted gold nanoparticles can enhance dose to endothelial cells surrounding a tumor by over 200 times depending on their concentration and energy of the irradiating X-ray photons. 16 Dose enhancement is often attributed to photoelectrons and Auger electrons generated from the X-ray irradiated nanoparticles. Photoelectrons are highly energetic, have a long-range (up to hundreds of micrometers) in surrounding water, and deposit a small fraction of their energy near the nanoparticle. Auger electrons have lower energy and shorter range (<1 μm), allowing most of the energy to be deposited close to the nanoparticle. Energy deposition by electrons will hydrolyze water molecules surrounding cells and their nuclei, producing free radicals that will induce DNA damage, eventually leading to cell death. Cell nucleus that contains DNA is thus considered to be the most sensitive to radiation exposure. 17−19 Because of major contributions from short-range Auger electrons, dose enhancement to nuclei is significantly different from that to the entire cell. A recent theoretical study indicates that nucleus dose enhancement factor (nDEF) or the ratio of dose delivered to nucleus with and without gold nanoparticles can be as high as 73 for endothelial cell nuclei. 20 Experiments have also shown that gold nanoparticles can be internalized inside cancer cells, which makes nanoparticle location control a feasible choice for dose enhancement. 21 In addition, although gold nanoparticles have been the prime choice for radiosensitizers due to their high biocompatibility, ease of conjugation to tumor targeting agents, and high X-ray absorption coefficients, nanoparticles of other heavy metals such as bismuth and platinum can also serve as promising alternatives to gold in radiotherapy. 22−27 However, there is no systemic investigation over potential benefits by controlling location and material composition of nanoparticles relative to cancer cells in X-ray radiation therapy.

We use an analytical approach developed by Ngwa et al. 16 to derive radiosensitizing abilities of bismuth, gold, and platinum nanoparticles under diagnostic X-ray conditions (50, 110, or 300 kVp). For each type of nanoparticles, doses delivered to endothelial cells and their nuclei are derived for particle sizes ranging between 2 to 400 nm in diameter and concentrations ranging between 7 to 350 mg of nanoparticles per gram of...
tumor tissue. The contributions from both photoelectrons and Auger electrons are derived. Unlike previous studies, this work primarily focuses on dependence of dose enhancements on material composition and size as well as location of nanoparticles using diagnostic X-ray sources (instead of using brachytherapy sources). In addition, the variation of nDEFs with respect to nanoparticle location has been discussed in the context of photoelectron and Auger electron generation. Although Auger electron cross sections are derived from a previous Monte Carlo simulation due to lack of such data, the theoretical results from this investigation can provide useful insights into choice of nanoparticles in terms of nanoparticle nature, size, and targeting location to achieve maximum efficacy in nanoparticle-enhanced X-ray radiation therapy of cancer.

2. METHODS

A slab of tumor endothelial cell with dimensions of 2 μm (thickness) × 10 μm (length) × 10 μm (width) has been considered in the following simulations (Figure 1).16 The radius of sphere with nanoparticle in center is equal to the range of emitted photoelectrons. Calculations are performed for spherical nanoparticles attached to the outer surface of the tumor endothelial cell. Nanoparticles of a wide range of size and targeting location to achieve maximum e

\[ D_w = \sum_E \Phi_E \left( \frac{\mu_{\text{en}}}{\rho} \right)_E \]  

\[
\text{where } \Phi \text{ is photon flux (photons/cm}^2\text{)}, E_{\text{en}} \text{ is energy per photon (J), and } (\mu_{\text{en}}/\rho) \text{ is mass absorption coefficient of water (cm}^2\text{)/g) at a given energy } E. \text{ The number of photons } (N_{\text{ph}}) \text{ incident on the nanoparticle is derived by multiplying photon flux by cross-sectional area of nanoparticle, } N_{\text{ph}} = \Phi \times \pi r^2, \text{ where } r \text{ is radius of nanoparticle. The probability } P \text{ of photoelectric interaction of incident photons with nanoparticle is given by } P \approx (\mu_{\text{en}}/\rho)_{NP}/N_{\text{ph}} \text{ where } (\mu_{\text{en}}/\rho)_E \text{ is the photoelectric absorption coefficient of nanoparticle at an energy } E, \rho_{NP} \text{ is density of nanoparticle, and } d_{\text{np}} = 4r/3 \text{ is the average distance traversed by photons through a spherical nanoparticle. A 50 kVp X-ray photon has an average energy } E \sim 29 \text{ keV. At } E = 29 \text{ keV, } (\mu_{\text{en}}/\rho)_{29\text{keV}} = 32.74 \text{ cm}^2/\text{g for bismuth resulting in } P \sim 8.54 \times 10^{-3} \text{ for } \rho_{\text{Bi}} = 9.78 \text{ g/cm}^3 \text{ and } r = 200 \text{ nm. Because the number of photoelectric interactions is equal to the number of emitted photoelectrons, the number of emitted photoelectrons per nanoparticle is derived from } N_{\text{PE}} = N_{\text{ph}} \times P. \]

