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Review Article

Advancements in Radiotherapy: The Role of Metal Nanomaterials in Enhancing Therapeutic Outcomes

Jie Wang[1]*, Mingfen Chen[3], Changan Chen[1], Boshu Zheng[1], Rong Wang[1], Yuxuan Guo[4], Yian Wang[4], Xianjie Jiang[5] and Jun Long[2]*

[1]*Department of Pathology and Institute of Oncology, The School of Basic Medical Sciences & Diagnostic Pathology Center, Fujian Medical University, Fuzhou, Fujian, China*

[2]*Shenzhen Key Laboratory of Energy Electrocatalytic Materials, Shenzhen Key Laboratory of Polymer Science and Technology, Guangdong Provincial Key Laboratory of New Energy Materials Service Safety, College of Materials Science and Engineering, Shenzhen University, Shenzhen, Guangdong, China*

[3]*Department of Radiation Oncology, The Second Affiliated Hospital of Fujian Medical University, Fujian Medical University, Quanzhou, Fujian, China*

[4]*The Key Laboratory of Model Animals and Stem Cell Biology in Hunan Province, School of Medicine, Hunan Normal University; The Engineering Research Center of Reproduction and Translational Medicine of Hunan Province, Changsha, Hunan, China*

[5]*Hunan Key Laboratory of Cancer Metabolism, Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan, China*

Abstract

Radiation therapy stands as a cornerstone in the arsenal against cancer. The burgeoning field of nanotechnology has ushered in a slew of innovative strategies for combating this malady. the efficacy of radiation therapy. This novel approach has captivated the radiation among these, the deployment of radiosensitizers, particularly those based on metal nanoparticles, marks a significant stride in augmenting oncology community, heralding a potent modality for cancer eradication. Metal nanoparticles, characterized by their high atomic numbers, exhibit distinctive photoelectric absorption properties, rendering them exceptionally efficacious as radiosensitizers. This review encapsulates the recent breakthroughs and the mechanistic insights into the application of metal nanoparticles in cancer radiotherapy. The insights gleaned from these advancements lay the groundwork for refining and clinically integrating the next generation of radiosensitizers derived from metal nanoparticles.

Keywords: Radiotherapy; Metal nanomaterials; Radiosensitizer

Introduction

Radiation therapy is a key treatment option for malignant tumors, utilizing various radiations like X-rays, gamma rays, electrons, neutrons, and charged particles to target cancer cells directly or indirectly by generating free radicals [1]. Despite advances in radiotherapy equipment and treatment protocols, such as combined radiochemotherapy and neoadjuvant chemotherapy with radiotherapy, recurrence and metastasis still pose significant challenges [2,3]. A major obstacle is the close proximity of tumors to normal tissues and Organs at Risk (OAR), which limits the maximum radiation dose deliverable to the tumor [4]. This has led to increased interest in radiosensitizers, compounds designed to enhance tumor cell sensitivity to ionizing radiation, as a crucial development in radiation oncology.

Metallic nanomaterials, especially those with high atomic numbers, are increasingly recognized for enhancing radiation therapy doses due to their strong photoelectric absorption [5,6]. These materials utilize the Enhanced Permeability and Retention (EPR) effect for preferential tumor accumulation, enhancing radiation effects while exhibiting low systemic clearance [7,8]. They are chemically inert and biocompatible, minimizing health risks and biotoxicity, making them suitable for clinical use [9]. However, their biodistribution can vary based on size, shape, surface chemistry, and modifications [10]. Despite efforts to standardize size for consistent quality, the radiosensitizing efficacy of these nanomaterials can differ across radiation doses and tumor models. Issues like surface coating degradation of gold nanoparticles under high radiation doses can reduce their effectiveness [11]. Moreover, their limited blood circulation time and uptake by immune cells within the tumor microenvironment can further limit their practicality [12].

Recent developments have led to the creation of novel metal nanomaterials designed to address these challenges in cancer radiotherapy. Advances in surface modification techniques have improved nanoparticle absorption, added stealth characteristics, and facilitated targeted tumor delivery. This review compiles the latest advancements in using metal nanomaterials as radiosensitizers, providing a detailed exploration of the physical, chemical, and biological mechanisms involved, thus supporting the continued evolution and application of metal nanomaterial-assisted radiotherapy.

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***Corresponding author:** Jie Wang, Department of Pathology and Institute of Oncology, The School of Basic Medical Sciences & Diagnostic Pathology Center, Fujian Medical University, Fuzhou, Fujian, China, E-mail: helenajie-wang@163.com

Jun Long, Shenzhen Key Laboratory of Energy Electrocatalytic Materials, Shenzhen Key Laboratory of Polymer Science and Technology, Guangdong Provincial Key Laboratory of New Energy Materials Service Safety, College of Materials Science and Engineering, Shenzhen University, Shenzhen, Guangdong, China, E-mail: longjun1988@126.com

Gold Nanoparticles

Gold Nanoparticles (GNPs) stand at the forefront of nanomaterial research, with extensive studies dedicated to their enhancement. Recent scientific efforts are focused on refining surface functionalities of GNPs to attain superior biocompatibility, extended circulation times, minimized cytotoxicity, enhanced targeting abilities, and improved tumor uptake.

Surface modification enhances the biocompatibility and circulation time of gold nanoparticles

Proteins are increasingly used for nanoparticle surface modification, particularly in the development of albumin-coated gold nanoparticles (Alb-GNPs) by Yao et al.

These nanoparticles demonstrate excellent biocompatibility, biosafety and biodegradability, alongside versatile surface modification options. Alb-GNPs have shown remarkable colloidal stability and prolonged blood circulation, with an average size of 205.06 nm ± 1.03 nm. In testing, they achieved A Radiosensitization Enhancement Ratio (SER) of 1.432, enhancing radiotherapy efficacy in a human non-small cell lung cancer mouse model while sparing healthy tissue [13].

