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The dosimetric feasibility of gold nanoparticle-aided radiation therapy (GNRT) via brachytherapy using low-energy gamma-/x-ray sources

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Abstract

The preferential accumulation of gold nanoparticles within tumors and the increased photoelectric absorption due to the high atomic number of gold cooperatively account for the possibility of significant tumor dose enhancement during gold nanoparticle-aided radiation therapy (GNRT). Among the many conceivable ways to implement GNRT clinically, a brachytherapy approach using low-energy gamma-/x-ray sources (i.e. $E_{\text{avg}} < 100$ keV) appears to be highly feasible and promising, because it may easily fulfill some of the technical and clinical requirements for GNRT. Therefore, the current study investigated the dosimetric feasibility of implementing GNRT using the following sources: ^{125}I , 50 kVp and ^{169}Yb . Specifically, Monte Carlo (MC) calculations were performed to determine the macroscopic dose enhancement factors (MDEF), defined as the ratio of the average dose in the tumor region with and without the presence of gold nanoparticles during the irradiation of the tumor, and the photo/Auger electron spectra within a tumor loaded with gold nanoparticles. The current study suggests that a significant tumor dose enhancement (e.g. >40%) could be achievable using ^{125}I , 50 kVp and ^{169}Yb sources and gold nanoparticles. When calculated at 1.0 cm from the center of the source within a tumor loaded with 18 mg Au g⁻¹, macroscopic dose enhancement was 116, 92 and 108% for ^{125}I , 50 kVp and ^{169}Yb , respectively. For a tumor loaded with 7 mg Au g⁻¹, it was 68, 57 and 44% at 1 cm from the center of the source for ^{125}I , 50 kVp and ^{169}Yb , respectively. The estimated MDEF values for ^{169}Yb were remarkably larger than those for ^{192}Ir , on average by up to about 70 and 30%, for 18 mg Au and 7 mg Au cases, respectively. The current MC study also shows a remarkable change in the photoelectron fluence and spectrum (e.g. more than two orders of magnitude) and a significant production (e.g. comparable to the number of photoelectrons) of the Auger electrons within the tumor region due to the presence of gold nanoparticles during low-energy gamma-/x-ray irradiation. The radiation sources considered in this study are currently available and tumor gold concentration levels considered in this investigation are deemed achievable. Therefore, the current results strongly suggest that GNRT can be successfully implemented via brachytherapy with low energy gamma-/x-ray sources, especially with a high dose rate ^{169}Yb source.

1. Introduction

In recent years, there has been growing interest in applying nanotechnology to cancer treatment and detection. Many of the current approaches are based on a phenomenon typically known as 'enhanced permeability and retention (EPR)' (Maeda *et al* 2003) due to passive extravasation of nanoparticles through 'leaky' vasculature of tumors (Dvorak *et al* 1988). In this phenomenon, nanoparticles passively leak into the tumor interstitium from blood vessels feeding the tumor, because by definition they are smaller (e.g. 1~100 nm) than the typical cutoff size of the pores (e.g. up to 400 nm) in the tumor vasculature (Umezaki *et al* 1996). This phenomenon alone has enabled an interesting strategy to concentrate nanoparticles specifically within the tumor, commonly known as 'passive targeting'. Moreover, the tumor specificity of nanoparticles can be further increased through so-called 'active targeting' (Qian *et al* 2008), in which nanoparticles are conjugated with antibodies or peptides directed against tumor markers such as the epidermal growth factor receptor (EGFR), human epidermal growth factor receptor-2 (HER2) and angiogenesis markers such as the vascular endothelial growth factor receptor (VEGFR).

The idea of enhancing tumor dose (or radio-sensitizing tumor) using high-atomic number (Z) contrast media or gold microspheres and kilo-/mega-voltage x-rays has been constantly sought over the years (Mello *et al* 1983, Dawson *et al* 1987, Iwamoto *et al* 1987, Rose *et al* 1994, Mesa *et al* 1999, Herold *et al* 2000, Robar *et al* 2002, Verhaegen *et al* 2005, Robar 2006, McMahon *et al* 2008). Taken this idea and the aforementioned EPR effect together, it is conceivable that an enhancement in tumor dose during radiation therapy could be achieved if enough gold nanoparticles passively and/or actively accumulate within tumors. In theory, this concept appears to be more promising than earlier approaches based on the use of high-Z contrast media such as iodine and gadolinium or gold microspheres, because of the higher atomic number of gold and/or better tumor specificity of nanoparticles. A previous animal study (Hainfeld *et al* 2004) actually tested this concept and found that irradiation of tumor-bearing mice after injecting gold nanoparticles indeed resulted in remarkable tumor regression and long-term survival without any significant toxicity compared to mice irradiated without gold nanoparticles. This dramatic outcome could be attributed to significant increase in the photoelectron fluence within the tumor (including blood vessels) loaded with high-Z gold nanoparticles during x-ray irradiation, resulting in greater physical damage to tumor cells and endothelial cells lining the blood vessels (Hainfeld *et al* 2008). A subsequent Monte Carlo (MC) study (Cho 2005) projected the potential clinical consequences of this animal study (Hainfeld *et al* 2004) by quantifying the amount of dose enhancement under typical radiation therapy treatment scenarios. The major finding of this MC study was that the macroscopic (or average) tumor dose enhancement would be dependent on gold concentration within the tumor and the photon beam quality, ranging from several hundred per cent for diagnostic x-rays to a few per cent for typical megavoltage photon beams. The results from this MC study were later confirmed by an independent non-Monte Carlo theoretical study (Roeske *et al* 2007) based on a systematic analysis of the mass energy absorption coefficients of various mixtures at different photon energies. Besides, many other recent studies have also demonstrated the tumor dose enhancement or radiosensitization *in vitro* and *in vivo* due to gold or other metal nanoparticles and x-ray or electron-beam irradiation (Foley *et al* 2005, Butterworth *et al* 2008, Chang *et al* 2008, Zhang *et al* 2008, Zheng *et al* 2008, Kong *et al* 2008).

