

Revolutionizing cancer therapy: Monoclonal antibodies in radiosensitization

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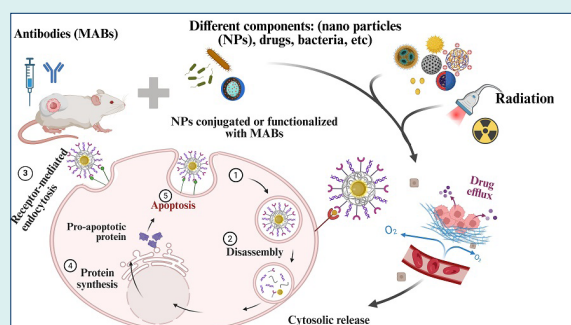
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Abstract

Cancer treatment has advanced significantly, yet traditional modalities such as radiotherapy still encounter challenges, including damage to healthy tissues and limited tumor specificity. Monoclonal antibodies (mAbs) have emerged as powerful tools in oncology, offering particular therapeutic options with reduced toxicity. Their capacity to enhance the efficacy of radiotherapy through radiosensitization presents

a promising strategy for improving cancer outcomes. This review synthesizes findings from the past decade, providing an in-depth analysis of the diverse roles of mAbs in radiosensitization. Key mechanisms are discussed, including targeting molecular pathways, modulation of immune responses, and integration with novel platforms such as nanoparticles and antibody-drug conjugates (ADCs). The review also highlights the successes of preclinical and clinical studies while addressing ongoing challenges like delivery inefficiencies, tumor resistance, and antigen heterogeneity. Additionally, emerging alternatives including aptamers, nanobodies, and engineered proteins are explored as potential solutions to these barriers. Advancements in mAb-based delivery systems and combination therapies remain crucial for achieving more personalized and effective cancer treatments.



Introduction

Cancer remains one of the leading causes of death globally, with the World Health Organization reporting nearly 10 million cancer-related deaths annually.¹⁻⁵ The high incidence and mortality rates associated with cancer highlight the urgent need for better and more effective

treatment strategies.⁶⁻⁹ Traditional cancer treatments such as surgery, chemotherapy, and radiotherapy have been the cornerstone of cancer therapy for decades.¹⁰⁻¹³ However, these methods often have significant limitations, particularly in targeting cancer cells while sparing healthy tissues.¹⁴⁻¹⁷ Chemotherapy and radiotherapy, for instance,



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not only target cancer cells but can also harm surrounding healthy tissues, leading to unwanted side effects.¹⁸

Radiotherapy, despite its effectiveness in treating certain cancers, also has the downside of damaging normal, healthy cells, which can result in various adverse effects.¹⁹ The inability of radiotherapy to discriminate between cancerous and healthy cells creates a pressing need for more targeted therapies.²⁰ One promising solution to this issue using monoclonal antibodies (mAbs), which offer a more precise approach by targeting cancer cells while minimizing harm to normal cells.²¹

Monoclonal antibodies are laboratory-engineered molecules designed to bind to specific antigens found on the surface of cancer cells.²² By recognizing and binding to these targets, mAbs can directly interfere with cancer cell growth and survival.²³ Additionally, monoclonal antibodies can be combined with other therapeutic agents, such as chemotherapy, nanoparticles, and bacteria, to enhance their effects.²⁴ This combination approach enables more effective treatment strategies and reduces the adverse side effects associated with traditional therapies.²⁵ Furthermore, monoclonal antibodies can sensitize cancer cells to radiotherapy, known as radiosensitization.²⁶

Radiosensitization refers to the process by which cancer cells become more sensitive to the damaging effects of radiation.^{27,28} This sensitivity can be achieved using antibodies targeting specific cell surface markers.²⁹ When monoclonal antibodies are used in conjunction with radiotherapy, they can enhance the effects of radiation by improving the delivery of radiation directly to the cancer cells while protecting healthy cells from damage.³⁰ This combination approach is auspicious in overcoming the limitations of radiotherapy, as it ensures that the radiation is more effectively absorbed by the cancer cells, increasing the likelihood of tumor regression and improving survival rates.³¹

