Monte Carlo Modeling of Reactive Oxygen Species Generation in Gold Nanoparticle-Enhanced FLASH Radiotherapy

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ABSTRACT

Purpose
To investigate the combined effects of gold nanoparticles (GNPs) and ultrahigh dose rate (UHDR) electron beams on reactive oxygen species (ROS) generation under FLASH radiotherapy conditions using Monte Carlo (MC) simulations.

Method
Geant4-DNA MC simulations were performed to model a spherical water phantom (10 µm diameter) embedded with a single GNP of varying sizes (5 - 100 nm diameter). Incident electron beams with energies of 100 keV and 1 MeV were simulated at ultra-high dose rates (UHDRs) of 60, 100, and 150 Gy/s. ROS yields, including H_3O^+, OH•, H_2O_2, OH^-, and H• radicals, were quantified at 10 ns post-irradiation. The yield enhancement factor (YEF) was calculated as the ratio of ROS generated with GNPs to that with water nanoparticles under identical conditions.

Results
Simulations revealed a strong dependence of ROS yield on GNP size, electron energy, and dose rate. For 1 MeV electrons, YEF increased with decreasing GNP size. At 60 Gy/s, the maximum YEF reached ~1.25 at 30 nm from a 5 nm GNP. Increasing UHDR from 60 to 150 Gy/s reduced YEF for small GNPs. For 100 keV electrons, YEF values were lower overall. Across all conditions, YEF declined sharply between 10 nm and 100 nm GNP sizes, indicating self-absorption and reduced secondary electron escape in larger particles. These findings highlight the fact that nanoparticle size and beam energy are dominant factors in optimizing radiosensitization under FLASH conditions.

Conclusions
This study demonstrates that nanoparticle size and beam parameters critically influence ROS generation during FLASH irradiation. Small GNPs under lower UHDR and higher electron energy conditions significantly enhance ROS yield, suggesting a potential strategy to optimize radiosensitization while preserving the normal tissue-sparing benefits of FLASH-RT. These findings provide a useful computational basis for designing nanoparticle-enhanced FLASH therapies and guide future experimental validation.

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INTRODUCTION

FLASH radiotherapy (FLASH-RT), characterized by ultra-high dose rates (UHDRs), has demonstrated a unique normal tissue–sparing effect while maintaining tumor control [1,2]. However, the underlying radiochemical mechanisms, particularly under nanoparticle enhancement, remain poorly understood. Gold nanoparticles (GNPs) are well-established radiosensitizers due to their ability to generate secondary electrons and amplify local reactive oxygen species (ROS) [3]. The interaction between GNP radiosensitization and FLASH-RT dose rates has not yet been systematically investigated. This study uses Geant4-DNA Monte Carlo simulations [4] to examine how GNP size, electron beam energy, and UHDR jointly influence ROS generation at nanometric scales, providing mechanistic insight relevant to nanoparticle-enhanced FLASH-RT.

METHODS AND MATERIALS

Monte Carlo simulations were performed using Geant4-DNA. The simulation geometry consisted of a spherical water phantom (10 µm diameter) with a single GNP placed at its center, as illustrated in Figure 1 and Figure 2. Incident monoenergetic electron beams (100 keV and 1 MeV) were directed toward the nanoparticle surface. GNP diameters of 5, 10, and 100 nm were modeled. Simulations were conducted at UHDRs of 60, 100, and 150 Gy/s. Radiolytic species—including H_3O^+, OH•, H_2O_2, OH^-, and H• radicals—were scored at 10 ns post-irradiation at radial distances from 10 to 30 nm from the GNP surface. The yield enhancement factor (YEF) was calculated as the ratio of total ROS generated in the presence of GNPs to that generated with equivalent water nanoparticles (WNPs) under identical irradiation conditions [5]:

$$\mathrm{YEF} = \frac{\mathrm{ROS_{GNP}}}{\mathrm{ROS_{WNP}}}$$

RESULTS

ROS production exhibited strong dependence on GNP size, electron energy, and dose rate. For 1 MeV electrons, YEF values increased with decreasing GNP diameter across all radial distances. As shown in Table 1, the highest enhancement (YEF ≈ 1.25) was observed at 30 nm from a 5 nm GNP under 60 Gy/s irradiation. Increasing the dose rate from 60 to 150 Gy/s resulted in a systematic reduction in YEF, particularly for smaller GNPs, indicating diminished radiosensitization at higher UHDR conditions (Table 1). This trend was consistent across all scoring distances. For 100 keV electrons, overall YEF values were lower than those obtained at 1 MeV. As summarized in Table 2, ROS enhancement decreased sharply with increasing GNP size. At 30 nm and 60 Gy/s, YEF dropped from approximately 0.8 for 5 nm GNPs to ~0.26 for 100 nm GNPs, demonstrating substantial size-dependent attenuation. Across both energies, YEF consistently declined as GNP diameter increased from 5 to 100 nm, reflecting reduced secondary electron escape and enhanced self-absorption in larger nanoparticles.

