Quantifying Physical Dose Enhancement and Chemical Radical Yield of HfO2 Nanoparticles: A Monte Carlo Study

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Abstract

Hafnium dioxide (HfO_2) nanoparticles are high-Z radiosensitizers with established potential for enhancing radiation-induced physical and chemical effects, yet the size-, energy-, and localization-dependent mechanisms underlying HfO_2-mediated radiosensitization remain incompletely quantified. In this study, we integrated TOPAS Monte Carlo simulations with TOPAS-nBio radiochemical modeling to investigate the physical dose enhancement and radiolytic species generation associated with HfO_2 nanoparticles. Single-particle size-comparison simulations were performed for HfO_2 nanoparticles with diameters ranging from 2.5 to 500 nm, whereas subsequent cellular radiochemical simulations focused on nanoparticles of 5 nm radius (10 nm diameter). The simulations revealed strong dependences of the dose enhancement factor (DEF) and radiochemical readouts on photon energy, nanoparticle size, and subcellular localization. Low-energy irradiation produced substantially greater near-field dose enhancement than MeV-scale irradiation, and nuclear placement yielded the largest whole-cell-averaged DEF values within the idealized 50 nm nanoparticle cell model. In the single-particle radiochemical analysis, ultrasmall HfO_2 nanoparticles exhibited higher mass-normalized and surface-area-normalized radiochemical metrics than larger particles, suggesting that their radiochemical advantage cannot be explained solely by increased surface area. In a whole-cell model containing 1,000 HfO_2 nanoparticles of 5 nm radius (10 nm diameter), the hydroxyl-radical G-ratio reached approximately 1.6 at 100 keV. Based on these simulation trends, ultrasmall HfO_2 nanoparticles were synthesized and characterized, and simplified in vitro experiments in 4T1 cells under 160 kVp X-ray irradiation showed enhanced ·OH-related fluorescence and a concentration-dependent reduction in cell viability. Overall, this study provides a comparative Monte Carlo framework linking HfO_2 nanoparticle size, radiation energy, subcellular distribution,

dose deposition, and radiochemical response. The findings support the potential relevance of ultrasmall HfO_2 nanoparticles for localized low-energy irradiation settings, while also indicating the need for further experimentally constrained modeling and organelle-specific validation.

Full Text

Preamble

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Carlo Study

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Abstract

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dose enhancement than MeV-scale irradiation, and nuclear placement yielded the largest whole-cell-averaged DEF

values within the idealized 50 nm nanoparticle cell model. In the single-particle radiochemical analysis, ultrasmall

HfO_2 nanoparticles exhibited higher mass-normalized and surface-area-normalized radiochemical metrics than

larger particles, suggesting that their radiochemical advantage cannot be explained solely by increased surface area.

In a whole-cell model containing 1,000 HfO_2 nanoparticles of 5 nm radius (10 nm diameter), the hydroxyl-radical

G-ratio reached approximately 1.6 at 100 keV. Based on these simulation trends, ultrasmall HfO_2 nanoparticles

were synthesized and characterized, and simplified in vitro experiments in 4T1 cells under 160 kVp X-ray

irradiation showed enhanced $\cdot$OH-related fluorescence and a concentration-dependent reduction in cell viability.

Overall, this study provides a comparative Monte Carlo framework linking HfO_2 nanoparticle size, radiation energy,

subcellular distribution, dose deposition, and radiochemical response. The findings support the potential relevance

of ultrasmall HfO_2 nanoparticles for localized low-energy irradiation settings, while also indicating the need for

further experimentally constrained modeling and organelle-specific validation.

Keywords

HfO_2 nanoparticles; Monte Carlo simulation; TOPAS-nBio; dose enhancement factor; water radiolysis;

radiosensitization

Introduction:

Radiotherapy is a cornerstone in the management of malignant tumors and remains one of the primary

treatment modalities in clinical oncology. Despite substantial technological advances, its therapeutic performance

remains constrained by several factors. Conventional radiotherapy uses high-energy X-rays or proton beams to

induce DNA damage together with broader membrane, mitochondrial, and other stress responses in tumor cells,

thereby suppressing tumor proliferation[1]. However, this strategy also injures surrounding normal tissues, leading

to adverse effects that limit further dose escalation[2]. In addition, many solid tumors, particularly those with

hypoxic microenvironments, show reduced oxygen availability and increased radioresistance, which further

compromises clinical outcomes[3, 4]. This effect is commonly interpreted in the context of the oxygen-fixation

hypothesis, whereby oxygen helps convert radiation-induced damage into less readily repairable lesions.