Based on the aforementioned studies, a radiation treatment modality referred to as gold nanoparticle-aided radiation therapy (GNRT) may be developed so that the tumor dose could be escalated beyond the current limits especially for those radioresistant tumors, while adequately sparing normal tissues surrounding the tumor. Note that the gold nanoparticles are singled out for this approach among various metal nanoparticles, as they are generally

fabricated from an inert metal (i.e. gold) and, as a result, are biologically non-reactive and molecularly stable. In principle, GNRT would be most effective with low-energy x-rays and gamma rays (i.e. $E_{\text{avg}} < 100$ keV) because such photons will interact with gold nanoparticles within the tumor predominantly via photoelectric effect, which is thought to be the main physical mechanism responsible for the dose enhancement. Due to their limited penetration into condensed media such as human tissue, however, low-energy x-rays and gamma rays may not be suitable for the delivery of GNRT via external beam radiation therapy (EBRT), unless tumors are located within a few cm depth (e.g. < 3 cm) in tissue. On the other hand, it is readily apparent that a brachytherapy implementation of GNRT is highly feasible. Moreover, it is conceptually possible to increase the tumor dose enhancement even further than that reported for an ^{192}Ir source by using radioisotopes emitting even lower energy gamma rays than ^{192}Ir or by using miniature x-ray devices producing low-energy x-rays (e.g. ~ 50 kVp). For example, a high-dose rate (HDR) ^{169}Yb source has an intensity-weighted average energy of about 93 keV (Medich *et al* 2006), which is significantly lower than that of the typical HDR ^{192}Ir sources (i.e. ~ 395 keV). Consequently, ^{169}Yb gamma rays have a higher probability of photoelectric absorption in a gold-loaded tumor than ^{192}Ir gamma rays and thereby would result in more tumor dose enhancement. A similar argument can be made for low-energy gamma rays from other brachytherapy sources such as ^{125}I and ^{103}Pd or x-rays from miniature x-ray devices reported previously (Birch and Blowes 1990, Gutman *et al* 2004, Rivard *et al* 2006). In fact, these possibilities were tested at least in part by previous computational studies (Cho and Krishnan 2007, Roeske *et al* 2007). Note that, the low-energy gamma-/x-rays below the K-edge (i.e. ~ 81 keV) of gold no longer interact with the K-shell electrons of gold but interact predominantly with the L-shell electrons during the photoelectric absorption process.

The main goal of the current MC study was to perform a rigorous testing of the idea mentioned above by estimating possible macroscopic dose enhancement during GNRT delivered with the following low-energy gamma-/x-ray sources: ^{125}I , 50 kVp and ^{169}Yb . The current MC study also aimed to demonstrate significant changes in the spectra and fluence of the photo/Auger electrons within a tumor loaded with gold nanoparticles during x-ray irradiation by the above sources, which can be correlated well with the tumor dose enhancement. Besides, the current presentation attempts to address some of the important technical issues omitted in a previous MC study (Cho 2005). Ultimately, the current presentation aims to provide the impetus for further investigation and clinical implementation of GNRT for many types of cancers that can be treated with brachytherapy.

2. Materials and methods

2.1. Estimation of the macroscopic dose enhancement factor

In this study, MC calculations were conducted to determine the macroscopic dose enhancement factor (MDEF), defined as the ratio of the average dose in the tumor region with and without the presence of gold nanoparticles after the irradiation of the tumor. In order to avoid some confusion between the current approach and a possible microscopic estimation of tumor dose enhancement, a more explicit term, ‘macroscopic dose enhancement factor (MDEF)’, has been used throughout the current presentation, instead of the ‘dose enhancement factor (DEF)’. The current study considered three different types of brachytherapy sources that could be used for GNRT. The first source was a commercially available ^{125}I seed source. It was modeled based on the source specifications available from a previous publication (Gearheart *et al* 2000). The second source considered in this investigation was an HDR ^{169}Yb source. For a direct comparison with previous results for an HDR ^{192}Ir source (Cho 2005), this source was modeled in the current study by replacing the iridium core of a commercial HDR ^{192}Ir source model with ytterbium. Although, an exact modeling of a currently available ^{169}Yb source was unnecessary for this study, the

material composition (i.e. ytterbium core encapsulated by stainless steel) and dimensions (i.e. active source length and diameter of 3.5 and 0.6 mm, respectively) of the current ^{169}Yb source model are similar enough to those of a commercial HDR ^{169}Yb source (Medich *et al* 2006). The details of the original ^{192}Ir source model that is the basis of the current ^{169}Yb source model, can be found elsewhere (Cho *et al* 1999). The third source considered in the current study was a point source emitting 50 kVp x-rays, typically available from miniature x-ray devices. The detailed modeling of a commercial miniature x-ray device was not attempted as it was beyond the scope of the current study. Table 1 lists detailed spectral lines of ^{125}I (noted as 'bare') and ^{169}Yb gamma rays used for the current Monte Carlo calculations as presented in published literature (Dillman and Von der Lage 1975, Medich *et al* 2006). Figure 1 shows the energy spectrum of 50 kVp x-rays (1.5 mm Al filter, 17° W target) obtained from Birch *et al* (1979).

The phantom geometry and material composition for MC calculations were similar to those used in a previous study (Cho 2005) for an easy comparison. The current phantom geometry represented a typical geometry used during the MC characterization of brachytherapy sources, namely, a source located at the center of a spherical phantom with the radius of 30 cm. The tumor region for ^{125}I and 50 kVp cases was taken as a 1.5 cm radius sphere centered at the origin of the spherical phantom excluding the region occupied by the source, while the tumor for the ^{169}Yb cases was assumed as a 3.5 cm radius sphere for a direct comparison with the ^{192}Ir results obtained for the same tumor size from a previous study (Cho 2005).

The material composition of the tumor and phantom was taken as the same as the four-component tissue (i.e. 10.1% hydrogen, 11.1% carbon, 2.6% nitrogen and 76.2% oxygen) defined by the International Commission on Radiation Units and Measurements (ICRU 1989). The phantom material within the tumor region was replaced by the ICRU four-component tissue loaded with gold nanoparticles at two different concentration levels: 7 and 18 mg Au g⁻¹ tissue, which were based on the animal data for 1.9 nm diameter gold nanoparticles from Hainfeld *et al* (2004). Note that, in the Hainfeld study, the latter value was not a concentration level inside the tumor but the blood content of gold, 2 min after a mouse was injected with 2.7 g Au kg⁻¹ body weight. Nevertheless, in this study, it was taken as an upper-bound value for a possible gold concentration level within a vascularized tumor at the time of irradiation. Note that, a very high tumor gold concentration more than 30 mg g⁻¹ tumor would be unachievable at least under a passive targeting scenario regardless of the particle size and shape, considering the reported tumor gold contents during various animal studies (Herold *et al* 2000, Hainfeld *et al* 2004, Zaman *et al* 2007, Qian *et al* 2008). The rest of the phantom was filled either with the ICRU four-component tissue or with the tissue altered for the concentration of 2 mg Au g⁻¹ tissue. The density of each gold-loaded tissue was increased from that of the ICRU tissue (i.e. 1 g cm⁻³) to the value reflecting the added weight of gold to the ICRU tissue (e.g. 1.007 g cm⁻³ for the tissue loaded with 7 mg Au g⁻¹), which was deemed reasonable for the current phantom cases. Figure 2 shows the difference between these materials in terms of their photon interaction cross-sections as obtained from XCOM software (Berger *et al* 2005). The photoelectric absorption edges for gold-loaded tissues become pronounced in this figure as the amount of gold within the ICRU tissue increases. Each gold-loaded tumor/tissue was assumed to have a uniform distribution of gold nanoparticles. Also, no physical interface between gold nanoparticles and tissue was assumed. Therefore, in the current model (i.e. uniform mixture model), a uniform distribution of gold nanoparticles throughout the ICRU tissue was approximated by a uniform distribution of gold atoms at a given weight fraction among other tissue elements. Although these assumptions might not be realistic, they could still be practical and reasonable within the scope of the current study (i.e. macroscopic estimation).

