REVIEW ARTICLE

Targeted Radiosensitization in Cancer Radiotherapy Using Functionalized Nanocarriers: A Systematic Review

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Abstract

Purpose: This study aims to provide a comprehensive review of recent advances in the application of nanocarriers for targeted drug delivery and radiosensitization in cancer Radiotherapy (RT), as well as to examine the challenges, solutions, and prospects of this technology.

Materials and Methods: This systematic review was conducted in accordance with PRISMA guidelines and protocol registered in PROSPERO (CRD420251154905). A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, identifying 373 records. Following PRISMA guidelines, 40 studies met the inclusion criteria focusing on functionalized nanocarriers in cancer RT. Data extraction covered nanoparticle types, functionalization, therapeutic payloads, cancer models, radiation modalities, and outcomes.

Results: Forty studies were analyzed, categorized into iron oxide-based (10), silver (10), bismuth-based (7), graphene-based (4), gadolinium-based (4), and titanium-based (2) nanoparticles (NPs). Bismuth-based NPs demonstrated superior radiosensitization with sensitizer enhancement ratios (SERs) of 1.25–1.48 and up to 450% increase in reactive oxygen species (ROS) in vivo, achieving ~70% tumor volume reduction without systemic toxicity. Silver NPs demonstrated dose enhancement factors (DEF) rising from 1.4 to 1.9 and synergistic effects with docetaxel plus 2 Gy radiation. Iron oxide NPs functionalized with HER2 and RGD ligands reduced cell viability by 1.95-fold and achieved DEF of 89.1 in targeted systems. Gadolinium NPs reached SERs up to 2.44 at 65 keV, while graphene-based systems enhanced ROS production by 75.2%. Titanium-based NPs increased ROS levels 2.5-fold. Combination therapies integrating chemotherapeutics, including cisplatin and curcumin with nanocarriers, yielded SERs up to 4.29. The radiation modalities included megavoltage X-rays (4–10 MV, n=24), synchrotron keV X-rays (n=2), gamma rays (0.38–1.25 MeV, n=3), and electron beams (6–12 MeV, n=3).

Conclusion: Bismuth-based NPs represent the most promising radiosensitizers due to their high efficacy, safety, and clinical relevance, supporting their advancement toward clinical translation.

Keywords: Nanocarrier; Targeted Drug Delivery; Radiosensitization; Cancer; Nanoparticle.

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1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, posing significant challenges in both diagnosis and treatment. This disease results from the uncontrolled growth and abnormal proliferation of cells, which can invade and destroy various tissues and organs [1]. Moreover, due to the great diversity of its types and biological complexities, cancer is considered one of the leading causes of mortality worldwide [2]. Radiotherapy (RT), as one of the main methods for cancer treatment, is used to destroy cancer cells through ionizing radiation. However, limitations, namely tumor resistance to RT and damage to surrounding healthy tissues, have reduced its effectiveness. Therefore, researchers are seeking solutions to increase the effectiveness of RT and reduce its side effects [3,4]. In recent years, nanotechnology, and especially functional nanocarriers, have attracted considerable attention as novel tools for improving radiosensitization and targeted drug delivery [5,6]. Nanoparticles (NPs), due to their small size, high surface-to-volume ratio, and the ability for surface modification, can selectively deliver drugs or radiosensitizing agents to cancer cells and prevent unnecessary contact with healthy tissues. This feature leads to increased treatment effectiveness and reduced side effects [7-9].

In this context, Shrista *et al.* (2021) demonstrated that smart NPs are capable of responding to internal stimuli, namely changes in pH, enzymes, hypoxia, and redox conditions, as well as external stimuli like light, temperature, ultrasound, and magnetic fields. This feature enables the drug or therapeutic agent to be released precisely at the required site and time [10]. The results of this study displayed that the use of smart nano-platforms in combination with chemotherapy, gene therapy, immunotherapy, and energy-based therapies not only increases treatment efficacy but also, by reducing drug dosage and side effects, can decrease drug resistance. The study concluded that this new generation of NPs has high potential for improving clinical outcomes in cancer treatment and can be used as a novel approach in combination cancer therapy [10]. Similarly, Katopodi *et al.* (2022), in their research, demonstrated that nanocarriers can deliver drugs and active molecules in a targeted and controlled manner to the tumor microenvironment [11]. One of the highlights of their study was the emphasis on the sensitivity of nanocarriers to specific tumor stimuli like pH, enzymes, and hypoxia, which leads to targeted drug release and reduced side effects. Additionally, these nanocarriers could enhance the antitumor immune response by modulating the tumor microenvironment and activating immune cells [11,12].

Recently, He *et al.* (2024), in a similar study, investigated the role of metal and metal oxide NPs in improving the effectiveness of RT. They explained that these NPs, by better absorbing ionizing radiation, increase the production of reactive oxygen species (ROS) and inhibit DNA repair genes. These processes lead to increased damage to cancer cells and reduced tumor resistance to RT [13]. It should be mentioned, not only metal NPs can act as imaging contrast agents [14-16] to improve the accuracy of RT, but also enhance the antitumor immune response [17]. They concluded that nanotechnology in RT, by increasing the precision and effectiveness of treatment and reducing side effects, has high potential for improving cancer treatment outcomes, and the development of new nanocarriers could lead to broader clinical applications [13,18]. On the other hand, Dankwa *et al.* (2020), in their studies, referred to the successful combination of chemotherapy and RT using nanocarriers, which leads to reduced drug and radiation doses and decreased side effects [19].

Other studies have also shown that porous nanocarriers and temperature-sensitive nanogels can serve as effective platforms for controlled drug release [20, 21]. Despite these advances, challenges namely the stability of nanocarriers, biosafety, and biological barriers in the body still hinder the widespread clinical application of these technologies [22]. Therefore, the primary objective of this systematic review was to comprehensively evaluate recent advances in the use of functionalized nanocarriers for tumor-targeted radiosensitization and drug delivery in cancer RT. Specifically, the study aimed to answer the following questions:

1) What types of functionalized nanocarriers are used in tumor-targeted radiosensitization for cancer RT?

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2) How do functionalization strategies improve targeting, radiosensitization, and drug delivery efficiency?

3) What are the safety profiles (toxicity, biodistribution, immune responses) of these nanocarriers in cancer therapy?

2. Materials and Methods

2.1. Research Protocol Registration and PICO Framework

A detailed protocol was developed before conducting the review, outlining the research objectives, eligibility criteria, information sources, and data extraction process to ensure methodological transparency and reproducibility. The review protocol was registered in the PROSPERO database (registration number: CRD420251154905). Additionally, this study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

Furthermore, the research question was structured using the PICO (Population, Intervention, Comparison, and Outcome) framework. As a result, the review focuses on cancer patients or relevant animal models undergoing RT. The intervention of interest includes functionalized nanocarriers, namely liposomes, dendrimers, or polymeric NPs, designed for targeted drug delivery and radiosensitization. Comparisons are made to conventional drug delivery methods or standard RT without nanocarrier intervention. The primary outcomes of interest include tumor radiosensitization, drug delivery efficiency, clinical efficacy, safety, and toxicity.

2.2. Eligibility Criteria

Studies were included if they investigated the use of functionalized nanocarriers for tumor-selective radiosensitization and/or drug delivery in the context of cancer RT. Eligible studies were required to present original experimental data (in vitro, in vivo, or clinical), demonstrate the use of functionalized nanocarriers for tumor targeting, and assess outcomes related to radiosensitization or combined drug delivery with RT. Only peer-reviewed articles published in English between January 2010 and July 2025 were considered. Exclusion criteria included reviews, conference abstracts without full data, editorials, studies lacking a functionalized nanocarrier or RT intervention, and articles not focused on cancer models.

2.3. Information Sources and Search Strategy

A comprehensive literature search was conducted in four electronic databases: PubMed, Scopus, Web of Science, and Embase, covering publications from Jan 2010 to July 2025. Two independent reviewers (F.Z., M.Sc. in Medical Physics, Shiraz University of Medical Sciences, and F.G., M.Sc. in Medical Physics, Shiraz University of Medical Sciences) screened the titles and abstracts for eligibility, followed by full-text assessment. Disagreements were resolved through discussion or consultation with a third reviewer (R.M., M.Sc. in Medical Physics, Tabriz University of Medical Sciences). The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords related to nanocarriers, functionalization, radiosensitization, drug delivery, and cancer RT. The search strategy in PubMed was as follows: ("cancer" [All Fields] OR "tumor" [All Fields] OR "neoplasm" [All Fields] OR "oncology" [All Fields] OR "malignancy" [All Fields]) AND ("functionalized nanocarriers" [All Fields] OR "nanoparticles" [All Fields] OR "liposomes" [All Fields] OR "dendrimers" [All Fields] OR "polymeric nanoparticles" [All Fields] OR "nano-carriers" [All Fields]) AND ("tumor targeting" [All Fields] OR "targeted delivery" [All Fields] OR "active targeting" [All Fields] OR "passive targeting" [All Fields]) AND ("radiosensitization" [All Fields] OR "radiotherapy" [All Fields] OR "radiation therapy" [All Fields] OR "radiation sensitizers" [All Fields]) AND ("radiosensitization"[All Fields] OR "radiation therapy" [All Fields] OR "tumor radiosensitization" [All Fields] OR "enhanced drug delivery" [All Fields] OR "drug delivery efficiency" [All Fields] OR "treatment efficacy" [All Fields]). The search was limited to English-language original research. The reference lists of included studies and relevant reviews were also screened manually to identify additional eligible studies.

