Dose enhancement in brachytherapy in the presence of gold nanoparticles: a Monte Carlo study on the size of gold nanoparticles and method of modelling

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Abstract. The aim of this study was to evaluate the effect of the size of gold nanoparticles (GNPs) on dose enhancement in brachytherapy with photon emitting sources. Four photon emitting sources, ^{125}I, ^{169}Yb, ^{103}Pd, and ^{192}Ir were simulated and dose rate constant and radial dose functions were compared with published corresponding data for these sources. Dose enhancement factor in the presence of gold nanoparticles of 30 mg/ml concentration was calculated separately for nanoparticles with a diameter of 50, 100 and 200 nm. Gold nanoparticles were simulated precisely as nanospheres utilizing a lattice option in the MCNPX Monte Carlo code and the results were compared with those obtained with a simple model in which gold atoms are distributed uniformly in tumor volume as a simple mixture. Among the four mentioned sources, the dose enhancement related to ^{125}I source is higher. Our results have shown that with gold nanoparticles of higher diameter, the level of dose enhancement is higher in the tested tumor. It has been also observed that the simple model overestimates the dose enhancement factor when compared with the precise model in which nanoparticles are defined according to the Monte Carlo code. In the energy range produced by the brachytherapy sources, the dose enhancement is higher when using brachytherapy sources with lower energy. Among the size range of gold nanoparticles used in medicine, it is predicted that nanoparticles with higher diameter can be more useful when are utilized in brachytherapy. It is also recommended that when calculating dose enhancements, a precise model be used for modelling of nanoparticles in the Monte Carlo simulations.

Key words: brachytherapy • dose enhancement • gold nanoparticles • Monte Carlo (MC)

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Introduction

The primary goal in radiotherapy is to achieve radiation damage to tumor cells while sparing the normal tissues. To reach this goal it is promising to use high atomic number media in the tumor volume to increase the tumor dose [25]. High atomic number contrast media have been studied for many years as dose enhancement agents in radiotherapy [2, 6, 9, 14, 18, 19, 26, 27, 29]. Animal studies have shown that gold nanoparticles can be used as a high atomic number material with accumulation in the implanted tumor and with little effect on the normal tissue [24]. Leung *et al.* have studied dose enhancement by gold nanoparticles in the 50 kVp to 6 MV energy range [15]. Cho *et al.* have studied dose enhancement by GNPs in brachytherapy with four photon emitting sources. In this study, gold nanoparticles were modelled as a simple mixture [5]. Zhang *et al.* have simulated a ^{192}Ir source and have used two models in defining gold nanoparticles: a simple model defining GNPs as a mixture of gold atoms in a water phantom; and a model incorporating cross section of gold nanoparticles in the Monte Carlo (MC) code [32]. Their results have shown that the simple model in some

points have up to 16% overestimation in quantification of dose in a tumor containing gold nanoparticles. Cho *et al*. have studied dose enhancement by gold nanoparticles in radiotherapy using ^{125}I, 50 kVp and [169]Yb sources using a simple model [6]. There are also recent studies in which dose enhancements by gold nanoparticles were sought from different points of view [21, 22, 28]. In this study, the dose enhancement by gold nanoparticles with different sizes was estimated in brachytherapy with photon emitting sources. The effect of modelling method of nanoparticles was also evaluated by comparing the obtained results with those assessed by a simple model in the simulation of nanoparticles.

Materials and methods

Radiation sources

In this study four photon emitting radionuclides were utilized as a radiation source in dose enhancement calculations: [125]I, [169]Yb, [103]Pd, and [192]Ir. The characteristics of these sources including model, half-life and energy range are listed in Table 1. The geometric information was adopted from the previous published literatures for these sources [3, 7, 17, 31] and also from the Car-

leton University database for TG-43 parameters of brachytherapy sources.

The details on the geometry of the four sources are illustrated in Fig. 1. The Amersham OncoSeed 6702 ^{125}I source is consisting of three active pellets. Each active pellet is composed of a resin sphere which has a density of 1.2 g/cm^3 and its chemical composition is $C_{12}H_{18}NCl$. The diameter of each resin bead is 0.600 mm. [125]I is coated on the spheres which have negligible thicknesses, not assumed in our study. The source capsulation is made of 0.050 mm thick titanium with an outer diameter of 0.800 mm [10, 31].