Additionally, Dendrimer-Entrapped Gold Nanoparticles (Au DENPs) have emerged as effective gene carriers, modified with amphiphilic ions to enhance biocompatibility and gene transfection efficiency. Yang et al. [14] developed a dual-mode nano-sensitizer using dendrimer-based gold nanoparticles for tumor radiotherapy, employing polyamidoamine dendrimers modified with 1,3-propanesulfonamide. These nanoparticles effectively deliver siRNA targeting the downregulation of hypoxiainducible factor-1α (HIF-1α) and its genes, reducing tumor invasion [14]. Another innovation, multifunctional dendrimer peptide-based nanoparticles (Au@SPP@DOX), uses amphiphilic micelles formed from polylysine, polyethylene glycol (PEG), and stearic acid (SA) to encapsulate Doxorubicin (DOX) and load gold nanoparticles (AuNPs). These nanoparticles exhibit excellent biocompatibility and accumulate at tumor sites via the EPR effect [15]. Furthermore, the Au@SA-QBA system, combining Sodium Alginate (SA) with 8-Quinolineboronic Acid (QBA) and modified with SA-QBA, responds to H2O2, inhibits oxidative stress, and reduces angiogenic factor expression. In vivo, this system significantly improved vascular normalization and increased perfusion units and endothelial cell coverage, thus enhancing radiotherapy efficacy [16].

Enhancing the radiotherapeutic efficacy of gold nanoparticles by loading drugs

The strategic loading of various drugs onto GNPs has proven to significantly amplify radiotherapy outcomes. Doxorubicin (DOX), for example, becomes protonated in the acidic tumor environment, enhancing its release from SPP-coated GNPs (Au@SPP@DOX). Under low-dose radiation, this triggers Reactive Oxygen Species (ROS) production, leading to mitochondrial dysfunction, cell cycle arrest, and tumor cell apoptosis, thereby boosting anti-tumor effects [15]. Similarly, gallic acid-loaded GNPs (GA-GNPs) effectively inhibit survival of U251 Glioblastoma Multiforme (GBM) cells more than GNPs alone, enhancing radiation-induced cell death by arresting the cell cycle and inducing apoptosis, indicated by increased BAX protein levels and decreased BCL-2 expression [17]. Wang et al. developed a novel gold nanoparticle (AuHQ), conjugating 8-hydroxyquinoline (HQ) with GNPs, creating a system that chelates iron ions to inhibit ROS production in tumor cells and reduce key angiogenic factor expression. In vivo, AuHQ treatment enhanced tumor vascular normalization, increased pericyte coverage, and blood perfusion, improving radiotherapy efficacy by 38% compared to unmodified Au NPs, and markedly increasing Au accumulation in the tumor [18].

Surface modification enhances the targeting of gold nanoparticles

Surface modification enhances the targeting capabilities of GNPs in cancer therapy. Folic acid (FA), stable and non-immunogenic, is an effective ligand due to its cancer cell specificity and straightforward conjugation. Ding et al. [19] developed GNPs coated with polyethylene glycol, FA, and a reactive sulfonamide group, 1,3-Cyclohexanedione (CHD), which react with proteins under oxidative stress, enhancing tumor fixation and retention. This significantly improves CT imaging and radiotherapy in mice [19]. Moreover, GNPs functionalized with anti-HER-2 aptamers deliver dasatinib precisely to breast cancer cells, enhancing targeted therapy outcomes [20]. Anti-CXCR4 antibody-conjugated GNPs intensify oxidative stress and DNA damage, boosting radiotherapy efficacy for Triple-Negative Breast Cancer (TNBC) [21]. PEGylated GNPs linked to Prostate-Specific Membrane Antigen (PSMA) antibodies induce a bystander effect on non-irradiated cells through medium transfer [22]. Zhao et al. created mitochondria-targeted GNPs (dAuNP-TPP) by adding triphenylphosphine and CHD to the nanoparticle surface, improving CT imaging and radiotherapy outcomes while ensuring high mitochondrial accumulation. This approach depletes ATP and causes significant mitochondrial damage, providing a potent radiosensitizing effect for breast tumor treatment. This marks a new era in precise and effective tumor treatment with subcellular targeting strategies (Figure 1) [23].

Figure 1: Endogenous ROS-mediated covalent immobilization of gold nanoparticles in mitochondria in tumor radiotherapy. Reprinted (adapted) with permission from [23]. Copyright {2022} American Chemical Society.

Recent studies have exploited the tumor microenvironment's unique features such as hypoxia and acidity, alongside tumor homing properties, to enhance the targeting capabilities of GNPs. Geng et al. [24] developed hypoxia-responsive gold nanoparticles (AuNNP@PAA/NIC NPs) that aggregate in situ within tumors under hypoxic conditions, facilitating second near-infrared window (NIR-II) photoacoustic (PA) imaging and improving radiosensitization. This aggregation increases nanoparticle accumulation and retention, with extended absorption into the NIR-II range due to

plasma coupling effects, significantly boosting PA intensity and enhancing treatment outcomes [24]. Zhang et al. created GNPs that aggregate in acidic conditions, serving as dual sensitizers for Radiotherapy (RT) and Photothermal Therapy (PTT) [25]. Wang et al. focused on improving nanoparticle transcytosis by degrading extracellular matrix components like collagen. Their collagenase-conjugated nanoparticles (Col-TNP) dissociate in acidic tumor environments, enhancing tissue penetration and radiosensitization in pancreatic cancer [26]. Additionally, the use of Mesenchymal Stem Cells (MSCs) for their tumor-homing capabilities has shown promise. A study demonstrated that MSCs effectively deliver GNPs to breast tumor xenografts in mice, enhancing radiation therapy efficacy [27].

Enhanced immunogenic cell death (ICD) induced by gold nanoparticles

Studies have also explored using GNPs to boost anti-tumor immunity. Qin et al. innovatively used tumor cells as bioreactors to produce biogenic gold nanoparticles (Au@MC38), which enhanced the effectiveness of radiotherapy and amplified immune responses. When combined with radiotherapy, Au@MC38 significantly increased radiation-induced DNA damage and ROS production, leading to greater cell apoptosis and necrosis. Its homologous targeting ability and promotion of cell phagocytosis resulted in exceptional tumor distribution. Moreover, local radiation triggered immunogenic cell death, initiating strong immune responses, evidenced by a notable increase in CD8a dendritic cells in treated mice [28]. Similarly, He et al. found that gold nanoparticles (AuNPs) could enhance immunogenic cell death induced by radiotherapy in glioblastoma, demonstrating the broad potential of AuNPs in cancer therapy [29].

