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The Influence of Au, Gd and I Nanoparticles on Radiation Dose Absorption during High Dose Rate Brachytherapy with ^{192}Ir Source

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Abstract: The efficacy of high dose rate (HDR) brachytherapy for cervical cancer is often constrained by the high radiation exposure to the healthy tissues that surround the tumor consequently diminishing the therapeutic benefits of the technique. A promising approach to mitigate this challenge is the use of high atomic number (Z) nanoparticles, such as Gold nanoparticles (GNPs), Gadolinium nanoparticles (GdNPs) and Iodine nanoparticles (INPs), which act as radioation dose enhancers. This study evaluates the influence of GNPs, GdNPs and INPs nanoparticles on dose absorption during 192Ir HDR brachytherapy using Geant4 based Monte Carlo (G4MC) simulation. The study deployed nanoparticles of various concentrations ranging from 3 mg/g to 30 mg/g. It was found that the presence of these nanoparticles significantly increases the dose in the tumor with GNPs causing higher dose deposition to the tumor than it is the case for GdNPs and INPs. It was further observed that the Dose Enhancement Factor (DEF) depends on the concentration and type of the nanoparticles. The maximum DEF was obtained at the concentration of 30 mg/g for each type of nanoparticle with the corresponding values being 1.82 for GNPs, 1.42 for GdNPs and 1.38 for INPs. These results indicate that incorporation of GNPs, GdNPs and INPs in HDR brachytherapy can enhance the efficacy of cancer tumor eradication. Hence, the use of GNPs during HDR brachytherapy at the concentration of 30 mg/g is recommended for effective cervical cancer treatment and management.

Keywords: Brachytherapy, Nanoparticles, Dose Enhancement Factor, Monte Carlo simulation.

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A Influência das Nanopartículas de Au, Gd e I na Absorção de Dose de Radiação durante a braquiterapia de alta taxa de dose com fonte ^{192}Ir

Resumo: A eficácia da braquiterapia para câncer cervical é frequentemente limitada pela alta exposição à radiação nos tecidos saudáveis que cercam o tumor, diminuindo, consequentemente, os benefícios terapêuticos da técnica. Uma abordagem promissora para mitigar esse desafio é o uso de nanopartículas de alto número atômico (Z), como nanopartículas de Ouro (GNPs), nanopartículas de Gadolínio (GdNPs) e nanopartículas de Iodo (INPs), que atuam como radio-sensibilizadores. Este estudo avalia a influência das nanopartículas de GNPs, GdNPs e INPs durante a braquiterapia HDR com 192Ir, utilizando simulação Monte Carlo (G4MC) baseada em Geant4. O estudo utilizou nanopartículas em várias concentrações, variando de 3 mg/g a 30 mg/g. Observou-se que a presença dessas nanopartículas aumenta significativamente a dose no tumor, com as GNPs causando uma maior deposição de dose no tumor em comparação com GdNPs e INPs. Também foi observado que o Fator de Aumento de Dose (DEF) depende da concentração e do tipo de nanopartículas. O DEF máximo foi obtido na concentração de 30 mg/g para cada tipo de nanopartícula, com os valores correspondentes sendo 1,82 para GNPs, 1,42 para GdNPs e 1,38 para INPs. Esses resultados indicam que a incorporação de GNPs, GdNPs e INPs na braquiterapia HDR pode aumentar a eficácia da erradicação do tumor cancerígeno. Portanto, recomenda-se o uso de GNPs durante a braquiterapia HDR na concentração de 30 mg/g para um tratamento e gerenciamento eficaz do câncer cervical.

Palavras-chave: Braquiterapia, Fator de Aumento de Dose, Simulação de Monte Carlo.

