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Recent Progress in the Development of Metal-Based Radiosensitizations for Cancer Therapy: A Review

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ABSTRACT

Radiotherapy (RT) remains an indispensable means in cancer treatment; however, its therapeutic efficacy is often limited by tumor radioresistance and side effect of damage to healthy tissue. The advances in nanotechnology have propelled metal radiosensitizers to forefront of precision medicine. These metal-based radiosensitizations enhance RT efficacy through multi-faceted mechanisms of physical dose amplification, chemical catalysis, and biological modulation. Compared to conventional way by employing high atomic number (high-*Z*) metal materials to enhance energy deposition, emerging strategies such as X-ray induced radiodynamic therapy (X-RDT) and Cerenkov radiation activated photodynamics therapy (CR-PDT), have been developed to synergize RT with deep-tumor reactive oxygen species (ROS) generation under lower radiation dose. In this review, we highlight recent progress in metal-based radiosensitization for cancer therapy, discuss key challenges hindering clinical translation, and emphasize innovations in material design, combinatorial therapies, and clinical oncology. Collectively, these advances may unlock the full potential of metal-based radiosensitizers, paving the way for curative RT with minimal damage to normal tissues.

1 | Introduction

Cancer remains one of the leading causes of death worldwide, making it critical to pursue diverse therapeutic strategies. Radiotherapy (RT) is central to cancer management, with more than half of all cancer patients receiving RT either as a standalone treatment or in combination with surgery and systemic therapies [1]. RT employs ionizing radiation, such as X-rays, γ-rays, electrons, protons, and heavy ions, to produce lethal DNA damage in cancer cells [2–4]. The therapeutic effect of RT is primarily mediated through two mechanisms. The first involves direct DNA damage: high-energy photons or particles can directly cleave DNA strands, with guanine bases being especially vulnerable because of their low ionization potential [5]. This results in double-strand breaks (DSBs), chromosomal aberrations, and subsequent cell death via apoptosis, necrosis, or mitotic catastrophe [6]. The second mechanism is indirect damage via reactive oxygen species (ROS). Ionizing radiation interacts with intracellular water molecules to produce a range of ROS, including hydroxyl radicals (•OH), superoxide anions ($\bullet O_2^-$), lipid peroxide radicals (ROO•), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), peroxynitrite anion ($ONOO^-$), hypochlorous acid (HOCl), etc.

These reactive molecules cause lipid peroxidation, membrane disruption, and oxidative DNA lesions, amplifying tumor cell killing [7, 8]. In fact, it is estimated that 60%–70% of the DNA damage caused by low-linear energy transfer (LET) radiation, such as X-rays, is attributable to ROS-mediated processes [9].

Despite its irreplaceable role in cancer treatment, RT still faces significant clinical barriers. (1) Normal tissue toxicity. The therapeutic window of RT is restricted by the radiosensitivity of healthy tissues. Even with modern precision techniques, surrounding organs at risk (e.g., lungs or intestines) may suffer from acute inflammatory reactions or late-onset fibrosis because of ROS-mediated injury [10, 11]. Attempts to escalate radiation doses to counteract tumor radioresistance are often constrained by toxicity thresholds, such as the spinal cord tolerance of 45–50 Gy [12, 13]. (2) Tumor heterogeneity and radioresistance. Genetic and microenvironmental diversity within tumors contributes to variable radiation responses [14, 15]. A key example is tumor hypoxia, which reduces ROS generation during irradiation, thereby impairing treatment efficacy in oxygen-deficient regions [11, 16–18]. (3) Physical and technical constraints. Since the mass energy absorption coefficients of tumors and surrounding normal tissues are nearly identical, achieving selective dose deposition remains extremely challenging [19–22]. (4) Patients exposed to thoracic or childhood irradiation are at higher risk of developing secondary malignancies, such as leukemia or lung cancer, as results of radiation-induced mutagenesis [23–25].

In recent years, nanomaterial-based radiosensitization has emerged as a promising strategy to enhance radiation absorption and boost ROS generation, thereby improving the therapeutic efficacy of RT [3, 26, 27]. These nano-based radiosensitizers are broadly classified into metal and non-metallic radiosensitizers according to their components. Non-metallic nanomaterials have gained particular interest because of their biodegradability and metabolic clearance within the body [28]. For instance, Yin et al. [29] developed carbon-iodine polydiacetylene nanofibers (PIDA), which functioned both as effective radiosensitizers and as computed tomography (CT) contrast agents, owing to their remarkably high iodine content (84 wt%). However, non-metallic radiosensitizers are also constrained by complex synthesis procedures and limited functional versatility [28]. In contrast, metallic nanomaterials have been extensively explored and applied in clinical contexts. They offer distinct advantages, including superior X-ray attenuation, robust chemical stability, tunable size and morphology, and efficient ROS generation capacity [30–32].

Metal nanomaterial-mediated radiosensitization has been investigated as a means to overcome the major barriers of conventional RT through several key strategies [33]. (1) Improved tumor selectivity. Optimal radiosensitizers preferentially accumulate in tumors either via passive targeting through the enhanced permeability and retention (EPR) effect or active targeting through ligand–receptor interactions [34, 35]. For instance, folate-conjugated gold nanoparticles (AuNPs) exhibit significantly higher tumor uptake compared to their non-targeted counterparts, thereby reducing off-target toxicity [32, 36, 37]. (2) Synergy with modern RT techniques. Radiosensitizers can enhance the performance of modern RT modalities across different energy ranges [38]. In clinical, X-rays typically have energies in the range of kiloelectronvolts (keV) to megaelectronvolts (MeV) [30]. At keV energies, high atomic number (high-*Z*) nanoparticles (NPs) maximize photoelectric interactions, whereas under MeV beams, they maintain effectiveness by enhancing Compton scattering and pair production [39]. Furthermore, functionalization of radiosensitizers with imaging agents enables real-time tumor visualization through PET, MRI, CT, or ultrasound, thereby guiding precise radiation delivery [40]. (3) Remodeling the tumor microenvironment (TME). Radiosensitizers can address intratumoral heterogeneity in oxygenation, proliferation, and genetic background. For instance, titanium dioxide nanoparticles (TiO_2 NPs) generate ROS under irradiation even in hypoxic conditions, thereby bypassing oxygen-dependent resistance [41]. (4) Minimization of normal tissue toxicity. In contrast to conventional RT, radiosensitizers preferentially accumulate in tumors and are activated only upon radiation exposure, thus restricting collateral damage to surrounding healthy tissues [39]. (5) Combination therapy. Multifunctional nanoplatforms allow integration of radiosensitization with complementary treatment modalities, such as chemotherapy and immunotherapy, providing synergistic effects that enhance therapeutic efficacy and help overcome radioresistance [4, 30, 42, 43].

Metal-based radiosensitizers enhance the efficacy of radiotherapy by integrating physical dose amplification, ROS-mediated chemical effects, and biological pathway modulation, thereby providing precise and multifunctional approaches to overcome the inherent limitations of RT [31]. These agents promote radiation-induced tumor cell death through several mechanisms: (i) physical enhancement of radiation dose deposition using high-*Z* metal materials, (ii) chemical sensitization by boosting ROS production, and (iii) biological modulation, including disruption of oxidative stress balance, inhibition of DNA repair, induction of cell cycle arrest, and remodeling of the TME [2, 39, 44]. With rapid progress in nanotechnology, personalized radiosensitization strategies hold great potential to reshape therapeutic outcomes in oncology [3]. In this review, we provide an overview of the mechanisms and design strategies underlying metal-based radiosensitization (Figure 1) with a focus on nanotechnology-enabled applications in cancer RT. We also discuss recent advances, existing clinical challenges, and future perspectives to accelerate the translation of metal radiosensitizers into clinical practice. Ultimately, we aim for this review to stimulate the development of innovative precision-driven strategies for next-generation cancer radiotherapy.

2 | Mechanisms of Metal-Based Radiosensitization

Metal-based radiosensitization is a multifaceted strategy to enhance the therapeutic efficacy of RT by amplifying tumor-specific radiation effects [5]. This enhancement arises from single or combined contributions of physical energy deposition, chemical generation of reactive species, and modulation of biological pathways [39, 44]. A clear understanding of these physical, chemical, and biological mechanisms is essential for overcoming tumor radioresistance while minimizing collateral injury to healthy tissues. In this review, we provide a

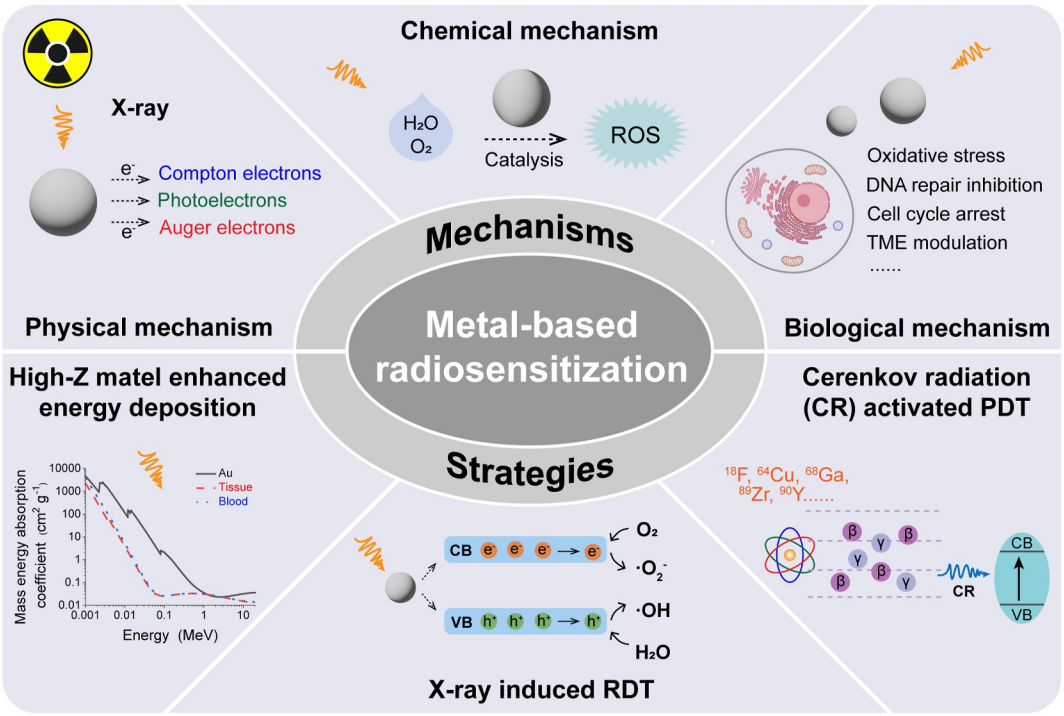

FIGURE 1 | Schematic illustration of the mechanisms and strategies of metal-based radiosensitizations.

comprehensive examination of the underlying mechanisms of metal-based radiosensitization across these three domains.