Selection of gold nanoparticles radiation dose

Recent research highlights the significant radiosensitizing effects of GNPs across various radiation doses, demonstrating their potential to enhance radiotherapy outcomes. One study on breast cancer rotational radiotherapy used GNPs with a 190 kV X-ray beam, achieving optimal dose enhancement and nanoparticle internalization with a dose enhancement factor of 1.33 ± 0.06 [30]. Another study explored the radiosensitizing effects of larger GNPs with a 200 MeV proton beam, showing a substantial increase in cell mortality-27.1% at 2 Gy and 43.8% at 6 Gy-compared to proton irradiation alone. This investigation also assessed the Linear Energy Transfer (LET) dependency of GNPs radiosensitization by irradiating cells at different positions along the proton depth-dose curve. Although combination therapy consistently resulted in increased cytogenetic damage across all depths compared to just proton therapy, the study could not conclusively determine the incremental LET increase [31].

Gadolinium-Based Nanoparticles

Gadolinium (Gd) is prized for MRI imaging and, with recent advancements, Gadolinium-Based Nanoparticles (GdNPs) have emerged as effective radiosensitizers in radiation therapy. Notably, AGuIX nanoparticles, composed of a polysiloxane network with Gd chelates, enhance DNA damage by disrupting homologous recombination repair pathways, thereby amplifying radiotherapy sensitivity via iron death promotion. Although AGuIX's radiosensitizing effects are well-documented, the precise cellular damage mechanism remains debated. Sun et al. discovered that AGuIX primarily impairs homologous recombination, leading to increased DNA damage, with iron death, potentially influenced by targeting the NRF2-GSH-GPX4 signaling pathway, playing a key role in radiosensitization (Figure 2) [32].

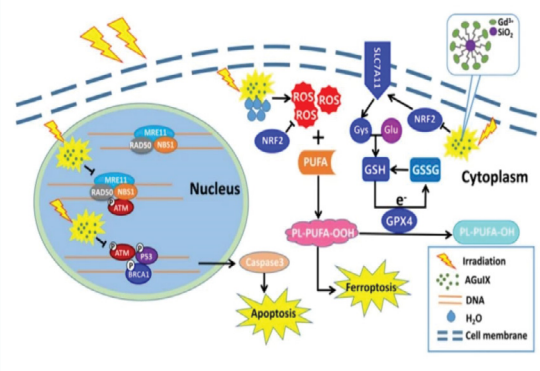

Figure 2: AGuIX nanoparticles enhance ionizing radiation-induced ferroptosis on tumor cells by targeting the NRF2-GPX4 signaling pathway. Reprinted (adapted) with permission from [32]. Copyright {2022} BioMed Central (Part of Springer Nature) under CC-BY 4.0.

Additionally, Zhang et al. developed Ovalbumin (OVA)-GdZol NPs, therapeutic gadolinium-based metal bisphosphonate nanoparticles, by chelating Gd ions with zoledronic acid and stabilizing them with ovalbumin. These nanoparticles significantly enhance radiosensitivity under X-ray irradiation, reduce cell colonies, and increase γH2AX-positive cells, indicating effective radiotherapy. Crucially, they also facilitate the maturation of dendritic cells and M1 polarization of macrophages, enhancing their role as immune adjuvants. Their use with X-ray irradiation significantly reduces tumor volume, improves survival rates, and decreases lung metastasis in osteosarcoma models, suggesting potential as dual-function agents for integrating vaccination with radiotherapy in cancer treatments (Figure 3) [33].

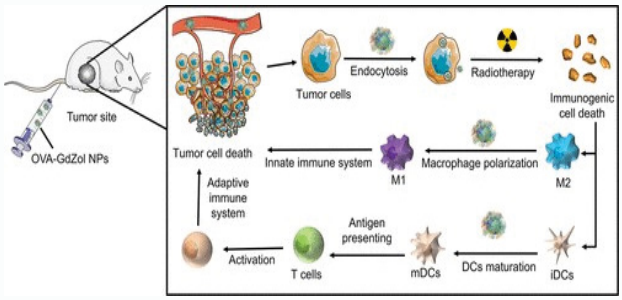

Figure 3: Gadolinium-based metal-bisphosphonate nanoparticles improve the radiotherapeutic effects by eliciting immune activation effects. Reprinted (adapted) with permission from [33]. Copyright {2022} American Chemical Society.

Iron-Based Nanoparticles

Metal-organic frameworks (MOFs) represent a sophisticated class of crystalline materials distinguished by their ordered porosity and the harmonious integration of organic ligands with inorganic metal ions or clusters [34]. Their remarkable properties, such as an expansive specific surface area, adjustable pore dimensions, straightforward functionalization, and the presence of numerous active sites, render them exceptionally versatile for a wide array of applications. Iron-based MOFs (Fe-MOFs), in particular, have

garnered extensive research interest due to their advantageous attributes and chemical versatility [34]. D-arginine-loaded MIL-100 (Fe)-based MOF nanoparticles, a prototypical MOF synthesized through the coordination between iron (III) ions and metabenzoic acid, escalate the radiosensitivity of osteosarcoma, simultaneously impeding lung metastasis in vivo. When administered to tumor sites, the trivalent iron ions within these nanoparticles engage in the Fenton reaction with hydrogen peroxide to amplify the production of ROS. Furthermore, the ROS generated by iron can react with Nitric Oxide (NO) derived from D-Arginine, leading to the formation of peroxynitrite anions (ONOO-) and other Reactive Nitrogen Species (RNS), which exert tumoricidal effects. D-Arginine, an enantiomer of L-Arginine that is metabolically stable, plays a critical role in this context by generating NO and suppressing hypoxiainducible factor-1α (HIF-1α), thereby mitigating tumor hypoxia. Moreover, the strategic incorporation of D-Arginine into these nanoparticles, along with the surface decoration using Hyaluronic Acid (HA), ensures targeted binding to cancer cells [35]. Xue et al. demonstrated that trimethyl iron nanoMOFs enhance radiotherapy by promoting electron diffusion under γ-radiation, leading to water radiolysis and hydroxyl radical production that destroys cancer cells at the nanoscale. Additionally, these nanoMOFs function as a "Trojan horse," delivering gemcitabine monophosphate (GemMP) into cancer cells to disrupt DNA repair mechanisms. The dual action mechanisms of nanoMOFs and doped Gem-MP synergistically amplify radiation efficiency, with a radiation enhancement factor of 1.8 [36]. The exploitation of the magnetic attributes of iron-based nanoparticles has marked a significant leap forward in the quest to amplify the efficacy of radiotherapy. Folic acid-coupled temozolomide-loaded SPION@PEG-PBA-PEG magnetite nanoparticles (TMZ-MNP-FA NPs) exemplify this progress, enhancing both Magnetic Resonance Imaging (MRI) as contrast agents and the cytotoxic effects of combined thermotherapy and radiotherapy, achieving a dose-enhancement factor of 1.65 [37]. Iron oxide (Fe3O4) nanoparticles further enhance radiotherapy for lung adenocarcinomas by enabling targeted delivery of siBIRC5 and Antisense Oligodeoxynucleotides (AS-ODN), advancing Magnetic Nanoparticle-Enhanced Radiotherapy (MNERT) strategies (Figure 4) [38]. These nanoparticles exploit their magnetic properties for localized hyperthermia under external magnetic fields and improved targeting through magnetic guidance, maximizing tumor eradication while sparing healthy tissue. Additionally, their MRI contrast enhancement capability enables precise tumor imaging, facilitating more accurate radiotherapeutic interventions. By leveraging the unique magnetic properties of these nanoparticles, researchers are developing more effective, targeted, and less invasive therapeutic modalities.