The M42 [169]Yb source is composed of an active ytterbium oxide core with a density of 7.10 g/cm^3. The active core has an inner and an outer capsules. The inner capsule, which is made of titanium, has a density of 4.51 g/cm^3. The outer 304 stainless steel capsule (density: 7.80 g/cm^3) is connected to a 306 stainless steel cable (density: 6.90 g/cm^3). The active core has a length of 6.0 mm and a diameter of 0.68 mm. The total length of the source complex is 8.2 mm and its diameter is 1.15 mm [3].

The Bebig IsoSeed [103]Pd source is composed of an active core, a gold radiographic marker and a capsule. The radioactive palladium is uniformly distributed within a shell made from alumina (Al_2O_3, density:

Table 1. Characteristics of four source models used in this study

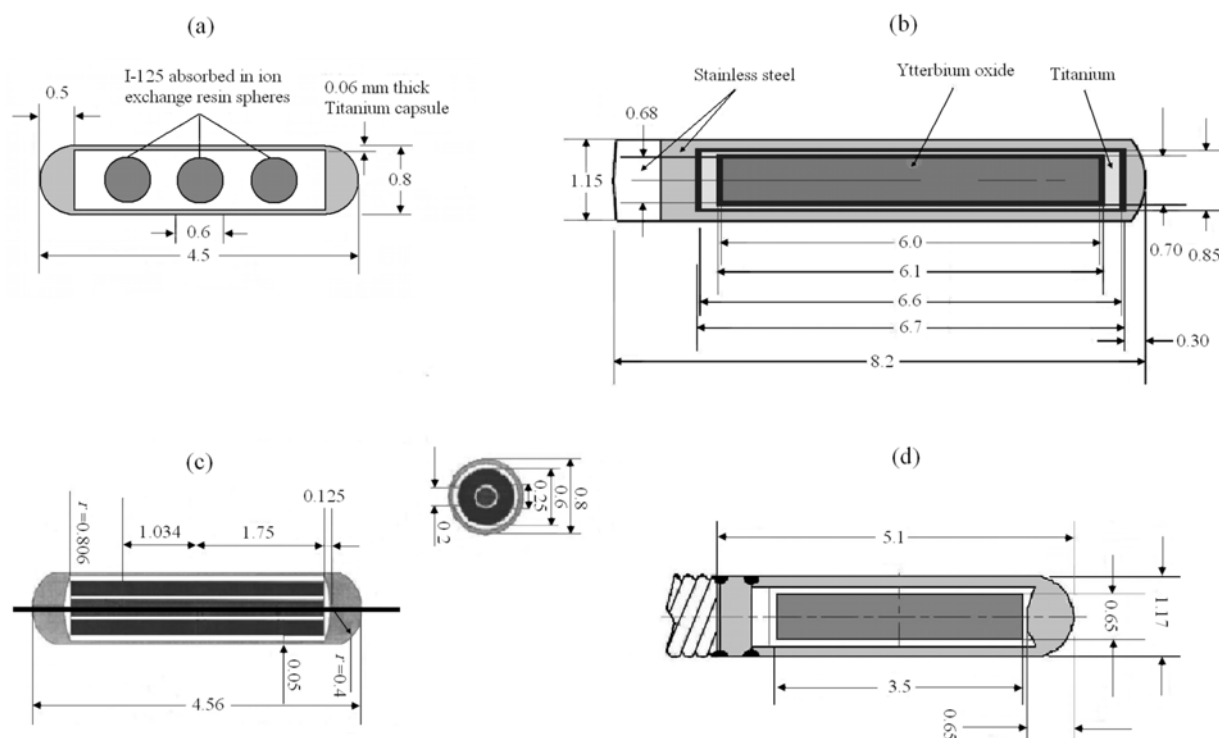| Radionuclide	Half-life (days)	Energy range (keV)	Source model	Reference
[125]I	59.40	27.202–35.492	Amersham OncoSeed 6702	[31]
[169]Yb	32.026	49.77–307.74	M42	[3]
[103]Pd	16.991	20.074–497.1	Bebig IsoSeed	[7]
[192]Ir	73.8	61.49–884.54	M-19	[17]