Consequently, improving tumor radiosensitivity while preserving healthy tissues remains a central goal in precision

radiotherapy. In recent years, nano-radiosensitizers have emerged as promising candidates for this purpose[2, 5].

Their rationale is to strengthen radiation-tumor interactions, increase local energy deposition, and modulate

radiation-induced biochemical processes. High-atomic-number (high-Z) nanoparticles, for example, can enhance

local dose deposition through stronger X-ray absorption, whereas catalytic nanomaterials may alter reactive oxygen

species (ROS)-related chemistry[6]. Together, these effects motivate a combined physical and radiochemical view

of nanoparticle-mediated radiosensitization. Among these agents, HfO2 nanoparticles have attracted substantial interest, exemplified by the approximately

50 nm formulation NBTXR3[7]. Their appeal stems from strong X-ray absorption, chemical stability, and favorable

biocompatibility. Previous studies have shown that HfO2 nanoparticles can increase the dose enhancement factor

(DEF) and alter the yield of low-energy secondary electrons under irradiation[7, 8], thereby intensifying local

physical damage. Recent work has also incorporated HfO2 into multifunctional systems, such as Hf-chelating gold

nanosensitizers or hafnium-based nanoscale metal-organic frameworks (Hf-nMOFs)[9, 10], to improve therapeutic

performance. In addition, HfO2 has been associated with increased ROS-related effects during irradiation[11], and

bio-carriers such as engineered bacteria have been explored to improve delivery and alleviate tumor hypoxia[12].

Despite this progress, several issues remain insufficiently resolved:

1. Quantitative integration of physical and chemical enhancement mechanisms: Most studies evaluate physical

dose enhancement and radiochemical effects separately, and the quantitative relationship between these readouts

remains incompletely defined. Recent work has explored multimodal radiosensitization strategies, for example

through chromatin modulation or additional catalytic mechanisms[13, 14], but the full radiosensitization profile of

HfO2 remains insufficiently characterized.

2. Quantitative evaluation of subcellular targeting strategies:

The radiosensitization performance of nanoparticles is strongly influenced by their intracellular fate, particularly

their accumulation near radiosensitive organelles such as the nucleus or mitochondria. Emerging evidence suggests

that organelle-specific localization can substantially amplify radiation-induced DNA damage and oxidative

stress[2]. However, it remains unclear which targeting strategy yields the greatest enhancement and how subcellular

localization parameters should be optimized for radiosensitization.

3. Energy dependence of radiosensitization mechanisms:

Limited research has examined how HfO2-mediated radiosensitization varies across radiation energy levels, from

low-energy X-rays to medium- and high-energy beams, at both the dose-deposition and radiochemical levels.

Recent studies suggest that nanoparticle catalytic radiosensitization depends on synthesis-dependent surface and

lattice properties[11, 15]. For localized low-energy modalities, such as electronic brachytherapy, orthovoltage

irradiation, or IORT, clarifying energy-dependent trends in dose deposition and ROS chemistry is important for the

rational design of next-generation radiosensitizers.

To address these knowledge gaps, this study integrates TOPAS-based Monte Carlo simulations with experimental

validation to delineate the physicochemical landscape of HfO2 nano-radiosensitization (Figure 1 [Figure 1: see original paper]). Specifically, the

manuscript is organized in two complementary parts. The first part compares physical dose-related metrics under

different photon energies and theoretical subcellular localization scenarios, with the main DEF figures primarily

reflecting the 50 nm particle analysis. The second part extends the radiochemical analysis into the ultrasmall

regime and then relates those radiochemical trends to experimental observations obtained with ultrasmall

synthesized particles. Collectively, these analyses provide a comparative framework for the rational design and

evaluation of HfO2-based radiosensitizers.

dose-related component, the radiochemical component, and the comparison of subcellular localization strategies

under low-energy irradiation.

Materials and Methods

Simulation Framework and Physics Models

Monte Carlo simulations were performed using the TOPAS and TOPAS-nBio toolkits (version 4.0, based on

Geant4 11.1.3). The G4EmDNAPhysics_option4 constructor was used to model low-energy photon interactions

and electron transport in water. This setting allows electron tracking to very low energies (approximately 0.025 eV)

and was used here to describe the water phase in the nanoscale simulations. Water radiolysis was simulated using

the G4EmDNAChemistry constructor. Simulation time steps were dynamically adjusted on the picosecond scale to

resolve the spatiotemporal evolution of key radiolytic species (e.g., $\cdot$OH, $e^{-}aq$, and H$\cdot$) from 10-12 to 10-6s. For each

configuration, 107-108 primary photon histories were simulated to reduce statistical noise; under these settings, the

relative statistical uncertainty of the reported DEF and radiochemical metrics remained below 1% for the scored

quantities.

