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REVIEW

Current Perspectives on Radiosensitizers in Cancer Radiotherapy

Hanguang Ruan[1–3], Yang Li[4], Songlin Chen[5]

[1]Department of Radiation Oncology, Jiangxi Cancer Hospital & Institute, Nanchang City, Jiangxi Province, People's Republic of China; [2]Department of Radiation Oncology, Jiangxi Cancer Center, Nanchang City, Jiangxi Province, People's Republic of China; [3]Department of Radiation Oncology, The Second Affiliated Hospital of Nanchang Medical College, Nanchang City, Jiangxi Province, People's Republic of China; [4]Department of Radiation Oncology, Harbin Medical University Cancer Hospital, Harbin City, Heilongjiang Province, People's Republic of China; [5]Department of Radiation Oncology, Nanchang People's Hospital, Nanchang City, Jiangxi Province, People's Republic of China

Correspondence: Songlin Chen, Email chensonglin_88@163.com

Objective: This review analyzes the multifactorial mechanisms of tumor radioresistance and evaluates the current landscape of innovative strategies to overcome this limitation, thereby improving the efficacy of radiotherapy.

Methods: We evaluated the key molecular and cellular drivers contributing to radioresistance. A comprehensive evaluation of contemporary radiosensitization strategies was then undertaken, with particular focus on nanomaterials (the predominant class discussed) while also covering nanomaterials, natural bioactive compounds, targeted molecular inhibitors, immunomodulators, and nucleic acid therapies. Each class of agents was subjected to a critical analysis spanning from mechanistic insights and supportive preclinical data to progress in clinical translation. Findings from foundational in vitro research, in vivo models, and preliminary clinical studies were consolidated to form a cohesive perspective.

Results: Tumor radioresistance is mediated by dynamic interactions between intrinsic cellular properties and the tumor microenvironment. Recent strategies have demonstrated potential through physical dose enhancement, multi-target modulation, precise interference with DNA damage repair and cell-cycle regulation, and combinatorial immunoradiotherapy. These approaches collectively enable selective tumor radiosensitization while modulating key resistance pathways.

Conclusion: Despite considerable preclinical promise, clinical adoption faces challenges including biological heterogeneity, suboptimal agent delivery, normal tissue toxicity, and a lack of validated predictive biomarkers. Future advances will rely on the development of intelligent multifunctional platforms, biomarker-guided patient stratification, and rationally designed combination therapies to achieve durable therapeutic gains.

Keywords: radiotherapy, radioresistance, radiosensitivity, strategy, radiosensitizers

Introduction

Radiotherapy (RT) remains a cornerstone of modern oncology, utilized in over half of all cancer cases across curative, adjuvant, and palliative settings.[1] Its efficacy relies on ionizing radiation to induce lethal DNA damage, predominantly DNA double-strand breaks (DSBs), in tumor cells.[2] Despite technological advancements that have improved precision, the clinical success of RT is frequently compromised by the development of tumor radioresistance, leading to locoregional recurrence and poor outcomes in numerous solid malignancies. This resistance is not a singular defect but a dynamic, multifactorial phenotype arising from complex interactions between tumor cell–intrinsic adaptations and extrinsic influences from the tumor microenvironment (TME).[3] Key intrinsic mechanisms include enhanced DNA damage repair, activation of pro-survival signaling pathways, dysregulated cell-cycle checkpoints, and the properties of cancer stem cells.[4–6] Concurrently, the hypoxic, acidic, and immunosuppressive TME further attenuates radiation response.[7–9] Overcoming these barriers is therefore critical to improving the therapeutic ratio of RT. This has spurred the development of diverse radiosensitizers designed to exploit these biological vulnerabilities. Moving beyond conventional chemotherapy, contemporary strategies encompass nanomaterials, natural products, molecularly targeted inhibitors, immunomodulators, and nucleic acid–based therapies.[10,11] Different classes

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of radiosensitizers differ considerably in their routes of administration. Nanomaterial-based agents, such as gold nanoparticles, AGuIX, and NBTXR3, are typically delivered via intravenous or intratumoral injection. Notably, NBTXR3 is administered intratumorally to circumvent the poor biodistribution associated with intravenous delivery. Natural products, including curcumin and resveratrol, can be administered orally; however, their low bioavailability often necessitates intravenous or intraperitoneal administration in preclinical studies. DNA damage repair inhibitors are primarily given orally, whereas immune checkpoint inhibitors and growth factor inhibitors are usually infused intravenously. Nucleic acid therapeutics face substantial delivery challenges and predominantly rely on nanocarriers for intravenous or local administration. Although intravenous injection remains the most common systemic route, its efficiency in delivering radiosensitizers to the tumor microenvironment is exceedingly low. It has been well documented that over 80–90% of intravenously administered nanoparticles are sequestered by the reticuloendothelial system in the liver and spleen. As a result, the fraction that reaches the tumor microenvironment is typically less than 10%, and in many cases may fall below 1–5%. Even when tumor accumulation occurs via the enhanced permeability and retention effect, the agents are largely confined to perivascular regions at the tumor periphery, with poor penetration into hypoxic cores. Furthermore, the enhanced permeability and retention effect is highly variable across patients, tumor types, and even within the same tumor over time, rendering the delivered dose unpredictable on an individual basis. This low delivery efficiency not only compromises therapeutic efficacy but also heightens the risk of radiation-induced injury to normal tissues due to off-target accumulation in healthy organs. These issues represent major barriers to the clinical translation of radiosensitizers. Accordingly, optimizing administration routes and improving tumor-targeted delivery efficiency are urgent priorities in the development of next-generation radiosensitizers.