Hafnium-Based Nanoparticles

The development of hafnium (Hf)-based Metal-Organic Framework (MOF) nanoparticles has significantly advanced radiosensitization in radiotherapy. These nanoparticles, such as the UiO-66-NH2 (Hf) MOF designed by Zhou et al., exhibit properties that counteract radiotherapy resistance and enhance treatment outcomes for cancers like esophageal cancer. With a diameter under 100 nm, UiO-66-NH2 (Hf) nanoparticles show remarkable stability in physiological environments and improve radiosensitivity due to their enhanced X-ray absorption properties, effectively inducing apoptosis in cancer cells. Their effectiveness has been validated through extensive in vitro and in vivo

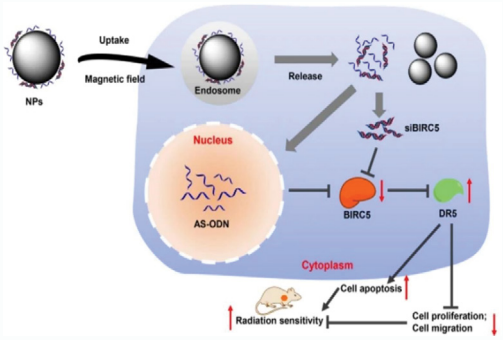

Figure 4: Fe3O4 magnetic nanoparticles inhibit tumor cell migration and increase DNA damage to enhance radiotherapy for lung adenocarcinoma via delivery of siBIRC5 and AS-ODN. Reprinted (adapted) with permission from [38]. Copyright {2021} BioMed Central (Part of Springer Nature) under CC-BY 4.0.

studies, positioning them as potent radiosensitizers [39]. Further innovations include nanoscale hafnium-based MOFs (Hf-nMOFs) encapsulating 3bromopyruvic acid (3-BrPA), developed by Fu et al. [40] this formulation enhances X-ray absorption and DNA damage while disrupting cancer cell metabolism by blocking glycolysis with 3-BrPA, effectively overcoming radiotherapy resistance and enhancing treatment efficacy [40]. Additionally, the introduction of folate-modified hafniumbased MOFs (HfMOF-PEG-FA) combined with imiquimod, a Toll-Like Receptor 7 (TLR7) agonist significantly increases radiation dose deposition, ROS generation, and promotes apoptosis through DNA Double-Strand Breaks (DSBs) and immune response activation, providing a multifaceted approach to cancer therapy [41].

The development of supramolecular nanoplatforms using hafnium oxide groups significantly advances cancer therapy by combining targeted drug delivery, advanced imaging, and enhanced radiotherapy outcomes. These nanoplatforms, coated with hydrofluoric acid and encapsulated in oleic acid and monomethoxy poly(ethylene glycol)-poly(ε-caprolactone) copolymer shells, specifically target cancer cells for precise drug accumulation and controlled release. Encapsulation of doxorubicin (DOX) within these platforms ensures targeted tumor delivery and responsive DOX release based on tumor environment triggers. This method has effectively lowered the IC50 values of DOX, indicating that lower drug doses are required compared to unencapsulated DOX, with minimal cytotoxicity observed in vitro. Additionally, X-ray irradiated cancer cells containing these nanoplatforms exhibit significantly higher mortality rates than those without, enhancing the cytotoxic effects of radiotherapy and potentially reducing necessary radiation doses [42]. Moreover, radiotherapy-activated hafnium oxide nanoparticles (NBTXR3) not only improve radiotherapy efficacy but also induce systemic anti-tumor responses. NBTXR3 increases immune cell infiltration in both treated and distant, untreated tumors, demonstrating a pronounced abscopal effect mediated primarily by CD8+ lymphocyte T-cells. This suggests NBTXR3's potential to convert the irradiated tumor into an *in situ* vaccine, promoting immune attacks on distant metastases [43].

Silver-Based Nanoparticles

Silver sulfide nanoparticles coated with alginate (Ag2S@Alg) act as potent radiosensitizers by generating ROS upon X-ray irradiation [44]. This ROS generation damages DNA, increasing

the cytotoxic effects of radiation on cancer cells. Additionally, alginate films embedded with silver nanoparticles (AgNPs-Alg film) introduce a novel method in radiotherapy. This technique uses the radiosensitizing properties of silver nanoparticles and the biocompatible and flexibility of alginate films, providing a versatile and effective adjunct to enhance radiotherapy [45].

Platinum-Based Nanomaterials

Platinum-based nanocrystals represent a significant advancement in the fields of biomedical imaging and radiotherapy. Ma et al. developed platinum-based nano-sized metal-organic frameworks (NMOF545@Pt) that enhance multimodal imaging and synergistic cancer therapy. These frameworks improve T1 relaxation, photoacoustic effects, and X-ray absorption, significantly boosting the efficacy of PTT and RT. Demonstrated both in vitro and *in vivo*, NMOF545@Pt effectively inhibits tumor growth without noticeable side effects or organ damage (Figure 5) [46]. Additionally, alginate-coated platinum nanoparticles (Pt@Alg) have been used as radiosensitizers in breast cancer treatments, enhancing X-ray therapy effects [47]. Behrends et al. attribute the radiosensitizing effect of biocompatible PtNPs to their catalytic action, rather than increased proton energy deposition [48]. This suggests a nuanced mechanism by which PtNPs amplify the destructive effects of radiotherapy on cancer cells, offering a promising avenue for the development of more effective cancer treatment protocols that minimize harm to healthy tissues.