To account for material heterogeneity, a hybrid physics strategy was used. Within HfO2 nanoparticles,

Livermore low-energy electromagnetic models were applied for photon interactions and electron transport because

Geant4-DNA does not provide cross sections for hafnium (Z = 72). In the surrounding aqueous medium,

Geant4-DNA was used to resolve electron tracks and chemical reactions in water with high spatial resolution[13,

14]. The chemical stage was simulated with the Independent Reaction Times (IRT) method provided by

TOPAS-nBio. Electron thermalization and solvation followed Ritchie (1994)[15], and diffusion coefficients and

reaction-rate constants for the primary radiolytic species were taken from the standard Geant4-DNA chemistry set.

Realistic Cell Model and Nanoparticle Geometry To move beyond a homogeneous water phantom, we constructed an idealized spherical cell model for

comparative simulations. The model consisted of a 4 μm-radius cell containing a concentric 2 μm-radius nucleus

and distributed mitochondria. Distinct elemental compositions and densities were assigned to the cytoplasm,

nucleus, and mitochondria according to ICRU/ICRP reference values, providing a simplified heterogeneous

geometry for comparing different targeting scenarios. This geometry should be interpreted as an idealized

comparative model rather than as a morphologically exact representation of a specific 4T1 cell.

HfO2 nanoparticles were modeled as solid spheres with a density of 9.68 g/cm^3. Particle diameters of 2.5, 5.0,

30, 40, 50, and 500 nm were investigated across the size-related simulations. The single-particle radiochemical

comparison shown in Figure 6 [Figure 6: see original paper] focuses on 2.5, 5, 50, and 500 nm particles, whereas the subsequent

energy-dependence and cell-level radiochemical analyses focus on HfO2 nanoparticles of 5 nm radius (10 nm

diameter). Nanoparticles were placed by a Monte Carlo algorithm within specified subcellular regions, and overlap

with organelle boundaries was prevented geometrically. Three localization scenarios were considered: cytoplasmic,

nuclear,

concentration-related trends in the scored DEF values. In the main DEF analysis shown in Figure 4 [Figure 4: see original paper], the reported

values correspond to the 50 nm particle case.

Quantities of Interest

mitochondrial

placement.

addition,

nanoparticle

loading

varied

examine

The DEF is defined as the ratio of the absorbed dose scored in the presence of nanoparticles (D_{enh}) to the absorbed dose scored in the corresponding control simulation without nanoparticles (D_{control}).

DEF = D_{enh} / D_{control}

where:

D_{enh}: absorbed dose within the target region in the presence of nanoparticles.

D_{control}: absorbed dose within the target region in the corresponding control simulation without

nanoparticles.

The radiochemical G value quantifies the number of molecules of a given species formed or consumed per

100 eV of absorbed energy. In addition to the standard G value, we report two derived comparison metrics for the

single-particle size-comparison analysis: a mass-normalized metric, G(X)/m_{NP}, and a surface-area-normalized

metric, G(X)/S_{NP}. The mass-normalized metric evaluates the radiochemical output per unit HfO2 mass, whereas

the surface-area-normalized metric evaluates the radiochemical output per unit nanoparticle surface area. These

quantities are used here as descriptive normalization metrics for within-study comparison and should not be

interpreted as conventional radiochemical G values, size-independent intrinsic material constants, or direct

predictors of cellular response. G(Product X) = N(Product X) / Eabs × 100 (molecules per 100 eV)

Mass-normalized comparison metric (X) = G(X) / m_{NP}

Surface-area-normalized comparison metric (X) = G(X) / S_{NP}

Where:

G(Product X): radiochemical G value of species X.

N(Product X): number of molecules of species X generated.

Eabs: absorbed energy in the medium.

m_{NP}: mass of the nanoparticle used for the single-particle size-comparison analysis, or total nanoparticle

mass when multiple particles are simulated (g).

S_{NP}: surface area of the nanoparticle used for the single-particle size-comparison analysis, calculated as S_{NP} =

$4\pi r^2$ for a spherical particle (nm^2).