More discussion on possible consequences from these assumptions will be provided in the discussion section.

The tissue containing 2 mg Au g^{-1} was introduced to investigate the possible effect of gold nanoparticles presented outside the tumor on the normal tissue dose during the gamma-/x-ray irradiation. It was created by altering the composition and density of the ICRU four-component tissue for the presence of 2 mg Au g^{-1} of tissue, which was the concentration level of gold nanoparticles in muscle when the tumor was loaded with 7 mg Au g^{-1} tumor (i.e. tumor-to-muscle gold concentration ratio of 3.5:1), according to the Hainfeld study. To provide estimation based on a realistic biodistribution of gold nanoparticles, this tissue was used only once during the current investigation, in conjunction with the tumor loaded at a concentration level of 7 mg Au g^{-1} tumor.

The MC calculations for all the cases in this task were performed with the MCNP5 code (X-5 Monte Carlo Team 2003). The default cross-sections of the MCNP5 system were used to generate particle interaction cross-sections for various concentration levels of gold nanoparticles. Only the photon-transport mode was used for the MCNP5 calculations assuming charged particle equilibrium at all detector sites, because the effect of electron transport can be insignificant for the MC dose calculations to estimate macroscopic dose enhancement around relatively low-energy gamma-/x-ray sources considered in this study. Each photon history was traced down to 1 keV, a default cutoff energy set by the MCNP5 code. The doses at radial distances along the transverse axis of the source (or phantom) between 1 and 10 cm were collected by concentric annuli (0.1 cm high and 0.1 cm wide in the cross-sectional dimensions) using the energy deposition tally (i.e. F6). The statistical uncertainty (1σ) was less than 1% at all radial distances after simulating 4×10^7 particle histories. More details about the MC simulation and MCNP5 code can be found elsewhere (Cho *et al* 1999, X-5 Monte Carlo Team 2003).

2.2. Calculations of secondary electron spectra within a gold-loaded tumor

In order to determine the secondary electron spectra within a gold nanoparticle-loaded tumor during brachytherapy with ^{169}Yb , ^{125}I and 50 kVp, the EGSnrc/DOSXYZnrc code (Kawrakow and Rogers 2003, Walters *et al* 2006) was modified to output the energy of any electron generated from Compton scattering, photoelectric absorption and atomic relaxation for a proper binning depending on the electron energy and interaction type. The EGSnrc/DOSXYZnrc code was chosen for this task because the source codes were immediately available for modification and the detailed modeling of source geometry was not absolutely necessary. Two separate simulations for each source were performed to determine electron spectra within a tumor with and without gold nanoparticles. Each electron spectrum was collected with 1000 energy bins either linearly or logarithmically spaced between the minimum and maximum energies of the spectrum. Only one level of tumor gold concentration at 7 mg g^{-1} tumor was considered for the calculations, as it is deemed the most probable and achievable based on existing animal data. Similar to the estimation of the MDEF, the ICRU tissue was the material for the phantom/tumor and the base material for the tumor loaded with gold nanoparticles during the application of a uniform mixture model described earlier.

The dimensions of the phantom and tumor were $30 \times 30 \times 30 \text{ cm}^3$ and $3 \times 3 \times 3 \text{ cm}^3$, respectively. The tumor was located centrally within the phantom and contained a source region (i.e. $0.01 \times 0.01 \times 0.01 \text{ cm}^3$) mimicking an isotropic point source at its center. The source spectra for the 50 kVp and ^{169}Yb sources were the same as those used for the estimation of MDEF. For EGSnrc/DOSXYZnrc calculations with a point isotropic ^{125}I source, a realistic energy spectrum measured outside a seed source was obtained from a previous study (Chen and Nath 2001; listed as 'seed' in table 1) for a better estimation of the

secondary electron spectrum. The particle interaction cross-sections for the EGSnrc/DOSXYZnrc code were generated using the PEGS4 code (Nelson *et al* 1985), a utility code to generate material cross-sections for MC calculations with the EGSnrc/DOSXYZnrc code system. The photon and electron cutoff energies were chosen as 0.001 and 0.512 MeV during the use of PEGS4 and EGSnrc/DOSXYZnrc codes respectively. Each secondary electron spectrum was obtained after a simulation running 10^9 source particles.

3. Results

3.1. The macroscopic dose enhancement factor

The MDEFs calculated from this study are shown in figures 3-5 as a function of radial distances from the center of the source (or phantom). Note, in these figures, that the factors beyond the tumor region are not truly the MDEFs but are the dose ratios between the cases with and without gold nanoparticles showing the dose reduction behind the tumor loaded with gold nanoparticles. In fact, the dose reduction as much as up to 80% was seen in these figures. As shown in figures 3-5, the MDEFs increased with the gold concentration within the tumor. In general, macroscopic dose enhancement over a tumor region was estimated to be remarkably large, especially at close radial distances from the center of the source. When calculated at 1.0 cm from the center of the source within a tumor loaded with 18 mg Au g⁻¹, macroscopic dose enhancement was 116, 92 and 108% for ¹²⁵I, 50 kVp and ¹⁶⁹Yb, respectively. For a tumor loaded with 7 mg Au g⁻¹, it was 68, 57 and 44% at 1 cm from the center of the source for ¹²⁵I, 50 kVp and ¹⁶⁹Yb, respectively. The current results for the 7 mg Au case with ¹²⁵I and 50 kVp may be compared with the theoretical values (i.e. 68% and 60% for ¹²⁵I and 50 kVp, respectively) from a previous study (Roeske *et al* 2007) in which 5 mg Au ml⁻¹ (or 0.5% by weight) was used as the tumor gold concentration. Interestingly, the current results are in excellent agreement with Roeske *et al*'s results, which means that their theoretical values for the 7 mg Au case would have been larger than the current results. This discrepancy could be attributed to the difference in the initial energy spectra of photon sources considered in both studies. More importantly, it could also be due to the fact that the theoretical values were estimated simply by taking the ratios of the photon energy absorption coefficients between water and materials mixed with gold at the initial photon spectra, while the current Monte Carlo results were obtained by actually transporting photons through detailed source/tumor geometry to properly take into account the changes in photon spectra throughout the phantom.