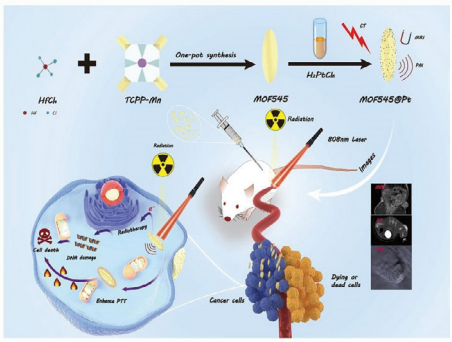

Figure 5: Schematic illustration of the preparation of NMOF545@Pt nanoparticles to integrate tumor CT/MRI/PAI imaging and PTT/RT. Reprinted (adapted) with permission from [46]. Copyright {2022} Frontiers under CCBY 4.0.

Palladium-Based Nanoparticles

Palladium-based nanoparticles, specifically sheet-like palladium nanosheets (Pd NSs), are emerging as effective radiosensitizers in radiotherapy. Yao et al. have demonstrated that these nanosheets, approximately 14 nm in diameter and 2nm thick, exhibit excellent cellular compatibility. Remarkably, Pd NSs alone do not affect cell viability even after 130 hours, highlighting their biocompatibility. However, their radiosensitizing capabilities become evident under X-ray irradiation, significantly reducing cancer cell viability by inducing more DSBs and enhancing ROS production compared to X-ray alone, resulting in higher apoptosis rates. In vivo studies confirm the radiosensitizing efficacy and biocompatibility of Pd NSs, suggesting they can improve radiotherapeutic outcomes with lower X-ray doses, potentially enabling more effective and safer radiotherapy protocols [49].

Multi-Metallic Nanoparticles

Multi-metallic nanocomposites are a breakthrough in nanotechnology, featuring complex metal-based hybrid structures with diverse compositions and morphologies. These composites combine at least two different metals, leveraging their collective properties to advance cancer therapy and imaging. Their multifunctionality extends to drug delivery, where their unique structural and chemical characteristics enable targeted and controlled release of therapeutic agents into the tumor microenvironment. This approach not only maximizes drug efficacy but also significantly reduces systemic side effects, offering a comprehensive strategy for cancer treatment.

Gold-iron composite nanoparticles

Gold-iron composite nanoparticles like Fe3O4@AuNPs (magnetic gold nanoparticles) are advancing cancer therapy by enhancing the synergistic effects of RT and PTT. Their magnetic properties allow for precise localization, while gold's plasmonic properties enable effective photothermal treatment [50]. Additionally, a multifunctional nanohybrid based on Graphene Oxide (GO), iron oxide, and gold nanoparticles improves dose factors for both RT and Radiofrequency (RF) treatment, with enhancement factors of 1.63 for RT and 2.63 for RF [51]. These nanoparticles have also shown significant radiosensitizing potential in glioblastoma radiotherapy and melanoma treatment, demonstrating their effectiveness across cancer types [52,53].

Gold palladium nanoparticles composite

Bimetallic nanoradiosensitizers, particularly those combining gadolinium and gold, such as Au@DTDTPA(Gd), are enhancing radiotherapy efficacy against glioblastoma by preventing tumor invasion and targeting cancer stem-like cells [54]. Gadolinium oxide and gold nanoparticles capped with bovine serum albumin (Gd2O3@BSA-Au NPs) amplify radiotherapy effects and have been validated in vivo for their exceptional radiosensitization capabilities without harming healthy organs [55]. These gold-iron and gold-palladium composites represent innovative approaches in oncology, offering multifaceted cancer treatment strategies.

Nanoparticles of gold and other metal compounds

The development of gold-based nanocomposite nanoparticles, combined with other metals, harness the unique synergistic properties of gold with other metals for more effective cancer targeting and treatment. Li et al. developed Ag@Au core-shell nanoparticles coated with Polyethylene Glycol (PEG) and GSGNPs adaptors, demonstrating superior tumor targeting and retention, notably prolonging survival in glioblastoma mouse models [56]. Xiao et al. introduced metal semiconductor nanoparticles (Au@AgBiS2), enhancing ROS production and DNA damage during radiotherapy, and inducing ferroptosis to prevent tumor growth and metastasis in BALB/c mice (Figure 6) [57]. Yang's study on Au-Pt nanoparticles revealed their ability to increase DNA damage and modulate the tumor microenvironment by decomposing H2O2 to O2, enhancing therapeutic efficacy [58]. Xu et al. explored copper selenide-coated gold nanoparticles (Au@Cu2-xSe NPs), which inhibit autophagy and DNA repair in tumor cells, significantly boosting radiotherapy effectiveness for glioblastoma [59].

Eutectic gallium indium

Eutectic Gallium Indium (EGaIn), a liquid metal alloy notable for its exceptional thermal conductivity, high dielectric constant, infinite deformability, and metallic conductivity, is ideal for flexible composite materials. Its unique properties have spurred interest

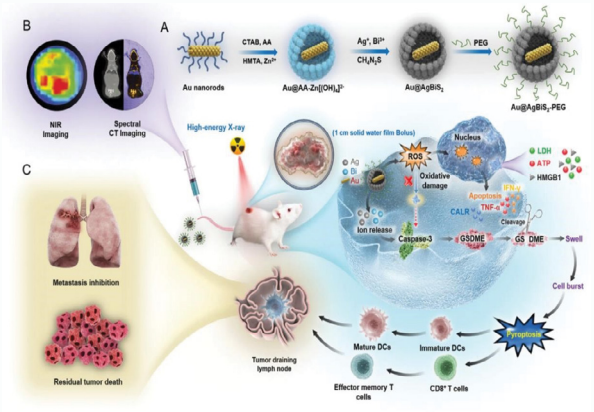

Figure 6: Schematic illustration of Au@AgBiS2-PEG design and anti-tumor application. Descriptions provided for the indicated panels (A–C). The synthesis of multifunctional Au@AgBiS2 core-shell structures using the intermediate layer conversion method (A). This composite exhibits the high efficacy as a radiosensitizer owing to the high level of ROS production and as an excellent pyroptosis inducer for boosting antitumor immunity (B) and effectively preventing lung metastasis (C). Reprinted (adapted) with permission from [57]. Copyright {2023} John Wiley and Sons under CC-BY 4.0.

in applications like tumor radiotherapy enhancement. Liu et al. developed RGD-PEG-PAA-MN nanoparticles, encapsulating EGaIn via ultrasonication to form nanoparticles that target tumor cells, responding to the acidic tumor microenvironment [60]. These nanoparticles convert Near-Infrared (NIR) light into heat and generate ROS under NIR or X-ray irradiation, enhancing therapeutic efficacy through both photothermal and radiosensitizing effects. Additionally, they improve radiation sensitivity under hypoxic conditions. Experiments with Hela tumor-bearing mice showed that RGD-PEG-PAA-MN@LM nanoparticles significantly reduced tumor volume and nearly eradicated tumors after NIR and X-ray treatment, demonstrating superior synergistic effects in cancer treatment.

