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Investigation of Tissue Components Impacts on Dose Enhancement Factor Using Monte Carlo Code

M. N. Al-Suhbani[1], N. E. H. Baghous[1], S. Serag[2*] , C. El Mahjoub[1], L. Ait-Mlouk[3], A. Zia[4], B. Hamid[5], M. Azougagh[5]

[1]*Laboratory of Material Physics and Subatomic, Department of Physics, Faculty of Sciences, Ibn Tofail University, BP 242, Kenitra, 14000, Morocco*
[2]*Department of Engineering - Università degli Studi della Campania "Luigi Vanvitelli," via Roma 29, Aversa 81031, Italy*
[3]*Velindre Cancer Centre, Velindre Rd, Cardiff CF14 2T, UK*
[4]*Faculty of Sciences, Abdelmalek Essaâdi University, BP. 2121 M'Hannech II, Tétouan, Morocco*
[5]*College of Technical Education (ENSAM), Mohammed V University, 6207 Avenue des Forces Armées Royales, Rabat 10100, Morocco*

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ABSTRACT

Despite the progress of science in cancer treatments and radiotherapy improvements, there are still several side effects that occur during tumors treatment, particularly on healthy tissues surrounded tumors. Newer treatment methods are being explored lately, one of which is the use of nanoparticles, wherein the tumor is injected with gold nanoparticles. Its aim is to enhance tumor sensitivity to radiation and reduce radiation damage to healthy tissues. Tissue type may play an effective role in enhancing the dose being received under the use of nanoparticles. This study aims to find the effect of different tissue components on dose enhancement factor through MCNP6 and GATE simulations, as well as to accurately compare the simulation results of these two code packages for dose enhancement factors. A ^{125}I brachytherapy source was simulated in phantoms for five tissues or materials (adipose tissue, breast tissue, soft tissue, water, and brain tissue). MCNP6 simulation code was validated by comparing its results with a previous study by Cho *et al*. Gold nanoparticles were injected as a mixture at a concentration of 7 mg/g into tissues inside a tumor. MCNP6 and GATE simulation results were compared. It was estimated from MCNP simulations that the highest radiation dose enhancement of 2.34 occurs in adipose tissue while lowest dose enhancement of 1.69 is in brain. In comparison, from GATE results, the estimates were that the highest value of dose enhancement factor also occurred in adipose tissue at 2.01, and the lowest value in brain at 1.48. The comparison between two codes suggest that they are compatible with the percentage difference in all tissues being less than 15 %. This study confirms that both MCNP6 and GATE codes could calculate DEF for different tissues under irradiation from a low-energy source.

INTRODUCTION

The main aim of radiotherapy is eliminating cancer cells while protecting healthy tissue. One of the methods that can be used to achieve this aim is to inject high-Z nanoparticles into the tumor volume to increase received dose during irradiation. Nanoparticles are defined as particles of 1 nm - 100 nm size. Several studies are being done on nanoparticles (NPs) because of their size-related characteristics, particularly for use in optics, electronics, and medicine [1].

The primary photon interaction within the tumor depends on photon energy and target atomic number. The probability for photoelectric effect is higher for keV-range photon energies under the presence of high-Z materials. It results in a higher absorbed dose. Equation (1) shows that photoelectric cross-section depends on Z since the energy is higher than the absorption edges.

$$\sigma \propto \left(\frac{Z}{h\nu}\right)^n \quad (1)$$

*Corresponding author.
E-mail address: saifhadimohsen.serag@unicampania.it
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In (1), σ is the cross-section, *hv is* photon energy, and *Z* is atomic number, while *n* is a constant that varies between 3 and 4 depending on photon energy.

Nanoparticles with high-*Z* are used for their ability to transfer energy from radiation to the medium. Radiotherapy use nanoparticles because of their ability to transfer energy from radiation to the medium. Therefore, it can be said that injecting the tumor with a high-*Z* substance increases tumor sensitivity to radiation, and thus the radiation dose inside tumor is enhanced, while in healthy tissues surrounding the tumor the dose is reduced [2,3,4,5].