2.1 | Physical Mechanism

The physical mechanism of metal-based radiosensitization is primarily driven by localized energy deposition through interactions between ionizing radiation and nanomaterials, particularly high-Z metal NPs. High-Z elements possess strongly bound inner-shell electrons that can be readily ionized, creating electron vacancies. Upon X-ray irradiation, these metals efficiently absorb energy and initiate a series of physical processes, including Compton scattering, the photoelectric effect, and Auger electron emission shown in Figure 1 [45]. In Compton scattering, X-ray photons undergo inelastic interactions with outer-shell electrons, transferring energy that ejects the electrons [46]. In the photoelectric effect, an inner-shell electron absorbs the entire energy of the incident photon, leading to its ejection and subsequent release of excess energy as secondary electrons, commonly referred to as Auger electrons [1, 44, 47]. The generated electrons can be captured by molecules at the target site, resulting in the formation of cytotoxic radicals that contribute to tumor cell death [2, 30].

High-Z NPs, such as gold (Au) and hafnium (Hf), enhance energy absorption predominantly through the photoelectric effect under low-energy X-ray irradiation, where incident photons eject tightly bound inner-shell electrons [48]. The subsequent relaxation of outer-shell electrons to fill these vacancies releases Auger electrons and fluorescence photons [13]. Auger electrons, characterized by their short range (on the order of micrometers) and high linear energy transfer (LET), generate dense ionization clusters that induce localized DSBs [47]. At keV X-ray energies (50–500 keV), the photoelectric cross-section scales proportionally to Z^3/E^3, making it highly dependent on both the atomic number of the material and the photon energy [1]. For example, AuNPs (Z = 79) exhibit 100–150-fold greater absorption compared to soft tissue, as demonstrated by Wang et al. [49]. At MeV energies of 4–25 MeV, Compton scattering becomes the predominant interaction, whereby photons impart partial energy to loosely bound electrons. At photon energies above 1.022 MeV, pair production occurs, generating electron–positron pairs, contributing to dose deposition [1]. Although these processes are less dependent on atomic number than the photoelectric effect, high-Z metals still enhance RT efficacy at MeV ranges due to their higher electron density and interfacial energy transfer properties [31]. Based on the Z^2 dependence of pair production, relative effect for high-Z metal of Au could amplify to about 127-fold ($79^2/7^2$), respectively, compared to soft tissue (Figure 1) [5].

Experimental evidence indicates that metal-based NPs often produce radiosensitization effects at keV energies that exceed theoretical predictions [39]. For instance, AuNPs demonstrated a 1.43-fold increase in cell killing under keV irradiation, despite the expected minimal contribution from the photoelectric effect [50]. Several mechanisms have been proposed to explain this discrepancy, including interfacial electron transfer, Auger cascade amplification, and nanoscale dose [49]. High-Z NPs can also lower the bandgap of nearby water molecules, promoting electron–hole (e^-–h^+) pair dissociation and localized redox reactions [30]. Even minimal photoelectric interactions can trigger cascades of low-energy electrons that substantially magnify DNA damage [6]. Auger electrons, with their nanometer-scale range, deposit highly concentrated energy near NPs and can overwhelm DNA repair mechanisms [7, 47]. However, physical models alone cannot fully account for the observed radiosensitization [51, 52]. For example, carbon-based NPs classified

as low-Z materials, have exhibited radiosensitization effects comparable to those of AuNPs, suggesting the involvement of additional non-physical mechanisms [53]. Moreover, nanoparticle properties such as size, shape, and aggregation state strongly influence energy deposition, further complicating accurate predictive modeling [1, 7].

2.2 | Chemical Mechanism

The chemical mechanism of metal-based radiosensitization primarily involves the generation of ROS and redox interactions at the nanoparticle–biological interface, thereby amplifying radiation-induced DNA damage in tumor cells [39]. The produced ROS in biological systems commonly include •OH, H_2O_2, $\bullet O_2^-$, $^1O_2$, and so on [31]. During RT, ionizing radiation induces water radiolysis, producing oxidative radicals and solvated electrons, a process that can be further enhanced by metal-based nanoparticles acting as catalytic amplifiers [39]. Specifically, the enhanced X-ray absorption by these nanoparticles promotes secondary electron emission and the formation of e^-–h^+ pairs. When the photon energy equals or exceeds the semiconductor band gap, electrons are excited from the valence band (VB) to the conduction band (CB), leaving holes in the VB [28]. These photogenerated charge carriers subsequently migrate to reactive sites, where they drive redox reactions and generate two key species, $\bullet O_2^-$ and •OH, as illustrated in Figure 1 [54]. These ROS amplify DSBs and genotoxic stress, rather than relying solely on direct DNA interactions with secondary electrons [2, 55]. In addition, metal NPs or their dissolved ions can promote ROS formation via redox cycling through Fenton and Haber–Weiss reactions, thereby sustaining oxidative stress and amplifying the radiobiological response [39, 56, 57]. For example, the manganese dioxide (MnO_2) incorporated into gold nanorod (AuNR)-based Janus nanoprobes has been shown to catalyze •OH generation through a Fenton-like reaction within tumor sites, enhancing radiosensitization [58]. Similarly, the release of Ag^+ ions from silver nanoparticles not only promoted ROS production by acting as an oxidant but also induced protein inactivation, resulting in synergistic cytotoxicity against tumor cells [59].

The extent of ROS-induced damage is influenced not only by the type and quantity of ROS generated but also by factors such as the duration of exposure and external cellular conditions, including temperature, oxygen availability, and the ionic and protein-rich environment of TME [1]. Consequently, although interactions with H_2O or O_2 contribute to the generation of reactive species, the radiosensitization effects are largely determined by the downstream biological processes occurring within tumor cells and tissues. These biological mechanisms, particularly those involving pathway modulation, will be discussed in detail in the following section.

2.3 | Biological Mechanism

Experimental studies consistently report radiosensitization effects of metal-based NPs that far exceed theoretical predictions based solely on the physical X-ray dose, suggesting the presence of additional, yet not fully understood, radiobiological interactions within cells [7]. Despite extensive investigation in recent years, the key biological mechanisms implicated in metal-based radiosensitization include the induction of oxidative stress, inhibition of DNA repair pathways, alterations in cell cycle regulation, and modulation of the TME [39, 44, 60].

Numerous studies have demonstrated that excessive ROS production can overwhelm cellular antioxidant defenses, resulting in DNA damage and lipid peroxidation [61]. For example, hafnium oxide (HfO_2)-based radiosensitizers have been shown to potentiate radiation-induced DNA damage and activate the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, thereby enhancing local antitumor immune responses [40]. Similarly, Au/Cu nanodots under ionizing radiation generate abundant ROS that intensify lipid peroxidation, leading to tumor cell apoptosis and significantly improving RT efficacy [62]. Another mechanism involved in metal radiosensitization is DNA repair inhibition. In RT, radiation itself induces DNA breakages, whereas the concurrent activation of DNA repair pathways is crucial for cell survival [7]. Thus, to exploit this vulnerability, numerous strategies have combined metal-based nanoparticles with inhibitors targeting DNA repair mechanisms, demonstrating enhanced radiosensitization effects in both preclinical and clinical settings [63–65].

Cellular sensitivity to radiation and the resulting biological effects are highly dependent on the cell cycle phase. Cells in the late S-phase are generally the most radioresistant, whereas those in late G2 and mitosis exhibit the greatest sensitivity to X-ray exposure [7, 39]. Metal-based radiosensitizers can enhance RT efficacy by disrupting cell cycle progression and promoting apoptosis. One approach involves synchronizing cells in radiation-sensitive phases such as G2/M [66, 67]. For instance, Kumar et al. [68] reported that AuNPs downregulated cyclin B1 and Cdc2 expression, thereby prolonging G2/M arrest and enhancing RT. Similarly, Asadi et al. [69] designed a zinc-based radiosensitizer (Zn@Alg-Dox) that increased the G2/M population by 18.5%, leading to improved RT outcomes. Alternatively, reducing the proportion of radioresistant S-phase cells has also been effective. Gold nanospikes, for example, suppressed DNA replication proteins and decreased S-phase populations, thereby augmenting RT efficiency [70–72].

Solid tumors are characterized by abnormal microenvironments, including hypoxia, acidity, and altered biomolecule levels. Thus, leveraging these unique features, metal-based radiosensitizers can enhance RT efficacy by reshaping the TME [33]. For example, MnO_2@CeO_x NPs with enzyme-mimicking activity catalyze the decomposition of H_2O_2 in acidic conditions, generating O_2 to alleviate tumor hypoxia and thereby reduce radioresistance [58, 73–75]. Similarly, gold-based nanomaterials have been shown to downregulate vascular endothelial growth factor (VEGF) expression in endothelial cells, improving blood perfusion and promoting tumor vascular normalization [76, 77]. Qiao et al. [78] developed selenium-doped Prussian blue nanoheterojunctions (Se@PB) as radiosensitizers, which deplete glutathione (GSH) and accumulate Fe^{2+} via a pro-Fenton reaction, disrupting redox homeostasis and enhancing the biochemical sensitivity of RT in the TME. The abscopal effect describes a systemic antitumor response induced by localized therapy and has been documented in both radiotherapy and radiosensitization [79, 80]. Radiation

induces cancer cell death, after which antigens and damage-associated molecular patterns (DAMPs) are released from the dead cells. This subsequently triggers the activation and recruitment of immune cells to the primary tumor site, initiating systemic immune responses against metastatic lesions. This process defined as immunogenic cell death (ICD), plays a central role in mediating such effects [81]. For instance, He et al. [82] demonstrated that AuNPs not only enhanced the efficacy of RT but also induced an abscopal effect through ICD, resulting in tumor suppression at non-irradiated sites. Moreover, metal ions such as Mn^{2+} and Zn^{2+}, released from nanoparticles, can regulate immune-related signaling pathways including cGAS–STING to reshape the immune microenvironment and boost antitumor activity during RT. As an example, the sustained release of Mn^{2+} from GSH-degradable MnO_2 nanoparticles, in combination with double-stranded DNA fragments released from irradiated tumor cells, co-activated the cGAS–STING pathway, thereby strengthening local immune responses and enhancing RT efficacy [75].

Therefore, the physical, chemical, and biological mechanisms of metal-based radiosensitization typically work in concert to enhance RT efficiency in radiosensitization process [83]. Physical processes increase localized energy deposition, whereas chemical mechanisms amplify DNA damage through ROS generation and redox cycling [31]. Then biological modulation targets DNA repair, cell cycle dynamics, and TME [7]. The persistent discrepancies between theoretical predictions and experimental observations highlight the complexity of nanoparticle–radiation interactions and underscore the need for interdisciplinary research collaborations [39]. Consequently, growing efforts are directed toward developing multifunctional nanoplatforms, such as integrating high-*Z* materials with catalytic agents, tailoring nanoparticle design to tumor genetics and microenvironmental factors, and improving tumor selectivity through advanced surface functionalization [4, 5, 84]. Hence, rational and personalized design strategies, metal-based radiosensitizers hold the potential to transform precision oncology, delivering curative radiation doses while minimizing collateral damage to normal tissues.