Furthermore, the development of EGaIn nanoparticles coated with sodium alginate (Alg) (EGaIn@Alg NPs) represents a significant advancement in nanotechnology for cancer therapy. The Alg coating prevents aggregation and oxidation in aqueous solutions, preserving EGaIn nanoparticle integrity and functionality. These nanoparticles form a gel in tumor microenvironments, particularly with calcium ions, enhancing targeted delivery and retention at tumor sites. This gelation maximizes therapeutic impact while reducing systemic effects. Under X-ray irradiation, EGaIn@Alg NPs generate ROS, damaging DNA and inducing apoptosis in cancer cells. They also serve as contrast agents in imaging techniques like CT and Photoacoustic Tomography (PAT), improving tumor localization and monitoring treatment progress. This dual functionality aligns with theranostic principles, combining therapeutic and diagnostic capabilities for personalized medicine [61].

Hafnium nanoparticles in composite with other metals

Bao et al. developed a sophisticated nanometal-organic framework (NMOF) utilizing Hf clusters and Mn(III)-porphyrin ligands, enhanced with folic acid for targeted cancer therapy. This multifunctional theranostic platform excels in MRI/CT/PAI imaging and supports PTT and RT, offering synergistic effects. It significantly outperforms existing contrast agents, with 1.7 and 3-5-times improvements in X-ray attenuation and T1 relaxation rates, respectively. The Mn(III)-porphyrin ligand converts H2O2 into O2, effectively suppressing tumor growth while sparing healthy tissue [62]. Furthermore, the cGAMP/Hf12-Ir MOL acts as both a potent radiosensitizer and a nanocarrier for STING agonists, enhancing cGAMP uptake in immune cells. This leads to increased maturation and activation of Antigen-Presenting Cells (APCs), inflammatory cytokine release, and type I interferons, amplifying immune responses and transforming tumors into immunologically active sites. The MOL structure also sensitizes tumors to radiation, reducing cancer cell proliferation and promoting the release of Tumor-Associated Antigens (TAAs) and damage-associated molecular patterns (DAMPs) from ICD. By binding to anti-PD-L1 antibody, it disrupts cancer cells' immunosuppressive shield and rejuvenates T cells for effective cancer cell elimination. This dual action strengthens the innate and adaptive immune linkage and induces a robust systemic anti-tumor response, positioning cGAMP/MOL as a promising candidate for an X-ray activatable cancer vaccine [63].

Other metal composite nanoparticles

Rageh MM and colleagues developed a novel honey-based method to synthesize Iron Nanoparticles (IONPs) and iron-silver bimetallic nanoparticles (IO@AgNPs). In studies comparing these with High-Dose Radiation (HRD) therapy, their combination with Low-Dose Radiation (LRD) significantly increased DNA damage by approximately 75% and reduced Ehrlich tumor growth by about 45%. Additionally, this method showed reduced hepatic toxicity, with half the Alanine Aminotransferase (ALT) levels compared to HRD therapy, suggesting a safer alternative [64]. Tsai et al. enhanced radiation therapy in cancer cells overexpressing Human Copper Transporter 1 (hCtr1) using iron-platinum nanoparticles (FePt NPs) that improve mitochondrial targeting [65]. Magnesium-doped copper spinel ferrite superparamagnetic nanoparticles (Mg(1-x) Cu x Fe2O4SPMNPs) were identified as effective radiosensitizers by increasing copper content to enhance cytotoxic effects [66]. A new theranostic agent, bismuth/selenium nanoparticles (Bi/Se NPs) combined with levatinib (Len), was developed for CT imageguided Stereotactic Body Radiation Therapy (SBRT) in Hepatocellular Carcinoma (HCC). This combination reversed hypoxic conditions and mitigated immunosuppressive states, precisely demarcating the therapy region and significantly enhancing radiotherapy sensitization in HCC mouse models [67].

Li et al. developed lipid-modified manganese diselenide nanoparticles (MnSe2lipid) responsive to the Tumor Microenvironment (TME), designed to combat radioresistance and reduce radiation side effects. Their formulation includes a pHsensitive bond that releases Mn2+ ions in acidic conditions, enhancing radiosensitization via ROS generation and cGAS-STING pathway activation. This approach aims to improve treatment for Esophageal Squamous Cell Carcinoma (ESCC) by enhancing radiosensitivity and immunostimulation while protecting healthy tissue [68]. Liu et al. introduced a bionic, coronavirus-inspired nanocarrier, HB@VHMBi-Gd, for MRIguided Photodynamic-Radiotherapy (PD-RT). Its unique surface enhances cellular uptake and decomposes in tumor lysosomes, improving X-ray attenuation and MRI contrast. This nanocarrier increases singlet oxygen production, activates apoptosis pathways, and causes significant DNA fragmentation, leading to up to 90% tumor suppression [69].

Wang et al. explored BaWO4 nanoparticles as radiosensitizers, synthesized hydrothermally and stabilized with polyvinylpyrrolidone (PVP). These nanoparticles generate hydroxyl radicals more efficiently than CaWO4 counterparts, showing enhanced oxidative stress and tumor suppression upon irradiation without systemic toxicity [70]. Additionally, europium-doped calcium fluoride (CaF2:Eu) nanoparticles demonstrated selective toxicity against osteosarcoma cells, augmenting adjuvant radiotherapy efficacy [71]. Zimmermann's study on Ti3C2Tx MXenes highlighted their potential to enhance radiation therapy effectiveness, with dose enhancement factors up to 2.5 in soft tissue sarcoma cells [72].