In a previous study [3], the MCNP5 algorithm was used to determine the dose rate distribution of AuNPs or GNPs (gold nanoparticles) at different concentrations in water and breast phantom. The authors found that the dose received by AuNP-injected tumor increased with increasing concentration of up to 10 %, and decreased for concentrations greater than 10 % [3]. Gold nanoparticles have been used in many studies due to their chemical properties that are harmless to tissues, as gold is chemically inactive, biologically nonreactive, and molecularly stable [6].

The authors in [5] investigated the impact of NP sizes, NP concentrations, and radiation beam intensity on radiotherapy dose augmentation. Their research project used gold, gadolinium, iodine, and iron oxide at different concentrations of (7, 18, 30) mg/g and different diameters of (25, 50, 75, 100, 125) nm. Furthermore, high- and low-voltage X-rays and ^{60}Co sources were used. The study found that the dose enhancement factor (DEF) is greatest at low energy and with gold nanoparticles, followed by gadolinium, iodine, and iron oxide nanoparticles. Also, the dose enhancement factor increases with increasing concentration and diameter of nanoparticles.

There are many studies that have examined the effects of GNPs in enhancing the dose. In one study [7], it was found that mice that were intravenously injected with GNPs and irradiated with 250 kV_p X-ray attained a survival rate of 86 %, while those that were exposed to radiation only without injection exhibited a 20 % survival rate [7]. In another research project, reported in [8], the effect of GNPs on normal tissues was studied for the cases of presence and absence of nanoparticles in phantom (eye and water) containing sources (^{125}I and ^{103}Pd) inside it. Different concentrations of GNPs were used. It was found that DEF increases with increasing concentrations. The concentration of DEF liquid is 2.45 % at 30 mg and 0.7 % at 7 mg [8]. In another study [9], four different concentrations and different volumes were use in eye and water phantoms. A Monte Carlo code was used to evaluate the effects of these concentrations and volumes on the dose that the tumor receives when a high-energy source is used. This study concluded that at a concentration of 30 mg and a volume of 100 nm, the eye structure is optimal. To obtain the highest dose sedimentation level for nanoparticles, therefore, the size and concentration of GNPs are considered as factors to increase the macroscopic dose in choroidal melanoma [9].

Furthermore, the authors in [10] investigated the characteristics of secondary electrons generated by X-ray interaction with GNPs and their dependency on the beam energy and NP size in a water medium using the Geant4 algorithm. The authors came to the conclusion that GNPs will damage cells more effectively when exposed to lower-energy photons. The authors in [11] used GNP injections directly into the prostate to imitate a novel ^{125}I brachytherapy method for high-risk prostate cancer. They found that using gold nanoparticles leads to an increased dose to in the prostate and to a reduced dose to the rectum and the urethra. Additionally, in a study using a Monte Carlo simulation package (MCNP), dosimetry effect of gold nanoparticles in prostate gland phantom was simulated in brachytherapy with ^{103}Pd source, and it was found that the use of GNPs leads to a significant DEF in the internal treatment of prostate cancer [12]. The authors in [13] utilized the MCNPX code package to examine the dose augmentation of gold and gadolinium NPs with such brachytherapy sources as ^{198}Au and ^{192}Ir. Three concentrations of NPs were simulated in a soft tissue phantom. The study found that gold nanoparticles improved the dose more than gadolinium particles. In Jones *et al*. [14], water phantom was use with gold nanoparticles and six different photon sources. A Monte Carlo code package was used in a study to estimate the DEF. The study concluded that for low-energy sources, the presence of gold nanoparticles significantly increases microscopic dose [14].

Many studies have focused on the effect of nanoparticles, in terms of both concentration, size, and type, as well as the energy source. Several studies examine the effect of different distances of the tumor from the source and used Monte Carlo code packages. However, the results of the Monte Carlo simulations in calculating the absorbed dose during radiotherapy using nanoparticles were not compared. The main contribution of this paper is to study the effects of gold nanoparticles in tissues, as summarized in the followings:

1. Studying the effects of different tissue components on the dose enhancement factor.
2. Using the Monte Carlo packages MCNP6 and GATE to check the accuracy and error rate in calculating the dose boost factor.

MATERIALS AND METHODS

Software

Simulations were performed using MCNP6 (Version 1) on an HP computer with a 64-bit Intel Core i5-6300U processor at 2.5 GHz, running Windows 10.