3 | Recent Advances in Radiosensitization Strategies

Metal-based radiosensitization has emerged as a transformative approach to enhance therapeutic efficacy in RT by overcoming tumor radioresistance and improving treatment safety. Advances in nanotechnology and radiobiology have given rise to three major strategies (Figure 1), including high-*Z* metal enhanced energy deposition, X-ray induced radiodynamic therapy (X-RDT), and Cerenkov radiation activated photodynamic therapy (CR-PDT).

3.1 | High-*Z* Metal Enhanced Energy Deposition

According to the physical enhancement mechanism, the atomic number is a critical factor influencing energy–matter interactions during irradiation [5]. High-*Z* materials, particularly metals and their compounds, possess markedly greater energy absorption capacity compared to soft tissues. This property amplifies radiation dose deposition at tissue interfaces through physical processes such as the photoelectric effect, Compton scattering, and Auger electron emission, thereby enabling more precise tumor targeting [5, 47]. Consequently, a wide range of high-*Z* metal NPs have been developed as radiosensitizers, including noble metals (Au, Ag, and Pt), rare earth elements (La, Ce, Gd, Ho, and Eu), and other heavy metals (Hf, Ta, W, Cs, and Bi) [49].

AuNPs are among the most widely studied radiosensitizers owing to their high atomic number and favorable biological properties [46, 85, 86]. Liu et al. [87] developed a multifunctional Au-modified platelet cell motor (PLT@Au@Urease) by integrating Au, platelets, and urease for targeted tumor radiosensitization. As shown in Figure 2A–J, this system markedly increased intracellular ROS generation under radiation, thereby intensifying DNA damage and achieving a sensitization enhancement ratio of 1.89, compared with 1.08 for PLT@Au alone. Lei et al. [89] engineered bacteria (PCM) functionalized with AuNPs to construct PCM@AuNPs, which significantly enhanced radiosensitization by amplifying local energy deposition within tumor cells, resulting in pronounced tumor growth inhibition. Beyond gold, other high-*Z* materials have also shown promise. Lyu et al. [90] designed platelet cell membrane-engineered hollow tantalum oxide (TaO_x) nanoparticles, which leveraged the strong photoelectric effect of tantalum to enhance RT efficacy and effectively eliminate tumors. Wang et al. [88] reported a mesoporous HfO_2 loaded with a Z-DNA inducer CBL0137 (CBL@HfO_2). As shown in Figure 2K–T, CBL@HfO_2 induced a conformational transition from B-DNA to Z-DNA, thereby enhancing DSBs approximately threefold compared with RT alone, and achieving a tumor suppression rate of 30%. Similarly, Zhang et al. [91] employed HfO_2 NPs to deliver a PROTAC prodrug, BPA771, which, upon reacting with H_2O_2, was converted to ARV771. This downregulated the BRD4–RAD51AP1 pathway, thereby sensitizing head and neck squamous cell carcinoma (HNSCC) tumors to RT. In another study, Wang's group developed a HfO_2-based radiosensitizer (ES@HM-HfO_2:Cu), which not only facilitated high-energy deposition but also released Cu^{2+} ions in the acidic tumor microenvironment. This triggered cuproptosis in tumor cells, producing a dual radiosensitization effect [92].

In addition, Chen et al. [93] developed a Hf-based metal-organic framework (MOF) for hypoxia imaging guided radiosensitization (Figure 3A–H). This multifunctional nanoprobe (HfC-Hy) enabled real-time imaging of tumor hypoxia levels and simultaneously guided radiosensitization, offering a promising approach for personalized clinical RT. Similarly, Luo et al. [94] reported a nanoscale Hf-based metal-organic layer (MOL), designed as a two-dimensional (2D) nanoradiosensitizer, which enhanced the antitumor effects of RT when combined with chemotherapeutics. In another study (Figure 3I–Q), Huang et al. [64] synthesized chiral vidarabine monophosphate-gadolinium nanowires (aAGd-NWs) through a coordination-driven self-assembly approach. These nanowires not only enhanced X-ray energy deposition at tumor sites but also inhibited DNA repair via the release of vidarabine monophosphate (ara-AMP), the key building block of the chiral coordination polymer. Moreover, they promoted radiation-induced in situ vaccination, thereby synergistically improving treatment efficacy against both

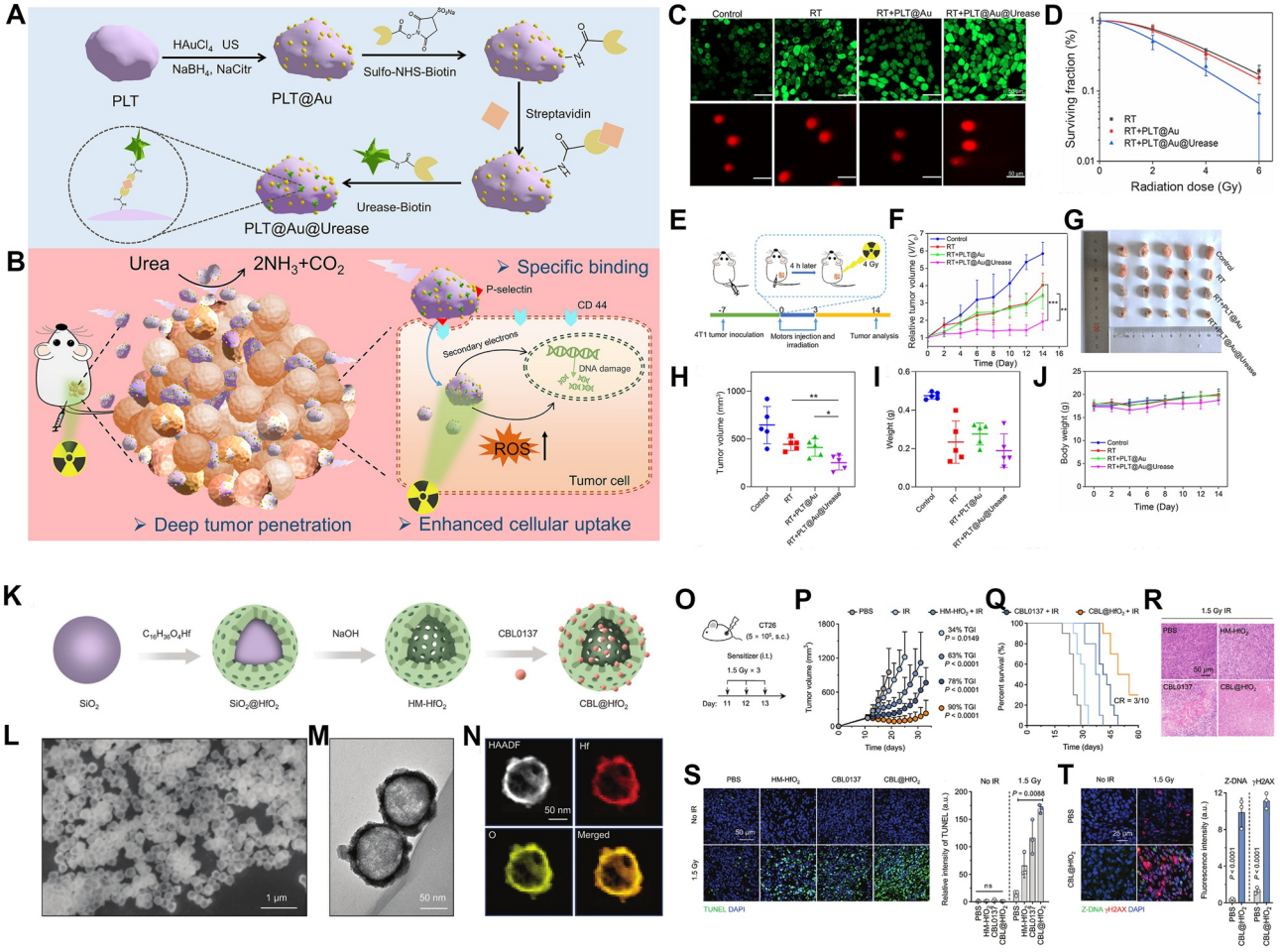

FIGURE 2 | The radiosensitizations of high-*Z* metal enhanced energy deposition. (A, B) Illustration of the fabrication and antitumor mechanism of gold engineered platelet cell motors (PLT@Au@Urease) for boosting cancer radiosensitization; (C) confocal laser scanning microscope (CLSM) images of intercellular ROS accumulation and DNA fragmentation by comet assay; (D) clonogenic survival fraction of 4T1 cells treated with engineered PLT@Au@Urease; (E–J) in vivo therapeutic effect of PLT@Au@Urease motors. Reproduced with permission from Ref. [87]. Copyright 2024 Elsevier. (K) Preparation of manipulating radiation-sensitive Z-DNA conformation of CBL@HfO_2 nanocapsules; (L–N) the scanning electron microscope (SEM), transmission electron microscope (TEM) and element mapping of CBL@HfO_2 nanocapsules; (O–T) in vivo radiosensitization with Z-DNA inducer in CT26 tumor-bearing mice. Reproduced with permission from Ref. [88]. Copyright 2024 Wiley.

primary and metastatic tumors when combined with immune checkpoint blockade therapy. Other gadolinium (Gd)-based nanosystems have also been explored. Liu et al. [95] reported a multifunctional gadolinium-based nanoprobe (GBD) that utilized bioorthogonal click chemistry to improve tumor retention, enabling both MRI detection and enhanced radiosensitivity. Kuang et al. [96] further introduced $Gd_2Hf_2O_7$ nanoparticles as high-*Z* materials for MRI-guided combination therapy, integrating chemotherapy, photothermal therapy, and RT to overcome treatment-resistant tumors.

