Dosimetric evaluation of gold nanoparticle aided intraoperative radiotherapy with the Intrabeam system using Monte Carlo simulations

F. Moradi\textsuperscript{a,b,*}, S.F. Abdul Sania\textsuperscript{a}, M.U. Khandaker\textsuperscript{b}, A. Sulieman\textsuperscript{c}, D.A. Bradley\textsuperscript{b,d}

\textsuperscript{a} Radiation Laboratory, Department of Physics, University of Malaya, Kuala Lumpur, Malaysia
\textsuperscript{b} Centre for Biomedical Physics, School of Healthcare and Medical Sciences, Sunway University, Bandar Sunway, Selangor, Malaysia
\textsuperscript{c} Radiology and Medical Imaging Department, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, Alkhurij, Saudi Arabia
\textsuperscript{d} Department of Physics, University of Surrey, Guildford, Surrey, UK

\section*{ARTICLE INFO}

\textbf{Keywords:} 
Gold nanoparticle  
Monte Carlo simulation  
Dose enhancement  
Intraoperative radiotherapy  
Intrabeam

\section*{ABSTRACT}

Radiosensitization using high atomic number nanoparticles (NPs) has been shown to be an effective method to enhance radiotherapy efficiency. The pathways by which NPs cause sensitization, are generally categorized as physical, chemical and biological effects. Specifically in the case of keV photon radiotherapy where the contribution of physical effects in radiosensitization mechanism is considerable, Monte Carlo (MC) simulations have been an efficient tool to predict the radioenhancement level and to calculate dose enhancement factor (DEF). To-date, several analytical, simulational and experimental studies have reported the radiosensitization effect of gold nanoparticles (GNPs) in various brachytherapy situations. In this work we report for the first time, the DEFs achievable in intraoperative radiotherapy through use of the Intrabeam system and its spherical applicators with addition of GNPs. The MCNPX Monte Carlo code was used for radiation transport and dose calculations. The results of macroscopic and microscopic analysis show that for the Intrabeam system and a homogeneous distribution of 50 nm diameter GNPs, respective DEFs of up to some 1.5, 2, 2.5 and 3 in the tumour bed can be achieved with 5, 10, 15 and 20 mg/g concentrations. Due to rapid change in electron spectra, DEFs greater than 1 mm separation from the applicator surface decrease with distance, offering an additional advantage.

\section*{1. Introduction}

Radiosensitizers have been studied from as long as six decades ago, typically in the form of chemical or pharmacologic agents offering the ability to enhance the toxicity of ionizing radiation to cells. The enhancement usually arises from chemical and biological mechanisms, as in for instance exclusive DNA strand breakage in hypoxic cells or DNA manipulation of active proliferating cells in an effort to reduce their radiosistance (Koch et al., 2012). A far more recent family of radiosensitizers concerns mediators of physical dose enhancement, obtained via metallic (high atomic number, Z) nanoparticles (NPs), the first such report concerning their use in an in vivo study, showing effectiveness in controlling tumour growth in mice, enhancing survival (Hainfeld et al., 2004). The procedure is typically to add a particular concentration of high Z NPs to the tumour tissue, either through direct injection into the tumour or via intravenous injection of bio-labeled NPs. Concerning photon beams, the cross section for photoelectric interactions in the NPs is many times greater than that of tissue (due to the \(Z^3\) dependence). Accordingly, the interaction of photons with NPs creates a large number of photoelectrons, the associated electron vacancies being filled by electrons from more distant orbits. The difference between atomic orbit binding energies is emitted in the form of fluorescence photons or Auger electrons, the otherwise often referred to Auger cascades. In respect of the photoelectrons and Auger electrons, with energies from just a few 10s of eV up to about 80 keV, the upper value depending on primary photon energy and NP Z value (Zygmanski and Sojo, 2016), these are of very short range in cells (from nm for the Auger electrons to a fraction of a nm for the photoelectrons). Accordingly, they cause an increase in energy deposition within the locality of the NPs, increasing the overall damage caused by the photon radiation. The dose enhancement and lower cancer cell survival rates were initially considered to be exclusively a result of physical radiosensitization. Subsequently, various chemical and biological processes have been more greatly appreciated to be contributing to the overall outcome; NP sensitization has been reviewed in detail by a number of authors (see for instance, Butterworth et al., 2012; Rosa et al., 2017; Cui et al., 2017). As it is now understood, only in the case of keV energy photons (below 100 keV) is the physical effect the dominant radiosensitization
mechanism, while for MeV photons and charged particles, the contribution of chemical and biological effects are the more pronounced (Martinez-Rovira and Prezado, 2015; Sotiropoulos et al., 2017; Butterworth et al., 2013).