The GATE MC Toolkit v8.2 is based on the GEANT4 environment (v10.4). Both GEANT4 and GATE tool kits were installed and built on an HP-Z800 workstation with an Intel Xeon CPU E5-2620 at 2 GHz with 24 cores.

Simulation System

This study encompassed two Monte Carlo code packages, MCNP6 and GATE. Both software packages were used to study their accuracy in calculating dose enhancement factors.

MCNP6 Simulation

The Monte Carlo N-Particle Transport (MCNP6) code was developed by Los Alamos National Laboratory to include all the features of the MCNPX and MCNP5 codes. This code is designed to track many types of particles across wide ranges of energies. It is a general-purpose radiation transmission code for continuous energy distribution, generalized geometry, and time-dependent simulation [15]. In this study, dosimetric estimations were performed using the f6 statistical tally to score absorbed dose in each voxel with a unit of MeV/g. The number of histories used was 10^9 for all simulations with both code packages.

GATE Simulation

GATE (Geant4 Application for Tomographic Emission) is an advanced open source software package based on the Geant4 code, in collaboration with the Laboratory for Corpuscular Physics (Computer Platform for Life Sciences Team). Other research institutes are involved in the development and validation of this simulation platform within the OpenGate collaboration.

GATE software offers high performance for nuclear medicine applications. The scope of it applications also extends to the fields of radiotherapy and brachytherapy [16].

Phantom simulation

A spherical phantom of 10 cm radius was defined. It included a cube-shaped tumor with dimensions of (1×1×1) cm^3 at a distance of 1.5 cm from the source which was located at the center of the phantom. Several voxels are defined by dimensions of (0.1×0.1× 0.1) cm^3 to depth of 3.4 cm. The first voxel is located at a distance of 0.09 cm from the center of the source inside the phantom, as shown in Fig. 1. These voxels were identified to obtain dose values in the accidental plane associated with source longitudinal axis in both cases when the phantom contains gold nanoparticles and without gold nanoparticles.

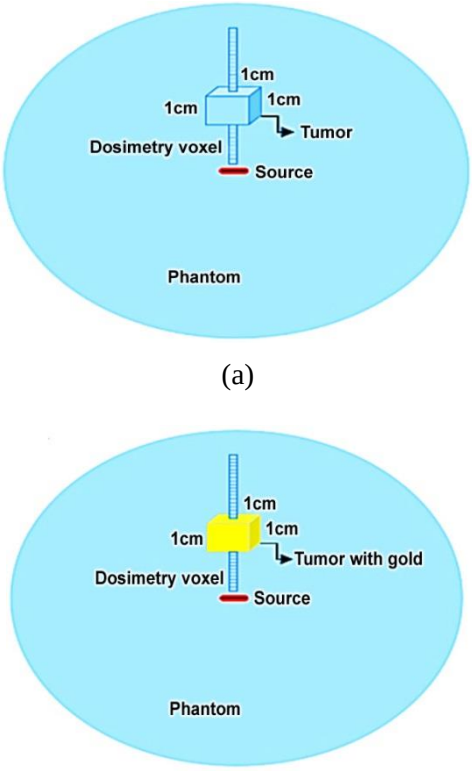

Fig. 1. Schematic illustrating brachytherapy source in center of phantom, tumor, and dosimetry voxels, as well as the dimensions simulated by the Monte Carlo code. (a) Tumor without nanoparticles. (b) Tumor with nanoparticles.

Radiation Sources

A commonly-used low-energy photon-emitting ^{125}I source is the GE HealthCare Model 6711. It has been the most widely used source of permanent transplant for brachytherapy since 1983. Figure 2 shows the structure and dimensions of the source, which consist of a titanium capsule with a length of 4.5 mm, and thickness of 0.06 mm, with welded end caps. Inside the capsule is a cylindrical

silver core with a length 3 mm and a diameter of 0.5 mm, coated with an Ag-halide compound with a thickness of 1 μm [17,18], as shown in Fig. 2.