The MDEFs were also found to depend on gamma-/x-ray energy spectra and radial distance. The fall-off of MDEFs through the tumor was more pronounced for ¹²⁵I and 50 kVp than for ¹⁶⁹Yb, due to increased attenuation of relatively lower energy gamma-/x-rays through a high-Z gold-loaded tumor. The current results also showed that such a fall-off was proportional to the gold concentration level within a tumor. For a tumor loaded with 18 mg Au g⁻¹, the MDEF decreased by 40 and 35% (i.e. 2.99 → 1.80 and 2.63 → 1.70) for ¹²⁵I and 50 kVp, respectively, as the radial distance increased from 0.5 to 1.25 cm from the source center. For a tumor loaded with 7 mg Au g⁻¹, it decreased by 19 and 18% (i.e. 1.94 → 1.57 and 1.81 → 1.49) for ¹²⁵I and 50 kVp, respectively, over the same radial distances as the 18 mg Au case. On the other hand, the MDEF for ¹⁶⁹Yb decreased only moderately, by about 10 and 3% (i.e. 2.08 → 1.88 and 1.44 → 1.40) for the 18 mg Au and 7 mg Au cases, respectively, as the radial distance increased from 1 to 3 cm.

Figures 3-5 also show the effect of gold nanoparticles present in the tissue surrounding a tumor, based on the gold concentration scenario explained earlier (i.e. 7 mg Au g⁻¹ tumor + 0 mg Au g⁻¹ tissue versus 7 mg Au g⁻¹ tumor + 2 mg Au g⁻¹ tissue). The current results show an increase in the tissue dose up to 26% for ¹²⁵I and 50 kVp and 14% for ¹⁶⁹Yb, due to the presence of gold outside the tumor, while the tumor dose remained almost the same.

However, the tissue dose was already reduced significantly due to increased photon attenuation through a gold-loaded tumor. Consequently, the effect of gold nanoparticles present in the tissue surrounding the tumor is deemed minimal, at least, for the tumor geometry considered in this study.

Figure 5 shows a comparison between ^{169}Yb and ^{192}Ir , in terms of their effectiveness to induce dose enhancement within a gold-loaded tumor. Note that the results for ^{192}Ir were from a previous MC study (Cho 2005). As seen in figure 5, the MDEF values for ^{169}Yb are remarkably larger than those for ^{192}Ir , on average by up to about 70 and 30%, for the 18 mg Au and 7 mg Au cases, respectively. In fact, the MDEF values for ^{192}Ir estimated at a somewhat unrealistic level of tumor gold concentration (i.e. 30 mg Au g^{-1} tumor) were smaller as much as by about 20% than those for ^{169}Yb estimated at a much lower concentration level of 7 mg Au g^{-1} tumor.

3.2. Photo/Auger electron spectra within a gold-loaded tumor

The results from this investigation are presented in figures 6-9. Note that the secondary electron spectra due to Compton scattering were also calculated from this study but are not shown here to focus on the role of secondary electrons due to photoelectric absorption/atomic relaxation on the dose enhancement. Note also no distinction between the Auger and Coster-Kronig electrons was made during the scoring of secondary electron spectra due to atomic relaxation. Figures 6-8 show a remarkable change in the photoelectron fluence and energy spectra within the tumor region due to the presence of gold nanoparticles during low-energy gamma-/x-ray irradiation. As shown in figures 6-8, the photoelectron fluence within a tumor with gold nanoparticles was significantly larger (e.g. more than two orders of magnitude) than that within a tumor without gold nanoparticles. Note that the current results were obtained based on the same assumptions as made for the estimation of MDEF (e.g. uniform mixture model). Some distinct peaks associated with each photoelectric absorption edge of gold (i.e. ~81 keV for K-edge, 12–14 keV for L-edge and 3 keV for M-edge) are also well shown in these figures. In general, ^{125}I and 50 kVp sources resulted in a similar pattern of increase in the photoelectron fluence within a tumor loaded with gold nanoparticles. Specifically, the difference in the photoelectron fluence between the two cases shown in each figure was more pronounced below the electron energy of about 20 keV, due to the increased photon interactions around gold L- and M-shell photoelectric absorption edges. On the other hand, a significant difference in the photoelectron fluence for the ^{169}Yb case was consistently shown across the entire energy range of photoelectrons, because the photoelectric absorption of ^{169}Yb gamma rays also occurred with gold K-shell electrons.

Figure 9 shows calculated fluence and energy spectra of the Auger electrons within the tumor region due to the presence of gold nanoparticles during low-energy gamma-/x-ray irradiation. As expected, no Auger electron above 1 keV (i.e. electron cutoff energy during the MC calculations) was noted for the ICRU tissue in the MC results. Consequently, the data shown in figure 9 are only for gold nanoparticles (i.e. gold atoms to be precise) uniformly distributed within the ICRU tissue at a weight fraction of 7 mg g^{-1} tissue. The current results clearly demonstrate the expected outcome from each irradiation scenario in a quantitative fashion. For example, Auger electrons due to the gold K-shell relaxation process appear only for the ^{169}Yb case around 50–80 keV energy range, while no such electrons are shown for other cases. Also, the fluence of Auger electrons due to gold L- and M-shell relaxation processes becomes prominent around 1–15 keV energy range for all the sources considered. A more quantitative summary of the results shown in figures 6-9 is presented in table 2. It can be seen from this table that, for a tumor gold concentration of 7 mg Au g^{-1} , the photoelectrons contribute to the local energy deposition significantly more (e.g. >a factor of 3) than the Auger electrons, even though the fluence of the photoelectrons

is comparable to that of the Auger electrons. However, the role of Auger electrons, particularly those with large abundance due to gold L- and M-shell relaxation processes, would become significant when one considers microscopic dose enhancement for the current cases on a cellular level to find some correlation with radiobiological effects. The significance of the current results (i.e. photo/Auger electron spectra) for this aspect will be discussed in the following section.