Although high-*Z* materials can significantly improve RT efficacy, several challenges hinder their clinical translation. Foremost among these is toxicity, as metal accumulation in organs such as the liver and spleen may cause unpredictable biological damage [2]. Many biodegradable metal NPs or renal-clearable ultrasmall NPs have been developed to reduce cytotoxicity [97, 98]. For instance, Jiang et al. [99] reported a metabolizable binary supracluster (BSCgal) composed of reversibly crosslinked cationic gold nanoclusters (AuNCs), which achieved 90.3% in vivo clearance within 4 weeks, thereby minimizing long-term toxicity. Similarly, Zhu et al. [9] designed ultrasmall dihydrolipoic acid-coated gold nanoclusters (AuNC@DHLA) that directly absorbed X-rays via the high-*Z* element Au, delivering strong radiosensitization performance while achieving negligible systemic toxicity through rapid clearance of ultrasmall size particles. In addition to safety considerations, radiation energy also influences radiosensitization efficiency. Jain et al. [38] demonstrated that AuNPs produced different sensitizer enhancement ratios (SERs) in MDA-MB-231 cells, measured at 1.41, 1.29, and 1.16 under 160 kVp, 6 MV, and 15 MV X-ray energies, respectively. These findings suggest that AuNPs exert varying radiosensitization effects depending on the irradiation energy. This is largely because photoelectric interactions dominate at keV energies, whereas their contribution diminishes at MeV energies [12]. However, clinical RT predominantly employs MeV beams due to their superior tissue penetration. To address this limitation, hybrid metal nanoparticles combining high-*Z* elements with catalytic components have been developed to boost ROS generation across a broader energy spectrum, even under high-energy irradiation [1]. For example, Zhang et al. [58] designed a biomarker-responsive

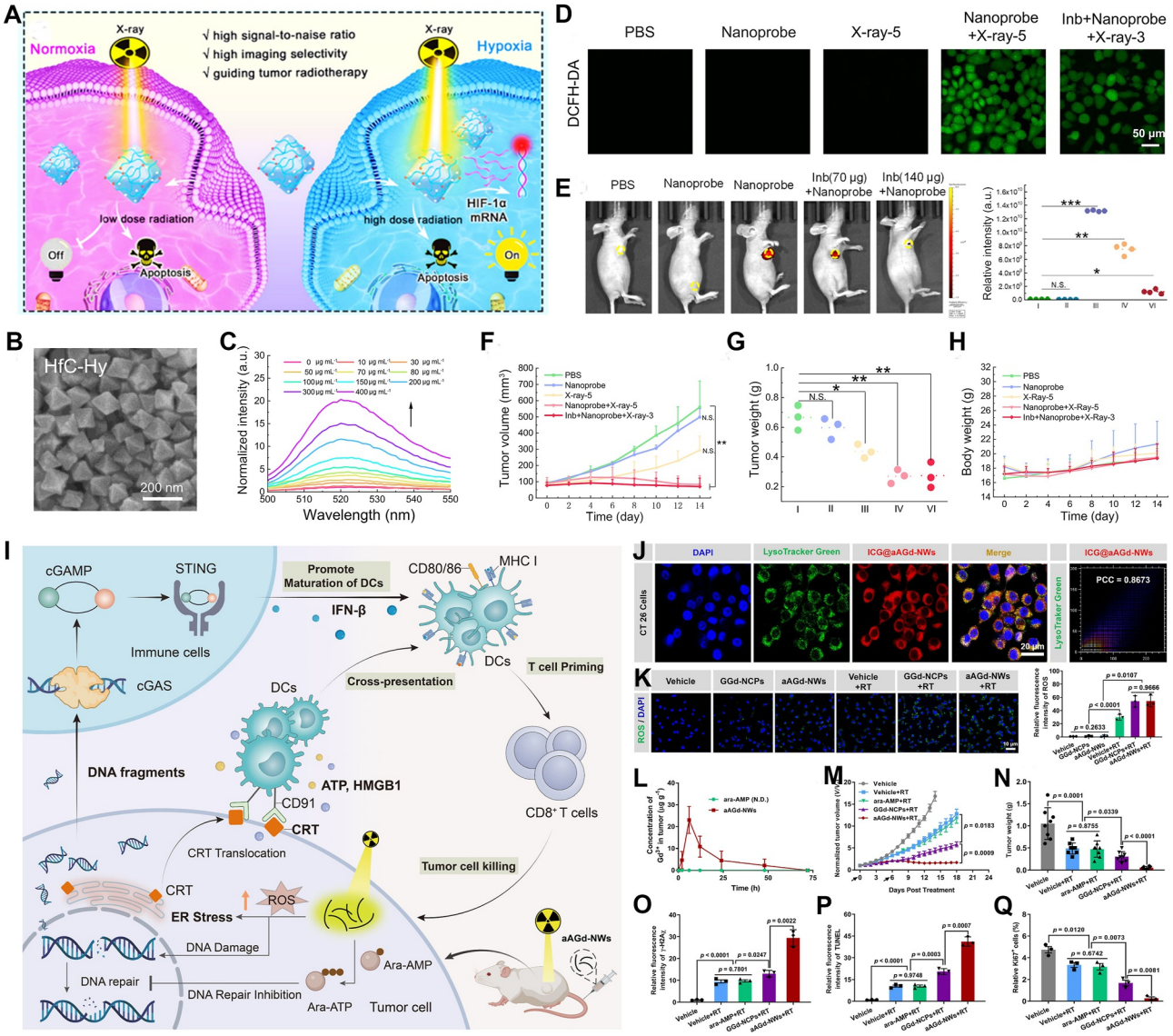

FIGURE 3 | The radiosensitization strategies using high-*Z* metal materials to enhance energy deposition. (A) Schematic illustration of MOF-derived multifunctional nucleic acid nanoprobes (HfC-Hy) for hypoxia imaging-guided tumor radiosensitization; (B, C) SEM image and ROS generation of HfC-Hy with X-ray irradiation; (D, E) the HfC-Hy nanoprobes used for hypoxia imaging in cells and mice models; (F–H) antitumor effect of HfC-Hy in mice with MCF-7 xenograft tumors. Reproduced with permission from Ref. [93]. Copyright 2023 American Chemical Society. (I) Scheme of chiral coordination polymer nanowires (aAGd-NWs) sensitized radiation for inducing potent in situ vaccination; (J, K) cellar uptake and ROS generation of aAGd-NWs under X-ray irradiation; (L–Q) pharmacokinetics and radiosensitization efficacy of aAGd-NWs in vivo. Reproduced with permission from Ref. [64]. Copyright 2024 Springer Nature.

Janus nanoplatform by integrating AuNR with MnO_2, which effectively enhanced RT efficacy while simultaneously enabling chemodynamic therapy.

3.2 | X-Ray Induced Radiodynamic Therapy (X-RDT)

Unlike traditional physical enhancement by high-*Z* nanoparticles, catalytic radiosensitization of X-ray induced radiodynamic therapy (X-RDT) focus on catalytic reactions and chemical products during radiation process [28, 49]. As discussed earlier, when a photoelectron is ejected from a lower atomic orbital under irradiation, an electron from a higher orbital fills the vacancy, leaving behind a "hole" [46]. This transition releases excess energy, which can either emit a fluorescent photon or ionize another electron in a higher orbital, resembling the mechanism of PDT [44]. X-RDT therefore acts as a bridge between RT and PDT, exploiting the deep tissue penetration of X-rays to activate nanocatalysts [49]. Thereby, benefiting from the rapid development of photosensitizers (PSs) and catalytic nanomaterials, a series of metal nanomaterials, such as MOFs, heterostructures, semiconductors, defective materials, and nanoenzymes, can serve as radiosensitizers for X-RDT [78, 100–108].

As illustrated in Figure 4A–F, Lv et al. [109] synthesized catalytic Janus-like Au-Fe_2C nanoparticles (AFCNPs) as radiosensitizers

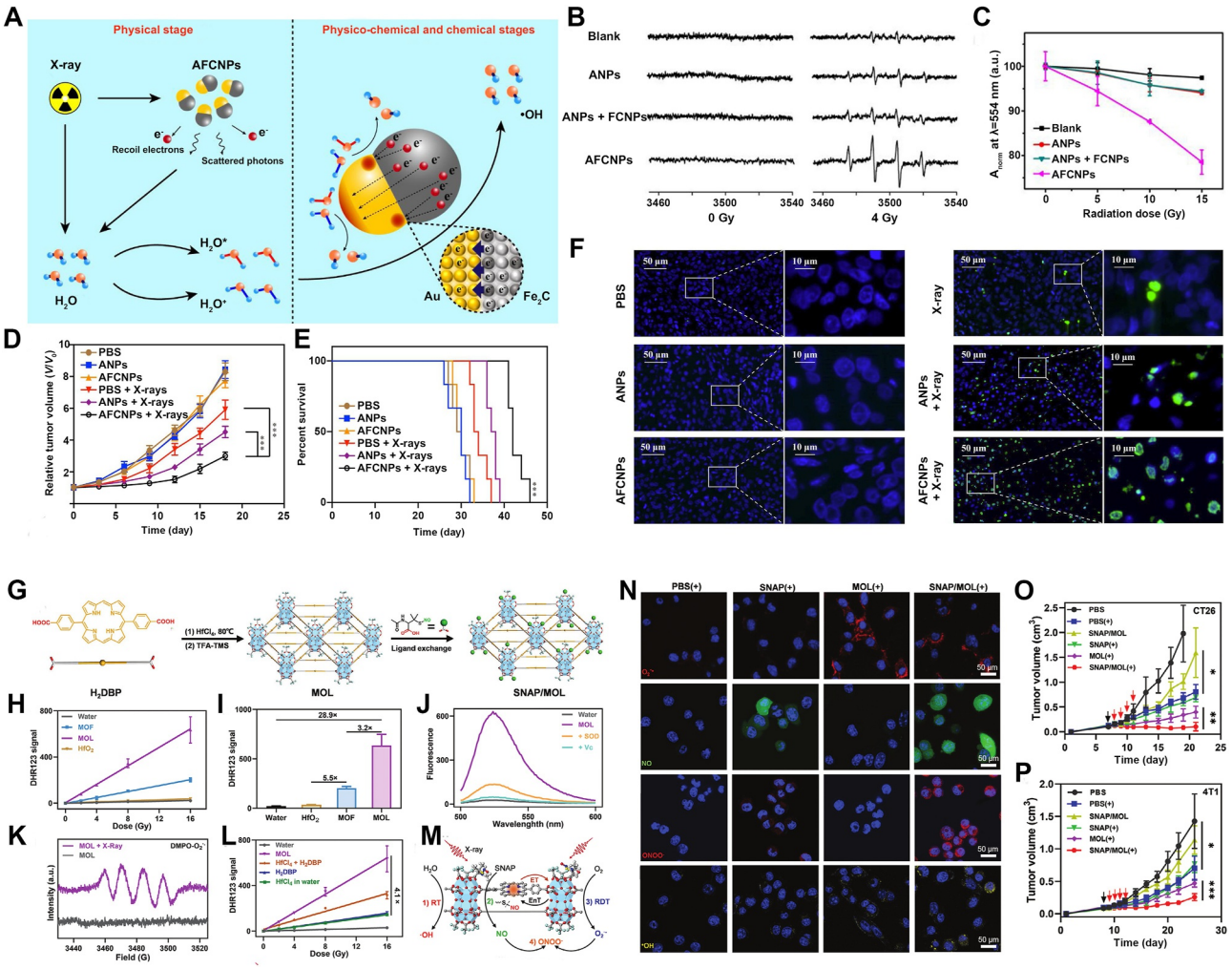

FIGURE 4 | The radiosensitizations using X-ray induced radiodynamic therapy (X-RDT) strategies. (A) Schematic illustration of structure-oriented catalytic radiosensitizer (AFCNPs) for X-ray-induced •OH generation; (B, C) the examination of •OH yield by electron spin resonance (ESR) and UV-Vis spectra of RhB under irradiation; (D–F) in vivo investigation of AFCNPs for radiosensitization. Reproduced with permission from Ref. [109]. Copyright 2020 Elsevier. (G) Synthetic scheme of nitric oxide (NO)-releasing nanoscale metal-organic layer (SNAP/MOL) to overcome hypoxia and ROS diffusion barriers and enhance cancer radiotherapy; (H–M) ROS generation and NO release under X-ray irradiation; (N) intracellular ROS and reactive nitrogen species (RNS) generation; (O, P) tumor growth profiles of CT26 and 4T1 tumor-bearing mice with different treatments. Reproduced with permission from Ref. [110]. Copyright 2024 Wiley.