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1. INTRODUCTION

Cancer continues to be a major global health challenge, ranking as the second leading cause of death worldwide after cardiovascular diseases [1]. In 2022, approximately 20 million new cancer cases were reported globally, with nearly 9.7 million deaths [2]. Due to population growth and rise in average life expectancy, cancer incidences are expected to rise, potentially reaching 35 million new cases annually by 2050 [2]. It follows that cancer treatment and management will continue to be a crucial part and parcel of the healthcare systems. Yet, the success of both cancer treatment and management relies on the performance of the various treatment methods including radiotherapy, which is one of the main treatments for localized tumors [3]. Among the various radiotherapy techniques, HDR brachytherapy is widely adopted due to its ability to deliver precise and high radiation doses directly to the tumor within a short time period. This technique involves placing a high-activity radioactive source, such as ^{192}Ir, close or inside the tumor, providing a concentrated dose with minimal fractions [4]. The technique is frequently used to treat cancers such as cervical, prostate and gynecological cancers [5].

Cervical cancer is a serious disease among women affecting the cervix [6]. The treatment of disease often requires precise strategies to manage it particularly at its advanced stages. In so doing, HDR brachytherapy has emerged as a cornerstone treatment modality for locally advanced cervical cancer, offering a focused approach that delivers high doses of radiation directly to the tumor. HDR brachytherapy treatment is typically administered in three or four fractions over several sessions, each planned to achieve optimal dose distribution. The high activity of ^{192}Ir allows the delivery of very high radiation dose in a short period which is crucial for efficient targeting and of tumors while minimizing exposure to sorrounding healthy tissues. Nevertheless, despite the precise tumor targeting in HDR

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brachytherapy, there is still a chance of radiation exposure to surrounding healthy tissues, which may potentially lead to tissue damage and secondary malignancies [7]. In efforts to address this issue, the use of nanoparticles has garnered significant attention in recent years [8]. These nanoparticles are used to enhance the sensitivity of tumor cells to radiation helping to concentrate the radiation dose in the tumor cell. This minimzes further the dose deposition to the surrounding tissues hence minimizing the damage to organs at risk [9].

Nanoparticles composed of high Z elements such as Gold (Au), Gadolinium (Gd) and Iodine (I), are particularly promising for radiosensitization. These nanoparticles interact with ionizing radiation through the photoelectric effect, which is dominant in the kilo-electron volt (keV) energy range and scales with Z3 [10]. Thus, when high-Z nanoparticles are introduced into the tumor environment, they drastically enhance the probability of photoelectric absorption, leading to the production of secondary electrons, such as photoelectrons and Auger electrons [11]. These secondary electrons deposit their energy within the tumor, causing localized DNA damage hence improving the therapeutic efficacy of radiotherapy [12].

Improvement of radiation dose deposition by the application of radiation enhancers has been previously demonstrated by various studies [13]. For instance, a study by Brivio and others in 2015 showed that the deposition of radiation dose during the External Beam Radiotherapy (EBRT) was enhanced by a factor of 1.97 when GNPs were used as radio-enhancers for photon beams in the keV energy range [14]. Yet, since the energy spectrum in HDR brachytherapy is quite different from that of EBRT, the effectiveness of GNPs, GdNPs and INPs in HDR brachytherapy could be very different from what is known in EBRT. It is therefore compelling to investigate the influence of high Z nanoparticles on the tumor dose absorption during HDR brachytherapy. Hence, the current study is set to explore the potential of radiation enhancement when the high atomic number nanoparticles are deployed in HDR brachytherapy using ^{192}Ir.

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In this study, the influence of using GNP, GdNPs and INPs as radiation dose enhancers during the ^{192}Ir HDR brachytherapy in cervical cancer treatment is evaluated. The study uses Geant4 Monte Carlo simulations to evaluate the extent to which these nanoparticles can enhance tumor radiation absorption during cervical cancer treatment using HDR brachytherapy by evaluating the DEF. By investigating the DEF of GNPs, GdNPs and INPs, this research seeks to identify the most effective nanoparticle for radiation enhancement in the context of HDR brachytherapy using ^{192}Ir for improving cancer treatment outcomes.