For a spherical HfO2 nanoparticle, m_{NP} = $\rho(4/3)\pi r^3$ and S_{NP} = $4\pi r^2$, where r is the particle radius and ρ is the

HfO2 density. The surface-area-normalized metric was introduced as an auxiliary descriptor to examine whether the

size-dependent radiochemical trend could be explained solely by differences in available nanoparticle surface area.

Scoring Geometries and Reported DEF Metrics

Two DEF-reporting configurations were used in this study.For the radial DEF analysis shown in Figure 2c [Figure 2: see original paper]-d, a

single nanoparticle was placed in water and dose was scored in concentric spherical shells surrounding the particle.

Radial DEF was defined as the ratio of the shell-averaged absorbed dose obtained with and without the

nanoparticle under otherwise identical irradiation conditions. This configuration was used to characterize the spatial

distribution of deposited dose as a function of distance from the nanoparticle center. For the subcellular-localization

analysis shown in Figure 4, DEF was defined on a whole-cell basis, namely as the ratio of the absorbed dose

averaged over the entire cell volume in the nanoparticle-containing simulation to that in the corresponding

nanoparticle-free control simulation. Accordingly, Figure 4 reports whole-cell averaged DEF values. Within the cell

model, the cytoplasm, mitochondria, and nucleus were assigned reference material definitions with distinct

compositions and densities. Under this modeling framework, the localization-dependent differences in Figure 4

represent the combined effects of nanoparticle spatial placement, heterogeneous material assignment, and

whole-cell dose averaging. Figure 4a-c correspond to cytoplasmic (upper left), mitochondrial (upper right), and

nuclear (lower left) localization, respectively, and show the concentration-dependent whole-cell DEF trends for

these three localization scenarios. Figure 4d (lower right) compares the whole-cell DEF values of the three

localization scenarios at 100 keV under a matched nanoparticle concentration.

Synthesis and Characterization of HfO2 Nanomaterials

(1) Preparation of HfO2: Hafnium tetrachloride was dissolved in anhydrous ethanol, followed by the addition of

trifluoroacetic acid. The mixture was stirred at 50 °C for 5 h and then vacuum-dried to obtain hafnium

trifluoroacetate powder. Subsequently, hafnium trifluoroacetate and oleylamine were introduced into a

round-bottom flask, heated to 110 °C under vacuum for 30 min, and then slowly heated to 330 °C under argon,

where the reaction was maintained for 1 h. After cooling to room temperature, excess ethanol was added to

precipitate the product, and the precipitate was washed three times with cyclohexane and ethanol to obtain hafnium

dioxide nanoparticles. (2) Characterization: The synthesized nanoparticles were characterized by transmission

electron microscopy (TEM; JEM2100Plus), and particle diameters were quantified from TEM images using Nano

Measure software. X-ray diffraction (XRD) patterns were recorded on a Bruker D8 Advance diffractometer using

Cu Kα radiation. (3) Detection of hydroxyl-radical generation under X-ray irradiation: Terephthalate (TA) was used

as a probe to detect hydroxyl radicals produced by HfO2 under X-ray irradiation. The final working concentrations

in the reaction system were 500 μmol/L for TA and 100 μg/mL for HfO2. (4) Cytotoxicity assay: 4T1 cells were

cultured at 37 °C in 5% CO2 using RPMI-1640 supplemented with 10% fetal bovine serum (FBS) and 1%

penicillin/streptomycin. Cells were seeded in 96-well plates (n = 8) at a density of 6,000-8,000 cells per well and

cultured for 24 h. The medium was then replaced with 100 μL of complete medium containing HfO2 at 0, 12.5, 25,

50, or 100 μg/mL. After incubation with HfO2 for the specified nanoparticle-incubation period, the medium was

replaced with fresh complete medium, and the cells were irradiated with X-rays (160 kVp, 6 Gy). After a further 24

h of culture, the medium was removed and replaced with 100 μL of fresh medium containing 10 μL of CCK-8

solution. After 1-2 h of incubation, absorbance at 450 nm was measured with a microplate reader.

Results and Discussion

simulations. (a) Dependence of DEF on nanoparticle volume fraction under different X-ray energies (6 MeV, 150

keV, and 100 keV). (b) Relationship between DEF and volume fraction, showing reduced incremental gains at

higher loadings. (c) Long-range (0-2500 nm) radial DEF scored in concentric water shells around a single

nanoparticle. (d) Short-range (0-120 nm) radial DEF scored in concentric water shells around a single nanoparticle,

highlighting near-field hotspots.