Various NPs have been investigated as potential radiosensitizers, \( \mu \text{Fe}, 47\text{Ag}, 53\text{Ir}, 60\text{Gd}, 78\text{Pt}, 79\text{Au} \) and 83Bi included (Kuncic and Lacombe, 2018). Of these, gold has tended to be the focus of the more extensive studies, due not only to its high photoelectric cross section but also to its excellent biocompatibility and ease of synthesis in various sizes (Hainfeld et al., 2008; Butterworth et al., 2013). External beam radiotherapy apart, NP radiosensitization has also been extensively studied for brachytherapy treatments. This is due to the simpler addition of nanoparticles to target tissue accessible via direct injection. Also, in regard to physical NP radiosensitization, the greatest dose enhancement tends to be for the lower photon energies of practical consequence, in particular that between 20 and 100 keV (Zygmanski et al., 2013; Zygmanski and Sajo, 2016), common in use of brachytherapy sources. This includes radionuclide and electronic brachytherapy sources, to-date radionuclide brachytherapy attracting the greater NP radiosensitization attention. For low-energy photon emitting radionuclide brachytherapy, with gold as the NP radiosensitizer, dose enhancement has been greatest at energies below the K-edge of Au i.e. 80.75 keV (Lechtman et al., 2011; Jones et al., 2010), according operatively with maximum photoelectric absorption at photon energies just below the K, L and M edges.

Considering the importance of the microscopic aspects of dose enhancement and acknowledging that short-range nanometer track lengths electrons dominate energy deposition, effectively localized to the vicinity of the NPs, it is clearly difficult to experimentally determine the actual physical dose enhancement level in NP-loaded tissues. This has led to extensive use of Monte Carlo (MC) simulations as the predominant tool in predicting or evaluating the dose enhancement factor (DEF) for different radiotherapy situations. As an aside, basic proof of principle efforts are being made through use of Au- and Pt-coated doped silica fibres of some 0.1 mm thickness/diameter, seeking to determine the coating thickness commensurate with optimal DEF, measured via fibre thermoluminescence yield (Alalawi et al., 2013; Abdul Sani et al., 2014). Presently, no attempt has been made to calibrate between coating thickness and Au concentration.

Herein DEF is defined as the ratio of calculated absorbed dose in tissue in the presence of NPs to that in their absence. For the calculation of dose enhancement, two simulation approaches are conceived, either within a uniform mixture of gold and water/tissue or with exclusive modeling of NPs in a homogeneous or random distribution. While the uniform mixture strategy allows for faster simulation, modeling of individual NPs is expected to provide more realistic results given that it additionally considers self-absorption by the NPs. It has been shown, depending on photon energy, size and concentration of NPs, that the mixture strategy may also result in different degrees of DEF over-estimation (Koger and Kirkby, 2016; Rasouli and Masoudi, 2019; Zhang et al., 2009).