Monoclonal antibodies have already shown great potential in preclinical and clinical studies, and their clinical translation has been one of the most successful in cancer therapy.³² Monoclonal antibodies have proven more effective in clinical settings³³ than other experimental treatments like aptamers and nanoparticles. They have been widely used in various cancer treatments, providing positive outcomes and becoming a standard in modern cancer immunotherapy.^{34,35} In addition to their direct action on cancer cells, monoclonal antibodies can influence various cellular pathways, further enhancing their therapeutic effects.³²

This review focuses, on using monoclonal antibodies in clinical and preclinical studies over the past decade. We examine how monoclonal antibodies have been combined with other therapeutic agents, such as nanoparticles and immune checkpoint inhibitors, to improve treatment efficacy. We also explore the molecular and cellular pathways affected by monoclonal antibodies, which

contribute to their therapeutic effects in cancer treatment. Finally, we address the current challenges in monoclonal antibody therapies, including tumor heterogeneity, resistance mechanisms, and delivery strategies. We conclude by discussing the prospects of monoclonal antibodies in cancer therapy and their potential to overcome the limitations of traditional treatments, offering more personalized and targeted approaches for cancer patients.

Monoclonal antibodies in cancer therapy

Antibodies are vital immune systems that identify and neutralize foreign substances, including pathogens and abnormal cells.³⁶⁻³⁹ These Y-shaped proteins are produced by B lymphocytes and are classified into five major isotypes: IgG, IgA, IgM, IgE, and IgD.⁴⁰⁻⁴³ Each isotype has unique structural and functional properties, enabling diverse roles in immune defense.^{41,44-46} Among these, IgG antibodies are the most abundant and are predominantly used in therapeutic applications due to their stability, prolonged half-life, and ability to mediate immune responses effectively.^{41,47,48}

Therapeutic antibodies can be further categorized based on their development and application. Polyclonal antibodies are mixtures that recognize multiple epitopes on an antigen, commonly used for passive immunization or diagnostic purposes.^{49,50} Monoclonal antibodies (mAbs), on the other hand, are engineered to recognize a single, specific epitope, providing high precision in targeting.⁵¹ Advances in genetic engineering have expanded the scope of mAbs, allowing for the development of chimeric, humanized, and fully human antibodies to minimize immunogenicity while enhancing therapeutic efficacy.⁵² Additionally, antibody-drug conjugates (ADCs), bispecific antibodies, and immune checkpoint inhibitors have emerged as innovative platforms in antibody engineering, further diversifying their clinical utility.^{53,54}

mAbs have emerged as a significant class of therapeutics, with notable applications in treating cancer.⁵⁵ These antibodies are engineered to target specific antigens present in cancer cells, facilitating tumor cell destruction through several mechanisms, including direct apoptosis induction, immune system activation, and enhanced chemotherapy sensitivity.⁵⁶ As of 2018, the FDA had approved over 80 mAbs, with a substantial portion of these approvals aimed at treating oncological conditions.⁵⁷ Approving 12 new mAbs that year alone highlighted their growing importance in cancer therapy.⁵⁷ The expanding therapeutic pipeline, with over 100 mAbs in development, further underscores their potential in clinical settings.⁵⁶

The development of mAbs has its roots in the hybridoma technique of the 1970s, which led to the creation of immortal B cell clones capable of producing specific antibodies.⁵⁸ However, early mAbs faced issues like immunogenicity, particularly when derived from murine

sources.⁵⁹ Over time, advances in genetic engineering have resulted in chimeric, humanized, and fully human mAbs, significantly improving their safety and efficacy profiles.⁶⁰ These therapeutic antibodies can be directed against tumor-associated antigens, such as the HER2 receptor in breast cancer, where trastuzumab (Herceptin) has proven effective in targeting overexpressed HER2, promoting immune-mediated tumor cell destruction through antibody-dependent cellular cytotoxicity (ADCC).^{61,62}

mAbs' ability to selectively target cancer cells while sparing healthy tissues represents a significant advantage over traditional chemotherapy, which often results in widespread toxicity.⁶³ Furthermore, recent innovations in mAb engineering have aimed to reduce off-target effects and enhance pharmacokinetics, ensuring more efficient delivery to the tumor site and improved clinical outcomes.⁶⁴ This efficient delivery has led to the development of bispecific antibodies and ADCs, which combine the specificity of mAbs with the cytotoxic power of chemotherapeutic agents, offering a promising avenue for improving cancer treatment.^{64,65}