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2.4. Study Selection

All identified records were imported into EndNote, and duplicates were removed. Based on study inclusion and exclusion criteria, two independent reviewers (F.Z. and F.G.) screened titles and abstracts for relevance. Full texts of potentially eligible articles were retrieved and assessed against the inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer (R.M.).

2.5. Data Collection Process

Data extraction was carried out independently by two reviewers (F.Z. & F.G.) using a standardized data extraction form, and any discrepancies were resolved through consensus or consultation with a third reviewer (R.M., expert in the field with ten years of experience). The extracted data included a comprehensive set of variables: study details (author, year, country), nanocarrier type, composition, and functionalization strategy, targeting mechanism (including ligand, antibody, peptide), therapeutic payloads (radiosensitizer, chemotherapeutic), cancer model (cell line, animal model, clinical), RT parameters (type and dose), and outcomes such as radiosensitization efficacy, tumor selectivity, drug delivery efficiency, toxicity, and safety. Additionally, key findings and limitations of each study were recorded.

3. Results

3.1. Study Selection

Figure 1 demonstrates the study selection process for this systematic review on nanoparticle-enabled hypoxia targeting and oxygen generation in RT. Initially, 527 records were identified from databases and manual searches. After removing 89 duplicates, 438 records were screened by title and abstract, excluding 371 irrelevant or non-original studies. Full texts of 67 articles were assessed, with 27 excluded due to lack of nanoparticle intervention, focus on RT, article type, language, or accessibility. Eventually, 40 studies comprising in vitro, in vivo, and combined preclinical designs were included in the final analysis.

3.2. Study Characteristics

As can be seen from Table 1, a total of 40 studies were included in the systematic review, with the majority of studies conducted between 2016 and 2024. The studies encompassed a range of experimental designs, including *in vitro* (26 studies), *in vivo* (12 studies), and Monte Carlo simulations (2 studies). The studies were primarily from diverse geographical locations, with contributions from countries including the United States, Iran, China, Egypt, Germany, and others. These studies focused on various cancer models, such as breast cancer (16 studies), glioma (8 studies), lung cancer (4 studies), and colorectal cancer (3 studies), among others. The nanocarriers used in these studies included a variety of nanoparticle types, such as iron oxide (IO), bismuth oxide (Bi_2O_3), silver (Ag), graphene oxide (GO), titanium dioxide (TiO_2), gadolinium (Gd), and gold (Au) NPs, each functionalized with different surface coatings and targeting ligands.

3.3. Types of Functionalized Nanocarriers

NPs employed for radiosensitization vary widely in composition, structure, and mechanism of action. In this systematic review, the included studies investigated a range of nanomaterials categorized primarily by their elemental core or functional properties. These include Fe_3O_4-based NPs for their magnetic targeting and biocompatibility, Ag NPs known for ROS generation, Bi-based NPs valued for high-Z and photoelectric efficiency, graphene and MXene nano-sheets offering surface area and oxidative stress enhancement, Gd-based NPs combining imaging and radiosensitization potential, and TiO NPs for ROS-mediated cytotoxicity. Each class presents unique physicochemical features, biological interactions, and radiation enhancement profiles, which are explored in the following subsections. Table 1 offers a comprehensive summary of each nanocarrier type, detailing their functionalization strategies, compositions, targeting mechanisms, and key findings from the studies reviewed.

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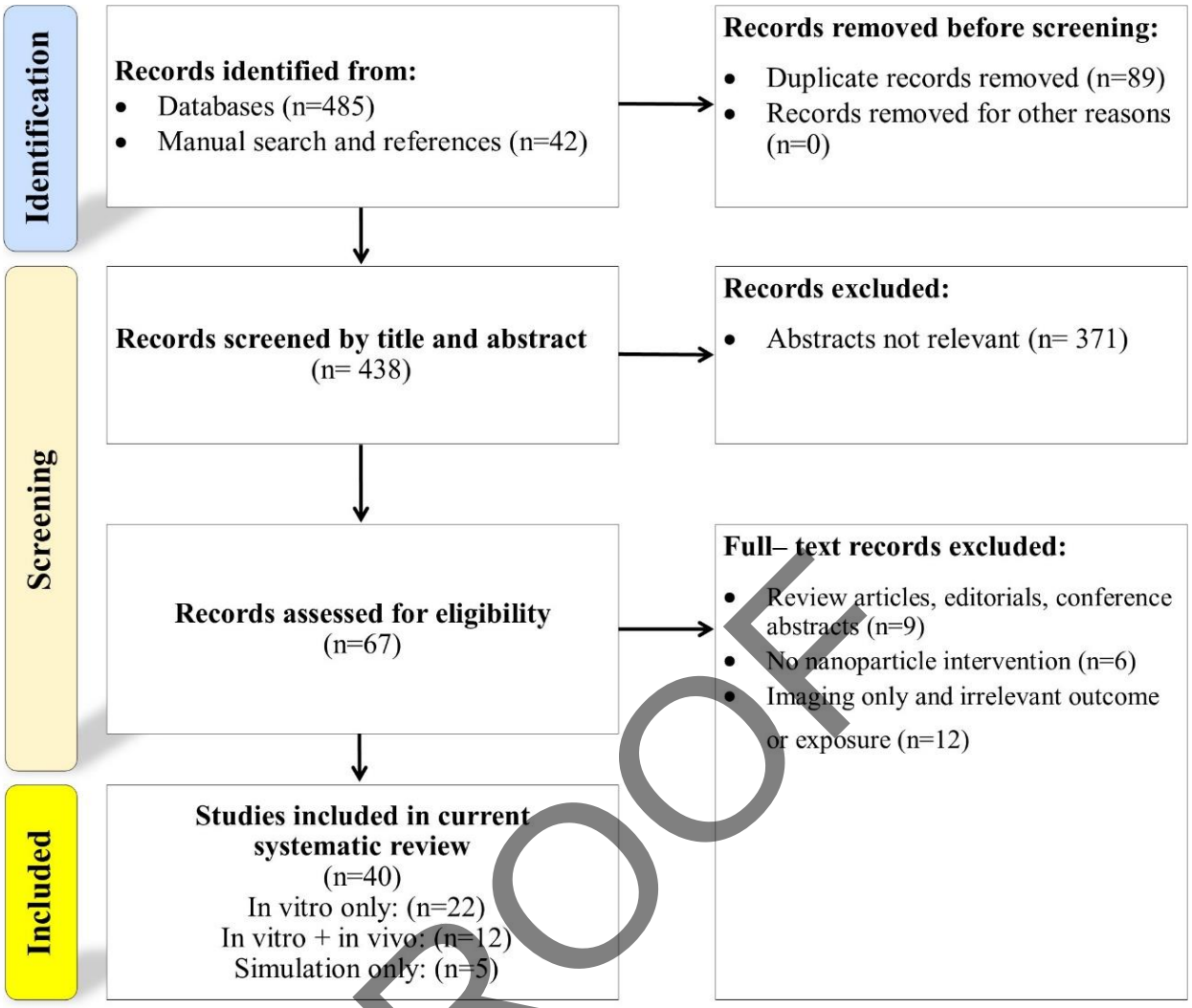

Figure 1. PRISMA flow diagram showing the study selection process for current systematic review study

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Table 1. Summary of nanoparticle types, mechanisms, and key outcomes in cancer radiotherapy

Nanoparticle Type	Number of Studies	Representative Mechanisms	Key Results	Justification
Iron Oxide	10	Magnetic targeting, ROS, Au coating	DEF 89.1 (targeted), Viability ↓1.95×	Excellent targeting, multifunctional potential
Silver	10	ROS, apoptosis, size-dependent uptake	Caspase ↑2.5×, DEF ↑1.9, ROS ↑	Strong ROS effect, synergistic with drugs
Bismuth	7	High-Z enhancement, tumor inhibition	SER 1.48, ROS ↑450%, Tumor ↓60–70%	Highest *in-vivo* efficacy, ROS generation, tumor inhibition
Graphene/MXene	4	ROS, apoptosis signaling	ROS 75.2% (MXene), Bcl-2 ↓40%	Apoptosis modulation, high ROS, emerging
Gadolinium	4	High-Z radiosensitization, MRI contrast	SER 2.44 (65 keV), Dose ↑30% (MC simulation)	High SER, dual-use for MRI, Monte Carlo-backed
Titanium	2	ROS, H_2O_2 delivery	ROS ↑2.5×, Apoptosis ↑40%	Redox-active, promising but underexplored

3.3.1. Iron Oxide-Based Systems

IO NPs, particularly superparamagnetic iron oxide NPs (SPIONs), were investigated in 10 studies for their radio-sensitizing potential. Their mechanisms primarily involved the generation of ROS, magnetic targeting, and high atomic number (Z) enhancement via surface modification with Au or Gd. Several studies used ligand-targeted NPs to improve tumor specificity. Abdollahi *et al.* (2022) employed HER2-targeted Fe_3O_4@Au NPs, observing a 1.95-fold reduction in breast cancer cell viability post-irradiation [24]. Similarly, Amraee *et al.* (2023) developed RGD-functionalized Fe_3O_4-Au/Gd NPs, achieving a dose enhancement factor (DEF) of 89.1 in targeted systems versus 59.1 in non-targeted systems [25]. Also, Fakhimikabir *et al.* (2018) demonstrated increased DNA damage in HeLa cells using folate-conjugated SPIONs under 6 MeV electron beam irradiation [26]. Other studies included variations of Fe_3O_4 NPs coated with APTES, PEG, polyglycerol, or silica to enhance biocompatibility and reduce cytotoxicity, with consistent findings of increased ROS production, apoptosis, and radiation sensitivity. Collectively, these studies underscore the versatility of IO NPs in preclinical radiosensitization strategies.