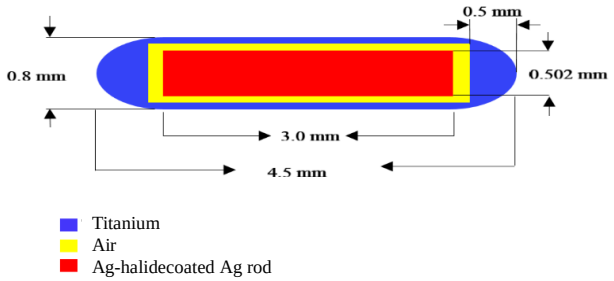

Fig. 2. Geometry of the GE HealthCare model 6711 ^{125}I LDR source. The dimensions are given in millimeters, and the origin of the coordinate system is at the center of the active core.

The phantom was filled with five different tissues (adipose tissue, breast tissue, water, soft tissue, and brain tissue) that were simulated separately tissue components were taken from ICRU-44 [19] as shown in Table 1.

Table 1. Tissue composition (in percent) and their density.

	Adipose tissue [19]	Brain tissue [19]	Soft tissue [19]	Water [20]	Breast tissue [21]
Density (g/cm^3)	0.95	1.040	1.00	1.00	1.02
H	11.4	10.7	10.1	11.2	10.6
C	59.8	14.5	11.1	-	33.2
N	0.7	2.2	2.6	-	3.0
O	27.8	71.2	76.2	88.8	52.7
Na	0.1	0.2	-	-	0.1
P	-	0.4	-	-	0.1
S	0.1	0.2	-	-	0.2
Cl	0.1	0.3	-	-	0.1
K	-	0.3	-	-	

Within the tumor, tissues were mixed with GNPs at a concentration of 7 mg/g, and this concentration is one of the concentrations used in a previous study by Hainfeld *et al*. [22]. The tumor volume was divided into ten parts each with a thickness of 0.1 cm with dimensions of (1×1×0.1) cm^3 in order to calculate the dose with and without GNP at different points within the tumor. Dose change was calculated as the GNP dose-enhancing factor (DEF), which is defined as the ratio of dose with GNP to dose without GNP at a certain point as in Eq. (2).

$$DEF = \frac{Averge\ dose\ with\ GNP}{Averge\ dose\ without\ GNP} \quad (2)$$

RESULTS AND DISCUSSION

In the first step, the results of dose enhancement for a MCNP6 code simulation of the ^{125}I source in soft tissue phantom with and without gold nanoparticles were compared with the results of a study by Cho *et al*. [23] to validate the simulation of MCNP6 in this study, to be considered as a reference for comparison with GATE code output.

Figure 3 shows simulation results for two studies at concentrations of 7 mg/g. As shown in Fig. 3, the values from the two studies are close, with the average DEF from the MCNP6 simulation was 1.82 %, while in Cho *et al*. study, the average DEF was 1.87 %. The average relative difference in DEF between our study and Cho *et al*. was 2.6 %. The differences in percentage between the results of the two studies may be due to the differences in the radii of the phantoms used. Whereas this study used a spherical phantom of 10 cm radius, the spherical phantom used in Cho *et al*. study was 4 cm in radius. The results are in good agreement and this confirms the reliability of MCNP6 code package in nanoparticle simulation.

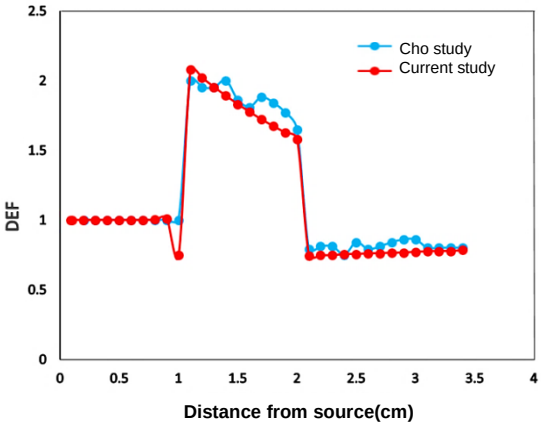

Fig. 3. Comparison of DEF estimate for ^{125}I source between the current study, using MCNP6, and the study by Cho *et al*., using MCNPX.

After validating MCNP6 simulation results, a low-energy source was simulated in a phantom center with five different tissues by MCNP6 and GATE.