In addition to their use in cancer therapy, mAbs have demonstrated potential in enhancing radiotherapy, particularly through radiosensitization.⁶⁶ Radiosensitization makes tumor cells more susceptible to radiation, which is crucial in overcoming resistance to radiotherapy.⁶⁷ Recent research has shown that mAbs can be engineered to bind to specific receptors on tumor cells, not only inhibiting their growth but also increasing their sensitivity to radiation.⁶⁸ This synergistic effect has been observed with mAbs targeting growth factor receptors and immune checkpoint inhibitors.⁶⁸ By improving the efficacy of radiotherapy, mAbs (Fig. 1) may offer an important strategy for treating tumors that are otherwise resistant to conventional radiation-based therapies, thus broadening the therapeutic options available for cancer patients.⁶⁸

Various applications of mAbs in radiosensitization

Only antibodies

Monoclonal antibodies (mAbs) as standalone radiosensitizers represent a targeted approach to overcoming tumor radiation resistance. While promising, their clinical efficacy varies across studies. This section critically examines recent evidence, emphasizing preclinical mechanisms and clinical findings, while highlighting limitations and future directions.

Hypoxia-induced radioresistance is a significant challenge in radiotherapy, and while SPINK1 has been identified as a key player in this process, its efficacy and limitations across different tumor types and stages remain underexplored. SPINK1 is secreted in response to severe hypoxia and can protect neighboring, oxygenated cells from radiation by activating EGFR- and Nrf2-dependent survival pathways. However, although the role

of SPINK1 in radiosensitization has been demonstrated in preclinical models, its therapeutic potential is likely to vary across cancer types due to differences in the tumor microenvironment, the degree of hypoxia, and the expression of SPINK1 across different malignancies. For instance, in some cancers like prostate and colon carcinoma, where SPINK1 is overexpressed even under normoxic conditions, its role as a predictive marker for tumor hypoxia may be less reliable. This unreliability highlights the necessity of evaluating SPINK1's function and predictive value in a broader range of cancer types to fully understand its utility as both a biomarker for tumor hypoxia and a target for radiosensitization.⁶⁹ Moreover, while anti-SPINK1 neutralizing antibodies have shown promise in radiosensitizing tumors in specific models, translating these findings to clinical settings is still uncertain, particularly considering the potential for off-target effects. For example, systematic inhibition of SPINK1 could increase the risk of pancreatitis, an issue requiring careful consideration in the design of future therapeutic strategies. Therefore, in addition to optimizing SPINK1-targeting treatments, it is crucial to explore more selective delivery methods, such as nanoparticle-based drug delivery systems, to minimize systemic toxicity. These challenges underline the need for additional research to refine our understanding of SPINK1's role in cancer therapy and to develop more effective strategies for exploiting its radiosensitizing properties.⁶⁹

Similarly, a preclinical study on head and neck squamous cell carcinoma (HNSCC) showed enhanced radiosensitization by simultaneously targeting β 1 integrin and EGFR using mAbs. The treatment inhibited FAK- and Erk1-mediated survival signaling, reducing clonogenic survival and improving tumor control in eight of ten cell lines. In vivo, xenografts treated with combined mAbs and radiotherapy showed better tumor control than single-agent therapies.⁷⁰ However, the study involved small sample sizes ($n = 12$ -16 per group), and potential systemic toxicities were not fully explored. Future investigations should evaluate this combination in models mimicking human immune and stromal components.⁷⁰

The phase II trial assessing panitumumab (anti-EGFR) combined with radiotherapy in 19 patients with KRAS wild-type locally advanced rectal cancer demonstrated mixed results. Although the treatment achieved a 41% grade 3 pathological tumor regression rate and a 95% sphincter-preservation rate, no complete pathological response (pCR) cases were observed.⁷¹ These results indicate partial efficacy but suggest that KRAS wild-type status alone is an insufficient biomarker for response prediction. When comparing these results to other similar studies, such as those investigating cetuximab in combination with radiotherapy, it becomes clear that while anti-EGFR monoclonal antibodies have shown some promise, their efficacy is limited. Cetuximab, for instance, has been