To quantify the spatial distribution of dose enhancement across different scales, radial DEF profiles were

computed around a centrally positioned isolated nanoparticle. The surrounding medium was partitioned into

concentric spherical shells, with the sampling resolution adjusted to resolve both the steep near-field gradients and

the longer-range deposition pattern. This single-particle configuration was used to minimize inter-particle

interference and to characterize radial energy deposition driven by nanoparticle-emitted secondary electrons in

water.

Before discussing size-dependent trends, it is useful to clarify the scope of the present hybrid simulations.

Following [16], discrepancies between condensed-history and track-structure models may become substantial at

nanometric scales. Here, Geant4-DNA track-structure physics was used in the aqueous near-field region, whereas

photon interactions inside HfO2 were handled with Livermore models because Geant4-DNA does not provide

hafnium cross sections. The present framework therefore provides a pragmatic hybrid description of dose

deposition and radiochemistry around high-Z nanoparticles, while interfacial charge-transfer and barrier effects

remain outside the model. We then examined how the reported DEF values changed with nanoparticle loading and

distance from the particle surface (Figure 2). Figure 2a shows that low-energy photons (100 and 150 keV) produced

much larger enhancement than 6 MeV photons, consistent with the stronger contribution of the photoelectric effect

in high-Z materials at lower photon energies[15]. Figure 2b-2d show that DEF depends strongly on both loading

and radial scoring distance. In the near field, especially within approximately 20 nm of the particle surface, the

local DEF can reach values on the order of 10^3 under low-energy irradiation. At larger distances, the enhancement

decays rapidly because most emitted low-energy secondary electrons have short ranges in water. Within the

simulated loading range, DEF increased with nanoparticle loading, although the incremental gain became smaller at

the highest loadings. Smaller particles also showed higher near-field DEF than larger particles under otherwise

matched low-energy conditions, consistent with stronger surface-dominated electron emission.

illustrating representative subcellular localization scenarios of HfO2 nanoparticles (yellow dots). (a) Nuclear

localization. (b) Cytoplasmic localization.

We performed subcellular-targeted DEF simulations to investigate how the reported whole-cell DEF varied

across organelle-specific localization scenarios. HfO2 nanoparticles were placed in the nuclear, mitochondrial, or

cytoplasmic region. To examine loading dependence, simulations were conducted at whole-cell concentrations of

100, 200, 300, 400, and 900 μM.

nm HfO2 nanoparticles. (a) Concentration-dependent whole-cell DEF profiles for cytoplasmic localization. (b)

Concentration-dependent whole-cell DEF profiles for mitochondrial localization. (c) Concentration-dependent

whole-cell DEF profiles for nuclear localization. (d) Comparison of whole-cell DEF values among mitochondrial,

nuclear, and cytoplasmic localization scenarios at 100 keV under a matched nanoparticle concentration.

The simulations show marked dependences on photon energy, subcellular localization, and nanoparticle loading.

Importantly, the DEF values reported in Figure 4 are whole-cell averaged quantities rather than nucleus-scored or

compartment-scored quantities. Under this definition, low-energy irradiation (approximately 100 keV) and nuclear

placement yielded the largest reported whole-cell DEF values among the tested localization scenarios. The

localization-dependent ordering should be interpreted as a model-dependent physical transport result arising from

the combination of nanoparticle source location, heterogeneous compartment materials, and the whole-cell scoring

definition, rather than as a direct biological ranking of organelle radiosensitivity. The loading dependence was

non-linear, with larger gains at low-to-intermediate loadings than at the highest tested values. Because Figure 4 was

generated primarily for 50 nm nanoparticles, these results should be interpreted as comparative physical-dose

trends for that particle size rather than as a complete size-dependence analysis spanning the ultrasmall regime.

distribution of secondary electron tracks generated by HfO2 nanoparticles, showing dense ionization events.

(Bottom) Corresponding spatial distribution of $\cdot$OH counts in the surrounding medium. The spatial overlap

illustrates the local coupling between secondary-electron transport and radical production in the water phase.