Fig. 1. Geometry of four photon emitting sources used in this study: (a) [125]I (Amersham OncoSeed 6702, [31]); (b) [169]Yb (M42, [3]); (c) [103]Pd (Bebig IsoSeed, [7]); (d) [192]Ir (M-19, [17]). All dimensions are in millimeters. The figures are schematic and are not to scale.

2.88 g/cm^3) with inner and outer diameters of 0.250 and 0.600 mm, respectively and a length of 3.50 mm. The gold marker is within the alumina core and has a 3.50 mm length and a diameter of 0.200 mm. The source capsule is a titanium tube with a 0.050 mm thickness and the external length and diameter of the capsule is 4.56 and 0.8 mm, respectively. The end welds are two titanium hemispheres which have an average thickness of 0.435 mm along the source's longitudinal axis [7, 11].

The M-19 ^{192}Ir source consists of a 3.50 mm long ^{192}Ir core and a stainless steel (AISI 306) capsule as well as a cable. The length of the active core is 3.5 mm and it has a diameter of 0.65 mm. The capsule is a shell with a 0.52 mm thick wall, its density being 7.80 g/cm^3. The capsule has an end weld which is a hemisphere with a 1.17 mm diameter. The cable is assumed to be a solid cylinder made of AISI 306 stainless steel with a density of 6.90 g/cm^3 [12, 17].

Calculation of TG-43 parameters

Dosimetric parameters recommended by task group No. 43 (TG-43) of the American Association of Physicists in Medicine (AAPM) [20] were calculated for the four mentioned sources. This was including three TG-43 parameters: air kerma strength, dose rate constant (DRC) and radial dose function (RDF). For this purpose, the source geometries were defined according to MCNPX (version 2.4.0) [30] input files. The method for calculation of air kerma strength was as outlined in our previous work [1]. The obtained value of air kerma strength for each source was used toward calculation of dose rate constant. A water phantom of 15 cm radius was employed in the MC code in calculation of dose rate constant and radial dose function.

To have a match between our method and a previous study [17] for M-19 ^{192}Ir source, the air kerma rate was obtained at a 100 cm distance from the ^{192}Ir source through simulation and then the air kerma strength was calculated from the value of air kerma rate. To obtain dose rate constant and radial dose function for the ^{192}Ir source, the source was defined in a water phantom of 40 cm radius.

Energy cutoff was set as 5 keV and 10 keV, respectively for photon and electron in air kerma strength simulations. In the calculation of dose rate constant and radial dose function, energy cutoff for electron was unchanged, but for photons an energy cutoff of 10 keV was defined.

Following running of the input files for enough photon histories, the output results were used for calculation of TG-43 parameters. In the simulations related to dose rate constant and radial dose function calculations of 10^8 photon histories were scored and the maximum MC statistical error was equal to 1.76%.

Dose enhancement calculations

Our calculations of dose enhancement were performed utilizing the MCNPX Monte Carlo code. With the purpose of dose enhancement calculations, the sources were defined in a soft tissue phantom with 15 cm in radius in our simulations. By adopting Report no. 44 of the