3.3.2. Silver-Based Systems

Ag NPs were utilized in 10 studies, largely due to their well-known ability to generate ROS and induce mitochondrial dysfunction, leading to enhanced cell death. The radiosensitization effect was often dependent on particle size and surface chemistry. Fathy (2020) exhibited that 10 nm Ag NPs produced the most potent radiosensitization effect, correlating with increased surface reactivity [27]. Recently, Hatami Zharabad *et al.* (2024) combined Ag NPs with docetaxel and 2 Gy radiation, leading to enhanced Caspase-3 expression and synergistic cytotoxicity in breast cancer cells [28]. In a simulation study, Çağlar *et al.* (2024) reported a DEF increase from 1.4 to 1.9 by optimizing the spatial distribution of Ag NPs in nanolattice structures [29]. Additional studies confirmed apoptosis induction, DNA double-strand breaks, and upregulation of apoptotic markers like Bax and caspase-9. Ag NPs were often surface-stabilized with PEG or PVP to improve colloidal stability and reduce toxicity. Overall, Ag NPs demonstrated consistent radiosensitizing efficacy across multiple cancer cell types, with enhanced ROS generation as a unifying mechanism.

3.3.3. Bismuth-Based NPs

Bismuth-based NPs (Bi NPs) appeared in seven studies, leveraging the element's high atomic number (Z = 83) to significantly enhance X-ray absorption and promote photoelectric interactions. These particles excelled in both *in vitro* and *in vivo* radiosensitization. Namely, Stewart *et al.* (2016) reported sensitizer enhancement ratios (SERs) of 1.48 and 1.25 at 125 kVp and 10 MV, respectively, when using Bi NPs in cancer cell models [30]. Also, Dastgir *et al.* (2024) demonstrated that Bi_2O_3 NPs loaded with 5-ALA and curcumin enhanced ROS generation by up to 450% and significantly reduced tumor volume [31]. Colak and Ertas (2024) developed a 3D-printed scaffold embedding Bi_2S_3@BSA NPs, which resulted in significant tumor inhibition (~70%) without systemic toxicity [32]. Further studies utilized PEGylated Bi_2O_3 NPs or photodynamic agents to boost radiosensitivity. These findings confirm the strong potential of Bi NPs as safe, high-Z radiosensitizers that work across multiple platforms and tumor models.

3.3.4. Graphene-Based Systems (Graphene Oxide and MXene Nanosheets)

Graphene-based systems, including GO and MXene nanosheets, were tested in four studies primarily for their ability to enhance ROS production and modulate apoptotic pathways. As an example, Zhou *et al.* (2023) showed that GO nanosheets downregulated anti-apoptotic protein Bcl-2 while increasing apoptosis in nasopharyngeal carcinoma cells [33]. Joze-Majidi *et al.* (2023) directly compared MXene and GO, finding MXene to be more potent in enhancing ROS production (75.2% vs. 65.2%) and inducing apoptosis [34]. More recently, Varzandeh *et al.* (2025) developed a bismuth nanosheet–reduced graphene oxide (BiNS–rGO) heterostructure, which demonstrated excellent photothermal stability. Drug release from the material was influenced by both pH and photothermal effects, with higher release observed in acidic conditions. The BiNS–rGO exhibited radiocatalytic ROS generation and showed promising anticancer activity, particularly with lower IC50

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values in combination therapies [35]. Despite the lower number of studies, graphene-based platforms exhibited strong potential in multifunctional therapeutic strategies, combining physical and biochemical radiosensitization.

3.3.5. Gadolinium-Based Systems

Gd-based NPs were explored in four studies for their radiosensitizing potential, particularly due to Gd's high-Z properties and suitability for MRI contrast. Taupin *et al.* (2015) observed SERs of 2.44 at 65 keV and 1.66 at 1.25 MeV in glioma cells treated with Gd NPs, confirming strong energy-dependent sensitization [36]. Delorme *et al.* (2017) validated these findings with Monte Carlo simulations showing over 30% localized dose enhancement [37]. Also, Amraee *et al.* (2023) incorporated Gd into Fe_3O_4–Au hybrid NPs, achieving significant radiosensitization in HER2-positive breast cancer [25]. Dufort *et al.* (2016) also used PEGylated Fe_3O_4–Gd particles, demonstrating increased radiosensitivity [38]. These studies not only confirmed the radiosensitizing efficacy of Gd NPs but also highlighted their dual role as imaging and therapeutic agents.

3.3.6. Titanium-Based Systems

Titanium-based NPs (Ti NPs) have been evaluated in two studies, focusing on their ability to generate ROS through photocatalytic and chemical mechanisms. Morita *et al.* (2021) designed polyacrylic acid-coated TiO_x NPs capable of delivering H_2O_2 intracellularly, leading to a 2.5-fold increase in ROS levels and enhanced radiation response in tumor cells [39]. Similarly, Ranjan *et al.* (2020) demonstrated that TiO_2-mediated oxidative stress alone induced a 40% apoptosis rate in colorectal cancer cells, even without the direct application of radiation [40]. While these results suggest that TiO_2 NPs hold potential for enhancing RT through redox modulation, it is important to note that the limited number of studies available in this area restricts the ability to draw broad conclusions. Further research with larger sample sizes, including studies incorporating clinical radiation settings, is needed to confirm the therapeutic potential of TiO_2 NPs in cancer treatment.

3.4. Comparative Evaluation of Radio-Sensitizing NPs: Efficacy, Biocompatibility, and Translational Potential

Upon analyzing the results of the reviewed studies, Bi NPs stand out as the most promising radiosensitizers in terms of efficacy, biocompatibility, and translational potential. Table 2 summarizes the comparative evaluation of these various functionalized radiosensitizing NPs, focusing on their efficacy (SER/DEF), biocompatibility, and potential for clinical translation.

Bi NPs, with a high atomic number (Z = 83), facilitate strong photoelectric interactions, making them highly effective under both kilovoltage and megavoltage radiation. This property enhances their radiosensitizing ability, offering superior efficacy across various radiation energies. For instance, Stewart *et al.* (2016) reported Sensitization Enhancement Ratios (SER) of 1.48 at 125 kVp and 1.25 at 10 MV, indicating significant radiosensitizing potential across both low and high-energy radiation [30]. Additionally, Dastgir *et al.* (2024) demonstrated a 450% increase in ROS generation and a significant tumor volume reduction *in vivo* using Bi_2O_3/CS@5-ALA-CUR systems, providing strong evidence of their therapeutic effectiveness in preclinical settings [31]. Likewise, Colak & Ertas (2024) showed tumor inhibition without systemic toxicity, confirming the biocompatibility and safety of Bi NPs, especially when embedded in 3D scaffolds, making them an ideal candidate for clinical applications [32].

In contrast, Ag NPs, also a promising radiosensitizer, demonstrated strong radiosensitization via ROS generation and drug synergy. For example, Hatami Zharabad *et al.* (2024) reported the combination of Ag NPs and Docetaxel (DTX) showing enhanced radiosensitization in triple-negative breast cancer (TNBC) cells, with increased cytotoxicity and ROS generation [28]. However, Ag NPs have fewer *in vivo* validations and lack broad energy applicability, limiting their clinical relevance compared to Bi NPs.