In this paper, the effect of gold nanoparticles at a concentration of 7 mg/ml on different tissue components, and the difference of dose enhancement factor (DEF) between one tissue and another, are studied. The analysis of the results can be divided into two parts. The first part is a discussion of the effects of different tissue components on DEF. The second part is a comparison of MCNP6 and GATE simulation results. In the first part, the dose was calculated for different depths ranging from 0.09 cm at source center to 3.4 cm inside the phantom. The average DEF for various depths is shown in Fig. 4.

It is noted that dose increased in tumor area in all tissues included in the study when gold nanoparticles were added at a concentration of

7 milligram per milliliter of tumor, which is located at a 1.5 cm distance from phantom center.

The results of MCNP6 simulation in Fig. 4 show highest improvement in DEF for adipose, breast, brain, and soft tissues, and water. The DEF in tumor areas in adipose tissue ranges between a maximum value 2.64 and a minimum value 2.08. In breast tissue, the maximum value of dose enhancement factor was 2.23 and its minimum value was 1.72. In soft tissue, the maximum value of DEF is 2.07, and the minimum value is 1.59. It can be seen in Fig. 4 that the DEF in water and brain are very close; whereas the maximum DEF in water was 1.98 and the minimum was 1.53, in brain tissue, which is considered as the lowest-DEF tissue, the maximum DEF was 1.94 and the minimum was 1.48.

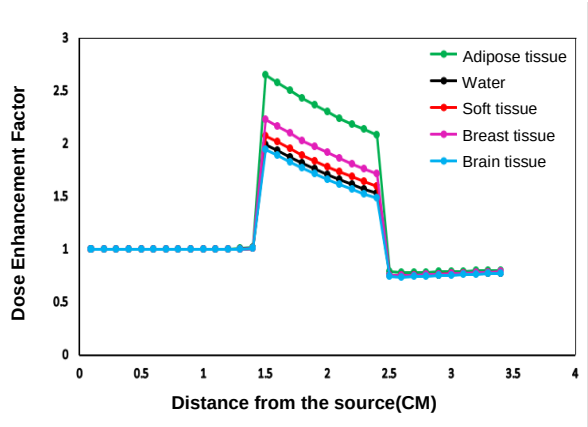

Fig. 4. Dose enhancement factor estimates from MCNP6 simulations for 7 mg/ml of gold nanoparticles for different tissues.

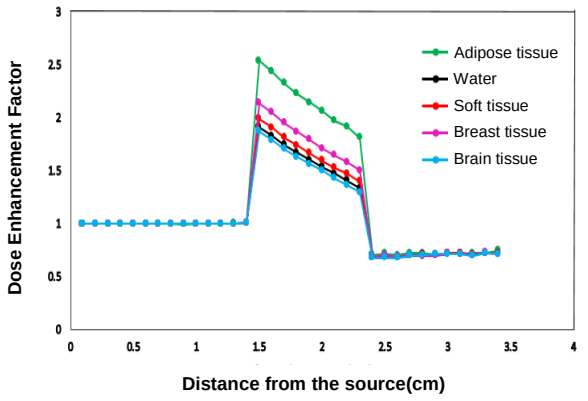

Fig. 5. Dose enhancement factor estimates from GATE simulations for 7 mg/ml of gold nanoparticles for different tissues.

Figure 5 shows the results of the GATE simulation. It is shown that when gold nanoparticles are added to the tumor, the adipose tissue shows highest dose enhancement factor, while brain tissue, the lowest. The maximum value of DEF in adipose tissue was 2.54 and the minimum value was 1.81. There was a clear difference between the DEFs of breast and adipose tissues, where the maximum value of DEF in breast was 2.14 and lowest value was 1.50. In descending DEF, soft tissue follows with a maximum DEF of 1.99 and a minimum of 1.40. As is the case with MCNP, GATE simulation clearly shows that DEF values of water and brain tissue are close. As shown in Fig. 5, the maximum DEF in water was 1.91 and the minimum was 1.33, while in brain tissue, the maximum was 1.87 and the minimum was 1.29.

As shown in Figs. 4 and 5, despite adipose tissue having the lowest density and effective atomic number of all tissues used in this study, it has the largest dose enhancement factor of 2.64 as determined through MCNP6 simulation and 2.54 through GATE simulation. This is due to its high hydrogen percentage; the hydrogen atoms produce an electron cloud in the path of photoelectrons, leading to an increase in DEF.