The next step is to determine the number of nanoparticles that attach on cell surface at given nanoparticle concentrations. The total mass of nanoparticles \( m_{\text{total}} \) in the entire volume of cell for a given concentration \( C \) (mg/g) is given by \( m_{\text{total}} = C \times V_{\text{cell}} \times \rho_{\text{EC}} \) where \( V_{\text{cell}} \) and \( \rho_{\text{EC}} \) are the volume and density of cell, respectively. The mass of nanoparticle is obtained as \( m_{\text{NP}} = (4/3)\pi r^3 \rho_{\text{NP}} \). Therefore, for any concentration \( C \) of nanoparticles, the number of nanoparticles that attach to cell is

\[ N_{\text{NP}} = \frac{m_{\text{total}}}{m_{\text{NP}}} = \frac{CV_{\text{cell}}\rho_{\text{EC}}}{\frac{4}{3}\pi r^3 \rho_{\text{NP}}} \]  

\[ (2) \]

The total number of emitted photoelectrons can now be calculated as \( N_{\text{PEtotal}} = N_{\text{PE}} \times N_{\text{NP}} \). To evaluate the range of emitted photoelectrons, the kinetic energy \( E_{\text{KE}} \) of emitted photoelectrons must be known, which is given by \( E_{\text{KE}} = E - E_{\text{edge}} \) where \( E_{\text{edge}} \) is relevant photoelectric absorption edge of nanoparticle. The average L-edge of bismuth is 15 keV, giving \( E_{\text{KE}} = 14 \text{ keV} \). As emitted photoelectrons interact with their surroundings, they will deposit kinetic energy in a sphere of interaction centered on the nanoparticle. The radius of interaction sphere defines the range \( R_{\text{tot}} \) of photoelectrons and is given by

\[ R_{\text{tot}} = 0.0431(E_{\text{KE}} + 0.367)^{1.77} - 0.007 \]  

\[ (3) \]

At \( E_{\text{KE}} = 14 \text{ keV} \), \( R_{\text{tot}} \) is 4.81 μm. For electron with kinetic energy between 20 eV and 20 MeV, Cole has derived an empirical relation28 between electron energy loss \( (dE_{\text{KE}})/dx \) (keV/μm) and range \( R_{\text{tot}} \) (μm)

\[ \frac{dE_{\text{KE}}}{dx} = 3.316(R_{\text{tot}} - x + 0.007)^{-0.435} + 0.0055 \]  

\[ (R_{\text{tot}} - x)^{0.33} \]  

\[ (4) \]

where \( x \) is the distance from photoelectron emission site. The total energy deposited by single photoelectron in cell volume is obtained by integrating differential energy loss from surface of nanoparticle \( (r) \) to maximum range \( (R_{\text{tot}}) \) of photoelectrons (Figure 1)

\[ E_{\text{EC}} = \int_0^{R_{\text{tot}}} \frac{H_{\text{ABC}} - C_{\text{XBY}}}{S_{\text{ABCD}}} \times \frac{dE_{\text{KE}}}{dx} \]  

\[ \text{dx} \]  

\[ (5) \]