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Table 2. Comparative evaluation of functionalized radiosensitizing nanoparticles (NPs), focusing on their efficacy (SER/DEF), biocompatibility, and potential for clinical translation. Superparamagnetic Iron Oxide (SPION)

Author, Year	Nanocarrier Type	Functionalization Strategy	Radiosensitization Efficacy (SER/DEF)	Biocompatibility/ Safety	Translational Potential
Afifi *et al.*, 2023 [41]	IO@AgNPs (Iron-Silver Bimetallic)	Honey-mediated synthesis, no targeting ligand	DEF: ~1.75, SER: ~1.45	Low ALT levels, reduced liver toxicity	Preclinical study, requires further validation
Emer *et al.*, 2023 [42]	SPIONs	Coating with APTES, no active targeting	SER: ~1.1 (limited radiosensitization)	Low cytotoxicity, minimal impact on clonogenic survival	*In-vitro* only, no clinical validation
Amraee *et al.*, 2023 [25]	RGD@Fe_3O_4-Au/Gd (Iron-Oxide, Gold, Gadolinium)	RGD peptide targeting αvβ3 receptors	DEF: 89.1 (targeted), 59.1 (non-targeted)	Low cytotoxicity in normal cells	Preclinical study, long-term safety not assessed
Abdollahi *et al.*, 2022 [24]	Fe_3O_4@Au	PEGylation + trastuzumab for HER-2 targeting	SER: ~1.95 (dose- and energy-dependent)	Increased cytotoxicity with radiation	*In-vitro*, needs *in-vivo* data and biodistribution
Askar *et al.*, 2022 [43]	QMNPs (Quercetin-conjugated Magnetite)	Biosynthesis via Aspergillus oryzae	SER: Not specified, but significant tumor growth inhibition	No significant toxicity, good safety profile	Preclinical only, radiation dose not specified
Anuje *et al.*, 2021 [44]	PEG-coated)	Polyethylene glycol coating	SER: Highest at 2 Gy with 0.25 mg/mL SPIONs	Low cytotoxicity, good biocompatibility	*In-vitro* only, no clinical validation
Russell *et al.*, 2021 [45]	SPIONs	No active targeting	SER: ~1.28 for 5 out of 6 cell lines	Low toxicity, no adverse effects *in-vivo*	Preclinical, no correlation with DNA damage
Klein *et al.*, 2021 [46]	NHDs (Pt–Fe_3O_4, Pd–Fe_3O_4, Au–Fe_3O_4 Nanoheterodimers)	Caffeic acid functionalization	No SER or DEF reported, enhanced ROS generation	No significant cytotoxicity in normal cells	Preclinical, no *in-vivo* data
Liu *et al.*, 2021 [47]	Fe_3O_4–TiO_2 nanocomposites	Surface coating with DOPAC, MIBG, EGF-mimicking peptides	SER: ~5-fold increase in radiosensitivity	No significant toxicity reported	*In-vitro*, mechanistic study needed
Fathy *et al.*, 2019 [48]	SIO-MNPs (Silica-coated Iron Oxide)	Silica shell coating	DEF: ~1.3× higher than uncoated IO-MNPs	Low cytotoxicity, biocompatible at tested concentrations	*In-vitro*, no *in-vivo* or clinical validation
Fakhimikabir *et al.*, 2018 [26]	FA-PG-SPIONs (Folic acid-conjugated Polyglycerol-coated Iron Oxide)	Polyglycerol coating, conjugation with folic acid	Not specified, but enhanced radiosensitivity	Low cytotoxicity, good biocompatibility	*In-vitro*, no *in-vivo* or clinical validation
Stewart *et al.*, 2016 [30]	Bi_2O_3 NPs	Platelet-shaped morphology, no active targeting	SER: 1.48 (125 kVp), 1.25 (10 MV)	Low toxicity, good biocompatibility	Preclinical, highly effective for gliosarcoma
Dastgir *et al.*, 2024 [31]	Bi_2O_3/CS@5-ALA-CUR (Bismuth Oxide + Chitosan)	Sol-gel synthesis, chitosan coating	Up to 450% ROS enhancement, significant tumor size reduction	No significant cytotoxicity in normal cells	Preclinical, dual imaging and therapeutic function

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Colak & Ertas, 2024 [32]	Bi_2S_3@BSA NPs (Bismuth Sulfide)	Coating with BSA, embedded in 3D-printed scaffolds	DEF: ~1.9, demonstrated significant ROS generation	No observable toxicity in major organs	Preclinical, 3D scaffolds reduce tumor recurrence
Hatami Zharabad *et al.*, 2024 [28]	Ag NPs + DTX (Docetaxel)	Low-toxic AgNPs, DTX at 0.25× IC_{50}	Significant increase in cytotoxicity vs. monotherapies	No significant toxicity at tested concentrations	*In-vitro*, no *in-vivo* validation
Morais *et al.*, 2023 [49]	Ag NPs	No active targeting, combined with everolimus	Enhanced radiosensitivity, potentiated everolimus effect	No significant toxicity, good biocompatibility	*In-vitro*, no *in-vivo* validation

Gd NPs, known for their high SER [36] and dual MRI functionality, also demonstrated significant radiosensitization. However, Gd NPs have been the subject of fewer studies, and their *in-vivo* validation remains limited, which narrows their clinical capabilities are promising, but the lack of extensive clinical data reduces their immediate applicability in clinical settings. Moreover, IO NPs and SPIONs excel in targeting specificity through ligand functionalization (RGD, folate, HER2), with enhanced magnetic modulation. However, their dose enhancement and radiosensitizing efficacy heavily rely on their surface chemistry and combination with other materials like Au or Gd. For example, Amraee *et al.* (2023) reported a DEF of 89.1 for RGD@Fe_3O_4-Au/Gd NPs compared to 59.1 for non-targeted NPs, highlighting the importance of targeting in enhancing efficacy [25]. Despite promising drug delivery results, the need for further optimization in surface functionalization and combination therapies constrains their clinical potential.

Graphene-based and MXene-based systems show promise in apoptosis modulation and ROS generation. Joze-Majidi *et al.* (2023) demonstrated that MXene NPs achieve 75.2% ROS generation, outperforming GO NPs (65.2%) in breast cancer cells under radiation therapy [34]. However, these materials remain in the early stages of development, with limited toxicity profiling and *in vivo* validation, restricting their clinical readiness. Ti-based NPs, while cost-effective and exhibiting ROS activity, have limited preclinical validation. In this context, Morita *et al.* (2021) demonstrated that PAA-TiO_x NPs significantly enhanced intracellular H_2O_2 levels and radiosensitivity compared to free H_2O_2. Despite these promising results, Ti NPs have minimal preclinical validation and are not as extensively studied as other nanoparticle systems, making their clinical potential still uncertain [39].

Taken together, Bi NPs provide the best balance of radiosensitizing potency, tumor selectivity, low cytotoxicity, and adaptability to various radiation types, making them the most promising candidate for future clinical translation in the field of tumor-targeted radiosensitization. They offer versatility for use under kilovoltage and megavoltage radiation and demonstrate outstanding biocompatibility, positioning them as a leading choice for clinical applications.

3.5. Drug Loading and Combination Strategies

A subset of eight studies integrated chemotherapeutic agents or radiosensitizers into nanoparticle platforms to enhance tumor specificity, synergize therapeutic effects, and overcome radioresistance. These combination strategies involved co-delivery of drugs namely cisplatin, docetaxel, curcumin, or 5-aminolevulinic acid (5-ALA) with high-Z or ROS-generating NPs, offering both spatiotemporal control and multimodal cancer treatment.

As a result, Dastgir *et al.* (2024) engineered a Bi_2O_3/CS@5-ALA-CUR nanoparticle system, co-loading curcumin (a natural antioxidant with radiosensitizing properties) and 5-ALA (a pro-drug for photodynamic therapy) [31]. The platform significantly increased ROS levels (~450% over control) and showed marked tumor volume reduction *in vivo*, indicating synergistic efficacy through combined photochemical and radiochemical mechanisms. In another high-impact study, Sisin *et al.* (2019) developed a hybrid platform combining cisplatin with BiO NPs, resulting in an exceptional

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sensitizer enhancement ratio (SER) of 4.29 in MCF-7 breast cancer cells. This strategy amplified DNA crosslinking damage while exploiting bismuth's radiosensitizing effects, showing superior potency compared to either agent alone [50]. Similarly, Hatami Zharabad *et al.* (2024) employed a tripartite combination of Ag NPs, docetaxel, and 2 Gy X-ray radiation, demonstrating a significant increase in Caspase-3 expression and apoptotic cell death in breast cancer cells [28]. The results emphasized the benefit of chemotherapeutic priming (via docetaxel) alongside ROS-amplifying Ag NPs, leading to enhanced cytotoxic synergy.

Other studies explored co-delivery systems using folate, dextran, or liposomal coatings to enhance drug loading efficiency and tumor targeting, though not all quantified dose enhancement ratios. Across these eight studies, combinatorial approaches consistently outperformed monotherapy counterparts, particularly when the nanoparticle carriers provided targeting ligands, pH-responsive release, or dual therapeutic functionalities.

3.6. Radiation Modalities and their Application in Radiosensitization

The use of various radiation modalities is a critical aspect of functionalized radiosensitizing NPs for cancer treatment, as it directly influences the radiosensitization efficacy and clinical applicability. The majority of the studies (n = 24) employed clinical X-ray beams in the megavoltage (MV) range, typically operating between 4–10 MV, although some did not specify the exact energy beyond indicating the use of MV beams. Two studies utilized synchrotron-based irradiation, delivering monochromatic X-rays in the kiloelectronvolt (keV) range (25–80 keV), which is

Table 3. Categorization of radiation modalities and dose specifications in the reviewed studies on functionalized radiosensitizing nanoparticles (NPs)