This review aims to summarize the current understanding of the molecular foundations of radioresistance and provide a comprehensive evaluation of these emerging radiosensitization strategies, discussing their mechanisms, preclinical evidence, translational progress, and future directions for clinical implementation.

The Mechanisms of Tumor Radioresistance

RT is a central component of cancer treatment by delivering ionizing radiation (IR), including X-rays, γ-rays, protons, and carbon ions.[12] Despite continuous technological advances, such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic body radiotherapy (SBRT), which have substantially improved dose conformity and normal-tissue sparing, treatment resistance remains a major obstacle to durable local control.[13,14] Radioresistance continues to contribute to locoregional recurrence and poor outcomes in multiple solid malignancies, including glioblastoma (GBM), pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), and head and neck squamous cell carcinoma (HNSCC), and so on.

Radioresistance represents a dynamic and multifactorial process resulting from the interplay between tumor cell–intrinsic mechanisms and the TME.[15–17] At the cellular level, intrinsic resistance is driven by several well-characterized pathways. Enhanced DNA damage response (DDR) enables tumor cells to efficiently repair IR-induced DSBs through upregulation of non-homologous end joining (NHEJ) and homologous recombination (HR), mediated by key regulators such as DNA-dependent protein kinase catalytic subunit (DNA-PKcs), ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3-related (ATR), and poly (ADP-ribose) polymerase (PARP). In parallel, activation of pro-survival signaling pathways, including epidermal growth factor receptor (EGFR) and downstream PI3K/AKT/mTOR and NF-κB cascades, promotes proliferation, suppresses apoptosis, and facilitates post-irradiation recovery.[18–22] Cell-cycle checkpoint dysregulation further permits cell cycle progression despite unresolved DNA damage. In contrast, cancer stem cells (CSCs) exhibit intrinsic radioresistance through quiescence, enhanced DNA repair capacity, and robust detoxification mechanisms.[23–25] Additionally, augmented antioxidant defenses, particularly elevated intracellular glutathione (GSH) levels, limit radiation-induced cytotoxicity by scavenging reactive oxygen species (ROS).[26–28]

The TME largely governs extrinsic determinants of radioresistance. Tumor hypoxia, arising from aberrant vascular architecture, reduces oxygen availability, thereby diminishing the oxygen fixation effect essential for maximal radiation-induced DNA damage.[21,29,30] Hypoxia-induced stabilization of hypoxia-inducible factor-1α (HIF-1α) further promotes angiogenesis, metabolic adaptation, and tumor invasiveness.[7,8,31,32] Acidic extracellular pH and elevated interstitial fluid pressure impede drug delivery and compromise therapeutic penetration, while simultaneously fostering an immunosuppressive microenvironment. Moreover, the accumulation of immunosuppressive cell populations, including regulatory

T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), attenuates antitumor immune responses that could otherwise synergize with RT-induced immunogenic cell death.[33–35]

Radiosensitizers are developed to exploit these biological vulnerabilities and improve the therapeutic ratio of RT. An ideal radiosensitizer should demonstrate preferential tumor selectivity, potent enhancement of radiation response at clinically achievable doses, compatibility with standard fractionation schedules, and an acceptable toxicity profile. While conventional chemoradiosensitizers such as cisplatin and 5-fluorouracil have demonstrated clinical benefit, their lack of specificity often limits therapeutic gain.[36–39] Recent advances in molecular targeting, immunomodulation, and nanotechnology have expanded the landscape of radiosensitizers, offering new opportunities for precision radiotherapy.[40]

Nanomaterial-Based Radiosensitizers

Physical and Chemical Mechanisms of Nanoradiosensitization

The interaction between high-atomic-number (high-Z) nanoparticles (NPs) and IR results in multiple mechanisms that enhance local radiation effects.[41,42] Figure 1 shows the details of the relationship between nanomaterial-mediated radiosensitization and irradiation. Related to multiple mechanisms, one is the Physical dose enhancement. High-Z elements such as gold (Au, Z = 79), hafnium (Hf, Z = 72), gadolinium (Gd, Z = 64), and bismuth (Bi, Z = 83) exhibit a substantially higher probability of interacting with kilovoltage X-rays through the photoelectric effect compared with soft tissues, which are primarily composed of low-Z elements (H, C, N, and O). These interactions generate secondary photoelectrons and Auger electrons with very short path lengths (nanometer to micrometer range), leading to highly localized energy deposition and clustered DNA damage in the immediate vicinity of the nanoparticles.[43,44] Monte Carlo simulations have played a critical role in quantifying the resulting dose enhancement factor (DEF) and elucidating its dependence on particle composition, size, and radiation energy.[45]