to enhance RT efficacy. These NPs significantly promoted radical conversion from H_2O substrates, resulting in nearly a fivefold increase in •OH generation compared with pure Au nanoparticles. Li et al. [48] further designed a hybrid radiosensitizer, AuNP@Hf-Ce6, which simultaneously enhanced physical dose deposition and $^1O_2$ production. Xiong et al. [110] employed 5,5′-di-*p*-benzoatoporphyrin to construct Hf-based nanoscale MOLs (Figure 4G–P), which produced abundant •OH and $•O_2^-$ during the X-RDT process, yielding unique radiotherapeutic effects. Thus, by conjugating the MOLs with the nitric oxide (NO) donor S-nitroso-N-acetyl-DL-penicillamine (SNAP), the resulting SNAP/MOL system further improved RT through the generation of long-lived and highly cytotoxic peroxynitrite anions ($ONOO^-$). In another study, Ma et al. [111] developed a cationic Hf-porphyrin-based coordination MOL (CMOL) capable of delivering small interfering RNAs (siRNAs), thereby achieving enhanced radiosensitization under low-dose X-ray irradiation. Zhen et al. [112] reported a Hf-based nanoscale MOF loaded with the chemotherapeutic drug SN38, which not only enhanced radiotherapeutic efficacy but also triggered the controlled release of SN38 under X-ray irradiation. As shown in Figure 5A–Q, Lin et al. [113] developed a multifunctional radio-enhancing system of Ce-based metaloxo clusters ($Ce(IV)_6$)-porphyrin (meso-tetra(4-carboxyphenyl)porphyrin, TCPP) framework loaded with L-arginine (LA@$Ce(IV)_6$-TCPP) to effectively heighten X-ray absorption and energy transfer in ROS generation. This system improved X-ray absorption and energy transfer for ROS generation while simultaneously achieving hypoxia-relief and gas therapy through the in situ production of O_2, NO, and highly cytotoxic $ONOO^-$. Thus, by alleviating tumor hypoxia and augmenting X-RDT and LA@$Ce(IV)_6$-TCPP demonstrated superior anticancer efficacy in RT.

However, the aforementioned studies involving organic PSs, are largely rely on organic PSs that primarily convert $^3O_2$ into $^1O_2$, a process limited by tumor hypoxia, similar to conventional type II

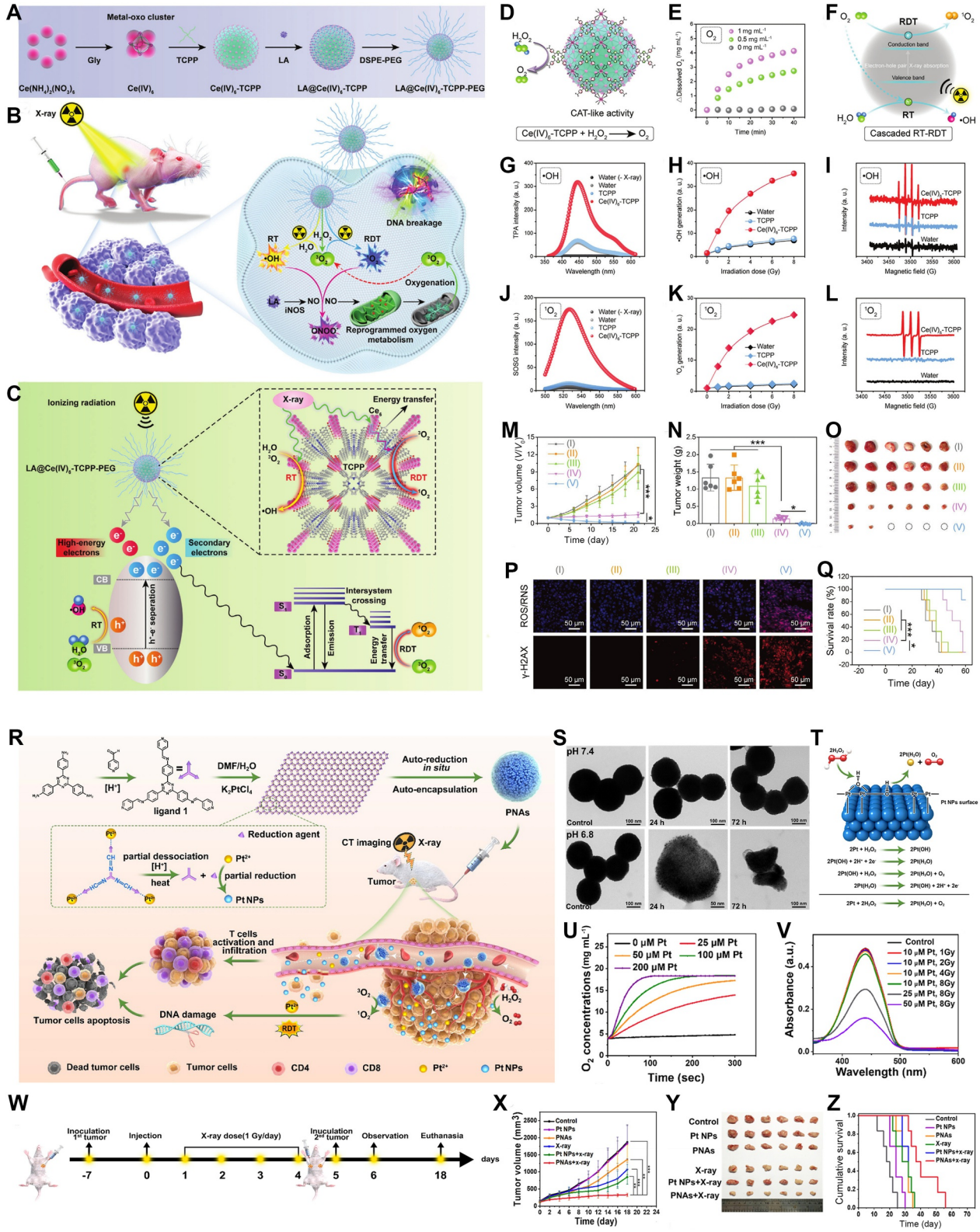

FIGURE 5 | The radiosensitization strategies of X-RDT. (A–C) Preparation and working mechanism of Ce-based rare-earth metal-porphyrin framework of LA@Ce(IV)$_6$-TCPP for oxygen-evolving X-RDT synergized with NO gas therapy; (D–L) in vitro O_2 supply capacity and X-RDT efficacy of Ce(IV)$_6$-TCPP; (M–Q) in vivo synergistic therapeutic effect of LA@Ce(IV)$_6$-TCPP-PEG. Reproduced with permission from Ref. [113]. Copyright 2024 Wiley. (R) Schematic illustration of mixed-valence Pt(0)/Pt^{2+} nanoassemblies (PNAs) for CT imaging guided radiotherapy; (S) TEM images of PNAs dispersed in pH 7.4 or 6.8 PBS solution with various times; (T) the catalytical mechanism for H_2O_2 decomposition to O_2 on the surface of PNAs; (U, V) oxygen and $^1O_2$ generation catalyzed by PNAs under X-ray irradiation; (W–Z) anti-tumor effects of PNAs combining with radiotherapy in bilateral tumor model. Reproduced with permission from Ref. [114]. Copyright 2023 Elsevier.

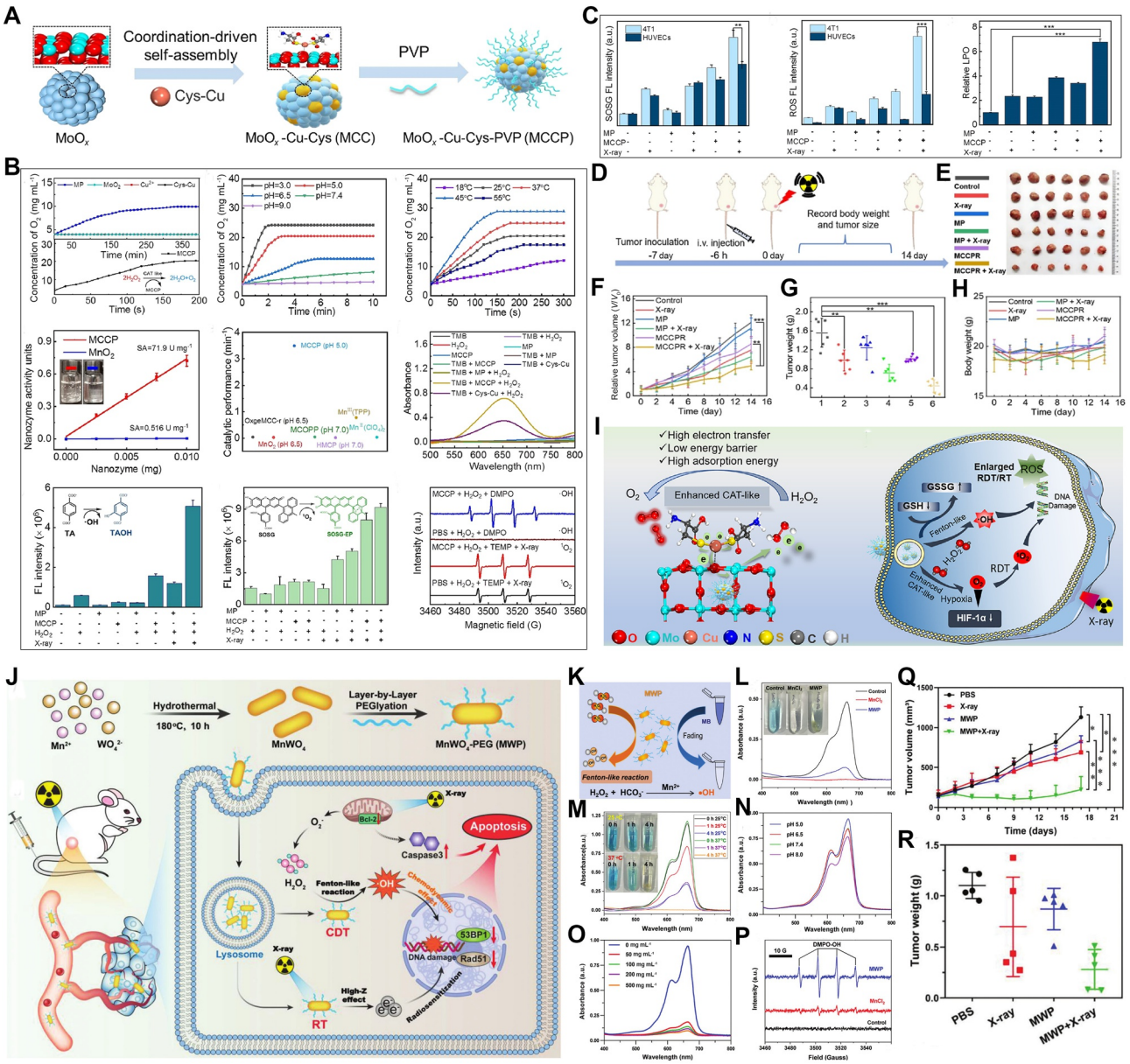

FIGURE 6 | The multifunctional radiosensitizers for X-RDT. (A) Schematic illustration of synthesis of high-loading Cu single atom nanozymes (MCCP SAzymes) for catalytic tumor-specific therapy; (B) high catalase (CAT)/Fenton-like activity and X-ray-triggered radiodynamic effect; (C) SOSG and DCF fluorescence intensity, and lipid peroxidation damage assessment under different treatments; (D–I) in vivo intratumoral penetration, antitumor efficacy, and mechanism of MCCP amplified RDT sensitized RT. Reproduced with permission from Ref. [116]. Copyright 2023 American Chemical Society. (J) Illustration of Catalytic $MnWO_4$ nanorods (MWP) for the synergistic CDT/RT-mediated chemodynamic therapy synergized radiotherapy; (K–P) fenton-like effect of MWP; (Q, R) in vivo anti-tumor effect of MWP-mediated CDT/RT. Reproduced with permission from Ref. [117]. Copyright 2023 Wiley.