4. Discussion

As of now, all of the low-energy gamma-/x-ray sources considered in this study are commercially available. Moreover, the tumor gold concentration around 1% by weight appears to be achievable at least in mice without significant toxicity by using 1.9 nm diameter gold nanoparticles under a passive targeting scenario (Hainfeld *et al* 2004,2008). Consequently, the current dosimetric results strongly indicate that it would immediately be feasible to implement GNRT via brachytherapy using ^{125}I , 50 kVp, ^{169}Yb , etc, provided that the biodistribution and toxicity data obtained from an animal study could be applicable in humans. In practice, gold nanoparticles are likely to be introduced into clinical trials as an investigational device rather than as investigational new drugs, further expediting their clinical translation. From a brachytherapy perspective, as was pointed out previously (Roeske *et al* 2007), the low-dose rate sources such as ^{125}I (or ^{103}Pd) would require a sustained release of gold nanoparticles or multiple injections of gold nanoparticles to induce the level of dose enhancement as predicted in this study. Otherwise, the level of dose enhancement would drop from the predicted maximum value to virtually zero as gold nanoparticles are cleared from the tumor and tumor vasculature over a typical biological half-life on the order of a few days (James *et al* 2007,Zhang *et al* 2009). Consequently, HDR brachytherapy treatments using 50 kVp x-ray and ^{169}Yb sources look more appealing than permanent implants using ^{125}I source. Between these two HDR brachytherapy options, one might find an HDR ^{169}Yb source more useful because of its capability of inducing more uniform dose enhancement throughout the tumor as shown in this study. Additionally, GNRT may be combined with hyperthermia (i.e. thermoradiotherapy) that also can be achieved using optically tunable gold nanoparticles such as the gold nanoshells or gold nanorods that can convert illuminated near-infrared light to heat. This combination can significantly improve the therapeutic ratios for radioresistant hypoxic tumors compared to GNRT or gold nanoshell-mediated hyperthermia alone (Diagaradjane *et al* 2008b).

As can be inferred from previous studies reporting the *ex vivo* analyses of gold nanoparticle distribution within a tumor (Hainfeld *et al* 2004, Diagaradjane *et al* 2008b), gold nanoparticles do not appear to be distributed uniformly within a tumor. Moreover, they typically aggregate and form clusters within the tumor. Furthermore, significantly more gold nanoparticles are found in close proximity to the tumor vasculature. As a result, there would be some heterogeneity across the tumor in terms of the amount of physical dose enhancement. Apparently, the current approach may not be suitable for predicting such heterogeneity because it assumes a uniform distribution of gold nanoparticles within the tumor. Nevertheless, one may argue that it is still a practical and effective approach to gauge the likelihood for the dose enhancement to occur with a given combination of gold concentration and radiation type under a passive targeting scenario. For example, one can easily see the difficulty of modeling spatio-temporal distribution of gold nanoparticles within the tumor during *in vivo* experiments, while no current imaging modality is capable of providing such information. In fact, the tumor gold concentration level is probably the only meaningful reproducible information available from *in vivo* studies for computational purpose. Therefore, at least as the first approximation, it would be reasonable to correlate biological dose enhancement with macroscopically-estimated physical dose enhancement through the two globally definable variables across the tumor such as average tumor gold

concentration and radiation quality. From the physical point of view, the net increase in energy deposition (i.e. physical dose enhancement) throughout the entire gold-loaded tumor region should, in principle, exactly match with the result obtained by applying the current approach. *In vivo* quantification of gold nanoparticles during future animal studies would be accomplished by applying the methods proposed by the current investigators and colleagues based on the diffuse optical spectroscopy (Zaman *et al* 2007) and gold K-fluorescence x-ray measurements (Siddiqi *et al* 2008).

Considering the data from previous studies (Hainfeld *et al* 2004, Chithrani *et al* 2006, James *et al* 2007, Zaman *et al* 2007, Qian *et al* 2008), the intra-tumoral and intracellular uptake of gold nanoparticles seems to be dependent on the particle size and shape. The current computational approach does not explicitly take such dependence into account but handles it indirectly via the use of the tumor gold concentration data derived from the biodistribution of a gold nanoparticle in question (e.g. 1.9 nm diameter spherical gold nanoparticle). Besides, it could be less capable of dealing with certain situations. For example, the current approach might provide a less accurate prediction for the likelihood of biological dose enhancement if gold nanoparticles themselves acted as a cytotoxic agent. Another example would be the cases involving an active targeting of gold nanoparticles as discussed below.

In theory, by active targeting of nanoparticles including gold nanoparticles to tumors and/or tumor vasculature using peptides, antibodies and oligonucleotides (Sokolov *et al* 2003, Cai *et al* 2006, Diagaradjane *et al* 2008a, McCarthy and Weissleder 2008, Qian *et al* 2008), the tumor loads of gold nanoparticles can be made higher due to tumor specificity, and the greater proximity of gold nanoparticles to nuclear deoxyribonucleic acid (DNA) increases the probability of creating DNA strand breaks, the primary mechanism of radiation-induced cytotoxicity, due to photoelectrons originating from gold nanoparticles. Therefore, active targeting would significantly increase the efficiency of the dual mechanisms of action (i.e. direct cell-killing and tumor blood vessel disruption) by gold nanoparticles and x-rays. Once active targeting becomes feasible, physical dose enhancement will need to be estimated on a nano-/micro- or cellular scale. One of the necessary information for this type of investigation is the secondary electron spectra as obtained from the current study because the spatial variation of physical dose enhancement on a cellular scale is closely related with the energy of secondary electrons, especially the photo/Auger electrons originating from gold nanoparticles. For example, in spite of an almost two-fold increase in photoelectron fluence as shown in this study, an actual increase in cell killing (i.e. biological dose enhancement) would be only due to those photoelectrons with sufficient energy to reach tumor and endothelial cells from the site of each gold nanoparticle or those originating from gold nanoparticles at close proximity to these cells.

Finally, it is worth emphasizing that the realization of GNRT will ultimately be dependent on whether or not gold nanoparticles can safely be administered to humans without causing any major short- and long-term harmful effects. As shown in a recent animal study about carbon nanotubes (Poland *et al* 2008), some nano-size materials may cause unexpected harmful effects in humans. Gold is known to be chemically inert, and gold nanoparticles have been found safe in previous animal studies (Hainfeld *et al* 2004, James *et al* 2007). Nevertheless, the safety of gold nanoparticles will have to be addressed successfully during future clinical trials of GNRT, especially because of their extraordinary capability to penetrate cell membranes/nuclei and the central nervous system.