Regarding brachytherapy NP radiosensitization, in use of MCNP5 code and gold in tissue concentration of 7 mg/g, Cho et al. (2009) calculated macroscopic dose enhancements for three brachytherapy sources: \( 125\text{T} \) (average energy 27 keV), 50 kVp x-rays and \( 160\text{Yb} \) (average energy ~93 keV). Respective enhancements of 68, 57 and 44% (i.e. DEF of 1.68, 1.57 and 1.44) were obtained. Lechtman et al. (2011), using a microscopic model within the confines of the MC code PENELOPE (simulating individual GNPs), obtained results for the various sources: \( 103\text{Pd} \) (average energy ~21 keV), \( 125\text{I} \), \( 160\text{Yb} \) and \( 192\text{Ir} \) (average energy ~395 keV). For doubling of dose their results showed need for gold in tumour concentrations in the range 5.33–6.26 mg/g. In low dose rate (LDR) brachytherapy obtained with \( 103\text{Pd} \) seeds and with a low concentration of gold NPs (GNPs), in vitro radiosensitization in the range 70–130% was reported by Ngwa et al. (2013). In yet one further MC study, this time using the MCNP6 code, it was shown in prostate brachytherapy that in addition to dose enhancement in the tumour the presence of the gold NPs (GNPs) acted as an effective shield, considerably decreasing dose to neighbouring tissue, the rectum and urethra included (Brivoio et al., 2017).

Among the various commercial low keV X-ray (electronic) brachytherapy sources are Xoft Axxent, Intrabeam and Esteya, Intrabeam currently being one of if not the most widely used system for intraoperative (IORT) radiotherapy. While NP radiosensitization in IORT is of interest due to the ease of control and localized delivery of NPs (Paunesku and Woloschak, 2017), the potential for radiosensitization using NPs during an Intrabeam system treatment has yet to be reported. Herein we carry out such study, using Monte Carlo transport simulations to evaluate the potential for dose enhancement from addition of different GNP concentrations to the tumour bed using the spherical applicators. The predictive capability is important, the photon spectral distribution being known to have significant impact on the level of radiosensitization and achievable DEF, with need for evaluation for the different brachytherapy sources and for various clinical situations.

2. Materials and methods

In previous work (Moradi et al., 2017) we reported Monte Carlo simulation of the Intrabeam X-ray source (Carl Zeiss Surgical, Oberkochen, Germany) with use of the spherical applicators, the results being validated against reference measurements. In addition to the photon spectra previously reported, here we calculate the on-surface electron spectra for the variously sized spherical applicators. In Fig. 1 shows the geometry of the X-ray probe and a 5 cm spherical applicator, simulated as the first phase in this study. Also shown is the schematic geometry simulated in a second phase set of simulations to this study. Both phases were modeled within the purview of the MCNPX code (version 2.6.0, LANL). In the first phase, electrons were accelerated through the evacuated X-ray probe, impinging upon the gold coating tip to the probe and producing X-rays. These photons were transported through the body of the applicator, the spectra of both photons and secondary electrons (generated by these photons) being scored at the surface of the applicators.

In the second phase, a spherical simulation setup was implemented, according with the spherical shape of the Intrabeam system applicators used in breast IORT. Spectra were calculated for emissions from the surfaces of spheres of appropriate diameter, limited to the smallest (1.5 cm diameter) and largest (5 cm diameter) of the Intrabeam system spherical applicators. In so doing, the photon spectra on the surface of all other spherical applicators can be expected to be encompassed between the scored results for these two sizes (Moradi et al., 2017). While spectral differences between the various applicator sizes have been shown to be minimal (mean energies between 27.8 and 29 keV), in acknowledging the importance of photoelectric interaction in radiosensitization and the radical changes in cross section of photoelectric interaction at such low photon energies, the potential for impact on DEF needs to be verified. Polyetherimide spherical applicator with mass density 1.27 g/cm³, composed of carbon, hydrogen, oxygen and nitrogen of respective weight fractions 75.00, 4.05, 16.22 and 4.73% were modeled. This ensured account of scattering from the applicators and possible impact on dose distribution.