Radical enhancement. To compare radiochemical trends across particle sizes, we evaluated the standard G

values together with two derived normalization metrics under 100 keV irradiation: the mass-normalized metric

G(X)/m_{NP} and the surface-area-normalized metric G(X)/S_{NP}. Because the size-comparison simulations were

performed for isolated single nanoparticles, direct comparison of absolute G values may be influenced by the large

differences in particle mass and surface area among different diameters. Therefore, the left column of Figure 6

reports the radiochemical output per unit HfO2 mass, whereas the right column reports the output per unit

nanoparticle surface area. This paired normalization strategy was used to distinguish a mass-efficiency effect from

a purely surface-area-driven effect, an issue also highlighted in previous nanoparticle radiolysis and

ROS-efficiency studies[17, 18] As shown in Figure 6, ultrasmall particles, especially the 2.5 and 5 nm particles, produced markedly higher

mass-normalized radiochemical metrics than the 50 and 500 nm particles for all examined species, including $\cdot$OH,

e^{-}_{aq}, H$\cdot$, and H2O2. This result indicates that, per unit HfO2 mass, ultrasmall particles are more efficient in

generating radiolytic species. This trend is consistent with the higher surface-to-volume ratio of smaller

nanoparticles and with the reduced probability of secondary-electron self-absorption within the particle.

Importantly, the size-dependent advantage of ultrasmall particles persisted after surface-area normalization. The 2.5

and 5 nm particles still showed higher G(X)/S_{NP} values than the larger particles, suggesting that the enhanced

radiochemical efficiency is not fully accounted for by increased available surface area alone. Instead, additional

nanoscale effects may contribute, including shorter electron transport distances from the particle interior to the

water interface, more efficient escape of low-energy secondary electrons, and more effective interfacial energy

deposition into the surrounding aqueous medium.

Among the examined species, the $\cdot$OH results are particularly relevant because hydroxyl radicals are highly

reactive products of water radiolysis and are closely associated with radiation-induced biological damage. Similar

trends for $e^{-}aq$ and $H\cdot$ indicate that particle size affects not only oxidative products but also the broader

water-radiolysis reaction network. For H2O2, the observed trend should be interpreted as a net chemical outcome,

because H2O2 accumulation depends on both radical generation and subsequent recombination or scavenging

reactions. Overall, the combined mass- and surface-area-normalized analyses support a surface-dominated but not

purely surface-area-controlled mechanism for the enhanced radiochemical output of ultrasmall HfO2 nanoparticles.

100 keV irradiation. Time-dependent evolution of mass-normalized G(X)/m_{NP} and surface-area-normalized

G(X)/S_{NP} metrics for four representative radiolytic species: $\cdot OH$, $e^{-}aq$, $H\cdot$, and H2O2. Particle sizes indicate

nanoparticle diameters. The left column shows the radiochemical output per unit nanoparticle mass, whereas the

right column shows the radiochemical output per unit nanoparticle surface area. For the single-particle

size-comparison simulations, $m_{NP} = \rho(4/3)\pi r^3$ and $S_{NP} = 4\pi r^2$. Ultrasmall particles maintained higher

normalized radiochemical outputs than larger particles under both normalization schemes, suggesting that their

enhanced radiochemical efficiency is not fully accounted for by surface area alone.

The above results indicate a pronounced size dependence in the simulated radiochemical response. Within the

present single-particle simulation framework, the 5 nm particles provided substantially larger radical-related

metrics than the larger-particle cases under both mass-normalized and surface-area-normalized comparisons and

were therefore selected for the subsequent energy-dependence analysis. These normalized metrics should be

interpreted as comparative descriptors within the present model rather than as conventional G values or universal

radiosensitization metrics.

diameter). Time evolution of the absolute G values for (a) ·OH, (b) H2O2, (c) H·, and (d) e⁻aq under irradiation

with X-rays of distinct energies (50 keV, 100 keV, 150 keV, and 1 MeV).

(10 nm diameter) at 50 keV, 100 keV, 150 keV, and 1 MeV. The absolute yields vary with photon energy and with

species. To examine the net effect at the cellular level, we additionally simulated a cell model containing 1,000

HfO2 nanoparticles of 5 nm radius (10 nm diameter) and calculated G-ratios relative to the corresponding

no-nanoparticle control (Figure 8 [Figure 8: see original paper]). Under the present idealized whole-cell geometry (cell radius, 4 μm), this

corresponds to an approximate total nanoparticle volume fraction of 1.95 × 10-6, a total HfO2 mass of 5.07 × 10-15 g,

and an equivalent whole-cell HfO2 concentration of 89.8 μM. In this whole-cell analysis, the hydroxyl-radical

G-ratio reached approximately 1.6 at 100 keV, indicating the largest relative ·OH enhancement among the tested

energies. The enhanced ·OH ratio at 100 keV is consistent with strong photoelectric absorption by hafnium and efficient

emission of low-energy secondary electrons into the surrounding water. It should be noted, however, that the

photoelectric cross section affects the initial physical interaction stage, whereas the time evolution of the chemical

species also depends on subsequent diffusion and reaction kinetics. The e⁻aq G-ratio stabilized at approximately

1.15-1.20. By contrast, the H2O2 G-ratio remained below 1, indicating a lower net yield in the

nanoparticle-containing system. One plausible interpretation is that the locally elevated radical density shifts the

reaction balance toward competing scavenging and recombination pathways, thereby favoring short-lived radical

species over accumulation of molecular H2O2. The H· ratio remained close to 1.10 under 100 keV irradiation.