where \( H_{\text{ABC}} = \text{area of hemisphere ABC} = 2\pi R_{\text{tot}}^2 \), \( C_{\text{XBY}} = \text{Area of hemispherical cap XBY} = 2\pi(R_{\text{tot}} - t) \), \( S_{\text{ABCD}} = \text{surface area of entire sphere ABCD} = 4\pi R_{\text{tot}}^2 \), and \( t \) is cell thickness. Assuming a homogeneous distribution of nanoparticles, and dose deposited in the entire sphere of interaction, the total energy deposited to cell by photoelectrons can be derived by multiplying \( E_{\text{EC}} \) by the total number of emitted photoelectrons; that is, \( E_{\text{ETotal}} = E_{\text{EC}} \times N_{\text{PEtotal}} \). This calculation does not take into account the hemispherical shell in the blood vessel and the spherical shell beyond the cell. Dose contributions from nanoparticles on the opposite side of blood vessel are relatively small and therefore have not been considered. The dose delivered to the entire cell by photoelectrons following nanoparticle and X-ray interactions is obtained by dividing energy deposited in cell by mass (volume × density) of cell:

\[
\text{dx} \text{doi.org/10.1021/jp306543q} J. \text{Phys. Chem. C 2012, 116, 23047–23052}
enzymes inside cell. It has been found that mean di
mostly hydroxyl radicals), but free radical chain reaction can
the same X-ray beam.
numbers and therefore similar Auger yields when exposed to
of 10
length of free radicals is in the range of 200 nm in the presence
particles using the same approach.
To derive contributions from Auger electrons, Auger
electron spectra obtained from Monte Carlo simulations for
tumors loaded with gold nanoparticles at 7 mg/g and irradiated
with a 50 kVp X-ray source are used.12 The energy deposited by
photons and Auger electrons (B) for 400 nm diameter nanoparticles
function of nanoparticle concentrations due to photoelectrons (A)
Figure 2. Endothelial cell dose enhancement factor (DEF) as a
function of local nanoparticle concentration due to photoelectrons (A)
and Auger electrons (B) for 400 nm diameter nanoparticles irradiated
by a 50 kVp external beam X-ray source. Endothelial cell dose
enhancement factor (DEF) as a function of nanoparticle radius (r) due
to photoelectrons (C) and Auger electrons (D) for 7 mg of
nanoparticles per gram of tumor irradiated by a 50 kVp external
beam X-ray source.

3. RESULTS AND DISCUSSION
Figure 2A shows the variation of cellular DEF due to
photoelectrons as a function of nanoparticle concentrations
for 400 nm diameter bismuth, gold, and platinum nanoparticles
when irradiated by a 50 kVp source. For any given
concentration, bismuth nanoparticles yield the highest dose
enhancement, whereas gold and platinum nanoparticles provide
similar enhancements. This is in accordance with differences in

\[
D_{NP} (PE) = \left( \frac{E_{EC\,q_{pp}}}{V_{EC\times q_{EC}}} \right).
\]

DEF due to photoelectrons is
given by

\[
\text{DEF (photoelectrons)} = \frac{\text{absorbed dose with nanoparticle}}{\text{absorbed dose without nanoparticle}} = \frac{D_W + D_{NP(PE)}}{D_W}
\]

A DEF of 1.0 refers to 0% enhancement, whereas a DEF of 2.0
refers to 100% enhancement. For bismuth nanoparticles, at a
concentration of 7 mg/g, DEF is 1.307, meaning that adding 7
mg of bismuth nanoparticles per gram of a tumor tissue
increases X-ray dose by 65% when only the photoelectrons are
considered for energy deposition. The calculations are repeated
for a series of nanoparticle concentrations ranging from 7 to
350 mg/g and radius ranging from 1 to 200 nm. DEFs due to
photoelectrons are calculated for gold and platinum nano-
particles using the same approach.

To derive contributions from Auger electrons, Auger
electron spectra obtained from Monte Carlo simulations for
tumors loaded with gold nanoparticles at 7 mg/g and irradiated
with a 50 kVp X-ray source are used.12 The energy deposited by
Auger electrons in the cell is determined as described for
photoelectrons. The average number of Auger electrons
generated per absorbed X-ray photon (at 7 mg/g nanoparticle
concentration) is 0.56, as derived from the Auger spectra. The
product of number of source photons and number of Auger
electrons per source photon gives the total number of Auger
electrons emitted. Number of Auger electrons per source
photon at higher nanoparticle concentrations is obtained by
scaling number of Auger electrons per source photon at 7 mg/
g, as described by Ngwa et al.16 For simplicity, the average
number of Auger electrons per source photon generated from
bismuth nanoparticles and platinum nanoparticles are also
taken as 0.56 when irradiated by the same 50 kVp source. This
is a reasonable approximation assuming that the difference in
Auger electron spectra of platinum (Z = 78), gold (Z = 79),
and bismuth (Z = 83) is negligible due to their similar atomic
numbers and therefore similar Auger yields when exposed to
the same X-ray beam.