The second one is catalytic generation of ROS (nanozyme activity). Beyond physical interactions, many nanomaterials exhibit intrinsic or surface-engineered enzyme-mimicking properties. For example, MnO_2, CeO_2, and certain metal sulfides can function as catalase mimics, decomposing hydrogen peroxide (H_2O_2) into molecular oxygen to alleviate hypoxia, or as peroxidase mimics that catalyze Fenton or Fenton-like reactions, involving Fe or Cu ions, generating highly cytotoxic

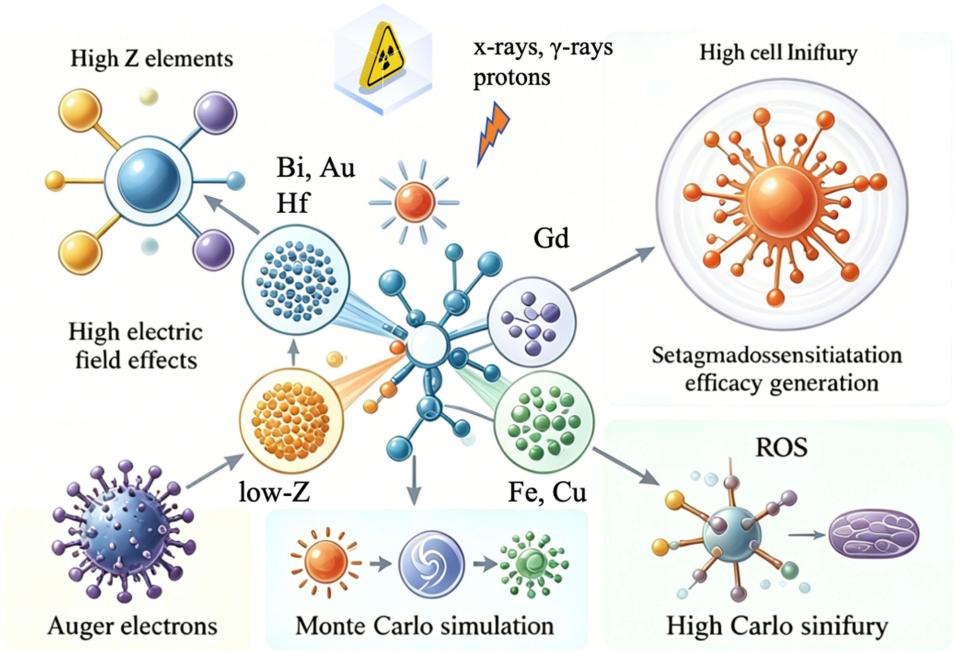

Figure 1 The Relationship Between Nanomaterial-Mediated Radiosensitization And Irradiation.
Abbreviations: GSH, Glutathione; ROS, Reactive Oxygen Species.

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hydroxyl radicals (•OH).[46,47] This chemically mediated radiosensitization directly amplifies the indirect effects of radiation and is particularly relevant in hypoxic or redox-adapted tumors.

The last is the TME modulation. Nanoparticles can also be rationally designed to disrupt protective features of the TME.[48] Representative strategies include depleting overexpressed glutathione (GSH) to impair redox homeostasis and in situ oxygen generation or release to reverse tumor hypoxia and restore radiation sensitivity.[49–51]

A comprehensive overview of representative nanomaterial-based radiosensitizers is presented in Table 1, detailing their diverse mechanisms and translational progress. These materials, including gold, gadolinium, hafnium oxide, and metal-organic frameworks, primarily function by physical dose enhancement through their high atomic numbers, which increase radiation absorption. Additional mechanisms include secondary electron emission, amplification of ROS, and disruption of cellular repair processes, such as homologous recombination. The table illustrates a clear translational pathway, with several agents advancing from preclinical studies to clinical trials. Notably, hafnium oxide nanoparticles (NBTXR3) have achieved EMA approval for soft tissue sarcoma, marking a significant milestone in nanomaterial-driven radiation oncology. These innovations are being evaluated across various tumor models, including breast cancer, glioblastoma, and head and neck squamous cell carcinoma, underscoring their broad potential in enhancing radiotherapy efficacy.

Gold Nanoparticles: Prototype and Evolution

Gold nanoparticles (AuNPs) remain the most extensively investigated nanoradiosensitizers owing to their favorable biocompatibility, ease of surface functionalization, and strong photoelectric absorption.