On the other end of DEF range, brain tissue has the highest density and the highest effective atomic number compared to tissues rest in this study, but both MCNP6 and GATE simulation results show it as having the lowest dose enhancement factor, with maximum values of 1.94 and 1.87, respectively. It can be interpreted that the ability to absorb energy depends largely on absorption region density, with the lesser range in the atomic number in absorbent medium.

As shown in Figs. 4 and 5, dose enhancement occurs inside tumor; outside the tumor the dose did not increase, and this is a useful feature in radiotherapy for tumor helps preserve healthy tissue surrounding the tumor.

In tumor area, DEF increases at the tumor beginning and then gradually decreases with increasing depth. This slight decrease in DEF is due to high scattering effects of low-energy photons with increasing depth inside tumor when interacting with gold nanoparticles.

The largest amount of dose was limited to inside the tumor, while dose decreased remarkably outside tumor with increased depth. It can be said that use of gold nanoparticles can make radiotherapy safer for tumor-surrounding tissues or healthy organs that are close to tumor and which are difficult to avoid when radiation is applied to tumor.

As previously mentioned, in the second part of the analysis, outputs from MCNP6 and GATE simulations were compared for the I-125 low energy source, to determine the accuracy of two calculations using the two software packages and the suitability of GATE as an appropriate tool for calculating dose enhancement factor in brachytherapy treatment using gold nanoparticles.

Simulation results in Fig. 6 show the average and highest DEF in the cases of adipose, breast, and soft tissues, water, and brain tissues, respectively.

Following the addition of gold nanoparticles to the tumor, the adipose tissue shows the highest dose improvement, while the lowest dose improvement is exhibited by brain tissue.

As shown in Fig. 6, MCNP6 and GATE simulations resulted in different DEF estimates. As shown in Fig. 6 (a), DEF estimates from MCNP6 simulations for adipose tissue, breast tissue, soft tissue, water, and brain are 2.34, 1.95, 1.82, 1.74, and 1.69, respectively, whereas GATE simulations resulted in estimates of 2.01, 1.69, 1.58, 1.52, and 1.48, respectively.

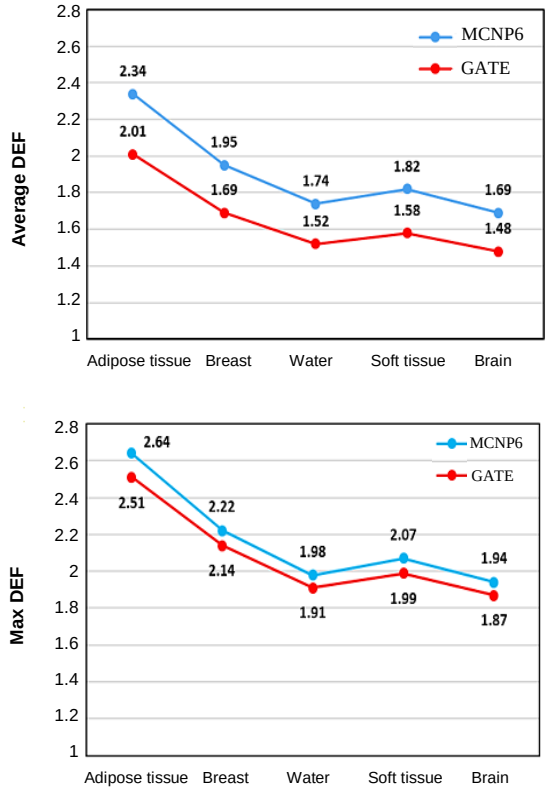

Fig .6. Dose enhancement factor estimates for different tissues from MCNP6 and GATE simulations. (a) average DEF and (b) maximum DEF.

By comparing the results of MCNP6 and GATE simulations, it became clear that the difference between results for adipose tissues is 14.1 %, which is the highest difference between the two for any of the tissues tested. As comparison, the difference is 13.3 % in breast tissue, 13.1 % in soft tissue, 12.6 % in water, and 12.4 % in brain tissue.