5. Conclusions

The current MC study suggests that a drastic tumor dose enhancement (e.g. >40%) could be achievable using low-energy gamma-/x-ray source such as ^{125}I , ^{169}Yb and 50 kVp source

and gold nanoparticles. When calculated at 1.0 cm from the center of the source within a tumor loaded with 18 mg Au g⁻¹, macroscopic dose enhancement was 116, 92, and 108% for ¹²⁵I, 50 kVp and ¹⁶⁹Yb, respectively. For a tumor loaded with 7 mg Au g⁻¹, it was 68, 57 and 44% at 1 cm from the center of the source for ¹²⁵I, 50 kVp and ¹⁶⁹Yb, respectively. The estimated MDEF values for ¹⁶⁹Yb were remarkably larger than those for ¹⁹²Ir, on average by up to about 70 and 30%, for the 18 mg Au and 7 mg Au cases, respectively. The current MC study also shows a remarkable change in the photoelectron fluence and spectrum (e.g. more than two orders of magnitude) and a significant production (e.g. comparable to the number of photoelectrons) of the Auger electrons within a tumor loaded with gold nanoparticles during low-energy gamma-/x-ray irradiation. The radiation sources considered in this study are currently available and gold concentration levels considered in this investigation are deemed achievable by either an intravenous injection or an intra-tumoral injection of gold nanoparticles. Therefore, the current study strongly suggests that GNRT can successfully be implemented via brachytherapy with low-energy gamma-/x-ray sources, especially with an HDR ¹⁶⁹Yb source, provided that gold nanoparticles themselves have no major short- and long-term harmful effects on humans.

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References

- Berger, MJ.; Hubbell, JH.; Seltzer, SM.; Chang, J.; Coursey, JS.; Sukumar, R.; Zucker, DS. XCOM: Photon Cross Section Database. version 1.3. NIST; Gaithersburg, MD: 2005.
<http://physics.nist.gov/xcom>
- Birch MJ, Blowes RW. A contact x-ray therapy unit for intracavitary irradiation. *Phys. Med. Biol.* 1990; 35:275–80. [PubMed: 2315382]
- Birch, R.; Marshall, M.; Ardran, GM. Scientific Report. Vol. 30. Hospital Physicists Association; London: 1979. Catalogue of spectral data for diagnostic x-rays.
- Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. *Adv. Drug Deliv. Rev.* 2002; 54:631–51. [PubMed: 12204596]
- Butterworth KT, Wyer JA, Brennan-Fournet M, Latimer CJ, Shah MB, Currell FJ, Hirst DG. Variation of strand break yield for plasmid DNA irradiated with high-Z metal nanoparticles. *Radiat. Res.* 2008; 170:381–7. [PubMed: 18763863]
- Cai W, Shin D-W, Chen K, Gheysens O, Cao Q, Wang SX, Gambhir SS, Chen X. Peptide-labeled near-infrared quantum dots for imaging tumor vasculature in living subjects. *Nano Lett.* 2006; 6:669–76. [PubMed: 16608262]
- Chang MY, Shiau AL, Chen YH, Chang CJ, Chen HHW, Wu CL. Increased apoptotic potential and dose-enhancing effect of gold nanoparticles in combination with single-dose clinical electron beams on tumor-bearing mice. *Cancer Sci.* 2008; 99:1479–84. [PubMed: 18410403]
- Chen Z, Nath R. Dose rate constant and energy spectrum of interstitial brachytherapy sources. *Med. Phys.* 2001; 28:86–96. [PubMed: 11213926]
- Chithrani BD, Ghazani AA, Chan WCW. Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. *Nano Lett.* 2006; 6:662–8. [PubMed: 16608261]
- Cho SH. Estimation of tumor dose enhancement due to gold nanoparticles during typical radiation treatments: a preliminary. Monte Carlo study *Phys. Med. Biol.* 2005; 50:N163–73.
- Cho SH, Krishnan S. Dosimetric feasibility of gold nanoparticle-aided radiation therapy (GNRT) using a Yb-169 source. *Proc. of the American Society for Therapeutic Radiology and Oncology 49th Meeting, Int. J. of Radiat. Oncol. Biol. Phys.* 2007; 69:S639.
- Cho SH, Muller-Runkel R, Hanson WF. Determination of the tissue attenuation factor along two major axes of a high dose rate (HDR) ¹⁹²Ir source. *Med. Phys.* 1999; 26:1492–7. [PubMed: 10501048]