Parameters Influencing Radiosensitization

Radiosensitizing efficacy depends on multiple physicochemical and treatment-related parameters, including particle size (often optimal in the 10–50 nm range for cellular uptake and retention), morphology (with nanorods and nanostars sometimes outperforming spherical particles), surface charge and coating (eg., polyethylene glycol for prolonged circulation), nanoparticle concentration, and radiation energy[52,53.] Notably, dose enhancement is more pronounced at kilovoltage energies than at megavoltage energies, reflecting the Z^3 dependence of the photoelectric effect. Morozov et al demonstrated size- and dose-rate–dependent radiosensitization of DNA, reporting a sensitizer enhancement ratio (SER) of 2.74 for 26-nm AuNPs at 200 kVp.[54]

Table 1 Representative Nanomaterial-Based Radiosensitizers: Mechanisms and Translational Status

Nanomaterial Class	Representative Examples	Primary Radiosensitization Mechanisms	Tumor Models/ Indications	Translational Status
Gold nanoparticles (AuNPs)	PEG-AuNPs, AS1411-AuNPs (NCT00356980) (NCT01679470)	Physical dose enhancement (photoelectric effect); secondary electron emission; ROS amplification	Breast cancer, GBM, NSCLC	Preclinical
Gadolinium-based NPs	AGuIX (NCT04881032) (NCT04789486)	Physical dose enhancement; impaired homologous recombination; ferroptosis induction	Brain metastases, HNSCC	Phase I/II clinical trials
Hafnium oxide NPs	NBTXR3 (Hensify) (NCT02379845) (NCT04862455) (NCT01433068)	Physical dose enhancement via high-Z interaction	Soft tissue sarcoma; HNSCC	EMA-approved (STS); ongoing trials
Metal–organic frameworks (MOFs)	Hf-BDC, UiO MnS (NCT03444714) (NCT05838729)	Combined physical enhancement; metabolic inhibition; hypoxia modulation; ROS generation	Pancreatic cancer, HNSCC	Phase I/II clinical trials
Silver nanoparticles	Thymoquinone-AgNPs	ROS overproduction; mitochondrial dysfunction	Breast cancer	Preclinical
Iron oxide nanoparticles	Fe_3O_4CuS-PEG	Fenton chemistry; nitric oxide generation; magnetic targeting	Colorectal cancer	Preclinical
Bismuth-based NPs	BiNPs, Bi_2S_3	Strong photoelectric absorption; ROS generation	Brachytherapy-relevant tumors	Preclinical

Abbreviations: GBM, Glioblastoma; NSCLC, Non-Small Cell Lung Cancer; ROS, Reactive Oxygen Species.

Functionalization and Active Targeting

To overcome the variability of the enhanced permeability and retention (EPR) effect in human tumors, active targeting strategies have been developed. Conjugation of AuNPs with the nucleolin-targeting aptamer AS1411 significantly increased cellular uptake and radiosensitization in breast cancer models.[55] Similar approaches using RGD peptides targeting αvβ3 integrin or folic acid targeting the folate receptor have also shown promising preclinical results.[56]

Combination Modalities

AuNPs are well-suited for multimodal therapy. Their strong absorption of near-infrared light enables photothermal therapy, which can act as a radiosensitizer by improving tumor perfusion and oxygenation and by inhibiting DNA repair pathways.[57,58] Sears et al demonstrated selective cytotoxicity in triple-negative breast cancer using triangular silver nanoparticles for combined photothermal therapy and radiosensitization, underscoring the potential of metallic nanostructures in combination strategies.[59]

Gadolinium- and Hafnium-Based Nanoplatforms

AGuIX Nanoparticles

AGuIX nanoparticles are sub-5-nm polysiloxane-based gadolinium chelates and are among the few nanoradiosensitizers to have advanced into clinical trials. These particles demonstrate efficient tumor accumulation, rapid renal clearance, and radiosensitization through multiple mechanisms. Preclinical studies indicate that AGuIX nanoparticles induce autophagy, impair homologous recombination repair, and promote ferroptosis by inhibiting the NRF2–GPX4 axis.[60] Simonet et al reported their efficacy in overcoming radioresistance in head and neck squamous cell carcinoma models.[61]

Hafnium-Based Nanomaterials

A Phase 2–3 trial assessed the safety and efficacy of radiotherapy-activated hafnium oxide (HfO2) nanoparticles, known as NBTXR3, compared with radiotherapy alone when used as a preoperative treatment for patients with locally advanced soft-tissue sarcoma. A total of 176 patients were analysed for the primary endpoint in the intention-to-treat full analysis set (87 in the NBTXR3 group and 89 in the radiotherapy alone group). The results showed that a pathological complete response was noted in 14 (16%) of 87 patients in the NBTXR3 group and seven (8%) of 89 in the radiotherapy alone group (p = 0. 044). Serious adverse events were observed in 35 (39%) of 89 patients in the NBTXR3 group and 27 (30%) of 90 patients in the radiotherapy alone group.[62] It has received European approval for intratumoral administration in locally advanced soft tissue sarcoma, primarily exploiting physical dose enhancement. Beyond simple oxide particles, hafnium-based metal–organic frameworks (nMOFs) are emerging as versatile platforms for radiosensitization. Fu et al developed Hf-nMOFs loaded with the glycolysis inhibitor 3-bromopyruvate, achieving simultaneous enhancement of dose deposition and interference with metabolism-dependent DNA repair.[63] Huang et al reported a UiO MnS core–shell nanostructure capable of TME-responsive hydrogen sulfide generation, relieving hypoxia and promoting ROS production to enhance immunogenic radiotherapy.[47]

Other Promising Nanomaterials

Silver nanoparticles, iron oxide nanoparticles, bismuth-based nanomaterials, and multi-component heterostructures have also demonstrated radiosensitizing potential through diverse mechanisms, including mitochondrial dysfunction, Fenton chemistry, and synergistic photothermal effects.[64–67] While these platforms offer compelling preclinical efficacy, their clinical translation requires careful evaluation of long-term toxicity, biodistribution, and normal tissue effects.