2. MATERIALS AND METHODS

2.1. Geant4 Monte Carlo Simulation Program

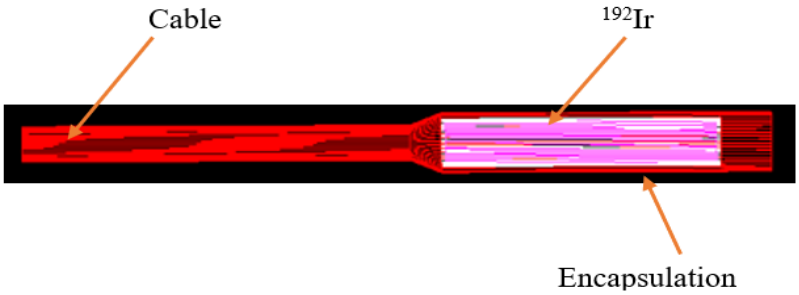
The Geometry and Tracking 4 (Geant4) code is a comprehensive multipurpose MC code utilized for simulating the interaction of particles with matter, extensively employed in fields like medical physics, high-energy physics and astrophysics. Such simulations are used when the experimental study is not possible due to the difficult, expensive, or even dangerous procedures (Hashemi et al. 2019). In the case of nanoparticle dose enhancement, simulation studies using software like Geant4 are employed to achieve physical assurance for clinical justification.

In this study, Geant4 (version 11.1.2) was used on a computer that run on the Ubuntu operating system with additional applications like compilers and ROOT for data analysis. The simulation geometry consisted of a tumor embedded within healthy tissue. Both structures were modeled as spheres, with radii of 60 mm for the tumor and 100 mm for the healthy tissue, placed within a rectangular world volume measuring 200 mm by 250 mm. The composition of these tissues adhered to International Commission for Radiological Units and Measurements (ICRU) guidelines, representing human soft tissue with a composition of

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11.2% carbon, 10% hydrogen, 2.6% nitrogen and 76.2% oxygen [15]. Spherical nanoparticles measuring 50 nm in size were employed within the tumor, as in vitro and in vivo studies have indicated their high cellular absorption rates [16]. ^{192}Ir was modelled as a cylindrical structure with a cross-sectional diameter of 0.6 mm and an active core length of 3.5 mm, having a density of 22.42 g/cm^3 [17]. As shown in Figure 1, the source was encapsulated with a steel of density 8.02 g/cm^3 made of manganese, silicon, nickel, chromium and iron, with their respective composition proportions being 2%, 1%, 12%, 17% and 68%, respectively [18].

Figure 1: The structure of ^{192}Ir HDR brachytherapy source as simulated in Geant4.



The encapsulation aimed at shielding the radioactive core of the source and absorption of the beta particles emitted during the decay of ^{192}Ir to ^{192}Pt. The source also had an air gap modelled as a cylindrical structure with a radius of 0.67 mm, separating the surface of the active ^{192}Ir core from the steel, ensuring a distance of 0.07 mm from the outer surface of the active core to the steel. At one end of the source, a cable with a length of 100 mm and a radius of 0.5 mm was attached to emulate the cable that is in the clinical setting connected to the microSelectron afterloader machine to transfer the source to the tumor.

After constructing the geometry, the primary particles of the source were set to photons in accordance to the ^{192}Ir source and all its properties including the decay mechanisms and energy of 380 keV. The source was allowed to emit radiation isotropically to ensure uniform dose distribution in the tumor. The interaction of radiation with the tumor or healthy tissues was guided by the chosen set of physics suited to the particles emitted in the decay of ^{192}Ir. Major types of interactions, such as the photoelectric effect, Compton interaction and gamma

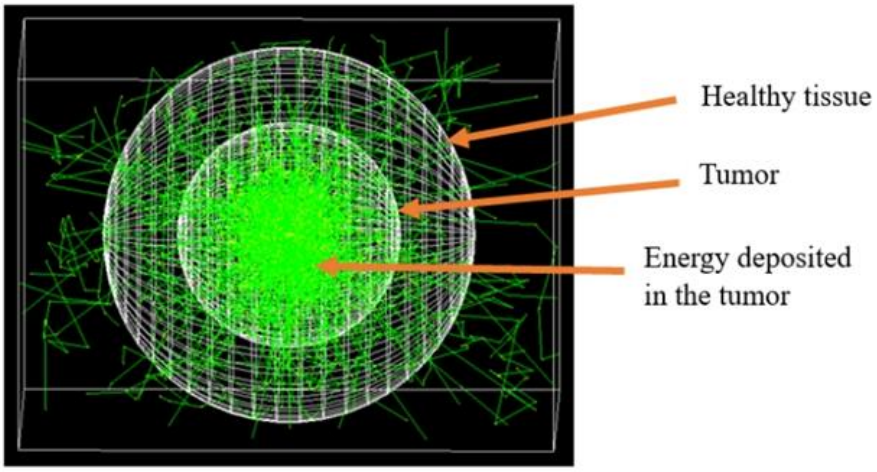
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conversion, were specified in the physics list class, with the energy cut-off ranging from 10 eV to 1 GeV and the track length of each interacting particle set to 0.1 mm.