Author	Nanocarrier Type	Radiation Modality	Energy/Beam Type	Dose (Gy)
X-ray Radiation				
Afifi *et al.* [41]	Iron-silver bimetallic NPs (IO@AgNPs)	X-ray Radiation	6 Gy (low dose), 12 Gy (high dose)	6 and 12
Amraee *et al.* [25]	RGD@Fe_3O_4-Au/Gd NPs	X-ray irradiation	6 MV X-rays	2
Abdollahi *et al.* [24]	Fe_3O_4@Au core–shell NPs	X-ray irradiation	6 MV, 18 MV	2, 4, 8
Anuje *et al.* [44]	PEG-coated SPIONs	X-ray photon beam	6 MV	0.5–2
Russell *et al.* [45]	SPIONs	X-ray (225 kVp)	1–2 Gy	1–2
Fathy *et al.* [48]	Silica-coated iron oxide NPs (SIO-MNPs)	X-ray Electron Beam Irradiation	-	0, 0.5, 1, 2, 4
Kirakli *et al.* [51]	Citrate-coated SPIONs	X-ray irradiation	6 MV	0–8
Dastgir *et al.* [31]	Bi_2O_3/CS@5-ALA-CUR NPs	X-ray irradiation	6 MV	2
Stewart *et al.* [30]	Bi_2O_3 NPs	X-ray irradiation	125 kVp, 10 MV	-
Sisin *et al.* [50]	Bismuth oxide NPs (BiONPs)	HDR brachytherapy (Ir-192)	0.38 MeV	0–4
Jamil *et al.* [52]	Bismuth oxide nanorods (Bi_2O_3-NRs)	X-ray photon beam	6 MV, 10 MV, 6 MeV, 12 MeV	0–10
Electron Beam Radiation				
Fakhimikabir *et al.* [26]	FA-PG-SPIONs	Electron beam irradiation	6 MeV	-
Specialized Radiation				
Robatjazi *et al.* [53]	Ag, Gd, Bi, Au, Pt, Fe NPs (50 nm)	Monte Carlo Simulation	30, 60, and 100 keV photon beams	-
Delorme *et al.* [37]	Gd NPs (3 nm)	Synchrotron X-rays, Co-60 γ-rays	50–80 keV, 1.25 MeV	-
Taupin *et al.* [36]	Gd NPs (3 nm)	Synchrotron X-rays, Co-60 γ-rays	65 keV, 1.25 MeV	-
Çağlar *et al.* [29]	Ag NPs	Monte Carlo Simulation	30–100 keV	-
Hatami Zharabad *et al.* [28]	Ag NPs + Docetaxel (DTX)	X-ray irradiation	2 Gy	2 Gy

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particularly valuable for investigating photoelectric enhancement effects at low energies [36]. Gamma radiation from radioisotopes, including cobalt-60 (Co-60) and iridium-192 (Ir-192), was used in 3 studies, with photon energies ranging from 0.38 to 1.25 MeV. Electron beam radiation was applied in 3 studies, with energies ranging from 6 to 12 MeV, mainly for preclinical or specialized irradiation protocols. Furthermore, 5 studies used simulation or phantom models with Monte Carlo codes, namely MCNP6.2 and EGSnrc, to model radiation interactions across a wide energy spectrum, from keV to MeV, offering insights into energy-dependent dose enhancement phenomena under controlled conditions [29] (Table 3).

3.6.1. X-ray Radiation

X-ray radiation is the most frequently used modality across the studies, with a significant number of experiments utilizing standard X-ray machines. X-ray radiation is employed for both preclinical and *in vitro* studies, often at varying energy levels (typically ranging from 100 kVp to 10 MV) to assess the radiosensitizing potential of NPs. Namely, studies by Afifi *et al.* (2023) [41], Stewart *et al.* (2016) [30], and Zhang *et al.* (2018) [54] applied X-ray radiation doses ranging from 2 to 10 Gy, with the energy typically set between 125 kVp and 10 MV. These studies demonstrated considerable DEFs, confirming the potential of various NPs to enhance radiation-induced DNA damage and increase tumor cell apoptosis. However, X-ray radiation is primarily used in preclinical settings and often lacks long-term safety data or human clinical validation.

3.6.2. Electron Beam Radiation

Electron beam radiation (6 MeV and 12 MeV) was used in several studies, particularly when simulating real clinical conditions or targeting specific tumor depths. For illustration, in the study by Fakhimikabir *et al.* (2018) [26], electron beam irradiation (6 MeV) was combined with functionalized IO NPs to enhance radiosensitization in HeLa cells. Similarly, Colak & Ertas (2024) utilized electron beam radiation to assess the efficacy of Bi sulfide NPs embedded in 3D scaffolds for localized treatment. Studies involving electron beam radiation typically focus on optimizing surface coatings and examining cellular uptake and the impact on radiosensitization efficiency [32]. This modality provides additional depth penetration compared to traditional X-rays, making it suitable for deeper tumors.

3.6.3. Gamma Radiation

Gamma radiation, such as Co-60 and Cs-137, is a well-established form of radiation therapy used in clinical settings. Several studies in this review, such as those by Afifi *et al.* (2023) [41] and Askar *et al.* (2022) [43], utilized gamma radiation at doses ranging from 0.5 to 12 Gy. These studies explored the enhancement of RT with various NPs, including Au and IO NPs, demonstrating significant tumor growth inhibition and apoptosis in cancer cells. Gamma radiation's role in RT allows for precise tumor targeting and deep tissue penetration, making it a relevant option for clinical application.

3.6.4. Specialized Radiation Techniques

Specialized radiation techniques such as synchrotron X-ray, High-Dose-Rate (HDR) brachytherapy, and Monte Carlo simulations were employed in some studies to explore the advanced capabilities of radiation. For instance, the study by Fathy (2020) used electron beam irradiation combined with thymoquinone-capped Ag NPs to explore radiosensitization in MDA-MB-231 cells [48]. Meanwhile, Monte Carlo simulations, as utilized by Robatjazi *et al.* (2021), modeled the effects of various NPs on photon energy interactions at different kilovoltage settings (30–100 keV), allowing for optimized radiation dose calculations [53]. These specialized techniques offer high precision in simulating real-world therapeutic conditions and understanding the biophysics of radiosensitizing NPs. Emerging radiation modalities, such as proton therapy and other particle-based techniques, are being explored in select studies but remain in early stages. As an example, specialized therapeutic techniques involving NPs like Bi sulfide NPs [32] have shown potential for tumor inhibition, although these modalities are yet to be widely implemented in clinical practice. These cutting-edge modalities are gaining attention due to their ability to minimize collateral damage to healthy tissues while enhancing treatment efficacy.

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4. Discussion

In recent years, significant advances have been made in the use of functional nanocarriers to improve the effectiveness of cancer RT. This novel technology, aimed at increasing the sensitivity of cancer cells to RT and enabling targeted drug delivery, has been able to reduce the limitations of traditional therapeutic methods like drug resistance and damage to healthy tissues [55,56]. Furthermore, given the biological complexities of tumors and the need for more precise and less risky treatments, the use of nanocarriers as multifunctional and smart tools has gained a special place in cancer research [57]. Here, the advantages and existing challenges were examined, and prospects for clinical applications were presented.

4.1. Functional Nanocarriers in Enhancing the Effectiveness of Cancer RT

Functional nanocarriers have shown significant potential in enhancing cancer RT by improving tumor-specific targeting and increasing radiosensitization. These nanocarriers enhance the production of ROS, modulate the tumor microenvironment, and inhibit DNA repair, leading to increased cancer cell damage and improved RT efficacy. Their ability to combine chemotherapy and RT in a controlled, targeted manner holds promise for reducing side effects and improving treatment outcomes. Further optimization and clinical validation are needed to maximize their potential in cancer therapy [58].

Recently, He *et al.* (2024) reported recent advances in the use of NPs to improve the effectiveness of RT in cancer treatment. This study aimed to describe the mechanisms of radiosensitization using various types of NPs, which include increasing the production of ROS, targeted RT, reduction of tumor hypoxia, enhancement of the anti-tumor immune microenvironment, and induction of cell cycle arrest at the G2/M phase. The results showed that metal and metal oxide NPs, through better absorption of ionizing radiation, increased ROS production and inhibition of DNA repair genes, leading to increased damage to cancer cells and reduced resistance to RT. Additionally, these NPs can act as imaging contrast agents to improve the precision of RT and enhance the anti-tumor immune response. Lastly, they established that nanotechnology in RT, by increasing the precision and effectiveness of treatment and reducing side effects, has high potential for improving cancer treatment outcomes, and it is expected that with the development of new nanocarriers, broader clinical applications will be achieved [13].

Similarly, Dankwa *et al.* (2020), examined the role of nanocarriers in improving cancer treatment through the combination of RT and chemotherapy effects. This research aimed to analyze four different strategies in which nanocarriers are used as platforms to coordinate the effects of RT and chemotherapeutic drugs to increase targeted damage to cancer cells and reduce side effects. The results showed that these nanocarriers, by providing selective drug release and targeted RT, lead to enhanced synergistic effects, reduced doses of radiation and drugs, and improved patients' quality of life. They ultimately concluded that nanocarriers, as effective platforms for the combined therapy of chemotherapy and RT, have high potential but require further studies for optimization of design and clinical evaluation [19].

Dong and Guan (2020) assessed nanoparticle-based drug delivery systems for cancer treatment. Compared to traditional drug delivery methods, these systems offer advantages including increased half-life of sensitive drugs, improved solubility of hydrophobic drugs, and the possibility of controlled and targeted drug release at the disease site. They mainly focused on NPs made from chitosan, silica, and poly (lactic-co-glycolic acid), introducing their fabrication methods and applications in cancer therapy. NPs, due to their specific physicochemical properties, enable drug targeting, reduce systemic toxicity, and increase therapeutic efficacy, playing an important role in overcoming drug resistance [59]. Furthermore, Khanna *et al.* (2023) addressed the application of stimuli-responsive nanocomposites in drug delivery and theranostics for combating cancer growth and drug resistance. These nanocomposites are capable of responding to internal stimuli, namely low pH, oxidative stress, enzymes, and hypoxia in the tumor microenvironment, as well as external stimuli including light, heat, and magnetic field. In addition, these nanocomposites possess the ability to combine therapy and diagnosis (theranostics), which improves treatment precision and monitoring of tumor response. They emphasized that the intelligent design of these

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systems can enhance the effectiveness of cancer therapy and reduce existing challenges in their clinical translation [60].