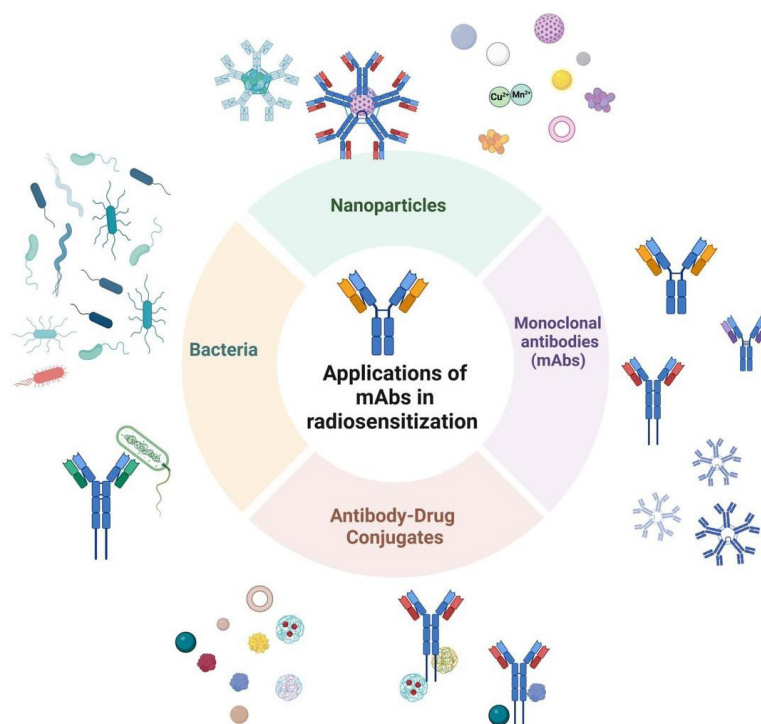


Fig. 1. Overview of strategies using mAbs for radiosensitization. **Nanoparticles:** Antibody-functionalized nanoparticles that deliver therapeutic agents or enhance the radiation response, making tumor cells more sensitive to radiation. **mAbs:** mAbs targeting tumor-specific antigens to block critical signaling pathways, thereby increasing the tumor cells' susceptibility to radiation therapy. **ADCs:** mAbs conjugated with cytotoxic drugs to target tumor cells. This combination sensitizes the cells to radiation by directly delivering toxic agents to the tumor. **Bacteria-based systems:** Engineered bacteria expressing or carrying antibody-based therapeutics that facilitate radiosensitization, improving the efficacy of radiation treatment against tumors.

associated with higher pCR rates in some studies, though not consistently across all cohorts. This discrepancy could be attributed to factors such as the treatment regimen, the sequencing of therapies, and the patient population. The significant changes in plasma TGF- α and EGF levels observed in responders emphasize the need for multi-biomarker approaches to refine patient selection and optimize therapeutic strategies. Interestingly, plasma TGF- α was significantly elevated in patients with a good response (grade 3 regression), which aligns with findings from other studies suggesting that increased TGF- α levels may correlate with enhanced tumor response in specific settings. However, the concurrent decrease in plasma EGF in these patients challenges the straightforward interpretation of EGFR pathway modulation. This dual biomarker trend underscores the complexity of EGFR inhibition in rectal cancer, where the dynamics between various EGFR ligands and other growth factor receptors, such as MET, may contribute to resistance mechanisms.⁷¹

A particularly notable case study involved the use of pembrolizumab (anti-PD1) followed by radiotherapy in a patient with non-resectable relapsed oral cavity carcinoma. This approach resulted in excellent local tumor control, attributed to T-cell activation mediated by checkpoint inhibition.⁷² Although promising, this report is based on a single patient, limiting its broader applicability. Large-scale clinical trials with defined endpoints, including immune response and survival

rates, are critical to validate these findings. Moreover, the potential for immune-related toxicities in combined regimens warrants careful monitoring.⁷²

Using monoclonal antibodies as standalone radiosensitizers demonstrates significant promise, especially in preclinical settings and small-scale clinical studies. However, variability in outcomes and limited patient cohorts underscore the need for refined patient selection, larger clinical trials, and exploration of combination strategies. By addressing these challenges, the full potential of mAbs in radiotherapy can be realized, paving the way for more effective and personalized cancer treatments.