Natural Products as Radiosensitizers

It is the non-nanoparticle radiosensitizers targeting specific radioresistance pathways in cancer that are detailed in Table 2. Unlike nanomaterials, these agents—including natural products, DDR inhibitors, cell-cycle regulators, and immunomodulators—act on biological mechanisms such as NF-κB signaling, PARP-mediated repair, and immune checkpoint pathways. While several, like PARP inhibitor olaparib and immune checkpoint blocker durvalumab, have

Table 2 Non-Nanoparticle Radiosensitizers Targeting Radioresistance Pathways

Radiosensitizer Class	Key Targets/Pathways	Representative Agents	Cancer Types Studied	Clinical Considerations
Natural products[68]	NF-κB, STAT3, HIF-1α, ROS balance	Curcumin, resveratrol, melatonin	Cervical, lung, breast	Favorable toxicity (low toxicity, oral administration and well tolerated); limited bioavailability
DDR inhibitors[69,70]	PARP, ATM, ATR, DNA-PKcs	Olaparib, VE-822, NU7441	BRCA-mutant tumors, HNSCC	Normal tissue toxicity; scheduling critical
Cell-cycle regulators[71,72]	CDK4/6, Wee1, CHK1/2	Palbociclib, adavosertib	Breast, lung cancers	p53 status influences efficacy
Growth factor inhibitors[73–75]	EGFR, PI3K/AKT/mTOR	Cetuximab, afatinib	HNSCC, NSCLC	Risk of enhanced radiation toxicity
Metabolic modulators[76]	Mitochondrial metabolism, glycolysis	CPI-613, GLUT1 inhibitors	Pancreatic cancer	Metabolic side effects
Immunomodulators[77]	PD-1/PD-L1, CTLA-4, STING	Durvalumab, pembrolizumab	NSCLC, melanoma	Timing and fractionation dependent
Nucleic acid therapeutics[78]	EGFR, Ku80, lncRNAs	siRNA, ASOs	GBM, lung cancer	Delivery remains key challenge

Abbreviations: DDR, DNA Damage Response; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; STAT3, Signal Transducer and Activator of Transcription 3; HIF-1α, Hypoxia-Inducible Factor 1-alpha; ROS, Reactive Oxygen Species; PARP, Poly(ADP-ribose) Polymerase; ATM, Ataxia Telangiectasia Mutated; ATR, Ataxia Telangiectasia and Rad3-related; DNA-PKcs, DNA-Dependent Protein Kinase Catalytic Subunit; CDK4/6, Cyclin-Dependent Kinase 4 and 6; CHK1/2, Checkpoint Kinase 1 and 2; PD-1/PD-L1, Programmed Cell Death Protein 1/Programmed Death-Ligand 1; CTLA-4, Cytotoxic T-Lymphocyte-Associated Protein 4; STING, Stimulator of Interferon Genes; GLUT1, Glucose Transporter 1; GI, Gastrointestinal; HNSCC, Head and Neck Squamous Cell Carcinoma; NSCLC, Non-Small Cell Lung Cancer; GBM, Glioblastoma.

entered clinical use, their translation is accompanied by significant considerations. Challenges include normal tissue toxicity, limited bioavailability (eg., with curcumin), and the critical importance of treatment scheduling and patient selection (eg., p53 status for cell-cycle drugs). The table also notes ongoing hurdles in delivering nucleic acid therapeutics, such as siRNA, effectively to tumors. These pathway-targeted agents represent a precision medicine approach to radiosensitization, aiming to overcome biological resistance while navigating complex clinical trade-offs between efficacy and safety.

Natural compounds derived from plants, fungi, and marine organisms represent a rich source of bioactive molecules with radiosensitizing potential. Their pleiotropic mechanisms, relatively favorable toxicity profiles, and historical use in oncology support continued investigation. However, it is important to explicitly state that for the vast majority of natural products discussed below, the evidence remains confined to in vitro or preclinical animal studies. Only a very limited number, such as curcumin, have been evaluated in small-scale clinical trials, and none have yet reached regulatory approval as radiosensitizers. The following descriptions of mechanistic and efficacy data should be interpreted with this evidence level in mind.