Research indicates functional nanocarriers with the ability to respond to internal and external stimuli, increase the production of ROS, and inhibit DNA repair play a key role in enhancing the sensitivity of cancer cells to RT. These technologies enable the effective combination of chemotherapy and RT and significantly improve therapeutic efficacy. However, further optimization of nanocarrier design is needed to enhance their stability and targeting capabilities [61].

4.2. Targeted Drug Delivery and Controlled Release in the Tumor Microenvironment

Targeted drug delivery and controlled release within the tumor microenvironment are essential strategies for improving the efficacy of cancer therapies while minimizing systemic side effects. Nanotechnology plays a crucial role in enhancing these approaches by designing multifunctional nanocarriers that can specifically target tumor sites and respond to environmental cues, such as pH, hypoxia, and enzyme activity. Figure 2 presents active and passive targeting strategies, highlighting how these nanocarriers can be tailored for optimal therapeutic outcomes.

In this case, Katopodi *et al.* (2022) investigated multifunctional engineered nanocarriers for controlled drug release in tumor immunotherapy. The results showed that these nanocarriers, by modulating the tumor microenvironment, activating immune cells like dendritic cells and macrophages, and reducing regulatory T cells, can enhance the anti-tumor immune response. Additionally, the use of nanocarriers sensitive to specific tumor stimuli (pH, enzymes, hypoxia) resulted in targeted drug release and improved therapeutic efficacy. Lastly, they concluded that multifunctional engineered nanocarriers, with the capability of controlled and targeted drug release, have high potential for improving cancer immunotherapy and can be used as innovative strategies to overcome drug resistance and enhance therapeutic outcomes [11].

Besides, Maity *et al.* (2018) reported the development of a smart, temperature-sensitive nanogel based on poly (N,N'-dimethylaminoethyl methacrylate) (PDMAEMA), capable of

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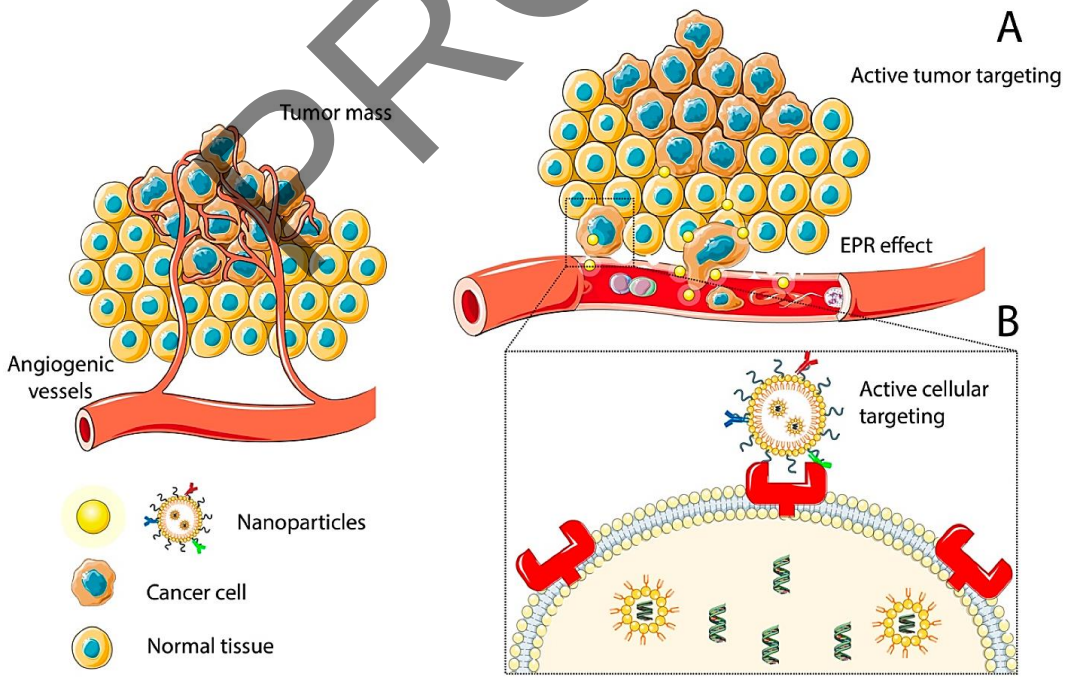

Figure 2. Nanoparticle targeting strategies in cancer treatment. (A) Passive targeting relies on nanoparticle size, tumor microenvironment abnormalities, and the EPR effect to enable nanoparticle diffusion into tumor tissues, while active targeting uses ligands and receptors to enhance nanoparticle-tumor cell interactions. (B) Active cellular targeting allows selective nanoparticle internalization by cancer cells, directing them to specific intracellular locations like the nucleus. Taken from [62]

simultaneously loading the anticancer drug doxorubicin (DOX) and albumin labeled with the radionuclide ^{131}I for combined chemo-radionuclide therapy. This nanogel remains in solution at room temperature and, after injection into the tumor, transforms into a gel at body temperature, a property that enables prolonged retention of the radionuclide at the tumor site and controlled drug release due to pH sensitivity. *In-vivo* experiments showed that their system increased therapeutic efficacy while reducing side effects compared to traditional chemotherapy or RT. This innovative strategy of using temperature-sensitive nanogels offers a promising platform for highly efficient and less toxic combination cancer therapy [20].

Moreover, Zhou *et al.* (2017), in a comprehensive study, assessed advances in magnetic IONPs as theranostic nanocarriers for targeted and guided cancer therapy. Due to their unique physicochemical properties, these NPs enable the combination of medical imaging (MRI) and therapy (chemotherapy, RT, photodynamic, and thermal therapies) in a single platform. Magnetic NPs, with their drug-targeting capability, enhance drug uptake in tumors and reduce systemic toxicity, thereby improving therapeutic efficacy. Additionally, these NPs can be used as MRI contrast agents for precise tumor imaging and treatment monitoring. Preclinical studies have shown that biocompatible-coated IO NPs are capable of loading various drugs and activating diverse therapeutic responses. Eventually, the authors emphasized that the development of theranostic magnetic NPs is an innovative approach for precision medicine in cancer treatment, which can improve diagnosis, targeted therapy, and simultaneous monitoring of therapeutic response [63].

Then, Sutresno and Ariga (2023) considered advances related to engineered porous nanoarchitectonics for cancer therapy. The results showed that mesoporous materials, due to their porous network structure, have a high capacity for drug loading and can provide controlled and targeted drug release. Ultimately, they concluded that engineered porous nanoarchitectonics, especially mesoporous materials, are promising platforms for the development of advanced drug delivery systems in cancer therapy, but further resolution of technical and safety challenges is required for clinical applications [64].

More recently, Zhou *et al.* (2025), investigated the applications of nanotechnology in cancer therapy. They explained that nanotechnology, through the design of targeted NPs, is capable of precisely delivering chemotherapeutic drugs to cancer cells while preventing damage to healthy tissues. This technology, by improving drug delivery, reducing systemic toxicity, and increasing therapeutic efficacy, mitigates the limitations of traditional methods, including chemotherapy and RT. Additionally, NPs can play an important role in medical imaging and early cancer diagnosis. Eventually, they emphasized that nanotechnology, by providing innovative and precise solutions, can create a major transformation in cancer treatment and offer a promising outlook for the development of personalized therapies [65]. Equally, Sabir *et al.* (2025) provided a comprehensive examination of the role of nanotechnology in overcoming cancer drug resistance. They first introduce the main factors contributing to drug resistance in cancer, including efflux pumps (ABC transporters), evasion of apoptosis, epigenetic changes, DNA repair mechanisms, and the tumor microenvironment. The authors highlight that systemic toxicity and resistance to conventional therapies highlight the necessity for alternative approaches, namely, nanotechnology. In this context, various nanomaterials, including carbon nanotubes, dendrimers, polymeric micelles, and liposomes, offer significant advantages in cancer diagnosis and therapy due to their biocompatibility, stability, permeability, selective accumulation in tumors, and the ability for targeted drug delivery. It was found that nanotechnology, by providing innovative solutions, can create a fundamental transformation in cancer treatment and overcome drug resistance; however, further research and optimization are required for widespread clinical application [66].

It was found that multifunctional nanocarriers sensitive to tumor microenvironment stimuli enable controlled and targeted drug release, resulting in reduced side effects and increased therapeutic efficacy [58,67]. Technologies, including magnetic NPs and temperature-sensitive nanogels, provide innovative tools for precise drug delivery. These approaches have

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created a promising outlook for combination and personalized cancer therapies.