Both photoelectrons and Auger electrons can cause radiolysis
of surrounding water, leading to the formation of free radicals
(mostly hydroxyl radicals), but free radical chain reaction can
be terminated by scavengers such as lipids in cell membranes
or enzymes inside cell. It has been found that mean diffusion
length of free radicals is in the range of 200 nm in the presence
of 10^{-5} M scavengers in aqueous solution. Therefore, to
ensure maximum DNA damage caused by photoelectron and Auger
electrons, it is necessary to position nanoparticles as close to
nucleus as possible. The slab model, used to calculate dose
enhancement to cell, is slightly adjusted to include a nucleus
that occupies 10% of cell volume (Figure 1).20 The nucleus has
a diameter of 0.5 μm and a thickness of 1.0 μm and is located at
the center of the 2 μm thick slab. The boundary conditions in
eq 5 are adjusted to include only the dose deposited by
electrons within 1 μm thick slab (KLMM) section containing
the nucleus. Energy deposited within 1 μm thick slab section
containing nucleus is calculated as

\[
E_{slab} = \int_{r_{int}}^{r_{out}} \frac{H_{ABC} - C_{ABC}}{S_{ABCD}} \times \frac{dE_{KE}}{dx} \, dx
\]

For a centrally located nucleus inside a 2 μm slab, \( C_{ABC} \) = area
of spherical cap A′B′C′ = 2πR_{tot}t (R_{tot} = t + 0.5 μm) and \( C_{ABC} \) =
area of spherical cap ABC = 2πR_{tot}t (R_{tot} = t + 1.5 μm), with t =
2 μm being the cell thickness. Plugging in parameters for 1.9
nm bismuth nanoparticles gives \( E_{slab} = 1.45 \) keV. The average
dose deposited in the slab section containing the nucleus is
given by

\[
D_{nucleus} = \frac{\text{volume}_{nucleus}}{\text{volume}_{slab}} \times \frac{E_{slab}}{\text{mass}_{nucleus}}
\]

The mass of nucleus is calculated from product of its volume
and density (1.0 g/cm³). The nDEF is obtained as follows

\[
nDEF = \frac{D_{nucleus}}{D_{slab}}
\]

where \( D_{slab} = 2 \) Gy is the arbitrary dose delivered to water
surrounding the nucleus. Plugging in values yields nDEF = 1.02
for photoelectrons and 8.24 for Auger electrons at 7 mg/g
concentration of 1.9 nm bismuth nanoparticles.
X-ray absorption cross sections of bismuth, gold, and platinum. At a concentration of 350 mg/g, bismuth nanoparticles provide 1.25 and 1.29 times higher dose enhancements than gold nanoparticles and platinum nanoparticles, respectively. Figure 2B shows the variation of dose enhancement due to Auger electrons with nanoparticle concentrations. Although, DEFs due to Auger electrons increase linearly with nanoparticle concentration, they are considerably higher than those from photoelectrons at the same concentration. This is attributed to the short-range (<1 μm) of Auger electrons, which causes them to deposit most of their energies in the vicinity of the X-ray irradiated nanoparticle. As a result of the near-particle energy deposition, dose contribution within several hundred nanometers from nanoparticle location is dominated by Auger electrons. Auger electrons from bismuth nanoparticles provide ~2 and 2.4 times higher enhancement than gold nanoparticles and platinum nanoparticles at 350 mg/g. Total dose enhancement factors are calculated by summing contributions from photoelectrons and Auger electrons. Table 1 summarizes total enhancement factors for three nanoparticle concentrations for three types of nanoparticles having a diameter of 400 nm.