Polyphenols and Flavonoids

Those radiosensitizers amplify radiation-induced oxidative stress by generating a massive burst of ROS, overwhelming the cancer cell's limited antioxidant defenses. This leads to sustained endoplasmic reticulum (ER) stress and mitochondrial membrane depolarization, triggering the intrinsic apoptotic pathway via caspase-9 and caspase-3. Additionally, they inhibit survival signaling pathways like NF-κB, PI3K/Akt, and STAT3, which normally help cells resist radiation-induced death.[79] One randomized controlled trial in cervical cancer demonstrated that curcumin supplementation during RT significantly enhanced survivin suppression, correlating with improved treatment response.[80] Nevertheless, this single trial does not provide conclusive evidence for clinical adoption; larger, multi-center studies are required to confirm efficacy and establish optimal dosing regimens. Resveratrol, quercetin, and genistein have similarly been shown to impair DNA repair and promote cell-cycle arrest or senescence, thereby enhancing radiosensitivity across multiple tumor models.[81,82] It should be noted that for these latter compounds, all available data derive from in vitro or in vivo animal models, and no clinical trial data on their radiosensitizing effects are currently available.

Terpenoids and Saponins

This large class of compounds, including paclitaxel and ginsenosides, primarily sensitizes cells by disrupting the cell cycle and inhibiting DNA repair. They cause G2/M cell cycle arrest, forcing more cells into the most radiosensitive phase of the cycle. They also inhibit HR and NHEJ, the two major pathways for repairing lethal DNA double-strand breaks (DSBs), by downregulating key proteins like ATM, ATR, DNA-PKcs, and RAD51.[79,83,84] This prevents cancer cells from fixing radiation-induced damage, leading to mitotic catastrophe and apoptosis. Ginsenosides, particularly ginsenoside Rg3, sensitize nasopharyngeal carcinoma cells by suppressing radiation-induced epithelial–mesenchymal transition and inhibiting nuclear translocation of EGFR.[85] Paclitaxel, although widely used as a chemotherapeutic agent, also functions as a radiosensitizer by inducing G2/M arrest, the most radiosensitive phase of the cell cycle.[86,87] Despite these promising mechanistic insights, the radiosensitizing effects of terpenoids and saponins, with the exception of paclitaxel, which is already established as a chemotherapeutic agent, have been demonstrated exclusively in preclinical models. No clinical trials have specifically evaluated their use as radiosensitizers, and caution is warranted when extrapolating the reported findings to human patients.

Alkaloids and Other Compounds

They inhibit checkpoint kinases like Chk1 and Chk2, effectively abrogating the G2/M checkpoint. This forces cells with unrepaired DNA damage to prematurely enter mitosis, resulting in mitotic catastrophe. They also directly inhibit the activity of topoisomerase I and II, creating persistent DNA breaks that compound with radiation damage. Furthermore, some alkaloids generate ROS and downregulate anti-apoptotic proteins like Bcl-2 and survivin, while upregulating pro-apoptotic Bax.[25] Berberine, papaverine, and related alkaloids have demonstrated radiosensitizing effects through metabolic inhibition and interference with DNA repair pathways.[88] Ononin, an isoflavone from Astragalus, has been identified as a novel radiosensitizer in lung cancer via inhibition of the HIF-1α/VEGF axis.[89] All of the aforementioned findings for alkaloids and related compounds are derived from in vitro or limited in vivo studies. The level of evidence for this class remains preliminary, and no clinical data are available to support their use as radiosensitizers at this time.

Melatonin

Melatonin exhibits unique dual properties, enhancing tumor cell radiosensitivity while protecting normal tissues. It downregulates the expression of repair proteins BRCA1, RAD51, and DNA-PKcs, suppressing both HR and NHEJ. Mechanistically, it increases ROS generation in cancer cells, impairs DNA repair, modulates estrogen synthesis, and reduces radiation-induced toxicity in normal tissues, making it an attractive adjunct in radiotherapy.[90,91] While melatonin has been investigated in a number of clinical studies as a radioprotective agent, its role as a tumor radiosensitizer remains less well established. Most of the radiosensitizing data come from preclinical models; well-controlled clinical trials specifically designed to assess radiosensitization are lacking. Therefore, the dual role of melatonin should be interpreted cautiously, and further clinical validation is required before it can be recommended as a radiosensitizer.

Discussion

Limitation and Toxicity

Nanomaterial-based radiosensitizers have demonstrated substantial potential to enhance the therapeutic ratio of radiotherapy through physical dose amplification, reactive oxygen species (ROS) overproduction, and disruption of DNA damage repair.[92] However, despite promising preclinical results, their clinical translation remains limited. The major hurdles are threefold: (i) toxicity, including chronic organ retention and off-target sensitization; (ii) biodistribution, characterized by reticuloendothelial system (RES) sequestration and poor tumor penetration; and (iii) clinical feasibility, encompassing manufacturing reproducibility, route of administration, and regulatory complexity.