PDT. To overcome this, type I PDT strategies have been explored, in which electron transfer from PSs to substrates (e.g., H_2O) generates $\bullet O_2^-$ and •OH in an oxygen-independent manner, making them suitable for radiosensitization. Leveraging the high-*Z* element platinum (Pt) to enhance energy deposition, Zhang et al. [114] developed mixed-valence Pt nanoassemblies (PNAs) [Pt(0)/Pt^{2+}] using a novel approach that introduced imine groups and reducing moieties into a MOF framework, imparting reversible redox properties (Figure 5R–Z). These PNAs not only catalyzed the conversion of H_2O_2 into O_2 but also released Pt ions that impaired cellular function, thereby improving radiodynamic therapy (RDT) efficacy and activating antitumor immune responses. Wang et al. [103] designed Schottky-type heterostructures of Au-Bi_2S_3 NPs, which effectively trapped X-ray induced electrons and transferred them to Au. This architecture promoted efficient e^-–h^+ separation, enabling robust generation of oxygen-independent ROS even under hypoxic conditions. Similarly, Chen et al. [115] employed TiO_2 nanoparticles to enhance electron transfer during low-dose X-ray irradiation, significantly increasing ROS production and inducing tumor cell death.

Zhou et al. [116] also presented a Cu single-atom nanozymes of MoO_x–Cu–Cys, aiming to achieve catalytic tumor-specific RT

(Figure 6A–I). In this system, Cu single atoms activated the catalase (CAT)-like activity of MoO_x NPs, promoting the decomposition of H_2O_2 into O_2 within acidic tumor microenvironments, thereby alleviating hypoxia and reducing radioresistance. At the same time, the Cu single atoms enhanced the production of •OH and $^1O_2$, enabling cascading X-RDT and achieving potent antitumor effects. Wang et al. [105] further developed heterostructured CuO@Graphdiyne (CuO@GDY) nanocatalysts, which combined NIR-photocatalytic oxygen evolution with X-ray–accelerated Fenton-like reactions of Cu^+, resulting in efficient O_2 generation and •OH production in hypoxic tumors. Recently, Zhao et al. [117] reported a single-component $MnWO_4$ material as a Fenton-like agent yet radiosensitizer shown in Figure 6J–R. In this system, tungsten (W) enhanced radiosensitization by elevating intratumoral H_2O_2 levels, whereas Mn^{2+} triggered chemodynamic activity that impaired DNA damage repair and synchronized tumor cells into radiosensitive phases. Together, these effects significantly amplified oxidative stress and improved RT outcomes.

In addition to external radiation, growing attention has been directed toward internal radiation sources, such as therapeutic radionuclides that emit α or β^- particles, for enhancing RT [83]. Ngwa et al. [118] provided the first experimental evidence of AuNP-mediated radiosensitization under continuous low-dose-rate (LDR) gamma irradiation, using low-energy brachytherapy sources from iodine-125 (^{125}I) seed plaques that emitted Auger electrons during decay. Similarly, Su et al. [119] employed ^{125}I to activate TiO_2 nanocatalysts, extending their application to cancer catalytic internal radiotherapy (CIRT). Zhang et al. [120] designed Mn-based radioimmunotherapy promoters of ^{211}At-ATE-MnO_2-(bovine serum albumin (BSA)), which achieved local RT and chemodynamic therapy by using an α-emitter of ^{211}At. Despite these advances, internal radiation sources can pose risks of systemic toxicity during intravenous administration, as radiation may interact with circulating blood components. Overall, metal-based X-RDT offers a promising strategy to enhance ROS generation and improve RT efficacy, providing new opportunities to broaden radiosensitization applications in clinical oncology. However, challenges such as limited energy conversion efficiency, oxygen dependence, radiation attenuation, and potential damage to normal tissues remain to be addressed to achieve more effective and safer radiotherapy [28, 49].

3.3 | Cerenkov Radiation Activated PDT (CR-PDT)

Beyond conventional radiosensitization strategies that rely on external radiotherapy equipment, novel internal RT approaches utilizing ionizing particles emitted during radionuclide decay have attracted growing interest. A key phenomenon is CR, which occurs when charged particles (e.g., β or α particles) travel faster than the speed of light in a given dielectric medium [121–123]. During this process, positrons or electrons emit UV-blue light (300–600 nm) that can serve as an intrinsic light source to activate PSs or catalytic materials, thereby generating ROS for intratumoral PDT [101, 124–127]. Numerous radionuclides have been identified as CR sources, including several clinically relevant isotopes such as fluorine-18 (^{18}F), copper-64 (^{64}Cu), gallium-68 (^{68}Ga), yttrium-90 (^{90}Y), iodine-124 (^{124}I), lutetium-177 (^{177}Lu), zirconium-89 (^{89}Zr), and others [128, 129]. The intensity of CR emission is proportional to the particle

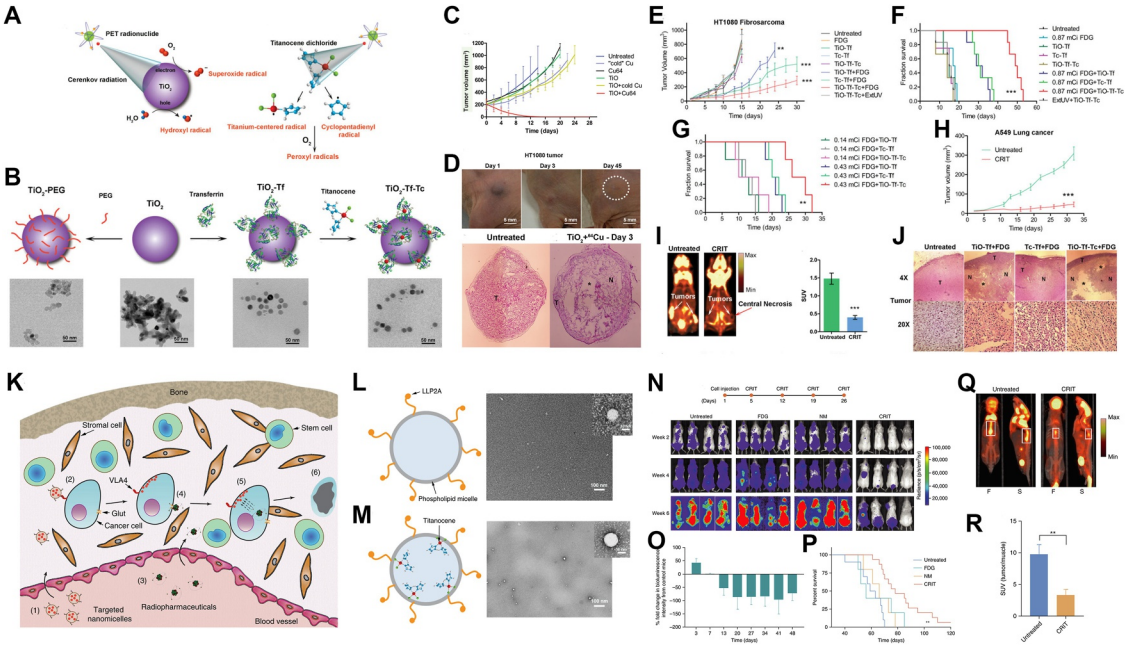

FIGURE 7 | The radiosensitizations of Cerenkov radiation activated PDT (CR-PDT). (A, B) Illustration of TiO_2 and Titanocene photoagents for CR-PDT; (C, D) CR-PDT through intratumoural administration of TiO_2 and ^{64}Cu; (E–J) evaluation of CR-PDT through systemically administered photoagents and ^{18}F-FDG. Reproduced with permission from Ref. [136]. Copyright 2015 Springer Nature. (K) Radionuclides transform chemotherapeutics into phototherapeutics: (L, M) orthogonal cancer targeting strategy using nanomicelles; (N–R) response of multiple myeloma to CR-PDT. Reproduced with permission from Ref. [41]. Copyright 2018 Springer Nature.