4.3. Clinical Challenges and Limitations of Nanocarriers in Radiosensitization and Drug Delivery

Investigation has shown that despite significant advances in the design of nanocarriers, important challenges, including potential toxicity, biological stability, biological barriers, and issues related to clinical translation, persist. Overcoming these limitations requires more extensive clinical studies, precise safety evaluation, and optimization of nanoparticle structures in order to achieve effective and safe clinical application.

Awasthi *et al.* (2018) examined the opportunities and barriers to the use of NPs in cancer therapy. They stated that NPs can revolutionize cancer treatment by enabling targeted drug delivery, reducing systemic toxicity, and overcoming multidrug resistance. The study highlights that successful clinical application of NPs requires precise design, optimization of physicochemical properties, and a better understanding of nanoparticle interactions with biological and cellular environments. Additionally, combining NPs with various therapeutic modalities and improving penetration into the tumor microenvironment are important strategies for enhancing treatment efficacy [22].

Sharma (2025) studied recent advances in the use of NPs for cancer treatment. This study showed that metallic NPs, carbon nanotubes, and extracellular vesicles, each with their specific characteristics, play a significant role in improving cancer diagnosis and therapy. Carbon nanotubes, due to their photothermal properties, have strong synergistic effects when combined with chemotherapy, while extracellular vesicles facilitate drug delivery because of their biocompatibility and ability to evade the immune system. Metallic NPs, with their optical and magnetic properties, are also used for imaging and targeted drug delivery. These NPs increase drug bioavailability, reduce systemic toxicity, and enhance therapeutic efficacy. Despite considerable progress, the number of approved nanomedicines remains limited, and further research is needed to optimize targeted drug delivery, reduce the effect of protein corona, and improve clinical translation [68]. Also, Brannon-Peppas (2004) examined significant advances in the field of targeted cancer therapy using NPs and targeted drug delivery systems. They highlight that targeting cancer therapy is achievable not only through the development of more specific anticancer agents, but also by improving drug delivery methods. They specifically refer to drug delivery methods using NPs, including biodegradable and non-biodegradable polymers, which can enhance drug accumulation at the tumor site and reduce systemic toxicity, thereby improving therapeutic efficacy. Generally, they demonstrate that nanoparticle and targeted systems can revolutionize cancer therapy by increasing precision, reducing side effects, and improving the therapeutic index, thus enhancing the quality of life for cancer patients [69].

Heath (2008) explains that advances in cancer biology have highlighted the need for novel technologies for multiparametric, precise, and cost-effective diagnosis. In this context, nanotechnology and tools including microfluidics and NPs enable sensitive and low-cost measurements, providing valuable clinical information with minimal samples and simple processing. In the field of therapy, nanodrugs and NPs with encapsulation and targeted delivery capabilities increase the precision of drug delivery to cancer cells and reduce toxicity to healthy tissues. These technologies not only enhance therapeutic efficacy but also minimize the side effects of traditional chemotherapies. Furthermore, multifunctional nanomaterials like magnetic NPs and quantum dots enable the integration of theranostics, which can revolutionize the process of cancer diagnosis and treatment monitoring. Eventually, they found that nanotechnology, by offering innovative solutions in early diagnosis, targeted drug delivery, and combination therapies, can transform the future of cancer treatment; however, challenges such as tumor biology complexity, safety, and clinical translation remain [70].

4.4. Emerging Technologies in Combination Cancer Therapy with Nanocarriers

Research has demonstrated that advanced nanocarrier technologies, especially co-delivery systems and hybrid nanocarriers, have high potential for improving combination cancer therapy. These

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technologies can reduce drug resistance, limit side effects, and increase therapeutic efficacy [71]. The future of cancer treatment, utilizing these technologies, promises improved quality of life for patients.

Yasin *et al.* (2024) examined the role of metal oxide NPs (MONPs) as efficient drug carriers for targeted cancer therapy and addressed challenges arising from chemotherapy-induced side effects such as neurological and cardiac disabilities. These NPs, including IO, zinc oxide, and copper oxide, possess unique physicochemical properties that enable drug loading and controlled release, contributing to reduced systemic toxicity and drug resistance. Recent advances in the synthesis and functionalization of MO NPs have improved their stability, drug loading capacity, and biocompatibility. By targeting drugs to cancer cells, these nanocarriers enhance therapeutic efficacy and reduce side effects. Ultimately, the authors emphasized that MO NPs are promising platforms for overcoming the limitations of conventional chemotherapy and improving the quality of life for cancer patients [72].

Similarly, Carvalho *et al.* (2021) analyzed nano-platform technologies capable of simultaneously delivering multiple therapeutic agents, including chemotherapeutics, gene therapy, immunotherapy, and radiosensitizers, to achieve synergistic therapeutic effects. These nanosystems, through intelligent design, enable controlled and targeted drug release and can reduce drug resistance. The results revealed that the use of these multifunctional nanocarriers increases therapeutic efficacy, reduces drug dosage and side effects, and improves the anti-tumor immune response [73].

Aan *et al.* (2025), in an innovative study, designed a tumor microenvironment-responsive nanocarrier that provides simultaneous and precise combination of radionuclide therapy and chemotherapy. This nanocarrier is based on a hybrid structure of hyaluronic acid (HA) and Human Serum Albumin (HSA) incorporating the metal-organic framework MIL-100(Fe). The chemotherapeutic drug DOX is loaded into this structure and labeled with the radionuclide ^{131}I. The ^{131}I radionuclide, through beta emission, destroys cancer cells, while the nanocarrier, in response to the tumor microenvironment, releases doxorubicin in a controlled manner, inhibiting DNA synthesis and sensitizing tumor cells to RT. *In vitro* and *in vivo* experiments demonstrated that this nanocarrier is biocompatible, the radionuclide labeling is stable, it accumulates selectively in the tumor, and drug release in the tumor microenvironment is well controlled. Moreover, dual-mode MRI/SPECT imaging enables real-time tracking of the nanocarrier and precise tumor diagnosis [74]. Experimental results showed that this combined therapeutic system significantly inhibits tumor growth. This approach offers a promising strategy for precise, simultaneous radionuclide-chemotherapy guided by imaging, which can improve the diagnosis and targeted treatment of cancer [75].

Tran *et al.* (2020) emphasized that despite therapeutic advances, breast cancer remains one of the leading causes of mortality in women, and chemotherapeutic treatments face challenges like drug toxicity and resistance. They introduced various commonly used nanocarriers, including liposomes, dendrimers, polymeric micelles, polymeric NPs, lipid particles, and carbon nanotubes. Each of these, through surface modification and loading of chemotherapeutic drugs, can target drugs to specific receptors that are overexpressed on breast cancer cells. Finally, they documented that nanotechnology-based approaches, by increasing drug penetration into tumors, reducing systemic toxicity, and overcoming drug resistance, offer a promising outlook for more effective and safer breast cancer treatment [76].

4.5. Surface Engineering and Nanoparticle Design for Enhanced Targeting and Reduced Side Effects

Surface engineering of NPs using polymeric coatings, ligands, and antibodies is crucial for enhancing targeted drug delivery and minimizing side effects in cancer therapies. This approach improves the precision of drug release at tumor sites, with lipid NPs and stimuli-responsive liposomes serving as successful examples of such strategies. These advancements are key to the future success of nanomedicine. Additionally, as illustrated in Figure 3, Surface modified targeted NPs contribute to

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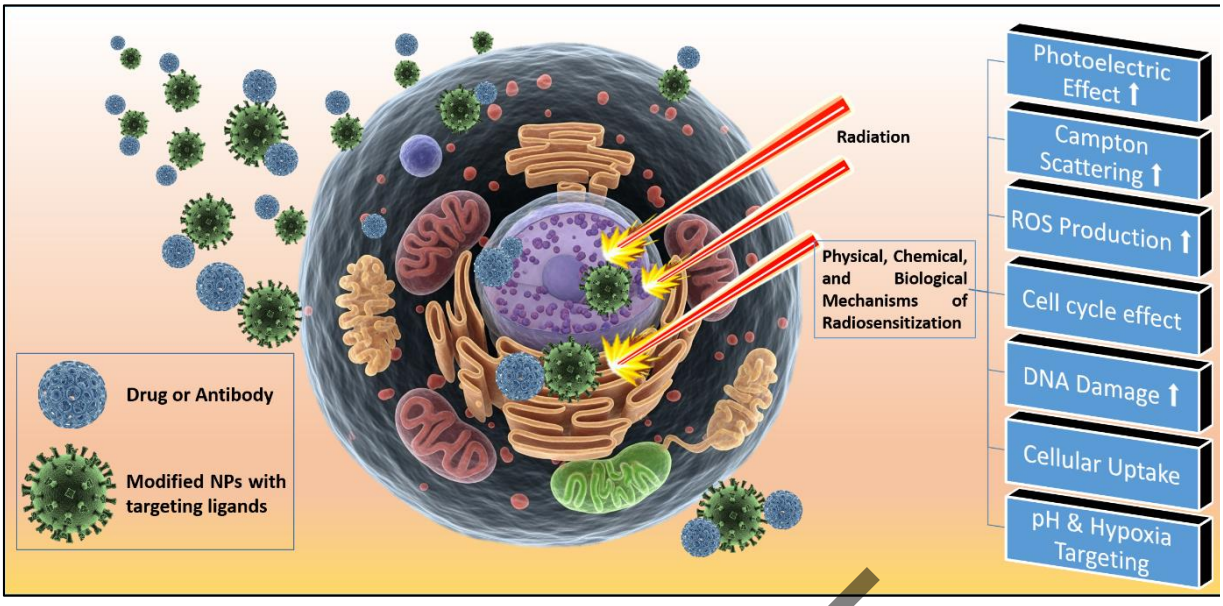

Figure 3. Schematic illustration of the physical, chemical, and biological mechanisms involved in radiosensitization through targeted nanoparticles (NPs). Reactive Oxygen Species (ROS)

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radiosensitization through various physical, chemical, and biological mechanisms, including the generation of ROS, which play a vital role in enhancing therapeutic outcomes.