The goal of radiosensitization is to amplify radiation effects exclusively within the tumor. However, when nanoparticles accumulate in healthy organs—particularly the liver, spleen, and kidneys—they sensitize these tissues to ionizing radiation, leading to unintended fibrosis, necrosis, or organ dysfunction. For example, gold nanoparticles (GNPs) with prolonged circulation can induce oxidative stress and chronic inflammation in RES-rich organs.[45,52] Many metallic nanoparticles, such as

Au, Gd, and Hf, are not readily biodegradable. They can persist in the RES for months to years, causing chronic inflammation, granuloma formation, or late-onset genotoxicity.[93] For biodegradable nanoparticles, dissolution and release of metal ions can disrupt cellular homeostasis, inhibit enzymatic activity, or induce ferroptosis in healthy tissues.[94,95] Furthermore, nanoparticle surfaces can activate the complement system and trigger cytokine storms, leading to vascular leakage and acute phase reactions.

Intravenously administered nanoparticles are predominantly captured by Kupffer cells and macrophages in the liver and spleen (often > 80–90% of the injected dose).[96] Real-time imaging studies have demonstrated that nanoparticles appear in the liver and spleen within 30 seconds of injection and remain there for days, drastically reducing tumor delivery and creating radiosensitive "hotspots" in clearance organs.[97,98] Heterogeneous tumor accumulation and poor penetration are other aspects of biodistribution. Even when nanoparticles reach the tumor via the enhanced permeability and retention (EPR) effect, they tend to accumulate at the tumor periphery near blood vessels. They fail to penetrate deeply into avascular, hypoxic regions—the most radioresistant compartments of the tumor. The EPR effect itself is highly variable across patients, tumor types, and even within the same tumor over time, making it impossible to predict the delivered dose of the radiosensitizer in an individual patient.[99,100]

Nanomaterial radiosensitizers have achieved some outcomes in preclinical experiments, but there are still many clinical challenges from Bench to Bedside. For example, nanoparticle suspensions are prone to aggregation during terminal sterilization. Lyophilization may extend shelf life, but reconstitution often induces aggregation. These stability issues directly impact clinical safety and efficacy. On the other hand, the route of administration dilemmas is also an important factor that makes clinical transformation challenging. Although intratumoral injection bypasses the issue of biological distribution, it is not suitable for deep, metastatic, or sporadic tumors.[101] In addition, image guidance is required for each radiotherapy session. Meanwhile, intravenous preparations will lead to poor tumor delivery and higher RES uptake. However, local or inhalation administration of nanomaterials is limited to specific cancers such as bladder cancer and lung cancer. The most advanced clinical candidate, NBTXR3 (Nanobiotix), illustrates these translational challenges. It is administered via intratumoral injection to circumvent issues with intravenous biodistribution.

Nanomaterial Radiosensitization Across Different Radiation Energies and Modalities

The foregoing discussion of nanomaterial-based radiosensitizers, particularly those utilizing high-Z) elements, predominantly relies on studies employing kilovoltage (kV) and megavoltage (MV) X-rays. It is important to clarify that the radiosensitization effects described—such as physical dose enhancement via the photoelectric effect—are highly energy-dependent. As noted in the present review, dose enhancement is substantially more pronounced at kV energies than at MV energies due to the Z^3 dependence of the photoelectric effect. However, the consistency of these effects across other radiation modalities, including γ-rays, protons, and carbon ions, remains insufficiently characterized. Protons and carbon ions deposit energy primarily through ionizing and excitational interactions along the Bragg peak, and the contribution of high-Z nanomaterials to additional dose deposition via secondary electron emission is less established and likely differs from that seen with photon irradiation. Furthermore, the radiosensitizing mechanisms mediated by catalytic reactive oxygen species generation or DNA repair interference may be influenced by radiation quality. Therefore, the conclusions drawn in this review regarding the efficacy of nanomaterial radiosensitizers should not be directly extrapolated to all radiation energies or all particle-beam modalities without further experimental validation. Future investigations are warranted to systematically evaluate nanomaterial radiosensitization under clinically relevant proton, carbon-ion, and emerging FLASH radiotherapy conditions, and to define the optimal energy windows and material designs for each modality.

Future Direction

The success of nanoparticles such as hafnium oxide (NBTXR3) has validated the potential of nanomaterial-based radiosensitizers, but future designs will likely move beyond passive energy deposition. Smart or stimuli-responsive nanosystems, such as pH-sensitive or enzyme-activated particles that release radiosensitizing payloads only within the tumor microenvironment, are under active development. Theranostic nanoparticles that combine real-time imaging, radiosensitization, and treatment monitoring may eventually enable personalized dose painting and adaptive radiotherapy.