In acquiring the dose in water in the first simulation setup, we considered a total of 30 concentric spherical shell cells enclosing the applicator surface, each 1 mm in thickness, providing thickness values up to 30 mm, the range within which the dose reduced towards zero. In the second series of simulations, 76 concentrically layered spherical shells were constructed around the applicator sphere, with those in the immediate vicinity of the applicator surface being thickness 10 mm, covering a range from 0 to 100 mm. Subsequent layers provided for exponential increase in thickness, incrementing in 100 nm steps from 100 nm to 1 μm, 1 μm steps from 1 to 10 μm, 10 μm steps from 10 to 100 μm and finally 100 μm steps to 1 mm. Further to the x-rays
produced at the tip of the Intrabeam X-ray probe and transferred to the applicator surface, such an arrangement examines the impact of secondary electrons produced in the interaction of x-rays within the body of the applicator. Consideration of these low energy electrons concerns the extent to which they impact upon the DEF, a matter to be elaborated in the results section. At distances > 1 mm from the applicator surface, shells in increments of 1 mm thickness were set up, through to 3 cm distance, as in that used in first setup.

By default, in the coupled photon electron transport mode, the MCNPX code considers photoelectric and Compton effects, Auger electron production, fluorescence emission and continuous slowing down approximation for transport of electrons. Absorbed dose in spherical shells was calculated using the *F8 tally function of the MCNPX code with respective division by mass. Dose was first calculated in water and then again in an homogeneous mixture of water and gold. The DEF was then calculated as the ratio of the dose in the gold-water mixture to that in water. The energy cut off for both photons and electrons was set to the minimum possible in the code, 1 keV. This provides for inclusion of the low energy electrons in the radiosensitization process. Choice of the number of initial particles from the applicator surface was such that an uncertainty of less than 1% in dose calculation was obtained for all shells (< 0.5% in most cases).

In this study four different concentrations of gold in water were considered: 5, 10, 15 and 20 mg/g (equal to 0.5, 1, 1.5 and 2% by weight). These were chosen since concentrations equal to or lower than 2% weight are considered achievable in vitro while avoiding significant long term toxicity (Hainfeld et al., 2004, 2008). In order to interpret the results, photon and electron spectra at various distances from the applicator surface were also calculated.

3. Results and discussion

3.1. Macroscopic dose enhancement

Fig. 2 shows photon and electron spectra calculated on applicator surfaces, subfigures A and B corresponding to the 1.5 cm and 5 cm diameter applicators. While the total numbers of electrons at the applicator surface are just $10^{-3}$ of the corresponding total photon fluence, the impact on DEF is nevertheless of interest. In first phase evaluations, photon dose at the surface of applicators was calculated, initially in water only and then in a 0.5% Au by weight aqueous mixture (equal to 5 mg/g). Fig. 3 shows the respective absorbed doses and DEF as a function of distance from applicator surface, comparable maximum DEFs (on the applicator surface) of 1.61 and 1.62 being obtained for the 1.5 and 5 cm applicators respectively. A similar pattern of decrease in DEF with distance is also observed. Results for the other available applicator sizes encompassed between these two diameters, are expected
to be similar. The decrease in DEF with distance, at this stage suggested to be due to the change in particle spectra, will be verified in the next section.

3.2. Microscopic dose enhancement

In the second series of simulations and as described in Section 2, spherical shells of thickness from 10 nm to 1 mm were modeled. The simulations, first performed for photons emitted from the surface of 1.5 cm and 5 cm applicators, were subsequently carried out with definition of both photon and electron spectra and associated emission probabilities. Absorbed dose was obtained for the spherical shells, calculated both in water and in a 5 mg/g (0.5% weight fraction) of aqueous Au. The DEFs were then calculated for the two situations.