International Commission on Radiation Units and Measurements (ICRU) [13], the composition of soft tissue was assumed as: 76.2% oxygen, 11.1% carbon, 10.1% hydrogen and 2.6% nitrogen. A tumor with $1 \times 1 \times 1$ cm dimensions at 1 cm radial distance from the source was then defined in the phantom. The composition in the tumor volume was defined by considering gold nanoparticles of different sizes of 50, 100 and 200 nm. Our rational for choosing these sizes of nanoparticles was that nanoparticles ranging in size from 10 to 200 nm are usually used in the field of nanomedicine [8]. It has been reported that optimal uptake in mammalian cells occurs with gold nanoparticles of 50 nm diameter [4]. So, 50 nm was chosen as a suitable size for nanoparticles and for evaluation of the size effect of nanoparticles on dose enhancement, we have selected two higher diameters of 100 nm and 200 nm as alternatives to 50 nm. The effect of size of nanoparticles was studied for a concentration of 30 mg Au per ml of soft tissue. Dose enhancement for each size of gold nanoparticles was studied separately in a single simulation. For definition of gold nanoparticles, rectangular parallelepiped (RPP) surfaces were used which is an option in MCNPX code for definition of lattice type cells in the problem. For example for gold nanoparticles with diameter of 100 nm and concentration of 30 mg/ml, a number of 2.97×10^{12} nanospheres were defined by the lattice cells in MCNPX code. Besides, a simple method was also utilized in simulation of nanoparticles, in which gold and soft tissue atoms were defined as a simple mixture. The results of this simple model were then compared with those obtained by precise definition of gold nanoparticles in the simulations as lattice. Input files were run for a number of 150 million photon histories and the resulted MC statistical error was less than 2.90%. However, for the ^{103}Pd source, it was required to run the input files for a larger number of photons (650 million photons) to have an acceptable value of MC statistical error (less than 3.04%). Our dose enhancement estimations were based on calculation of dose enhancement factor (DEF) value for different sources and sizes of gold nanoparticles. DEF was calculated as the ratio of dose at a point with the presence of nanoparticles in the tumor to the dose at the same point without the presence of nanoparticles in the tumor. The DEF values were obtained for the five voxels in the tumor on the transverse plane and the average value over the five voxels was calculated. The dose ratios for those points located on the transverse plane under and above the tumor region were also calculated. In the calculation of dose enhancement factor for each source, the source was defined including its core and capsule located at the centre of the phantom in the simulations.

Results and discussion

TG-43 parameters

Dose rate constant (cGy·h^{-1}·U^{-1}) and radial dose function values for ^{125}I, ^{169}Yb, ^{103}Pd and ^{192}Ir sources obtained through our MC simulations are presented in Table 2 and Fig. 2a. The maximum percent combined error in radial dose function values in the present study was 1.57%,

Table 2. Dose rate constant values (cGy·h^{-1}·U^{-1}) for the ^{125}I, ^{169}Yb, ^{103}Pd and ^{192}Ir sources

Radionuclide	This study	Other studies	Reference	Ratio (%) (this study to other study)
^{125}I	1.02	1.04	[23]	98.9
^{169}Yb	1.16	1.22	[3]	95.4
^{103}Pd	0.710	0.664	[7]	106.9
^{192}Ir	1.12	1.13	[17]	99.0
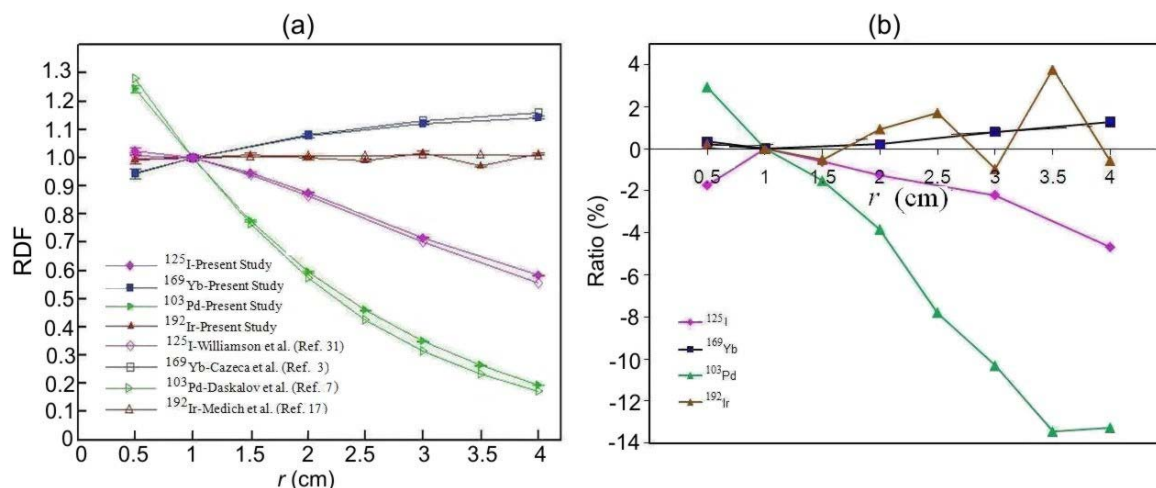
Fig. 2. (a) Radial dose functions for the ^{125}I, ^{169}Yb, ^{103}Pd and ^{192}Ir sources; (b) the percent ratio (%) of our results over those reported by other studies.