Hypoxia remains a major obstacle to effective radiotherapy. Next-generation radiosensitizers are being designed not only as oxygen mimetics such as nimorazole derivatives, but also as agents that actively remodel the tumor microenvironment.[100] Examples include inhibitors of HIF-1α and metal-organic frameworks or gold-based nanoclusters that generate reactive oxygen species independent of oxygen levels.[102]

The convergence of radiotherapy and immunotherapy has opened new opportunities for radiosensitizers. Agents that enhance DNA damage while triggering immunogenic cell death (ICD) can convert the irradiated tumor into an in-situ vaccine.[15] Combining such radiosensitizers with immune checkpoint inhibitors, STING agonists, or TLR agonists may amplify abscopal effects, leading to regression of distant metastases.[103]

Instead of broadly increasing radiation sensitivity, future radiosensitizers are expected to target DDR pathways specifically. Inhibitors of PARP, ATM, ATR, and DNA-PKcs are already in clinical trials.[21] Pairing these molecular radiosensitizers with advanced radiation techniques such as FLASH or proton therapy could achieve synergistic tumor control while minimizing normal tissue toxicity.[104] Predictive biomarkers, including DDR gene mutations, will be essential for patient selection, moving radiosensitization into the realm of precision medicine.

The emergence of FLASH radiotherapy creates both opportunities and challenges for radiosensitizers. While FLASH spares normal tissue (the FLASH effect), not all tumors respond equally. Radiosensitizers that preferentially accumulate in tumors and enhance sensitivity under FLASH conditions, without compromising the protective effect on healthy tissue, represent a high-priority research area. High-atomic-number materials with short-lived excitation states, such as gold or bismuth nanoparticles with tailored surface chemistry, are among the candidates.

Future directions of radiosensitizers in cancer radiotherapy are moving away from one-size-fits-all radiosensitization toward intelligent, tumor-selective, and immune-activating systems. Advances in nanotechnology, molecular targeting, and immunomodulation, aligned with emerging radiotherapy modalities such as FLASH, may soon yield radiosensitizers that not only improve local tumor control but also convert localized therapy into systemic antitumor immunity. Moreover, future preclinical studies should explicitly model clinically relevant fractionation schedules rather than relying solely on single high-dose irradiation. Comparative testing of radiosensitizers across multiple fractionation regimens would reveal agent-specific dependencies. Similarly, orthotopic and genetically engineered mouse models that recapitulate the histopathology and microenvironment of human tumors are preferred over subcutaneous xenografts for evaluating tumor-type-specific barriers. For clinical trial design, adaptive or platform trial designs that allow simultaneous evaluation of multiple radiosensitizers or schedules within a single disease context should be considered. Regulatory science for radiosensitizers would also benefit from early engagement with health authorities to qualify surrogate endpoints and imaging biomarkers that can serve as early indicators of radiosensitization activity, thereby reducing the cost and duration of pivotal trials.

Conclusion

The development of radiosensitizers has evolved from cytotoxic agents toward mechanism-driven strategies, including nanomaterials, natural products, targeted inhibitors, and immunomodulators. However, as discussed in this review, each class exhibits inherent limitations and toxicity that hinder clinical translation. Nanomaterials offer physical dose enhancement but suffer from reticuloendothelial system sequestration, chronic organ retention, and off-target sensitization of healthy tissues. Natural products demonstrate pleiotropic effects and favorable safety profiles but are limited by poor bioavailability and inconsistent pharmacokinetics. Molecularly targeted inhibitors provide precision against specific resistance pathways yet carry risks of normal tissue toxicity and require biomarker-guided patient selection. Immunomodulators and nucleic acid therapeutics face delivery barriers, timing-dependent efficacy, and potential immune-related adverse events. Addressing these challenges—poor tumor delivery, unpredictable biodistribution, normal tissue toxicity, and lack of predictive biomarkers—will be critical for successful clinical translation. Future directions should prioritize: (i) smart stimuli-responsive nanosystems for tumor-selective activation; (ii) combination with immunotherapy to harness abscopal effects; (iii) integration with emerging modalities such as FLASH radiotherapy; and (iv) biomarker-driven patient stratification to enable precision radiosensitization. Interdisciplinary collaboration remains essential to translate these advances into improved therapeutic outcomes.

Abbreviation

RT, Radiotherapy; IMRT, Intensity-Modulated Radiotherapy; IGRT, Image-Guided Radiotherapy; SBRT, Stereotactic Body Radiotherapy; NHEJ, Non-Homologous End Joining; HR, Homologous Recombination; ATM, Ataxia Telangiectasia Mutated; ATR, Ataxia Telangiectasia and Rad3-Related; PARP, Poly (Adp-Ribose) Polymerase (Parp); EGFR, Epidermal Growth Factor Receptor; CSCs, Cancer Stem Cells; GSH, Glutathione; ROS, Reactive Oxygen Species; TAMs, Tumor-Associated Macrophages; MDSCs, Myeloid-Derived Suppressor Cells; HIF-1α, Hypoxia-Inducible Factor-1α; GBM, Glioblastoma; PDAC, Pancreatic Ductal Adenocarcinoma; NSCLC, Non-Small Cell Lung Cancer; HNSCC, Head and Neck Squamous Cell Carcinoma.

Data Sharing Statement

This review study has no raw data and has generated analysis data.

Ethics Approval and Consent to Participate

This study does not require ethics approval.

Author Contributions

Hanguang Ruan and Yang Li are co-first authors of the article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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