Fig. 4 shows the calculated results normalized to per primary particle emitted from the source. As before, while the total numbers of electrons at the applicator surface are just $10^{-3}$ of the corresponding total particle fluence, within their short range they nevertheless give rise to significant energy deposition. In neglecting scattered electrons from the body of the applicator underestimation of dose is evident for distances < 30 μm (3 × 10^4 nm) from the applicator surface, but with no effect on dose distribution beyond 30 μm, clearly resulting from the limited range of these electrons.

Calculated DEFs using the gold-water mixture in a macroscopic Monte Carlo simulation model can be converted to absorbed dose in water using conversion factors calculated by Koger and Kirkby (2016). In this self-absorption by the nanoparticles has been considered, neglected prior to this in the gold-water mixture simulation strategy. In the foresaid study, conversion factors to convert the dose in gold and tissue mixture to dose in tissue have been calculated for various gold nanoparticle diameters, various concentrations and for a range of mono-energetic photon and electron beams using PENELOPE MC simulations. Since in present work we have applied the photon and electron spectra (and not mono-energetic particles) acquired on applicator surfaces, to use the conversion factors of Koger and Kirkby, the weight of photon intensity at each energy bin in the spectra has been considered. The intensity fraction at each energy bin was multiplied by the conversion factor of that mono-energetic beam. This is mathematically shown in Equation (1), where $TCF$ is total correction factor. The summation in the denominator ($\sum_{i=1}^{E_{\text{max}}}$) represents the total intensity of photons in the spectra from minimum energy (1 keV due to the cut off energy in MCNP simulation) to the maximum energy (variable depending on the applicator size) present in the spectra. $CF(i)$ is the correction factor for the mono-energetic beam of energy $i$.

For a GNP diameter of 50 nm which is probably the most appropriate in practice given that it provides the greatest cellular uptake (Chithrani et al., 2006), and for different concentrations of 5, 10, 15 and 20 mg/g of gold in water, the calculated conversion factors for the 1.5 cm applicator were 0.934, 0.907, 0.892 and 0.884 respectively while for 5 mg/g and the 5 cm applicator size a value of 0.941 was obtained. Here one notes that increase in GNP concentrations results in
an expected increase in self-absorption and therefore a greater correction factor i.e. greater deviation from unity. Fig. 5 shows the calculated microscopic DEF at the applicator surface for the 1.5 cm diameter applicator (A) and the 5 cm diameter (B) with and without consideration of scattered electrons, corrected for GNP self-absorption.

In disregarding scattered electrons from the body of the applicator, the overestimated DEF in the vicinity of the applicator surface is comparable to that in the vicinity of a NP, a matter reported by Zygmanski et al. (2013), consideration being made of the photon beam exclusively instead of the complete phase space file including scattered electrons. In considering the scattered electrons, the increase in dose absorption is smaller. In Fig. 5 the corrected DEF (considering both photon and electron emissions and NP self-absorption) are lower in value compared to the previous plots. From the surface of the applicator up to 1 μm distance, the corrected DEF is observed to be only about 10%. The corrected DEF subsequently increases from 1.13 at 1 μm, up to 1.5 at around 30 μm, then remaining almost constant until 1 mm. It then decreases from 1.48 at 1 mm to 1.21 at 1 cm (for 1.5 cm applicator) and 1.51 at 1 mm to 1.25 at 1 cm (for the 5 cm applicator) and continues to decrease in value through to 3 cm distance whereupon it achieves values of 0.94 and 0.97 for 1.5 and 5 cm applicators respectively. This demonstrates reduction in dose for points further than 2.3 cm (for 1.5 cm applicator) and 2.5 cm (for 5 cm applicator) due to the shielding provided by the presence of gold in the tissue. Depending on the amount of dose needed to be delivered to different depths in the tumour bed, present findings suggest effective dose enhancement at distances from a few micrometers up to 2 cm from the applicator surface and dose reduction at greater distances, a matter which can be of significant interest in saving dose to normal tissues.