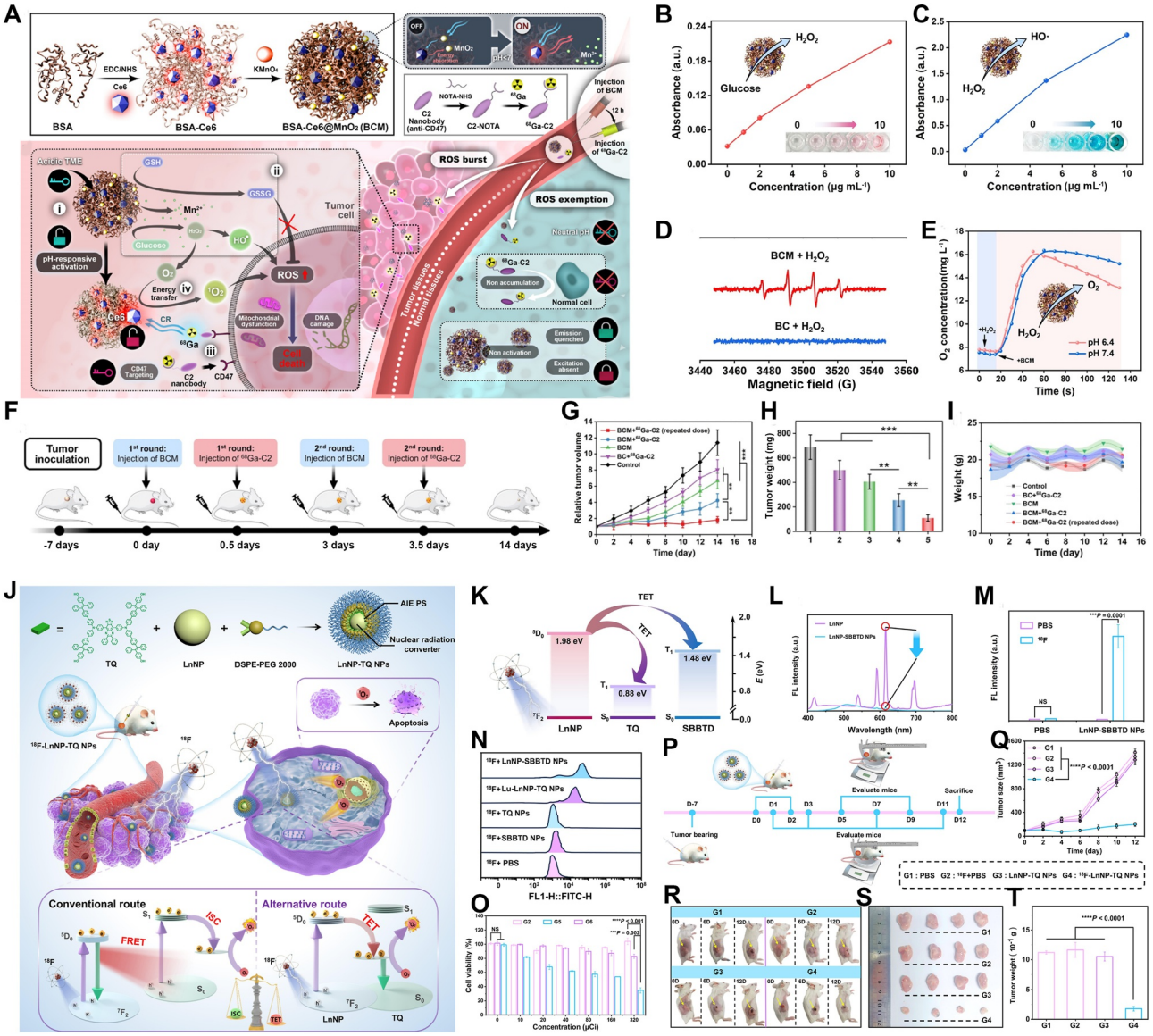

FIGURE 8 | Radionuclide derived CR luminescence to activate PDT. (A) Design of bifunctional BCM with pH-activatable nature for efficient and safe CR-PDT; (B–E) the multiple enzyme-mimicking activities of BCM; (F–I) in vivo anti-tumor efficacy and therapeutic mechanism of BCM-boosted CR-PDT. Reproduced with permission from Ref. [137]. Copyright 2023 Elsevier. (J) Schematic representation of a lanthanide NP and aggregation-induced emission (AIE) photosensitizer complex system (LnNP–TQNP) driven coupled triplet energy transfer (TET) for enhanced CR-PDT; (K, L) exploration of energy transfer and ROS generation; (M–O) in vitro radio-photodynamic therapeutic effects of hybrid system; (P–T) evaluation of therapeutic efficacy and biosafety in vivo. Reproduced with permission from Ref. [138]. Copyright 2025 American Chemical Society.

energy [130]. In terms of emission brightness, ^{90}Y, ^{124}I, and ^{68}Ga could emit higher intensities than those of ^{18}F and ^{64}Cu. As for the duration of emission, the luminescence from ^{89}Zr, ^{124}I, and ^{177}Lu lasts longer (several days) than those of ^{68}Ga and ^{18}F (several minutes) [129]. Thus, the intrinsic properties of each radionuclide determine its suitability for distinct biological and clinical applications [121, 131].

In addition to imaging applications, researchers have demonstrated that radionuclide decay produces sufficient luminescence to activate PSs, leading to the development of Cerenkov radiation activated photodynamic therapy (CR-PDT) [132, 133]. This approach effectively addresses the inherent limitation of light penetration in conventional PDT, thereby enabling treatment of deep-seated tumors and achieving improved therapeutic outcomes [126, 134, 135]. In 2015, Kotagiri et al. [136] reported the first use of radionuclide-derived CR luminescence to activate TiO_2, an oxygen-independent nano PS, overcoming both the shallow tissue penetration of external light sources and the dependence on oxygen for generating cytotoxic radicals (Figure 7A–J). In vivo administration of transferrin-coated TiO_2 nanoparticles together with clinical radionuclides (^{18}F and ^{64}Cu) resulted in either complete tumor remission or significantly prolonged median survival in mice. This work established the foundation for depth-independent CR-activated therapies using low-radiance-sensitive PSs. Three years later, Kotagiri et al. [41] advanced this concept by developing a radiopharmaceutical-induced photoactivation strategy to treat disseminated cancers.

As shown in Figure 7K–R, they employed an orthogonal-targeting approach with a photoactivatable titanocene, enabling selective tumor ablation while sparing resident stem cells and minimizing off-target effects.

Recently, Wu et al. [137] proposed a dual-locked CR-PDT strategy involving a radiosensitizer that combined a pH-activatable PS of BSA-packed chlorin e6 (Ce6) and MnO_2 nanodots (referred to BCM), and ^{68}Ga-labeled CD47-targeting C2 nanobody (donated as ^{68}Ga-C2) (Figure 8A–I). This system employed two activation mechanisms to achieve selective ROS generation at tumor sites, thereby improving both treatment safety and therapeutic efficiency. Once delivered to the tumor, ^{68}Ga-C2 emitted CR to activate Ce6, producing $^1O_2$ and this effect was further amplified by MnO_2 nanodots, which alleviated tumor hypoxia through catalytic oxygen generation. Li et al. [139] also developed an NH_2-$Ti_{32}O_{16}$ nanocluster (NTOC), which enabled efficient •OH generation when irradiated by CR derived from ^{18}F-FDG, providing a promising approach for cancer therapy. As shown in Figure 8J–T, An et al. [138] designed a strategy to enhance CR-PDT by doping lanthanides (Ln) into aggregation-induced emission (AIE) PSs. The resulting LnNP-TQNPs optimized radionuclide decay energy transfer and sensitized the AIE PSs via triplet energy transfer (TET)-mediated processes. Notably, when activated by the clinical radionuclide ^{18}F, LnNP-TQNPs generated abundant $^1O_2$ and significantly suppressed tumor growth.

Despite its inherent advantages in cancer diagnosis and therapy, the clinical application of CR-PDT remains challenging. One major limitation is the extremely low photon emission efficiency of CR, which accounts for less than 0.006% of the total energy released during the radioactive decay of ^{18}F [140, 141]. Another critical hurdle is achieving synchronized accumulation of both the radionuclide and the PSs at the same tumor site and at the optimal time. These obstacles present significant barriers to clinical translation and highlight the need for innovative strategies to enhance RT. To address these issues, several approaches have been explored to improve radionuclide–PS co-localization. First, systematic studies of the temporal biodistribution of intravenously administered radionuclides and PSs are required to ensure that their peak concentrations coincide at the tumor site. Second, conjugating the two components into a single hybrid entity offers a potential solution; however, this strategy carries the risk of toxic side effects during systemic circulation. Alternatively, local delivery methods such as intratumoral injection or transcatheter arterial embolization—can maximize therapeutic accumulation within the tumor while minimizing systemic exposure, thereby improving treatment safety and efficacy.

Overall, radiosensitization strategies based on high-*Z* materials, X-RDT, and CR-PDT represent paradigm-shifting approaches to enhance RT efficacy. However, challenges such as toxicity, limited energy conversion efficiency, low CR intensity, and barriers to clinical scalability continue to hinder their translation into clinical practice. Nevertheless, interdisciplinary innovations at the interface of nanotechnology, radiochemistry, and oncology hold great promise for overcoming the limitations of single-modality approaches and unlocking their full therapeutic potential. For instance, Zhu et al. [142] developed a cerium oxide (CeO_2)-based radiosensitizer formulated as CMCS/CeO_2&Ca nano-enema, which not only enhanced energy deposition through the high-*Z* property of Ce but also amplified ROS generation via the intrinsic catalytic activity of CeO_2. Furthermore, this system promoted macrophage polarization toward the M1 phenotype, thereby improving the tumor immune microenvironment and achieving radio-immunosensitization. Thus, the future of metal-based radiosensitization may lie in the design of smart multifunctional nanoplatforms capable of dynamically adapting to tumor biology, ensuring greater precision, safety, and therapeutic benefit in cancer treatment.

4 | Clinical Translations of Metal-Based Radiosensitization

Numerous studies have demonstrated the potential of metal-based radiosensitizers, particularly HfO_2 NPs and AuNPs, to amplify radiation effects through three primary mechanisms of physical dose enhancement, chemical radiosensitization of catalyzing ROS generation, and biological pathway modulation [2, 143]. Currently, no metal radiosensitizers have been approved by the U.S. Food and Drug Administration (FDA) for clinical use in RT; however, one HfO_2 NP formulation has received approval from the European Medicines Agency (EMA) [144]. Several candidates, including NBTXR3, AGuIX, and other formulations, are currently advancing through clinical trials, as summarized in Table 1 based on data from ClinicalTrials.gov.

NBTXR3 (commercially known as Hensify or EPE503) is a nanoformulation composed of crystalline HfO_2 NPs (50–100 nm) and has been approved for the treatment of several cancers via intratumoral injection [31]. The intratumoral delivery route offers the advantage of achieving markedly higher local doses compared to intravenous administration, thereby reducing acute systemic toxicity. The first clinical use of NBTXR3 was reported in 2011 in a phase I trial for patients with extremity soft tissue sarcoma (NCT01433068) [145]. This study primarily evaluated the feasibility, safety, and optimal dosing of NBTXR3 when administered alongside RT (50 Gy over 5 weeks at 2 Gy per fraction). Subsequently, a multicenter phase II–III clinical trial (NCT02379845) was conducted between 2015 and 2020 across several countries to further assess the safety and efficacy of NBTXR3 in patients with extremity and trunk wall soft tissue sarcoma, with participants randomized into two treatment arms [146]. Since then, additional trials have expanded the evaluation of NBTXR3 to other malignancies, including rectal cancer, liver cancer, prostate cancer, and head and neck squamous cell carcinoma (Table 1). Moreover, studies investigating NBTXR3 in combination with surgery, chemotherapy, and immunotherapy have shown encouraging results, demonstrating strong tumor control with minimal toxicity.

Another notable formulation is AGuIX, a polysiloxane-based nanoparticle chelating Gd, designed to provide both radiosensitization and MRI-based tumor imaging following systemic administration. The first phase I clinical trial, Radiosensitization of Multiple Brain Metastases Using AGuIX Gadolinium-Based Nanoparticles (NANO-RAD) (NCT02820454), was conducted between 2016 and 2019 in patients with brain metastases, with the primary aim of assessing safety, tolerability, optimal dosing, and the therapeutic benefit of combining AGuIX with RT [147].

TABLE 1 | Metal-based radiosensitizers in clinical trials.