- Costantini DL, Hu M, Reilly RM. Peptide motifs for insertion of radiolabeled biomolecules into cells and routing to the nucleus for cancer imaging or radiotherapeutic applications. *Cancer Biother. Radiopharm.* 2008; 23:3–24. [PubMed: 18298325]
- Dawson P, Penhaligon M, Smith E, Saunders J. Iodinated contrast agents as radiosensitizers. *Br. J. Radiol.* 1987; 60:201–3. [PubMed: 3815019]
- Diagaradjane P, Orenstein-Cardona J, Colon-Casasnovas NE, Deorukhkar A, Shentu S, Kuno N, Schwartz DL, Gelovani JG, Krishnan S. Imaging epidermal growth factor receptor expression *in vivo*: pharmacokinetic and biodistribution characterization of bioconjugated quantum dot nanoprobe. *Clin. Cancer Res.* 2008a; 14:731–41. [PubMed: 18245533]
- Diagaradjane P, et al. Modulation of *in vivo* tumor radiation response via gold nanoshell mediated vascular-focused hyperthermia: characterizing an integrated antihypoxic and localized vascular disrupting targeting strategy. *Nano Lett.* 2008b; 8:1492–500. [PubMed: 18412402]
- Dillman, LT.; Von der Lage, FC. MIRD Pamphlet. Vol. 10. Society of Nuclear Medicine; New York: 1975. Radionuclide decay schemes and nuclear parameters for use in radiation dose estimation.
- Dvorak HF, Nagy JA, Dvorak JT, Dvorak AM. Identification and characterization of the blood vessels of solid tumors that are leaky to circulating macromolecules. *Am. J. Pathol.* 1988; 133:95–109. [PubMed: 2459969]
- Foley EA, Carter JD, Shan F, Guo T. Enhanced relaxation of nanoparticle-bound supercoiled DNA in x-ray radiation. *Chem. Commun.* 2005:3192–4.
- Gearheart DM, Drogin A, Sowards K, Meigooni AS, Ibbott GS. Dosimetric characteristics of a new ¹²⁵I brachytherapy source. *Med. Phys.* 2000; 27:2278–85. [PubMed: 11099194]
- Gutman G, Sozontov E, Strumban E, Yin F-F, Lee S-W, Kim JH. A novel needle-based miniature x-ray generating system. *Phys. Med. Biol.* 2004; 49:4677–88. [PubMed: 15566167]
- Hainfeld JF, Dilmanian FA, Slatkin DN, Smilowitz HM. Radiotherapy enhancement with gold nanoparticles. *J. Pharm. Pharmacol.* 2008; 60:977–85. [PubMed: 18644191]
- Hainfeld JF, Slatkin DN, Smilowitz HM. The use of gold nanoparticles to enhance radiotherapy in mice. *Phys. Med. Biol.* 2004; 49:N309–15. [PubMed: 15509078]
- Herold DM, Das IJ, Stobbe CC, Iyer RV, Chapman JD. Gold microspheres: a selective technique for producing biologically effective dose enhancement. *Int. J. Radiat. Biol.* 2000; 76:1357–64. [PubMed: 11057744]
- ICRU. ICRU Report. Vol. 44. ICRU; Bethesda, MD: 1989. Tissue substitutes in radiation dosimetry and measurement.
- Iwamoto KS, Cochran ST, Winter J, Holburt E, Higashida RT, Norman A. Radiation dose enhancement therapy with iodine in rabbit VX-2 brain tumors. *Radiother. Oncol.* 1987; 8:161–70. [PubMed: 3562895]
- James WD, Hirsch LR, West JL, O'Neal PD, Payne JD. Application of INAA to the build-up and clearance of gold nanoshells in clinical studies in mice. *J. Radioanal. Nucl. Chem.* 2007; 271:455.
- Kawrakow, I.; Rogers, DWO. National Research Council Report PIRS-701. NRCC; Ottawa: 2003. The EGSnrc code system.
- Kong T, Zeng J, Wang XP, Yang XY, Yang J, McQuarrie S, McEwan A, Roa W, Chen J, Xing JZ. Enhancement of radiation cytotoxicity in breast-cancer cells by localized attachment of gold nanoparticles. *Small.* 2008; 4:1537–43. [PubMed: 18712753]
- Maeda H, Fang J, Inutsuka T, Kitamoto Y. Vascular permeability enhancement in solid tumor: various factors, mechanisms involved and its implications. *Int. Immunopharmacol.* 2003; 3:319–28. [PubMed: 12639809]
- McCarthy JR, Weissleder R. Multifunctional magnetic nanoparticles for targeted imaging and therapy. *Adv. Drug Deliv. Rev.* 2008; 60:1241–51. [PubMed: 18508157]
- McMahon SJ, Mendenhall MH, Jain S, Currell F. Radiotherapy in the presence of contrast agents: a general figure of merit and its application to gold nanoparticles. *Phys. Med. Biol.* 2008; 53:5635–51. [PubMed: 18812647]
- Medich DC, Tries MA, Munro JJ III. Monte Carlo characterization of an ytterbium-169 high dose rate brachytherapy source with analysis of statistical uncertainty. *Med. Phys.* 2006; 33:163–72. [PubMed: 16485423]

- Mello RS, Callison H, Winter J, Kagan AR, Norman A. Radiation dose enhancement in tumors with iodine. *Med. Phys.* 1983; 10:75–8. [PubMed: 6843516]
- Mesa AV, Norman A, Solberg TD, DeMarco JJ, Smathers JB. Dose distribution using kilovoltage x-ray and dose enhancement from iodine contrast agents. *Phys. Med. Biol.* 1999; 44:1955–68. [PubMed: 10473207]
- Nelson, WR.; Hirayama, H.; Rogers, DWO. The EGS4 code system SLAC-265. SLAC; Stanford, CA: 1985.
- Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WAH, Seaton A, Stone V, Brown S, MacNee W, Donaldson K. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat. Nanotechnol.* 2008; 3:423–8. [PubMed: 18654567]
- Qian X, Peng X-H, Ansari DO, Yin-Goen Q, Chen GZ, Shin DM, Yang L, Young AN, Wang MD, Nie S. *In vivo* tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. *Nat. Biotechnol.* 2008; 26:83–90. [PubMed: 18157119]
- Rivard MJ, Davis SD, DeWerd LA, Rusch TW, Axelrod S. Calculated and measured brachytherapy dosimetry parameters in water for the Xofigo x-ray source: an electronic brachytherapy source. *Med. Phys.* 2006; 33:4020–32. [PubMed: 17153382]
- Robar JL. Generation and modeling of megavoltage photon beams for contrast-enhanced radiation therapy. *Phys. Med. Biol.* 2006; 51:5487–504. [PubMed: 17047265]
- Robar JL, Riccio SA, Martin MA. Tumor dose enhancement using modified megavoltage photon beams and contrast media. *Phys. Med. Biol.* 2002; 47:2433–49. [PubMed: 12171332]
- Roeske JC, Nunez L, Hoggarth M, Labay E, Weichselbaum RR. Characterization of the theoretical radiation dose enhancement from nanoparticles. *Technol. Cancer Res. Treat.* 2007; 6:395–402. [PubMed: 17877427]
- Rose JH, Norman A, Ingram M. First experience with radiation therapy of small brain tumors delivered by a computerized tomography scanner. *Int. J. Radiat. Oncol. Biol. Phys.* 1994; 30:24–5.
- Siddiqi A, Cheong S, Cho S. Detection of gold fluorescence x-rays for the *in vivo* quantification of gold concentration during gold nanoparticle-aided radiation therapy (GNRT). *Med. Phys.* 2008; 35:2694.
- Sokolov K, Follen M, Aaron J, Pavlova I, Malpica A, Lotan R, Richards-Kortum R. Real-time vital optical imaging of precancer using anti-epidermal growth factor receptor antibodies conjugated to gold nanoparticles. *Cancer Res.* 2003; 63:1999–2004. [PubMed: 12727808]
- Unezaki S, Maruyama K, Hosoda J-I, Nagae I, Koyanagi Y, Nakata M, Ishida O, Iwatsuru M, Tsuchiya S. Direct measurement of the extravasation of polyethyleneglycol-coated liposomes into solid tumor tissue by *in vivo* fluorescence microscopy. *Int. J. Pharm.* 1996; 144:11–7.
- Verhaegen F, Reniers B, Deblois F, Devic S, Seuntjens J, Hristov D. Dosimetric and microdosimetric study of contrast-enhanced radiotherapy with kilovolt x-rays. *Phys. Med. Biol.* 2005; 50:3555–69.
- Walters, BR.; Kawrakow, I.; Rogers, DWO. National Research Council Report. NRCC; Ottawa: 2006. DOSXYZnrc users manual. PIRS-794revB
- X-5 Monte Carlo Team. MCNP—A General Monte Carlo N-Particle Transport Code LA-UR-03-1987. Version 5. Los Alamos National Laboratory; Los Alamos, NM: 2003.
- Zaman RT, et al. *In vivo* detection of gold nanoshells in tumors using diffuse optical spectroscopy. *IEEE J. Sel. Top. Quantum Electron.* 2007; 13:1715–20.
- Zhang G, Yang Z, Lu W, Zhang R, Huang Q, Tian M, Li L, Liang D, Li C. Influence of anchoring ligands and particle size on the colloidal stability and *in vivo* biodistribution of polyethylene glycol-coated gold nanoparticles in tumor-xenografted mice. *Biomaterials.* 2009; 30:1928–36. [PubMed: 19131103]
- Zhang XJ, Xing JZ, Chen J, Ko L, Amanie J, Gulavita S, Pervez N, Yee D, Moore R, Roa W. Enhanced radiation sensitivity in prostate cancer by gold-nanoparticles. *Clin. Invest. Med.* 2008; 31:E160–7. [PubMed: 18544279]
- Zheng Y, Hunting DJ, Ayotte P, Sanche L. Radiosensitization of DNA by gold nanoparticles irradiated with high-energy electrons *Radiat. Res.* 2008; 169:19–27.