2.2. The Influence of GNPs, GdNPs and INPs on Radiation Dose Absorption during ^{192}Ir HDR Brachytherapy

Initially, the concentration of GNPs was set to 0 mg/g to obtain the dose deposited in the tumor in the absence of nanoparticles. As radiation interacts with the tumor and healthy tissues, a sensitive volume for dose scoring set via the G4SDManager in the detector construction was used to record the dose deposited in the tissues. Within this sensitive volume, the hits due to particles interacting with the tumor were collected using the score writer approach implemented in the simulation program. The path of each interacting particle was traced in the scoring volume using the G4SteppingAction functionality, calculating the accumulated dose at the end run. To limit the scoring to the tumor volume only, particles exiting the tumor were not traced. However, since the study also aimed to calculate the dose deposited in the healthy tissues surrounding the tumor, the scoring volume was set to these tissues in the other scenario of the simulation and G4SteppingAction was configured to trace particles' interaction within them as well. Figure 2 depicts the energy deposition during the interaction of the photons with the tumor.

Figure 2: The view of the tumor exposed to radiation from ^{192}Ir source.



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Following the completion of the entire simulation, the accumulated doses in both tumor and healthy tissue were calculated, saved in ROOT files and printed to the console. The concentration of GNPs was then set to 3 mg/g, and the dose deposited in the tumor was obtained using the same procedures. Given that the study used concentrations ranging from 3 mg/g to 30 mg/g, the concentration was incremented by 3 mg/g for each step. For each of these concentrations, the dose deposited in the tumor was calculated and saved. To assess the extent of dose enhancement due to the impact of GNPs, a thorough comparison was made between the dose obtained in the absence of GNPs and the dose obtained in their presence. The simulation procedure was repeated with GNPs replaced by first GdNPs followed by INPs.

3. RESULTS AND DISCUSSIONS

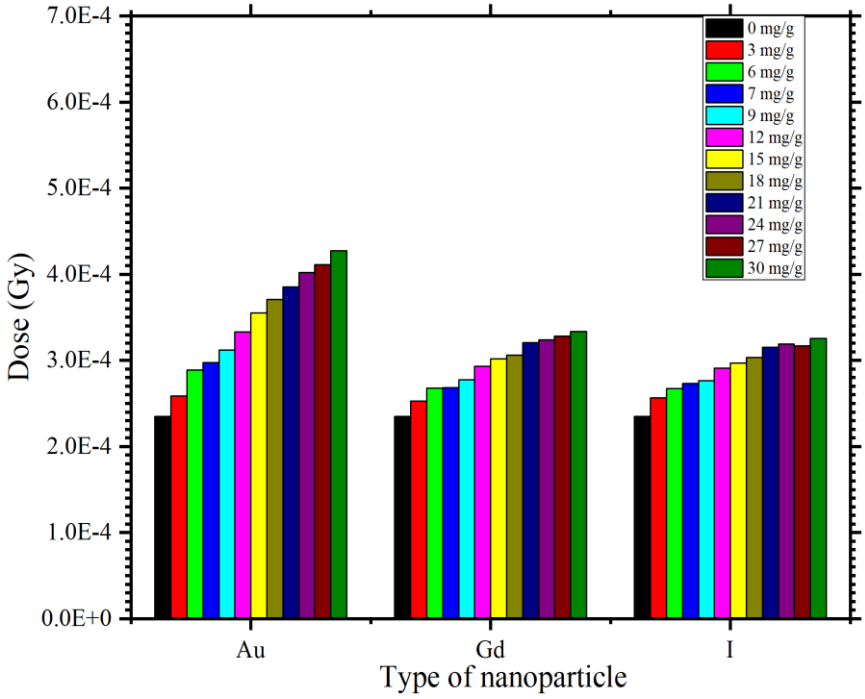
3.1. The influence of nanoparticle concentrations on the dose absorption by the cervical cancer tumor