Overall, the cell-level results suggest that 100 keV produced the largest relative ·OH enhancement in the present

simulations, whereas absolute species yields and local physical DEF values should be interpreted separately.

HfO2 nanoparticles of 5 nm radius (10 nm diameter). Time evolution of the G-ratios (yield with nanoparticles

divided by yield without nanoparticles) for (a) ·OH, (b) H2O2, (c) e^{-}aq, and (d-f) H· under different energies. The

results show the largest relative ·OH enhancement in the present whole-cell simulations at 100 keV, while the H2O2

ratio remains below unity.

Transmission Electron Microscopy (TEM) image showing the uniform morphology and dispersity of the

synthesized HfO2 nanoparticles (~5 nm). (b) X-ray Diffraction (XRD) pattern confirming the high-purity

monoclinic phase structure (JCPDS No. 06-0318) (c) Fluorescence spectra of the TA probe detecting hydroxyl

radical generation, showing significantly enhanced intensity in the HfO2 + X-ray group compared to X-ray alone.

(d) Cytotoxicity assessment of 4T1 cells treated with varying concentrations of HfO2 under 160 kVp X-ray

irradiation, demonstrating a concentration-dependent therapeutic effect.

Based on the simulation results, we synthesized ultrasmall HfO2 nanoparticles and examined whether they could

enhance irradiation-associated effects in vitro. TEM indicated particles mainly in the 1-10 nm range, consistent

with an ultrasmall-particle preparation. XRD confirmed the monoclinic HfO2 phase. The TA assay showed higher

fluorescence in the HfO2 + X-ray group than in the X-ray-only group, consistent with increased ·OH-related signal.

In the 4T1 assay performed under 160 kVp irradiation, cell viability decreased with increasing HfO2 concentration.

Because a robust organelle-specific targeting platform was not established in the present experimental system, these

biological experiments were intended as simplified uptake-and-effect validation for ultrasmall particles rather than

as direct experimental validation of the theoretical localization scenarios in Figure 4. The experimental results

therefore qualitatively agree with the simulation-based expectation that ultrasmall HfO2 particles can enhance

radiation-associated physicochemical effects.

Conclusion

This study combines TOPAS-based Monte Carlo simulations with TOPAS-nBio radiochemical modeling to

examine how HfO2 nanoparticle size, photon energy, and subcellular placement influence dose-related and

radiochemical readouts. The simulations showed substantially larger low-energy enhancement than MeV-scale

irradiation, and the whole-cell ·OH G-ratio reached approximately 1.6 at 100 keV in the 1,000-particle cell model.

Within the present model, nuclear placement yielded the largest reported whole-cell DEF values.

Particle size also influenced the reported radiochemical metrics. Under both mass-normalized and

surface-area-normalized comparisons, the ultrasmall regime produced larger radical-related values than the

larger-particle cases in the single-particle simulations. The persistence of the size-dependent trend after surface-area

normalization suggests that the ultrasmall-particle advantage is not merely a consequence of increased surface area,

but may also reflect reduced secondary-electron self-absorption and more efficient interfacial energy transfer to the

surrounding water. These findings are consistent with the general view that nanoparticle radiosensitization is

governed by a combination of material mass, available surface/interface, electron transport, and subsequent

water-radiolysis chemistry.