Figure 2C shows the effect of nanoparticle size (r = radius) on dose enhancement due to photoelectrons alone at 7 mg/g for three different types of nanoparticles. The enhancement factor remains constant with increase in particle size from 2 to 400 nm. Figure 2D shows that the enhancement factor due to Auger electrons decreases with increase in particle size. Following an ionizing event, photo or Auger electrons must escape nanoparticle before causing damage to surrounding cells; however, the percentage of electrons emitted from nanoparticle upon X-ray excitation strongly depends on particle size, with a majority of low-energy and short-range Auger electrons being absorbed more readily within nanoparticle of increasing size. Because more Auger electrons can escape from smaller nanoparticles, the overall energy deposited to surrounding cell is higher for smaller nanoparticles, resulting in higher dose enhancements. The percentage of energy escaping as photoelectrons and characteristic X-rays remains unchanged with increase in particle size, thereby, maintaining an almost constant dose enhancement.

As shown in Figure 2C,D, for any given size (and concentration), bismuth nanoparticles provide the maximum dose enhancement, whereas platinum nanoparticles have slightly lower DEFs than gold nanoparticles. The total enhancement including both Auger and photoelectrons with respect to particle size is calculated by summing the individual contributions from Auger and photoelectrons.

Figure 3A,B shows variations in nDEFs with nanoparticle concentrations for photoelectrons and Auger electrons, respectively, when irradiated by an external 50 kVp X-ray source. Because smaller nanoparticles have high Auger electron yield (due to low self-absorption), the nanoparticle diameter used to calculate nDEF is 1.9 nm instead of 400 nm to emphasize influence of Auger electrons. Bismuth nanoparticles provide the highest nDEFs for a given nanoparticle concentration, size, and location. The total nDEFs can be obtained by adding nDEF values for photoelectrons and Auger electrons. Table 2 summarizes nDEFs due to photoelectrons and Auger electrons for a centrally located nucleus using three different concentrations with nanoparticle diameter of 1.9 nm. The location-dependent variation of nDEF is studied for photoelectrons and Auger electrons. The zero position is taken as the location where nanoparticle is closest to the nucleus or just inside the nucleus. Figure 3C,D show how the cellular dose enhancements due to photoelectrons and Auger electrons varies as the nanoparticle is moved away from the nucleus, with regards to the energy distributions from photoelectrons and Auger electrons, respectively. The concentration of nanoparticles is chosen to be 7 mg/g. The long-range photoelectrons deposit their energy relatively uniformly over the entire cell volume, with nDEF remaining fairly constant as the nanoparticle is moved away from the nucleus. In contrast, short-range Auger electrons deposit more energy closer to the nanoparticles; therefore, the highest nDEFs are achieved for nanoparticles that are located closest to the nucleus.
platinum nanoparticles, respectively. For each type of particle, the diameter is taken at 400 nm. Figure 4D shows the results obtained at nanoparticle concentration of 350 mg/g. In addition to 50 kVp source, two additional X-ray sources, 110 and 300 kVp (average energy ~100 keV), are used to study the energy dependence of cellular dose enhancements. Our results are consistent with previous studies that used Monte Carlo simulations and reveal a general trend of increasing dose enhancement with decreasing energy of X-ray sources for a given nanoparticle type. The k-edge energies of bismuth, gold, and platinum are 91, 81, and 78 keV, respectively. The 50 and 110 kVp sources have average energies below k-edge, whereas the 300 kVp source has an average energy above k-edge of particles. An abrupt increase in photoelectric absorption coefficients is observed only when the average energy of the primary X-ray photons matches k-edge energies or when a monochromatic X-ray source with the same energy as k-edge of nanoparticles is used. Low-energy diagnostic X-ray sources are therefore ideal for nanoparticle enhanced therapeutic applications, particularly for the treatment of surface cancers. However, treating deeply buried cancers would still require high-energy X-ray beams that can penetrate deeper inside the body.

4. CONCLUSIONS

In this work, an analytical approach is adopted to obtain dose enhancements for tumor cells and their nuclei using bismuth, gold, and platinum nanoparticles. Energy depositions from both photoelectrons and Auger electrons, generated by X-ray photons matches k-edge energies or when a monochromatic X-ray source with the same energy as k-edge of nanoparticles is used. Low-energy diagnostic X-ray sources are therefore ideal for nanoparticle enhanced therapeutic applications, particularly for the treatment of surface cancers. However, treating deeply buried cancers would still require high-energy X-ray beams that can penetrate deeper inside the body.

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