This study examined the radiation dose absorption by the cervical cancer tumor during HDR brachytherapy in the presence of GNPs, GdNPs and INPs. It was found that the dose absorption by the tumors depends on both the type and concentration of the nanoparticles used as displayed in Figure 3. The general trend of data shows that the dose deposited in the tumor increases as the concentration of the nanoparticles increases. Meanwhile, the absorbed dose was greatest when GNPs were used followed by GdNPs. It follows that, even though all three nanoparticles result to the increase in the dose absorbed by the tumor, the greatest enhancement factor during HDR brachytherapy treatment with ^{192}Ir could be achieved when using the GNPs. The high efficiency of GNPs is attributed to the high Z of Au compared to those of Gd and I [8]. This finding aligns with the literature, which reports the superiority of GNPs in dose enhancement during treatment with low-energy EBRT [19]. Generally,

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nanoparticles with high Z are found to be effective for dose enhancement during treatment of cervical cancer by HDR brachytherapy.

Figure 3: Dose deposited in the tumor in the presence of GNPs, GdNPs and INPs at various concentrations.

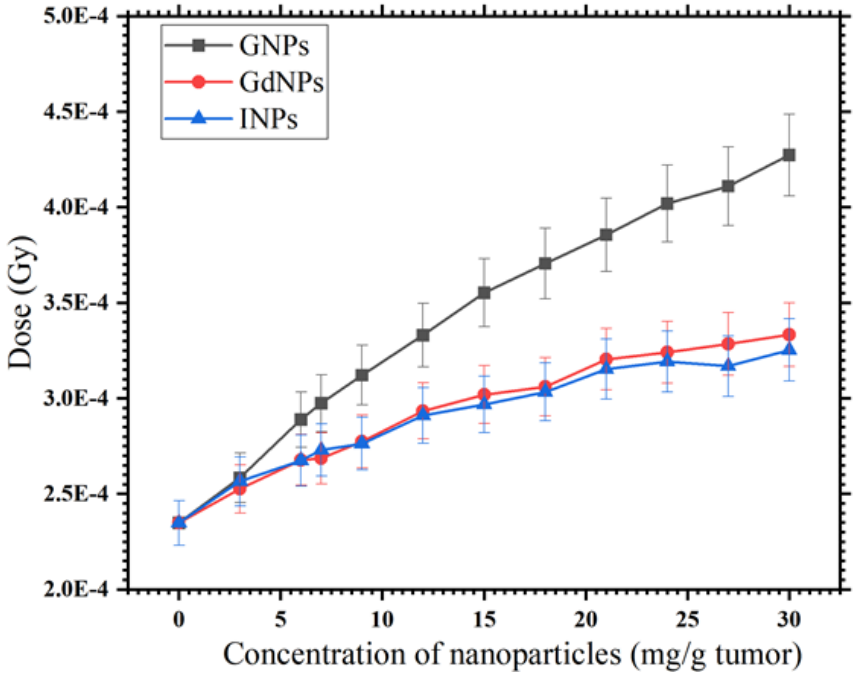


3.2. Comparison of Nanoparticles at Different Concentrations

As previously observed, different concentration of nanoparticles contributes to different absorbed doses by the tumor. However, the extent of dose absorption enhancement by nanoparticles is also dictated by the type of nanoparticles applied. The study was therefore compelled to compare the absorbed doses resulting from the use of different nanoparticles at different nominal concentrations. To do this, two scenarios were considered. In the first scenario, the tumor was treated in the absence of nanoparticles, and the total dose deposited was observed to be 2.35×10^{-4} Gy. In the other scenario, the tumor was treated with the presence of GNPs, GdNPs or INPs at various concentrations ranging from 0 mg/g to 30 mg/g. The dose absorbed by the tumor for each case was then recorded and plotted as shown in Figure 4.