Name	NPs type	Condition	Administration method	Clinical trail[a]
NBTXR3	HfO_2 NPs	Soft tissue sarcoma, rectal cancer, liver cancer, prostate cancer, head and neck squamous cell carcinoma, esophageal adenocarcinoma, metastasis from skin, bladder, cervix, NSCLC, breast carcinoma, etc.	Intratumoral injection	NCT01433068, Phase I, completed (2011–2015) NCT01946867, Phase I, recruiting (2014–2023) NCT02379845, Phase II–III, completed (2015–2020) NCT02465593, Phase I–II, terminated (2015–2021) NCT02721056, Phase I–II, terminated (2016–2020) NCT02805894, Phase I–II, terminated (2017–2020) NCT02901483, Phase I–II, terminated (2014–2020) NCT03589339, Phase I, recruiting (2019–) NCT04484909, Phase I, recruiting (2020–) NCT04505267, Phase I, recruiting (2021–) NCT04615013, Phase I, recruiting (2020–) NCT04834349, Phase II, terminated (2021–2022) NCT04862455, Phase II, active, not recruiting (2021–) NCT04892173, Phase II–III, recruiting (2022–) NCT05039632, Phase I–II, recruiting (2023–) NCT06667908, Phase II, recruiting (2024–)
AGuIX	Polysiloxane Gd-based NPs	Brain metastases, glioblastoma, advanced pancreatic adenocarcinoma, ductal adenocarcinoma of the pancreas, non-small cell lung cancer, unresectable pancreatic cancer, etc.	Intravenous administration	NCT02820454, Phase I, completed (2016–2019) NCT03308604, Phase I–II, recruiting (2021–) NCT03818386, Phase II, recruiting (2019–2025) NCT04094077, Phase II, terminated (2020–2021) NCT04789486, Phase I–II, recruiting (2021–) NCT04784221, Phase II, not yet recruiting (2024–) NCT04881032, Phase II, active, not recruiting (2021–) NCT04899908, Phase II, recruiting (2021–2025)

(Continues)

TABLE 1 | (Continued)

Name	NPs type	Condition	Administration method	Clinical trail[a]
Ferumoxytol	Iron oxide NPs	Liver cancers	Intravenous administration	NCT04682847, Phase I, active, not recruiting (2020–2024)

[a]Information was collected from Clinicaltrial.gov on August 20, 2025.

Subsequently, the indications were expanded to include advanced pancreatic adenocarcinoma, ductal adenocarcinoma of the pancreas, non-small cell lung cancer, and unresectable pancreatic cancer in the phase I–II clinical trial NCT04789486, which commenced in May 2021 [148]. This trial was designed to first establish a safe dose level (phase I), followed by an evaluation of treatment efficacy when AGuIX was combined with stereotactic body radiation therapy (SBRT). Results highlighted the dual advantage of AGuIX, offering both MRI contrast enhancement and radiosensitization via ROS amplification, thereby significantly improving treatment outcomes [39].

In addition, several other nanomaterials have advanced toward clinical applications in tumor radiosensitization. Ferumoxytol, an FDA-approved iron oxide NPs formulation (~30 nm), was initially indicated for the treatment of iron deficiency in patients with chronic kidney disease and end-stage renal disease [149]. Its scope of application has since broadened to include anemia, oncology, infectious and inflammatory disorders, regenerative medicine, and neural modulation via magnetic stimulation [150, 151]. In 2020, a phase I clinical trial (NCT04682847) was launched to investigate the use of Ferumoxytol in enhancing RT with the Elekta MR-Linac for patients with primary or metastatic hepatic carcinoma, hepatic atrophy, and liver cirrhosis [144]. AuNPs-based products are also progressing toward clinical translation, given the extensive preclinical evidence supporting their efficacy in cancer treatment. For example, CYT-6091, a formulation of tumor necrosis factor-α (TNF-α)-conjugated AuNPs, demonstrated dual radiosensitization and immunomodulatory activity in animal models when combined with RT [152]. This formulation has since advanced to phase I clinical trials (NCT00356980, NCT00436410) to determine its maximum tolerated dose in humans [153].

Although NBTXR3 and AGuIX have achieved important milestones in clinical translation, significant challenges remain. For example, the administration method limits the applicability of NBTXR3 in treating deep-seated tumors, and its energy dependence results in variations in RT efficacy between keV and MeV radiation sources [38]. Clinically, keV radiation sources are mainly applied to superficial tumors because of their shallow penetration depth (< 5 cm), representing only a small fraction of RT indications. In contrast, most deep-seated tumors require MeV radiation sources to ensure adequate dose delivery [19]. Although metal radiosensitizers demonstrate stronger photoelectric effects at keV energies, MeV sources are still widely used in clinical practice due to the requirement for treating deep-seated tumors with radiosensitizers [154]. For AGuIX, key limitations reported in trials include the risk of neurotoxicity from Gd deposition, low tumor enrichment efficiency, and the inherent trade-off between rapid renal clearance and sufficient nanoparticle accumulation [147]. These translational barriers underscore the need for further optimization in radiosensitizer design. Future research should prioritize the development of intelligent and efficient targeted delivery systems, sensitizers compatible with MeV radiation, and biodegradable metal-based platforms such as ultrasmall AuNCs. These strategies aim to minimize organ toxicity, enhance tumor selectivity, and incorporate immune-regulatory functions, ultimately advancing toward a synergistic therapeutic paradigm that combines precise local radiosensitization with systemic antitumor immunotherapy.

5 | Conclusions and Outlooks

RT remains a cornerstone in cancer therapy; however, its efficacy is often hindered by tumor radioresistance and severe side effects on healthy tissues. Over the past decades, advances in nanotechnology and radiobiology have introduced metal-based NPs as powerful radiosensitizers, offering new opportunities to overcome these challenges [155]. In this review, we have highlighted recent progress and three major strategies for metal-based radiosensitization: high-Z enhancement, X-RDT, and CR-PDT. Although these approaches show great promise, their clinical translation continues to be constrained by unresolved safety issues and technical limitations.

The first challenge lies in preclinical limitations. Most studies provide insufficient depth and data on hypoxia and the TME, despite their critical roles in reducing ROS generation and contributing to radioresistance [17]. Furthermore, passive tumor targeting through the EPR effect typically achieves less than 5% uptake, whereas active targeting strategies are hindered by protein corona formation, which interferes with targeting efficiency [35, 156]. Another concern is the mismatch between experimental and clinical radiation sources: preclinical models predominantly employ keV beams, which favor photoelectric effects, whereas clinical RT primarily utilizes MeV beams dominated by Compton scattering. This discrepancy often results in inconsistent findings between laboratory research and clinical practice [39]. The second major challenge involves barriers to clinical translation. High-Z nanoparticles tend to accumulate in the liver and spleen, raising concerns regarding long-term toxicity [7]. Additionally, large-scale manufacturing poses difficulties due to batch-to-batch variability in nanoparticle size and surface chemistry, complicating regulatory approval processes [31]. A further obstacle is the absence of validated biomarkers to identify patients most likely to respond to radiosensitizer-enhanced RT, limiting opportunities for effective patient stratification.

Herein, we aim to summarize actionable solutions to advance these technologies toward clinical maturity. (1) Advanced design of radiosensitizers. Although clinical needs must remain the priority, current research is often centered on multifunctional platforms and synergistic therapies that are conceptually appealing but rarely feasible in practice. Future designs should integrate input from researchers, clinicians, and patients to ensure alignment with real-world clinical demands. Emphasis should be placed on developing stimuli-responsive, precisely targeted, biodegradable, or renal-clearable NPs with high radiosensitizing efficiency and minimal toxicity. Next-generation platforms are expected to integrate radiosensitization with complementary therapies (chemotherapy, immunotherapy, etc.) and diagnostic tools (PET, MRI, etc.) to create multimodal theranostic systems. For instance, functionalized AuNPs have been shown to induce ICD, enabling RT to act as an in situ vaccine that suppresses metastasis and enhances abscopal effects [82]. Moreover, energy-tunable radiosensitizers can be engineered to optimize interactions with low-dose X-rays in external RT or radionuclides in internal RT, thereby reducing unnecessary radiation exposure and side effects. The emergence of artificial intelligence (AI) further provides an opportunity to guide the rational design of next-generation nanomaterials by addressing persistent challenges in toxicity and translation [157]. For example, Blind et al. [158] used GATE simulations to demonstrate linear and affine relationships between radiophysical parameters, irradiation dose, and nanoparticle concentration. This enabled the development of predictive models for radiophysical events and cell death, providing a powerful framework for the design and optimization of radiosensitizers.

Despite the clear advantages of multifunctional radiosensitizers, their structural and functional complexity often creates manufacturing challenges. Consequently, large-scale production and clinical translation require radiosensitizers to be designed with simplicity while retaining high therapeutic efficacy. (2) Clinical trial optimization. To improve preclinical relevance, it is essential to harmonize in vitro models (e.g., 3D spheroids and organoids) with in vivo systems such as patient-derived xenografts. Additionally, direct intratumoral administration (as in the case of NBTXR3) offers distinct benefits by bypassing systemic circulation, reducing toxicity, and achieving higher tumor retention compared with intravenous delivery. Radiosensitization could also be potentiated through co-administration with hypoxia-modifying agents (e.g., nimorazole) or DNA repair inhibitors (e.g., olaparib). (3) Patient stratification. Identifying and validating predictive biomarkers such as hypoxia-inducible factors will be critical for selecting patients most likely to benefit from radiosensitizer-mediated RT. Such biomarker-driven stratification can maximize therapeutic efficiency and accelerate personalized applications of radiosensitization in the clinic.

Metal-based radiosensitization represents a paradigm shift in oncology, offering precision and synergy with emerging modalities of X-RDT and CR-PDT. Although significant challenges remain, particularly those related to toxicity, biodistribution, and clinical translation the future of the field lies in interdisciplinary innovation. Advances in the design of novel metal-based nanomaterials, when combined with gene engineering, AI-assisted material optimization, and multimodal theranostic platforms, hold great promise for addressing current barriers. These next-generation systems will enable intelligent, tumor-adaptive radiosensitization strategies that integrate localized radiation enhancement with systemic immune modulation. Overall, such innovations are expected to accelerate the realization of truly personalized radiotherapy, delivering curative outcomes with minimal collateral damage to normal tissues.

Author Contributions

Xiao-Xia Wu: conceptualization, data curation, funding acquisition, methodology, resources, writing – original draft. **Ding-Hu Zhang:** conceptualization, funding acquisition, resources. **Chuan Hu:** conceptualization, funding acquisition, resources. **Yi-Nan Ding:** conceptualization, funding acquisition, resources. **Kun Chen:** conceptualization, resources. **Yi Jiang:** methodology, resources. **Jun Luo:** methodology, resources. **Fei Cao:** resources. **Wei-Yuan Hao:** resources. **Bin-Yan Zhong:** funding acquisition, resources. **Jie Lin:** funding acquisition, writing – review and editing. **Dong Xu:** writing – review and editing. **Jia-Ping Zheng:** funding acquisition, project administration, supervision, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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