Clinical Studies of Metal-based Nanomaterials for Radiotherapy Sensitization

Recent advancements in oncology have highlighted the potential of metal-based nanomaterials in enhancing radiotherapy efficacy. Specifically, gadolinium-based nanoparticles, such as AGuIX, have demonstrated promising results in clinical trials for their diagnostic and radiosensitizing capabilities. The phase I NANO-RAD trial (NCT02820454) investigated AGuIX nanoparticles in combination with whole-brain radiotherapy for patients with multiple brain metastases from various cancers including lung (NSCLC), melanoma, colon, and breast cancer. Out of 14 evaluable patients, 13 showed clinical benefits such as stable or reduced tumor volume. MRI analysis confirmed a significant correlation between contrast enhancement and tumor response, validating AGuIX's radiosensitizing effect [73,74]. Additional studies include the NANO-GBM trial (NCT04881032) for newly diagnosed glioblastomas, using AGuIX with radiotherapy and temozolomide [75], a phase I study (NCT03308604) exploring its use in advanced cervical cancer, underscoring its versatility across cancer types [76] and a phase I and II trail (NCT04789486) in centrally located lung tumors and locally advanced unresectable pancreatic ductal adenocarcinoma (Table 1).

NBTXR3, comprising negatively charged phosphate-coated crystalline hafnium oxide (HfO2) nanoparticles, is another innovative class of radiation enhancers selected for clinical development due to their superior X-ray absorption and safety profile. A phase I study (NCT01433068) assessed the safety and feasibility of NBTXR3 combined with External Beam Radiation Therapy (EBRT) for preoperative treatment of locally advanced Soft Tissue Sarcoma (STS) in adults. The treatment proved viable and produced promising objective response rate (ORR) of 42.9%, establishing a recommended dose equivalent to 10% of the tumor volume, based on MRI measurements, at a concentration of 53.3 g/L (Table 1) [77].

In the significant phase II/III Act.In.Sarc clinical trial (NCT02379845), the efficacy of the radiation enhancer NBTXR3 combined with radiotherapy was evaluated against radiotherapy alone for treating patients with locally advanced soft tissue sarcoma. The study demonstrated that NBTXR3, activated by preoperative radiotherapy, effectively doubled the rate of complete pathological remission post-resection—16.1% versus 7.9% with radiotherapy alone (P=0.045). Additionally, 77.0% of patients achieved R0 resection (complete tumor removal with clear margins) with the combination therapy, compared to 64.0% with radiotherapy alone (P = 0.042). Regarding safety, Serious Adverse Events (SAEs) related to NBTXR3 occurred in 10.1% of patients receiving the combination therapy, while SAEs related to radiotherapy alone were comparable between groups (5.6% each). Importantly, NBTXR3 did not adversely affect patients' Health-Related Quality of Life (HRQoL) [78,79]. Additionally, a phase I study (NCT01946867) assessed the safety of NBTXR3 intratumoural injection in elderly or frail patients with locally advanced Head and Neck Squamous Cell Carcinoma (HNSCC), who were unsuitable for standard radiotherapy. This study enrolled 19 patients across different dosage levels without reaching the Maximum Tolerated Dose (MTD), observed no dose-limiting toxicities (DLTs), or SAEs related to NBTXR3. Minor adverse events (grades I-II) related to NBTXR3 and/or intratumoral injections confirmed the nanoparticle's confinement to the tumor without affecting surrounding healthy tissues. The recommended phase II dose (RP2D) was established at 22% of the baseline tumor volume, with an ORR of 68.8% [80]. These findings support the ongoing trials of NBTXR3 in treating other solid tumors (NCT04615013, NCT04892173, NCT04484909, NCT04505267, NCT03589339, NCT05039632, NCT04862455) highlighting its potential as a powerful adjunct to radiation therapy across various cancer types [81]. Moreover, the combination of these metal nanomaterial-based radiotherapies with other chemotherapies or immunotherapies may be critical for improving the prognosis of a larger number of patients (Table 1).

Future Outlook

Metallic nanoparticles are increasingly pivotal in radiotherapy, enhancing treatment efficacy through diverse biological mechanisms. This review delves into optimizing these nanoparticles to improve biological processes, thereby boosting sensitization and synergistic effects of radiotherapy. Key mechanisms include oxidative stress induction, cell cycle disruption, DNA repair inhibition, ferroptosis initiation, autophagy regulation, and ICD induction. Future research will focus on detailing the roles of metal-based nanosensitizers within complex biological contexts, especially changes in the tumor microenvironment and immune system modulation, to enhance radiosensitization customization. Despite known radiosensitization effects, the impact of different radiation doses on therapy outcomes is underexplored, highlighting a gap in systematic evaluation and standard setting. Studies on metal oxide nanoparticles like SiO2, TiO2, HfO2, as well as TiN and Au nanoparticles across various radiation types have shown mixed results. For instance, while gold nanoparticles excel under kV irradiation due to the photoelectric effect, this advantage reduces with MV photons and proton therapies. In contrast, HfO2 nanoparticles maintain radiosensitization properties under MV photon and proton treatments, and TiO2 nanoparticles consistently exhibit radiosensitization across all settings due to their radiocatalytic activity enhancing hydroxyl radical production [82]. This discrepancy underscores the need for further research into nanoparticle radiosensitizer design tailored to specific treatment modalities. Such studies are crucial for refining radiotherapy and optimizing nanotherapy, setting the stage for more effective cancer treatments. The administration route of metal nanomaterials is crucial for optimizing therapeutic efficacy and is a key focus of research. For example, MRI studies from the NanoRAD trial involving 15 patients showed significant uptake of AGuIX nanoparticles in brain metastases following intravenous injection, highlighting the need for detailed pharmacokinetic studies, especially when transitioning from animal to human models. While intravenous administration is commonly preferred

Table 1: Clinical trials of metal-based nanomaterials for radiotherapy sensitization.