In contrast, ADCs offer a more potent strategy for radiosensitization by not only targeting tumor antigens but also delivering cytotoxic agents directly to the tumor cells.^{71,73} This method combines the precision of monoclonal antibodies with the tumor-killing potential of chemotherapy, thus providing a more robust approach to overcoming radiation resistance. ADCs, such as those targeting EGFR or other tumor-specific antigens, are designed to maximize the local concentration of toxic drugs within tumor cells, which may significantly enhance radiosensitivity.^{71,72,74} However, while ADCs offer the advantage of delivering targeted chemotherapy, their efficacy can be affected by the tumor's ability to internalize the conjugated drug and its heterogeneity. Furthermore, ADCs often face challenges related to off-target toxicity

and the complex pharmacokinetics of drug release. The advantage of ADCs over standalone mAbs lies in their ability to sensitize tumors to radiation and induce direct tumor cell killing, a key benefit when targeting highly resistant tumors.⁷²⁻⁷⁴

On the other hand, mAbs are generally less toxic and more specific in their targeting mechanism, but their efficacy is sometimes limited by the tumor's resistance mechanisms, such as the downregulation of target antigens or activation of alternative survival pathways.⁷⁴ For example, while EGFR-targeted mAbs like cetuximab have shown some efficacy in radiosensitization, their success can be limited by the tumor's ability to bypass EGFR signaling through other compensatory mechanisms.^{72,74} By delivering a cytotoxic payload, ADCs can potentially overcome this issue by directly killing tumor cells that would otherwise evade mAb-mediated inhibition. Therefore, combining of ADCs with radiotherapy may offer a synergistic approach, exploiting both the radiosensitizing effects and the direct cytotoxicity of the conjugated drug, making them a compelling alternative to standalone mAbs in specific contexts.^{72,73}

Antibody-drug conjugates

ADCs represent a promising strategy for improving the efficacy of radiotherapy by selectively delivering cytotoxic agents to tumor cells.^{73,75} This approach leverages the specificity of antibodies to target tumor-associated antigens, thus enabling the precise delivery of potent drugs to malignant cells while minimizing systemic toxicity. However, while ADCs show great potential, several factors must be optimized to enhance their therapeutic impact in radiotherapy.⁷³

Lewis and his colleagues explored using an ADC targeting the radiation-inducible antigen TIP1 on non-small cell lung cancer (NSCLC). A summary of key findings from this and other relevant studies is provided in Supplementary file 1 (Table S1). The study demonstrated that the ADC, composed of the anti-TIP1 antibody 7H5 conjugated to the cytotoxic drug MMAE, significantly enhanced the radiosensitization of cancer cells.⁷⁴ This conjugate exhibited prolonged circulation times in the bloodstream, allowing continuous drug delivery to the tumor during radiotherapy. Combining 7H5-VcMMAE with radiation resulted in a 70% reduction in viable cells, delayed tumor growth, and improved survival in NSCLC tumor models. These findings underscore the potential of ADCs in improving tumor response to radiotherapy, but they also highlight the need for further optimization of ADCs for specific tumor types and radiation protocols. The cytotoxic agent's antigen specificity and effectiveness, such as MMAE, must be carefully tailored to the tumor's molecular profile.⁷⁴

In contrast, Guster et al combined radiotherapy with EGFR-targeting antibodies like cetuximab in HNSCC, which showed less favorable results. Although cetuximab

is widely used as a radiosensitizer, the study revealed that it failed to enhance the radiosensitivity of HPV-positive HNSCC cell lines significantly.¹⁰⁵ This outcome suggests that the effectiveness of ADCs in combination with radiotherapy may vary across cancer types and patient populations.¹⁰⁵ A critical takeaway is the necessity for individualized treatment approaches considering tumor heterogeneity and molecular characteristics. Furthermore, this study highlighted those alternative approaches, such as PARP inhibition, might provide more effective radiosensitization in some cancers, indicating that ADCs may not always be the optimal choice in all contexts.¹⁰⁵