Through comparing the results of simulations with both MCNP6 and GATE for water phantom with the result of the study by Cho *et al*., it was found that the average dose enhancement factor in MCNP6 simulation was 1.74, while in GATE simulation, it was 1.52, whereas in Cho *et al*. study, it was 1.87. The average relative difference in DEF between MCNP6 and Cho *et al*. was 6.95 %, average relative difference in DEF between GATE and Cho *et al*. was 18.71 %. Therefore, it turns out that MCNP6 code is more accurate than GATE code.

Moreover, in Fig. 6 (b), the maximum DEF values were calculated for five tissues for both codes. Maximum DEF from MCNP6 simulations for adipose tissue, breast, water, soft tissue, and brain were (2.64, 2.22, 1.98, 2.07, and 1.94), respectively, whereas GATE-estimated maximum DEF for adipose tissue, breast, water, soft tissue, and brain were (2.51, 2.14, 1.91, 1.99, and 1.87), respectively.

The maximum values of DEF results for the two codes are convergent. Obviously, difference percentages of maximum DEF between two codes are much less than in average DEF. For average DEF, the percentage difference was 4.92 % for adipose tissue, which is the highest percentage difference between the code packages. For other tissues, it was 3.60 % for breast tissue, 3.53 % for water, 3.86 % for soft tissue, and 3.61 % for brain tissue. The convergence percentage of values was greater between results of MCNP6 and GATE for average DEF.

On the other hand, Table 2 presented the uncertainty of dose estimate from MCNP6 and GATE simulation results, both with and without adding gold nanoparticles to tumor.

Table 2. The maximum uncertainty of dose estimates from MCNP6 and GATE for different tissues.

Tissues	The maximum uncertainty in MCNP6 %		The maximum uncertainty in GATE %	
	Dose without Gold	Dose with Gold	Dose without Gold	Dose with Gold
Adipose Tissue	0.61	0.68	1.83	2.10
Soft Tissue	0.73	0.82	1.90	2.21
Water	0.76	0.85	1.92	2.22
Breast Tissue	0.70	0.79	2.18	2.18
Brain Tissue	0.67	0.74	1.95	2.25

Table 2 shows the uncertainties of doses estimated from MCNP6 and GATE simulation results, with and without adding gold nanoparticles to the tumor. The uncertainty in MCNP6 and GATE calculations of dose before and after addition of gold nanoparticles to tumor was compared for the five tissue or material types. It was observed that maximum uncertainty values for doses with and without the addition of gold nanoparticles in MCNP6 are lower than maximum values in GATE for all tissues.

The same number of particles was used to make the comparison between codes fair. The time taken to simulate each tissue in MCNP6 with addition of gold particles and without gold particles was 8.5 h in a separate simulation and GATE

code package took 24 h to simulate each tissue. Table 3 shows that MCNP6 is faster in simulation than GATE. In addition, the relative error of MCNP6 is less than 1 %, and GATE is less than 2 %.

Table 3. Comparison between MCNP6 and GATE.

	Number of Particles	Relative Error	Computing Time (h)
MCNP6	10^9	0.3 %	8.5
GATE	10^9	1 %	24

The current results of this study indicate that MCNP6 provides more accurate estimations than GATE. However, the two code packages' results were fairly convergent; the differences were acceptable, with the relative difference being less than 15 %. The difference between MCNP6 and GATE may be due to data processing methods and particle transfer algorithms. Accordingly, it can be said that GATE can be used to calculate the dose increase factor in topical treatment with nanoparticles.

CONCLUSION

From the results obtained by Monte Carlo simulations for a low-energy source, it was found that DEF differs from one tissue to another according to the properties of each tissue, whether its soft tissue, adipose tissue, water, breast tissue, or brain tissue. Additionally, good dose enhancement was observed in tumors using GNP gold nanoparticles. It can be said that gold nanoparticle use can make radiotherapy more effective in protecting the tissues surrounding the tumor or the healthy organs close to the tumor. This study confirmed that MCNP6 and GATE codes can account for DEF in different tissues for a low-energy source. The results of GATE were close to those of MCNP6. The differences between the two codes in all tissues were less than 15 %. The differences between the results of the two codes may be due to differences in Monte Carlo packages and simulation algorithms.

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AUTHOR CONTRIBUTION

M. N. Al-Suhbani is the main contributor of this paper. All authors read and approved the final version of the paper.

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