In investigating the reason behind the fall-off in DEF for distances beyond 1 mm surface, calculation has been made of the spectra of electrons at 1 mm, 1 cm and 3 cm from the surface of the applicator. As seen in Fig. 6, it is evident that the energy distribution of electrons and the mean energy of the spectra in water with and without gold are comparable, clearly suggesting that DEF is directly correlated to the ratio of electron intensity in the presence of gold to that in its absence. With increase of distance beyond 1 mm from the surface, the electron fluence in the gold/water mixture decreases, becoming smaller than that in pure water, the DEF being less than 1 at 3 cm distance. A further observation is that the mean energy of the electron spectra progressively increases with distance from the surface, from 15.8 keV at 1 mm to 19.2 keV at 30 mm distance, a beam hardening effect of Au filtration.

In this final part of the study, the effect of change in concentration
of GNPs in the medium was investigated, the weight fraction of gold in water being increased from 5 mg/g to 20 mg/g, the density of gold/water mixture accordingly increasing from 1.005 to 1.020 g/cm³. The graph of Fig. 7-A shows the absorbed dose in terms of distance from the 1.5 cm applicator surface while the graph of Fig. 7-B demonstrates microscopic DEF for various GNP concentrations corrected for self-absorption of GNPs (B).

In the present work we calculated DEFs assuming that diffusion of GNPs in the tumour results in a homogeneous distribution in tissue. This is not intended to negate results from previous studies showing NP penetration through tissue and tumour diffusion to be highly complex. Accordingly, the situation is difficult to predict, with dependency on a multitude of parameters including the injection method, NP type and size, NP surface charge and coating, tumour type, collagen content and orientation of the fibre net in the tumour tissue (Miao and Huang, 2015). This can give rise to patterns such as linear or exponential decrease from the tumour centre to its borders, or even inversely (England et al., 2015).

4. Conclusion

In recent years radiosensitization using high Z nanoparticles has become a matter of great interest. In pursuit of this, Monte Carlo simulation has been shown to provide a reliable means for predicting the level of radiosensitization. In particular, and as shown herein, it can provide capability for obtaining rationalized results in the case of low energy photon brachytherapy sources. In the present work we have reported for the first time MC simulations predicting the dose enhancement that can result from the use of gold nanoparticles in intraoperative radiotherapy using the Intrabeam system and its associated spherical applicators. A macroscopic dose enhancement factor (DEF) of about 1.6 at the surface of the applicator has been shown to be almost independent of applicator size due to the similarity in photon spectra. It has also been shown that in neglecting consideration of scattered electrons on the applicator surface this will result in significant over-estimation of DEF in the close vicinity of the applicator surface. For concentrations of 5, 10, 15 and 20 mg/g of gold in water, as considered in this study, the microscopic DEF corrected for the self-absorption produced by the NPs has been shown to be variable from 1 to 3, depending on the distance from applicator surface and GNP concentration. Variation in DEF with distance was rationalized through calculation of the electron spectra at various depths in the medium, electron fluence being shown to be reduced at more distal values due to the shielding produced by the gold. An important reduction in dose (DEF < 1) was observed at distances beyond about 2 cm from the applicator surface (depending on concentration), due to the shielding effect of GNPs. This can be seen to be an advantage in dose saving to healthy tissues but should be carefully taken into account in possible future therapeutic applications. The result of this study encourages further investigation in regard to GNP radiosensitization in association with the Intrabeam intraoperative radiotherapy system, also in potential cell studies and also in seeking experimental verification in animal studies.

CRediT authorship contribution statement

F. Moradi: Conceptualization, Writing - original draft, Investigation, Methodology, Software, Data curation. S.F. Abdul Sani: Funding acquisition, Supervision, Writing - review & editing. M.U. Khandaker: Writing - review & editing, Data curation. A. Sulieman: Funding acquisition, Data curation. D.A. Bradley: Writing - review & editing, Data curation.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.
Acknowledgement

This work was supported by the University of Malaya RU Grant [GPF036B-2018] and Malaysia Ministry of Education FRGS Grant [PP032-2017A].

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