Table 3. Dose enhancement factors for nanoparticles with 50, 100 and 200 nm diameter and the simple model. All values are related to gold concentration of 30 mg/ml in a soft tissue phantom

Radionuclide	50 nm	100 nm	200 nm	Simple model
^{125}I	2.98	3.62	3.89	4.09
^{169}Yb	1.96	2.48	2.84	2.98
^{103}Pd	1.88	2.13	2.21	2.27
^{192}Ir	1.10	1.16	1.20	1.21

so while the error bars in RDF points are indicated in Fig. 2a, they are not clearly seen in all points.

The results were compared by the corresponding values for the same source models from the previous published studies. The comparisons are based on the percent ratio of our result over the value reported by other studies for that source model.

As it is evident from Table 2 and Fig. 2b, the maximum discrepancy between our values and other studies is 13.3% which is related to the radial distance of 4 cm for the ^{103}Pd source. With respect to the percentage ratios, our simulations of the source models are in agreement with the corresponding published values and were used toward our dose enhancement evaluations using these sources. Although differences up to 13.3% were observed between our results of radial dose function and the values by Daskalov *et al.* for the IsoSeed ^{103}Pd source, there are other studies in which the same difference values were observed for a ^{103}Pd source [16].

Dose enhancements

Dose enhancement factors for gold nanoparticles of 50, 100 and 200 nm diameter for the four mentioned sources are summarized in Table 3. Besides, the results

of dose enhancement factors which were obtained by a simple mixture model were listed in the table.

As can be noticed from the data in Table 3, the dose enhancement factors are higher for the ^{125}I source. The effect can be related to source energy, since ^{125}I emits photons with lower mean energy compared to other three sources. The most contribution in dose enhancement is originated from the photoelectric effect which depends on the inverse of the third power of photon energy ($1/E^3$).

Dose enhancement factors for gold nanoparticles with concentration of 30 mg/ml and diameters of 50, 100, 200 nm are plotted in Fig. 3. In this figure, the dose enhancement factor in the transverse plane was plotted on the vertical axis, while the radial distance from the source centre was plotted in the horizontal axis. The sources (^{125}I, ^{169}Yb, ^{103}Pd and ^{192}Ir) were located in the centre of phantom in the simulations. In the study of the effect of size of nanoparticles and type of modelling on dose enhancement (the data presented in Table 3 and Fig. 3), the percentage combined error in dose enhancement factor values was less than 4.22%.