Another study on histone deacetylase (HDAC) inhibition in bladder cancer (BC) radiosensitivity revealed a potential synergy between ADCs and radiation. The selective inhibition of HDAC6, when combined with radiotherapy, increased radiosensitivity by inducing gene expression changes that counteracted the radiation-induced effects on tumor migration and metastasis.⁷⁸ These findings suggest using ADCs as standalone therapies and in conjunction with epigenetic modulators or other therapeutic agents to enhance their impact further. This result suggests that multi-pronged treatment strategies involving ADCs could be particularly beneficial in overcoming the tumor's adaptive responses to radiation and limiting metastasis.⁷⁸

In pancreatic cancer, another research study conducted by Azad et al⁹⁵ has shown that combining radiotherapy with anti-PD-L1 antibodies can enhance the tumor response, particularly at higher radiation doses. The addition of PD-L1 blockade promoted CD8+ T cell infiltration into the tumor, improving overall radiotherapy efficacy. This effect points to the emerging role of ADCs that can also modulate the immune microenvironment to enhance the immune response alongside traditional therapies. The challenge lies in selecting ADCs that can effectively influence the tumor's immune landscape while sensitizing it to radiation.⁹⁵

A study (Fig. 2), which was conducted by Hingorani, focusing on a trimodal approach integrating chemotherapy, radiotherapy, and immunotherapy using auristatin-based ADCs showed that MMAE-conjugated antibodies could sensitize tumors to radiation and boost immune responses (Table S1).⁸¹ The combination led to durable tumor control and the development of immunologic memory, emphasizing the growing importance of combining ADCs with immunotherapies to amplify therapeutic effects. However, these strategies' success will require thorough clinical trials testing to evaluate long-term outcomes and identify any potential off-target effects or resistance mechanisms that could undermine their efficacy.⁸¹

In conclusion, while ADCs offer a promising avenue for enhancing the efficacy of radiotherapy, several challenges remain in optimizing their use. Personalized treatment