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Figure 4: Dose deposited in the tumor in the presence of GNPs, GdNPs and INPs at various concentrations.



When GNPs were introduced into the tumor at a concentration of 3 mg Au/g, the dose deposited in the tumor slightly increased to 2.58×10^{-4} Gy. This increase in dose was equivalent to a 10% increase compared to the dose obtained in the absence of GNPs. As the concentration of GNPs increased, the dose deposited in the tumor continued to rise until it reached its maximum value of 4.27×10^{-4} Gy, which is equivalent to 82% increase in dose obtained when at a concentration of 30 mg Au/g.

On the other hand, both GdNPs and INPs have shown absorbed doses of 2.53×10^{-4} Gy and 2.56×10^{-4} Gy which show an increase in the absorbed dose equivalent to 8% and 8.5% respectively. This shows that the two nanoparticles cause almost the same influence on dose absorption when applied at a concentration of 3mg/g. However, an increase in the concentration of GdNPs resulted in more tumor dose deposition compared to the absorbed dose in the presence of INPs. At the maximum concentration of 30 mg/g used in this study, GdNPs exhibited a dose increase of 42%, while INPs showed an increase

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in the dose of 38% meaning that GdNPs have a superior influence than INPs. Nevertheless, although both GdNPs and INPs fall significantly short of the dose absorption enhancement caused by GNPs at the same concentrations, it is worth noting that at concentrations below 3 mg/g, the dose deposited in the tumor is similar for all three types of nanoparticles. This suggests that at low nanoparticle concentrations, the impact of low-energy electrons, such as photoelectrons and Auger electrons, is not significant. It follows that precise concentrations of nanoparticles are required to achieve the desired enhancement of dose absorption by the tumor cells. Moreover, GNPs are observed to outperform other nanoparticles even for HDR brachytherapy as one can realize through Figure 4. Yet, this can be further underlined by the DEF for each type of studied nanoparticles.

3.3. Evaluation of Dose Enhancement Factor for GNPs, GdNPs and IGPs at Various Concentrations

The Dose Enhancement Factor (DEF) is a measure used to quantify the increase in radiation dose delivered to a target area, such as a tumor, in the presence of dose-enhancing materials like nanoparticles. It is calculated by comparing the dose absorbed by the tumor with and without these nanoparticles. Evaluating DEF is crucial for identifying the optimal nanoparticles that can enhance dose deposition in tumors during HDR brachytherapy using ^{192}Ir. This factor quantifies the extent to which the dose in the tumor is altered when specific nanoparticles are used in tumor treatment. In this study, DEF was determined by simulating dose distributions with G4MC simulations, where each nanoparticle type (GNPs, GdNPs and IGPs) was incorporated at specific concentrations (from 0 mg/g to 30 mg/g) within the tumor model. The results are presented in Table 1.

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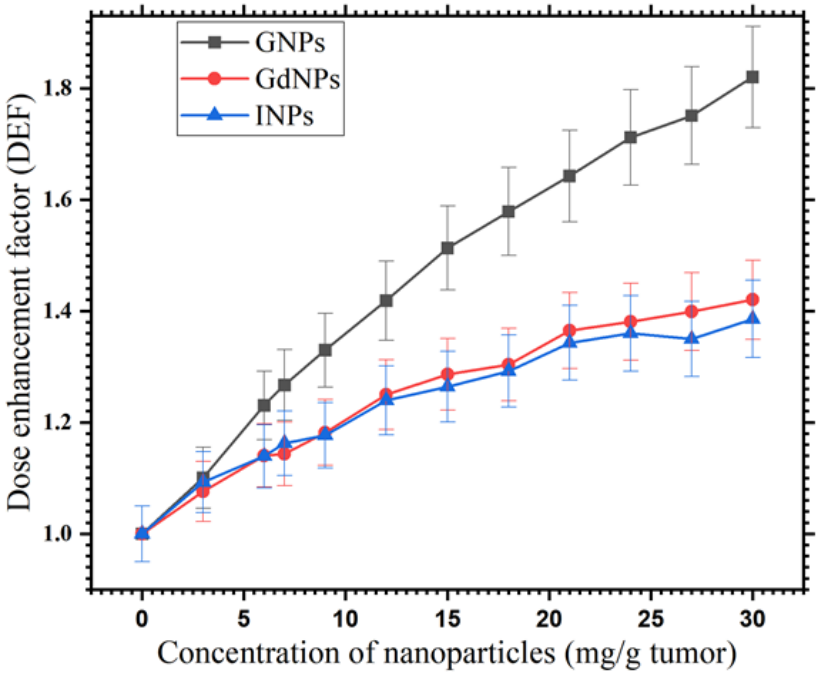
Table 1 : DEF due to the application of GNPs, GdNPs and IGPs at various concentrations.