Conclusions

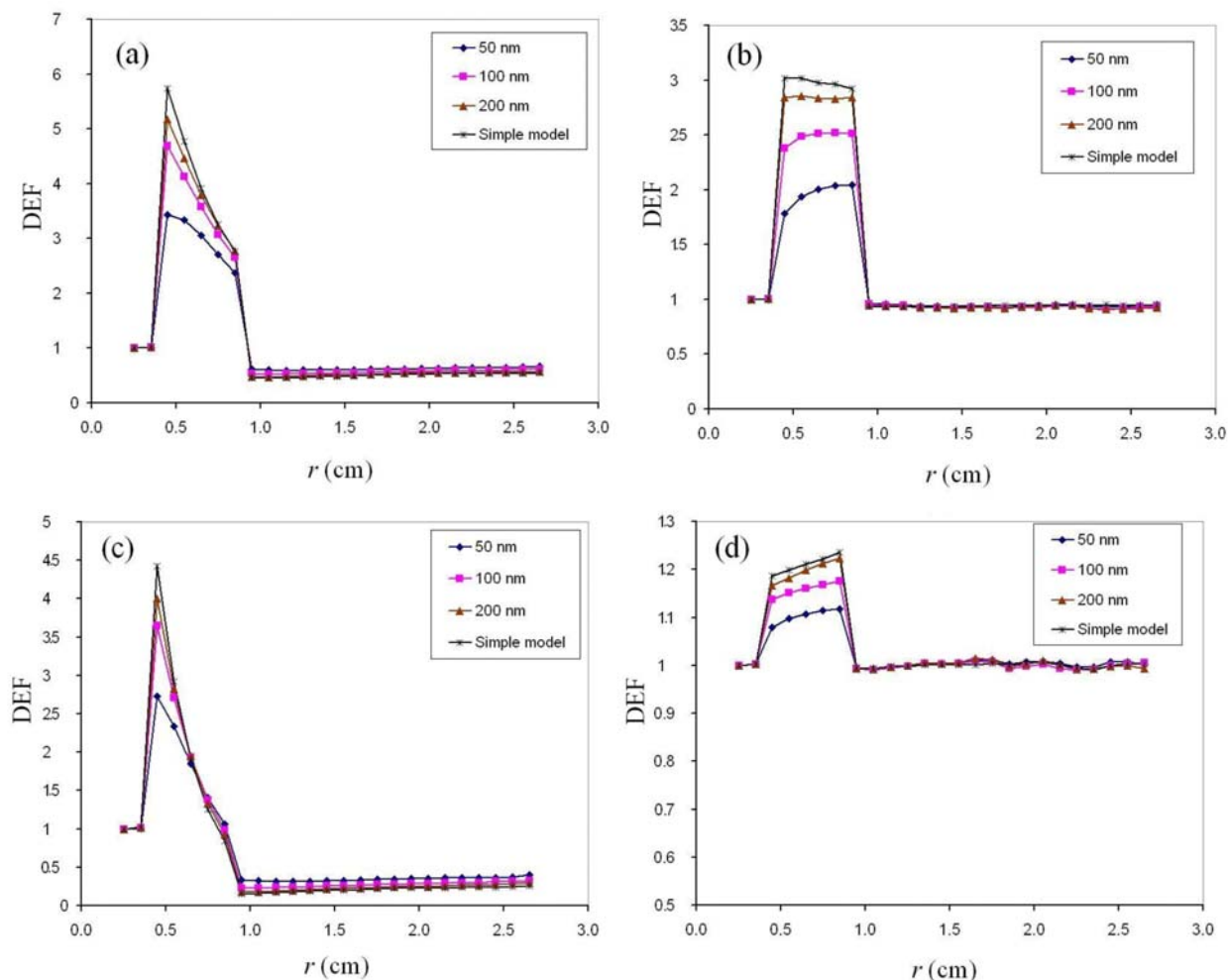In the present work we studied tumor dose enhancement by gold nanoparticles of different sizes in

Fig. 3. Dose enhancement factors for gold nanoparticles of 50, 100 and 200 nm as well as for the simple model: (a) for ^{125}I; (b) for [169]Yb; (c) for [103]Pd and (d) for ^{192}Ir source. All values are related to gold nanoparticles with concentration of 30 mg/ml.

brachytherapy for four photon emitting sources. Acceptable agreement was observed when our results of dose rate constant and radial dose functions were compared with the corresponding published data for the four sources. Our results of dose enhancement factors have shown that from dose enhancement point of view, brachytherapy with sources of lower energy and with gold nanoparticles with higher diameters (among 50, 100 and 200 nm diameters) can be of more clinical usefulness. Our results are implying that a simple model in which nanoparticles are not simulated equally, overestimates the dose enhancement level in the tumor and the overestimation in DEF value can amount up to 1.10 (the difference between the dose enhancement factors for the precise model for GNPs with 50 nm diameter for ^{125}I source and that obtained by the simple model for ^{125}I source) in some cases in brachytherapy with photon emitting sources. It is recommended that when calculating dose enhancements with the presence of nanoparticles in a tumor, a precise model be used in modelling of nanoparticles in MC simulations.

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