Mitchell *et al.* (2021) examined the principles of engineering precise NPs for drug delivery. They stated that designing NPs with consideration of factors including size, shape, surface charge, composition, and release properties enables more accurate targeting and increased drug efficacy. The authors emphasized that precise nanoparticle engineering can lead to the development of more targeted drugs and reduced side effects, playing a significant role in personalized medicine [77]. Also, Cheng *et al.* (2025), in their study, investigated the applications of liposomes and lipid NPs in cancer therapy. These NPs, due to their lipid bilayer structure, are capable of encapsulating both hydrophilic and hydrophobic drugs and can deliver them specifically to cancer cells. Liposomes enhance therapeutic efficacy and reduce side effects by protecting drugs from premature degradation and enabling controlled release. Furthermore, these nanocarriers can be surface-modified with targeting ligands and exhibit increased penetration into the tumor microenvironment. Recent advances include the development of environmentally responsive liposomes (including pH- and temperature-sensitive) and solid lipid NPs with high stability and biocompatibility, allowing for more precise drug release. It was found that these technologies offer a promising outlook for personalized cancer therapies and can help overcome the limitations of traditional treatment methods [78].

Wang *et al.* (2016), in a comprehensive study, examined fabrication methods and surface engineering of polymeric NPs for targeted drug delivery to cancer. They accurately focused on two key biocompatible and biodegradable polymers, PLGA (poly(lactide-co-glycolide)) and chitosan, both approved by the FDA and EMA and advanced from laboratory research to clinical application. They described various nano/microencapsulation methods, including top-down techniques, for producing these NPs, and analyzed the roles of organic and aqueous phases in emulsion systems and their effects on the final nanoparticle characteristics.

In the section on surface engineering, studies revealed different strategies for surface modification of NPs to improve physicochemical properties, increase stability, reduce toxicity, and enhance targeting to cancer cells. These surface modifications include coating with polymers such as PEG to increase circulation time and reduce recognition by the immune system, or conjugation with ligands, antibodies, and specific peptides for active targeting of tumor cells. These approaches increase nanoparticle accumulation

in tumor tissue and reduce systemic side effects. It's clear that polymeric NPs with advanced surface engineering have high potential for targeted and effective delivery of anticancer drugs and can significantly improve therapeutic efficacy and patient quality of life [79].

4.6. Clinical Challenges and Future Research Directions

While functionalized nanocarriers show great promise in enhancing radiosensitization and enabling targeted drug delivery for cancer RT, significant clinical challenges remain that must be addressed before these technologies can be widely implemented. Key impediments include the stability of nanocarriers, potential toxicity, biodistribution, and the immune system's response to foreign materials. Moreover, overcoming biological barriers such as the blood-brain barrier, tumor heterogeneity, and the complex tumor microenvironment further complicates their clinical translation.

The long-term safety of these nanocarriers, including how they degrade and clear from the body, is not fully understood. For instance, the study by Dastgir *et al.* (2024) showed promising results in reducing tumor volume and increasing ROS generation with Bi_2O_3/CS@5-ALA-CUR NPs in preclinical models, but the long-term effects and clearance of these nanocarriers are still uncertain. Similarly, Bi NPs have demonstrated superior radiosensitizing efficacy, with SERs up to 1.48 and a 450% increase in ROS *in vivo* [30], but translating these results into clinical settings presents challenges, including optimizing nanocarrier design for human trials and ensuring patient safety.

Future research should focus on several strategic advancements to enhance the effectiveness of nanocarriers in radiosensitization and targeted drug delivery. First, optimizing nanocarrier design through precise control of drug release and improved targeting achieved via surface engineering techniques such as ligand or antibody conjugation can significantly enhance therapeutic efficacy while minimizing systemic toxicity. The development of multifunctional and stimuli-responsive nanocarriers, which respond to specific physical (magnetic field, light, temperature) or chemical (pH, enzyme presence) stimuli, offers exciting potential for site-specific and controlled drug release within the tumor microenvironment. Additionally, it is essential to prioritize safety and biocompatibility by utilizing biodegradable and non-toxic materials to reduce adverse effects and improve clinical acceptability. To bridge the gap between laboratory findings and clinical implementation, comprehensive preclinical and clinical studies are required to validate the efficacy, safety, and biological behavior of these nanocarriers. Incorporating imaging agents into nanocarriers is also a promising strategy, enabling real-time monitoring of drug delivery, improving treatment precision, and evaluating therapeutic outcomes. Finally, diversifying nanoparticle structures and compositions, including liposomes, polymeric NPs, metallic systems, and hybrid platforms, can be tailored for specific diagnostic and therapeutic applications. This helps to increase the versatility and functionality of nanomedicine in oncologic treatment, providing new avenues for personalized cancer therapies. By focusing on these areas, future research can accelerate the clinical translation of nanocarriers, making them a cornerstone of cancer treatment in the near future.

4.7. Limitations

While the studies included in this review show promising results for the use of functionalized nanocarriers in radiosensitization and targeted drug delivery, there are several important limitations to consider.

First, most of the studies reviewed are preclinical or *in vitro*, with only a few providing clinical data. For example, studies like those by Afifi *et al.* (2023) [41] and Abdollahi *et al.* (2022) [24] primarily focus on *in-vivo* and *in-vitro vitro* models, and while they provide valuable insights, their relevance to human trials is still uncertain. Second, there's considerable variability in the design and functionalization of nanocarriers across studies. Different NPs are used with different strategies, making it challenging to compare their effectiveness. This lack of standardization complicates the generalization of results across diverse tumor models and radiation techniques. Third, many studies, like those by Dastgir *et al.* (2024) and Stewart *et al.* (2016), focus mainly on short-term outcomes like tumor shrinkage and ROS generation. However, long-term data regarding the safety,

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toxicity, and biodegradation of these nanocarriers are often lacking, which is essential for assessing their potential for clinical application, particularly concerning clearance and long-term side effects.

Fourth, there is considerable variation in radiation therapy parameters, such as dose, energy, and technique, across studies, making it difficult to interpret results consistently. For example, studies like those by Liu *et al.* (2018) [80] and Jamil *et al.* (2021) [52] don't always clearly specify radiation doses, which challenges the ability to assess the reproducibility of radiosensitization effects. Fifth, while some studies have evaluated tumor-specific accumulation, a more comprehensive understanding of the biodistribution and immune system interactions of these nanocarriers is still needed. As seen in studies, while some nanocarriers accumulate well in tumors, their behavior in the body and interaction with the immune system require more exploration.

Finally, the considerable diversity in radiation parameters (particle, energy, dose), nanoparticle types, cancer models, and functionalization strategies across the studies makes it impossible to conduct a meta-analysis. Studies use different NPs and cancer models (breast, prostate cancer, and glioma), which introduces significant heterogeneity. This diversity in experimental designs and outcomes prevents meaningful statistical aggregation, hindering the ability to summarize the findings quantitatively. These limitations underscore the need for more rigorous preclinical studies and early-phase clinical trials to better understand the challenges of translating nanocarrier-based therapies into clinical practice.

5. Conclusion

Recent advances in nanocarrier technology have fundamentally transformed cancer treatment by enabling targeted and controlled drug delivery, enhancing radiosensitivity, and minimizing systemic side effects. Functionalized nanocarriers including magnetic NPs, nanogels, and stimuli-responsive liposomes, offer unique physicochemical properties that facilitate personalized therapeutic strategies and improve patient quality of life. This systematic review highlights the superior radiosensitizing efficacy of bismuth-based NPs, which demonstrate significant tumor volume reduction and ROS generation with minimal toxicity, positioning them as leading candidates for clinical translation. Ag, IO, Gd, graphene-based, and Ti NPs also show promising radiosensitization and drug delivery capabilities, often enhanced through ligand functionalization and combination therapies with chemotherapeutics.

Despite these promising outcomes, several challenges remain. Potential toxicity, biological stability, physiological barriers, and hurdles in clinical translation continue to limit widespread application. Addressing these issues requires further optimization of nanocarrier design, development of highly biocompatible and biodegradable materials, and extensive preclinical and clinical validation. Additionally, integrating advanced imaging modalities and engineering multifunctional, stimuli-responsive nanocarriers tailored to the tumor microenvironment will be critical to enhancing treatment precision and efficacy.

Largely, the evidence underscores a highly promising future for nanotechnology-driven cancer therapies. Continued interdisciplinary research focusing on overcoming clinical challenges, improving biocompatibility, and leveraging combinatorial nanocarrier applications will be essential to fully harness the potential of these innovative platforms, ultimately delivering safer, more effective, and tumor-selective treatments for cancer patients.

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