Concentration of nanoparticles (mg/g)	DEF in the presence of nanoparticles		
	GNPs	**GdNPs**	**INPs**
0	1.000	1.000	1.000
3	1.101	1.076	1.093
6	1.230	1.141	1.139
7	1.267	1.144	1.163
9	1.330	1.182	1.177
12	1.419	1.250	1.239
15	1.513	1.286	1.264
18	1.579	1.303	1.292
21	1.642	1.365	1.343
24	1.712	1.380	1.360
27	1.751	1.399	1.350
30	1.820	1.420	1.386

The DEF in the presence of GNPs exhibited a significant increase as the concentration of nanoparticles in the tumor increased. Furthermore, at the concentration of 3 mg/g all three nanoparticles showed the DEFs that are slightly close, with GNPs having a higher value than the others. As the concentration of nanoparticles increases, the values of DEFs increased for all nanoparticles, with GNPs having more prominent values than GdNPs and IGPs. It was also found that, the maximum DEF was 1.82, 1.42 and 1.38 for GNPs, GdNPs and INPs respectively. This DEF trend showed that the dose enhancement capabilities of GdNPs and INPs is almost half that of GNPs at the same concentration as illustrated in Figure 5.

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Figure 1: Centered DEF in the presence of GNPs, GdNPs and INPs at various concentrations ranging from 0 mg/g to 30 mg/g.



These findings highlight the potent impact of nanoparticle concentration on dose enhancement in HDR brachytherapy, particularly at higher concentrations where the differences become more pronounced. GNPs are found to be exceptionally effective for dose enhancement during ^{192}Ir HDR brachytherapy. Furthermore, the optimal concentration identified in this study was 30 mg/g, as this concentration resulted in the highest dose deposition in the tumor, significantly increasing the DEF. This makes GNPs at 30 mg/g an optimal choice for maximizing therapeutic efficacy in HDR brachytherapy.

4. CONCLUSIONS

This study has evaluated the dose enhancement capabilities of GNPs, GdNPs and INPs when applied in conjunction with HDR brachytherapy. Specifically, the study sought to determine the influence of each of these nanoparticles on dose enhancement during HDR

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brachytherapy using a ^{192}Ir source. The results showed that without nanoparticles, a tumor received 2.35×10^{-4} Gy during ^{192}Ir HDR brachytherapy whereas upon the introduction of nanoparticles, the dose received by the tumor increased substantially. The dose was observed to reach a maximum of 4.27×10−4 Gy, 3.33×10^{-4} Gy and 3.25×10^{-4} Gy when 30 mg/g of GNPs, GdNPs and INPs were respectively applied.

The factor by which the radiation dose absorbed by the tumor increased was observed to depend on the type and concentration of the nanoparticles used. GNPs are deemed more effective in enhancing the dose during HDR brachytherapy. Therefore, the incorporation of GNPs during HDR brachytherapy is hereby recommended for improving cervical cancer treatment. However, as this study concentrated on HDR brachytherapy using ^{192}Ir source, it is recommended that other sources such as ^{60}Co and ^{169}Yb which are in some cases employed in HDR brachytherapy are also considered in future studies.

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CONFLICT OF INTEREST

The authors of this article wish to declare no conflict of interest in this work.

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