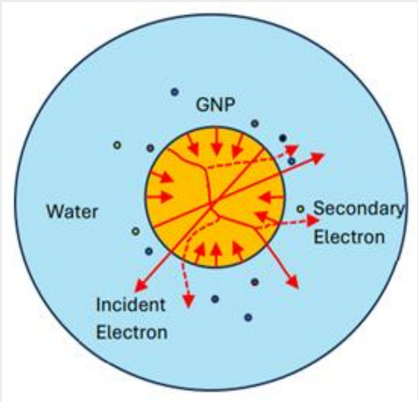

Figure 1. Figure 1: A GNP, orange with diameters of 5, 10, or 100 nm is placed at the center of a water sphere (light blue) with a radius of 5 µm. ROS, incident electrons, and secondary electrons are represented by multicolored dots, solid red lines, and dashed red lines, respectively.

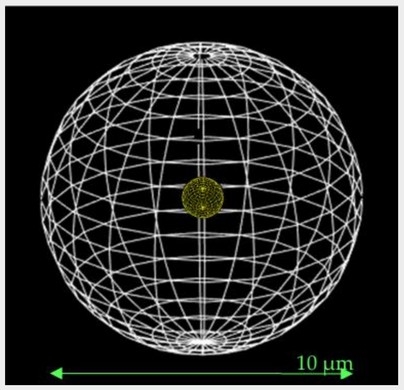

Figure 2. The MC simulation setup consists of a spherical water phantom (10 µm in diameter) embedded with a GNP of varying size.

Table 1. YEF as a function of GNP size (5, 10 and 100 nm) at distances of 10, 15, 20, 25, and 30 nm from the GNP surface under different UHDR conditions (60, 100, and 150 Gy/s) for 1 MeV incident electrons.

Distance (nm)	Diameter (nm)	YEF @ 60 Gy/s	YEF @ 100 Gy/s	YEF @ 150 Gy/s
10	5	1.15	1.1	1.05
10	10	0.85	0.8	0.75
10	100	0.13	0.12	0.1
15	5	1.1	1.05	1
15	10	0.8	0.75	0.7
15	100	0.18	0.17	0.15
20	5	1.15	1.1	1.05
20	10	0.75	0.7	0.65
20	100	0.22	0.2	0.18
25	5	1.1	1.05	1
25	10	0.7	0.65	0.6
25	100	0.24	0.22	0.22
30	5	1.25	1.05	1
30	10	0.65	0.6	0.55
30	100	0.26	0.24	0.22

Table 2: YEF as a function of GNP size (5, 10 and 100 nm) at distances of 10, 15, 20, 25, and 30 nm from the GNP surface under different UHDR conditions (60, 100, and 150 Gy/s) for 100 keV incident electrons.

Distance (nm)	Diameter (nm)	YEF @ 60 Gy/s	YEF @ 100 Gy/s	YEF @ 150 Gy/s
10	5	1	0.95	0.9
10	10	0.7	0.65	0.6
10	100	0.13	0.12	0.1
15	5	0.95	0.9	0.85
15	10	0.65	0.6	0.55
15	100	0.18	0.17	0.15
20	5	0.9	0.85	0.8
20	10	0.6	0.55	0.5
20	100	0.22	0.2	0.18
25	5	0.85	0.8	0.75
25	10	0.55	0.5	0.45
25	100	0.24	0.22	0.2
30	5	0.8	0.75	0.7
30	10	0.5	0.45	0.4
30	100	0.26	0.24	0.22

DISCUSSION

This Monte Carlo study demonstrates that gold nanoparticle–mediated ROS enhancement under FLASH radiotherapy conditions is strongly dependent on nanoparticle size, beam energy, and dose rate. Among these factors, GNP size is the primary determinant of radiosensitization. Smaller nanoparticles consistently produced higher YEFs, particularly within 10–30 nm from the particle surface. This behavior is attributed to more efficient secondary electron escape from smaller GNPs, whereas larger nanoparticles experience increased self-absorption, limiting their radiolytic effectiveness. Electron beam energy also influenced ROS enhancement, with 1 MeV electrons producing higher YEFs than 100 keV electrons across all nanoparticle sizes. Higher-energy electrons generate broader secondary electron spectra capable of inducing more extensive water radiolysis, highlighting the importance of matching nanoparticle dimensions with beam parameters. A key finding is the reduction of YEF with increasing UHDR. Increasing dose rate from 60 to 150 Gy/s suppressed ROS enhancement, particularly for small GNPs. This suggests that FLASH conditions may reduce effective radical availability through mechanisms such as increased radical recombination at high instantaneous concentrations. These results indicate that nanoparticle radiosensitization and FLASH effects interact, rather than act independently, and must be jointly optimized.

CONCLUSIONS

This Monte Carlo study demonstrates that small gold nanoparticles irradiated with higher-energy electrons at lower UHDRs produce the greatest enhancement of ROS generation under FLASH-RT conditions. Increasing dose rate and nanoparticle size significantly reduces radiosensitization due to self-absorption and suppressed radical chemistry. These findings establish a quantitative nanoscale framework for optimizing nanoparticle-enhanced FLASH radiotherapy, balancing ROS-mediated tumor damage with the normal tissue-sparing benefits of FLASH-RT. The results provide clear guidance for future experimental validation and translational study design.

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