Therapy	Conditions	Clinical trial No. Phase & Status	Efficacy	Safety	Ref.
AGuIX (15, 30, 50, 75 or 100 mg/kg) + Whole Brain Radiotherapy (WBRT) (30 Gy, 10 fractions of 3 Gy)	Multiple brain metastases patients with primary Non-Small Cell Lung Cancer (NSCLC), melanoma, breast, and Table 1. Clinical trials of metal-based nanomaterials for radiotherapy sensitization colon tumors	NCT02820454 Phase I Completed	Disease control rate (DCR): 92.9%, intracranial progression-free survival (PFS): 5.5 months, overall survival (OS): 5.5 months	No dose-limiting toxic effects were observed up to AGuIX 100 mg/kg	[73, 74]
AGuIX (50, 75 or 100 mg/kg) + RT (60 Gy in 6 weeks) + Temozolomide (TMZ) 75 mg/m^2 per day from the first day of RT until the last day	Patients with grade IV glioblastoma, not operated or partially operated, with a KPS ≥ 70%	NCT04881032 Phase I, II Recruiting	\	\	[75]
AGuIX (20, 30 or 50 mg/kg) +External Beam Radiotherapy (EBRT) (45 Gy in 5 weeks) + uterovaginal brachytherapy (15 Gy in 2 weeks) + cisplatin (40 mg/m^2, 5 cycles)	Locally advanced (LA) cervical cancer	NCT03308604 Phase I Recruiting	\	\	[76]
AGuIX (100 mg/kg) + WBRT (30 Gy, 10 fractions of 3 Gy)	Multiple brain metastases	NCT03818386 Phase II Recruiting	\	\	\
AGuIX + stereotactic brain-directed radiation	Brain metastases at higher risk of local recurrence	NCT04899908 Phase I Recruiting	\	\	\
AGuIX + Stereotactic Body Radiation Therapy (SBRT)	Centrally located lung tumors and locally advanced unresectable pancreatic ductal adenocarcinoma	NCT04789486 Phase I, II Recruiting	\	\	\
AGuIX (100 mg/kg at day 4 and day 8) + + strereotactic radiation from day 8 to day 15 as per standard practice	Brain metastases	NCT04094077 Phase II Terminated	\	\	\
AGuIX + hypofractionated Protontherapy	Recurrent tumors	NCT04784221 Phase II Not yet recruiting	\	\	\
NBTXR3 (53.3 g/L) + EBRT	Adult soft tissue sarcoma	NCT01433068 Phase I Completed	ORR: 42.9% (3/7)	The most serious (grade 3) adverse events (SAEs) were reversible in all cases. One patient experienced two grade 3 AEs: injection site pain and a postoperative wound complication requiring a flap, which may be due to the radiotherapy itself or to the association	[77]

Arm A: NBTXR3 (53.3 g/L) + EBRT (50 Gy in 25 fractions)
Arm B: EBRT
	Soft tissue sarcoma	NCT02379845
		Phase II, Ш
		Completed
			A *vs* B:
			pCRR 16.1% vs 7.9%, P =0.045;
			tumor necrosis: 20.0% vs 10.0%, P = 0.014;
			R0 resection 77.0% vs 64.0%, P = 0.042)
				SAEs of all grades related to NBTXR3: 10.1% (9/89)	[78,79]

NBTXR3 + Intensity Modulated Radiation Therapy (IMRT)	Patients with LA Head and Neck Squamous Cell Carcinoma (HNSCC)	NCT01946867 Phase I Active, not recruiting	ORR: 68.8% CR: 31.3% PR: 37.5%	No DLTs or serious adverse event (SAEs) related to NBTXR3	[80]
NBTXR3 + IMRT + chemotherapy	Adenocarcinoma of the esophagus	NCT04615013 Phase I Recruiting	\	\	\

NBTXR3 + IMRT (70 Gy in 35 fractions) ± cetuximab	LA HNSCC	NCT04892173 Phase Ш Recruiting	\	\	\
NBTXR3 + RT	LA or borderline-resectable pancreatic cancer	NCT04484909 Phase I Recruiting	\	\	\
NBTXR3 + RT	Inoperable recurrent non-small cell lung cancer	NCT04505267 Phase I Recruiting	\	\	\
NBTXR3 intratumoral injection + RT + anti-PD-1 therapy	Cohort 1: advanced HNSCC resistant to anti-PD-1 therapy; cohort 2: advanced HNSCC naive to anti-PD-1 therapy; cohort 3: inoperable NSCLC, malignant melanoma, HCC, RCC, urothelial cancer, cervical cancer or TNBC with metastases and resistant to anti-PD-1 therapy	NCT03589339 Phase I Recruiting	\	\	\
NBTXR3 intratumoral injection + RT + anti-PD-1/PD-L1 therapy	Advanced solid malignancies	NCT05039632 Phase I, II Recruiting	\	\	\
NBTXR3 + RT + pembrolizumab	Recurrent or Metastatic HNSCC	NCT04862455 Phase II Recruiting	\	\	\
NBTXR3 + SBRT (45 or 50 Gy)	Liver cancers	NCT02721056 Phase I, II Terminated	\	\	\
NBTXR3 + 5-FU/capecitabine + RT	Rectal cancer	NCT02465593 Phase I, II Terminated	\	\	[81]
NBTXR3 + IMRT only or brachytherapy & IMRT	Prostate adenocarcinoma	NCT02805894 Phase I, II Terminated	\	\	\

for its clinical applicability, intratumoral (i.t.) injection is a viable alternative for directly targeting accessible tumors, ensuring precise delivery and minimizing material usage [83]. Exploring additional pathways such as intraperitoneal, inhalation, and oral routes could provide diverse strategies for nanoparticle delivery based on tumor location and patient condition [84-87].

Furthermore, the synergistic potential of metal nanomaterials with therapies like immunotherapy and Photodynamic Therapy (PDT) opens new avenues for treatment enhancements. Notably, nanoparticles conjugated with targeted agents against PD-L1 and CD47 have shown promising results in increasing uptake and prolonging effects in both in vitro and in vivo studies, enhancing targeted radiosensitization and PD-L1 MRI detection [88-91]. Additionally, integrating photosensitizers with AGuIX nanoparticles for PDT achieves targeted tumor therapy while sparing healthy tissues. These nanoparticles utilize the enhanced permeability and retention effect for tumor targeting, with MRI contrast enhancement aiding in precise tumor imaging and guiding PDT [92]. Emerging research also indicates the potential of multifunctional AGuIX-designed nanoparticles with MRI contrast agents and specific targeting ligands for cell-specific targeting, like M2-type macrophages [93]. However, the limited drug-loading capacity of metal nanoparticles poses challenges in carrying multiple or large molecules, potentially restricting the therapeutic window [94]. The evolving landscape of metal nanoparticle research in cancer therapy highlights the balance between sophisticated nanoparticle design and clinical practicality. While intricate engineering allows for targeted actions and enhanced outcomes, the complexity may complicate understanding of their behaviour in biological systems and hinder clinical translation [95-97]. Addressing these challenges requires a pivot towards simplifying metal-based therapeutic designs, focusing on ease of manufacturing and scalability. Establishing standardized production processes is crucial to ensuring consistency, safety, and efficacy, facilitating the successful integration of metal nanoparticles into routine clinical practice [98].

Authors' Contributions

JW collected the related paper and finished the manuscript. JW and JL gave constructive guidance and made critical revisions. MC, CC, BZ, RW, YG, YW and XJ participated in the design of this review. All authors read and approved the final manuscript.

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