While this study provides comparative insight into HfO2-mediated radiosensitization, several limitations

remain. The hybrid framework uses Geant4-DNA for water and Livermore models for HfO2, so interfacial charge

transfer and barrier effects are not explicitly modeled. The cell geometry is idealized, and the reported DEF values

depend on the chosen scoring volumes and particle-placement rules. In addition, the main DEF analysis shown in

provide a complete DEF-based comparison between the 50 nm benchmark and the ultrasmall regime. The mass-

and surface-area-normalized metrics in Figure 6 should be interpreted as comparative descriptors within the present

single-particle simulation framework rather than as conventional G values, intrinsic material constants, or direct

predictors of cellular response. The IRT radiochemistry model uses diffusion coefficients and reaction constants

derived largely from bulk water, whereas subcellular microenvironments may differ in viscosity, ionic strength, and

pH. Moreover, the experimental validation was performed under 160 kVp irradiation and was limited to simplified

uptake-and-effect experiments without direct organelle-specific targeting validation; therefore, it does not provide a

one-to-one validation of each simulated monoenergetic or localization condition. Future work integrating more

realistic cellular geometries, better defined scoring regions, experimentally constrained nanoparticle distributions,

and a more explicit ultrasmall-particle DEF analysis will help refine the link between nanoscale physics and

biological response. From a clinical-medical-physics perspective, the present results are best interpreted as

comparative trends that may inform future studies of localized low-energy modalities rather than as direct

treatment-planning parameters.

In the radiochemical simulations, the nanoparticle-containing system also showed a reduced H2O2 ratio

despite enhanced ·OH-related signals. This pattern is consistent with a shift in the local reaction network under

high radical density, although the precise balance between interfacial physics and bulk-water chemistry warrants

further investigation.

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AUTHOR CONTRIBUTIONS

Zhi-Bo Zhao: Conceptualization, Methodology, Software, Formal analysis, Investigation, Visualization,

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Funding acquisition, Project administration, Writing –review and editing. All authors read and approved the final

manuscript.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable

request. The simulation input files, processed datasets, and source data used to generate the figures will be made

publicly available in an appropriate repository before publication.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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Radiosensitization.

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Legend of Figures

dose-related component, the radiochemical component, and the comparison of subcellular localization strategies

under low-energy irradiation.

(a) Dependence of DEF on nanoparticle volume fraction under different X-ray energies (6 MeV, 150 keV, and 100

keV). (b) Relationship between DEF and volume fraction, showing reduced incremental gains at higher loadings. (c)

Long-range (0-2500 nm) radial DEF scored in concentric water shells around a single nanoparticle. (d) Short-range

(0-120 nm) radial DEF scored in concentric water shells around a single nanoparticle, highlighting near-field

hotspots.

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representative subcellular localization scenarios of HfO2 nanoparticles (yellow dots). (a) Nuclear localization. (b)

Cytoplasmic localization.

HfO2 nanoparticles. (a) Concentration-dependent whole-cell DEF profiles for cytoplasmic localization. (b)

Concentration-dependent whole-cell DEF profiles for mitochondrial localization. (c) Concentration-dependent

whole-cell DEF profiles for nuclear localization. (d) Comparison of whole-cell DEF values among mitochondrial,

nuclear, and cytoplasmic localization scenarios at 100 keV under a matched nanoparticle concentration.

distribution of secondary electron tracks generated by HfO2 nanoparticles, showing dense ionization events.

(Bottom) Corresponding spatial distribution of ·OH counts in the surrounding medium.

keV irradiation. Time-dependent evolution of mass-normalized G(X)/m_{NP} and surface-area-normalized

G(X)/S_{NP} metrics for four representative radiolytic species: ·OH, e^{-}aq, H·, and H2O2. Particle sizes indicate

nanoparticle diameters. The left column shows the radiochemical output per unit nanoparticle mass, whereas the

right column shows the radiochemical output per unit nanoparticle surface area. Ultrasmall particles maintained

higher normalized radiochemical outputs than larger particles under both normalization schemes.

Time evolution of the absolute G values for (a) ·OH, (b) H2O2, (c) H·, and (d) e^{-}aq under irradiation with X-rays

of distinct energies (50 keV, 100 keV, 150 keV, and 1 MeV).

HfO2 nanoparticles of 5 nm radius (10 nm diameter). Time evolution of the G-ratios for (a) ·OH, (b) H2O2, (c) e^{-}aq,

and (d-f) H· under different energies.

image showing the morphology and dispersity within the ultrasmall size regime. (b) XRD pattern confirming the

monoclinic phase. (c) Fluorescence spectra of the TA probe indicating stronger ·OH-related signal. (d) Cytotoxicity

assessment of 4T1 cells under 160 kVp X-ray irradiation.

DEF, dose enhancement factor; ROS, reactive oxygen species; ·OH, hydroxyl radical; e^{-} q, hydrated electron; TA,

terephthalate; TEM, transmission electron microscopy; XRD, X-ray diffraction.

Note: Figure translations are in progress. See original paper for figures.