Figure 1.

X-ray spectrum for a 50 kVp x-ray source (1.5 mm Al filter, 17° W target). Spectral data are obtained from Birch *et al* (1979).

Figure 2.

Total photon interaction cross-sections for various materials considered in this study. The data are obtained using XCOM software (Berger *et al* 2005). The photon absorption edges for gold-loaded tissues become pronounced in this figure as the amount of gold within the ICRU tissue increases.

Figure 3.

The calculated macroscopic dose enhancement factor (MDEF) for ^{125}I cases as a function of radial distance along the transverse axis of the source. The factors shown from $r = 2$ to 10 cm are not the MDEFs but show the decrease in the doses behind the tumor loaded with gold nanoparticles. The radius of a spherical tumor centered at the origin is 1.5 cm. The statistical uncertainty (1σ) of each data point is comparable to the size of the symbols. The amount of gold shown in the figure legend is per gram of tumor or tissue.

Figure 4.

The calculated macroscopic dose enhancement factor (MDEF) for 50 kVp cases as a function of radial distance along the transverse axis of the phantom. The factors shown from $r = 2$ to 10 cm are not the MDEFs but show the decrease in the doses behind the tumor loaded with gold nanoparticles. The radius of a spherical tumor centered at the origin is 1.5 cm. The statistical uncertainty (1σ) of each data point is comparable to the size of the symbol. The amount of gold shown in the figure legend is per gram of tumor or tissue.

Figure 5.

The calculated macroscopic dose enhancement factor (MDEF) for ^{169}Yb cases as a function of radial distance along the transverse axis of the source. The ^{192}Ir results obtained from a previous study (Cho 2005) are also shown in this figure. If less than unity, the factors shown from $r = 4$ to 10 cm are not the MDEFs but show the decrease in the doses behind the tumor loaded with gold nanoparticles. The radius of a spherical tumor centered at the origin is 3.5 cm. The statistical uncertainty (1σ) of each data point is comparable to the size of the symbol. The amount of gold shown in the figure legend is per gram of tumor or tissue.

Figure 6.

Photoelectron spectra within a $3 \times 3 \times 3 \text{ cm}^3$ tumor irradiated by ^{125}I gamma rays from a source located at the center of the tumor. The spectra are shown for a tumor loaded with gold nanoparticles at 7 mg g^{-1} and for a tumor without gold nanoparticles.

Figure 7. Photoelectron spectra within a $3 \times 3 \times 3 \text{ cm}^3$ tumor irradiated by 50 kVp x-rays from a source located at the center of the tumor. The spectra are shown for a tumor loaded with gold nanoparticles at 7 mg g^{-1} and for a tumor without gold nanoparticles.

Figure 8.

Photoelectron spectra within a $3 \times 3 \times 3 \text{ cm}^3$ tumor irradiated by ^{169}Yb gamma rays from a source located at the center of the tumor. The spectra are shown for a tumor loaded with gold nanoparticles at 7 mg g^{-1} and for a tumor without gold nanoparticles.

Figure 9.

Auger electron spectra within a $3 \times 3 \times 3 \text{ cm}^3$ tumor irradiated by ^{125}I , 50 kVp and ^{169}Yb sources located at the center of the tumor. The spectra are shown only for a tumor loaded with gold nanoparticles at 7 mg g^{-1} , because Auger electrons above 1 keV are not seen for a tumor without gold nanoparticles. No distinction between the Auger and Coster-Kronig electrons is made for these spectra.

Brachytherapy source spectra used for MC calculations. ¹²⁵I gamma ray spectral data for seed and bare sources are from Chen and Nath (2001) and Dillman and Von der Lage (1975), respectively. ¹⁶⁹Yb gamma ray spectral data are from Medich *et al* (2006).

Table 1

¹²⁵ I (Seed)			¹²⁵ I (Bare)			¹⁶⁹ Yb		
half-life: 59.4 days			half-life: 59.4 days			half-life: 32.0 days		
Energy (keV)	Relative intensity		Energy (keV)	Relative intensity		Energy (keV)	Relative intensity	
22.1	0.25		3.7	0.2226		49.5	0.532	
25.2	0.07		27.2	0.3906		50.7	0.940	
27.4	1.00		27.4	0.7615		57.6	0.295	
31.4	0.25		30.9	0.2056		59.1	0.082	
35.5	0.06		31.8	0.0426		63.1	0.442	
			35.4	0.0666		93.6	0.026	
						109.8	0.175	
						118.2	0.019	
						130.5	0.113	
						177.2	0.222	
						198.0	0.358	
						261.1	0.017	
						307.7	0.101	

Total fluence and fluence-weighted total energy of photo/Auger electrons per photon from each source located at the center of a $3 \times 3 \times 3 \text{ cm}^3$ tumor loaded with gold nanoparticles at 7 mg Au g^{-1} (PE: photoelectron, AE: Auger electron). The origin of electrons, either gold or tissue elements within a gold-loaded tissue, is noted in each column where applicable.

Table 2

Source	Total PE Fluence gold	Total PE Energy (keV) gold	Total PE Fluence tissue	Total PE Energy (keV) tissue	Total PE Energy (keV) gold	Total AE Fluence gold	Total AE Energy (keV)
^{125}I	0.337	5.28	0.332	7.24	12.5	0.622	2.25
50 kVp	0.307	4.84	0.311	6.62	11.5	0.569	2.07
^{169}Yb	0.068	2.85	0.048	1.76	4.61	0.126	0.47