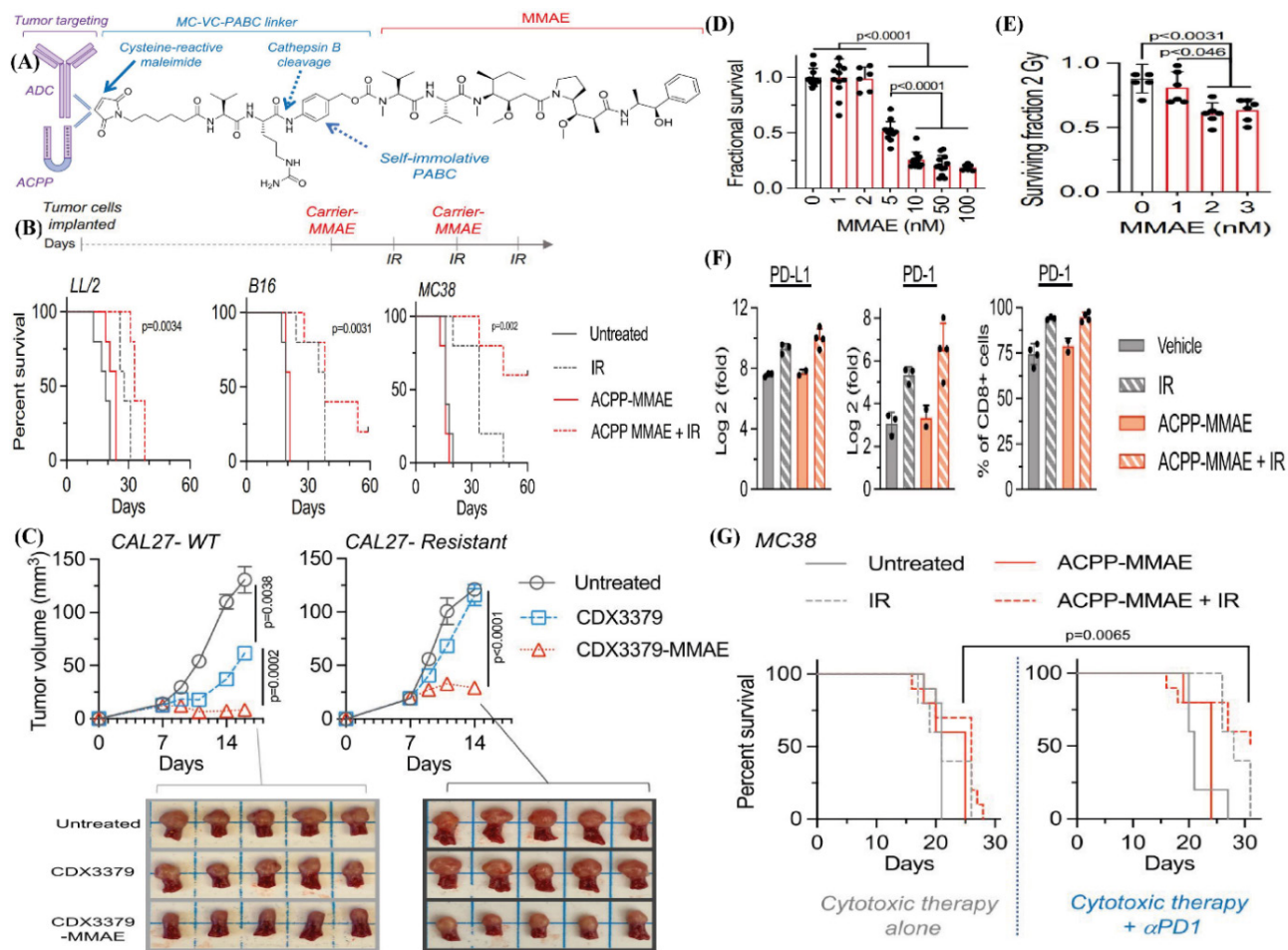


Fig. 2. MMAE-based conjugates enhance cancer therapy via targeted delivery, radiosensitization, and immune modulation. (A) Schematic of MMAE conjugated to antibodies and cell-penetrating peptides using MC-VC-PABC linkers. (B) Treatment plan for tumor-bearing mice showing improved survival with ACPM-MMAE and IR. (C) Reduced tumor size in CAL27-resistant models after ACPM-MMAE treatment. (D) Dose-dependent decrease in B16 cell survival after MMAE treatment. (E) Combined MMAE and radiation increases sensitivity and reduces survival of tumor cells. (F) Enhanced immune response with increased CD8+ T cells and PD-L1/PD-1 modulation. (G) Triple therapy with MMAE, radiation, and anti-PD-1 antibody prolongs survival in MC38 tumors. **Statistical analysis:** Mean $\pm$ SEM; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. These results demonstrate the synergistic therapeutic effects of MMAE-based conjugates with radiation and immunotherapy in targeting cancer cells. Abbreviations: ACPM, activatable cell-penetrating peptide. This figure is reproduced from⁸¹ under the CC BY license.

regimens that account for tumor heterogeneity, specific antigen profiles, and immune responses are essential to maximize the therapeutic benefits of ADCs. Additionally, the development of combination therapies, incorporating ADCs with other modalities such as immunotherapy or epigenetic modifiers, holds significant promise in overcoming the limitations of single-agent therapies. Ongoing research and clinical trials will be critical in refining these strategies and establishing ADCs as a mainstay in radiotherapy.

Nanoparticles

Nanotechnology offers state of the art approaches for combating cancer.¹⁰⁶⁻¹¹⁰ Integrating nanoparticles with monoclonal antibodies presents an innovative strategy to enhance radiotherapy outcomes by combining radiosensitization, targeted therapy, imaging capabilities, and immune modulation.^{106,111,112} This multifaceted approach addresses critical limitations in traditional cancer treatments, such as resistance to therapy and

lack of specificity, offering promising advancements in glioblastoma and other malignancies.¹¹²⁻¹¹⁴

Nanoparticles provide a unique platform for transporting monoclonal antibodies across biological barriers, exemplified by a study utilizing gold nanoparticles coated with insulin to traverse the blood-brain barrier (BBB) and deliver cetuximab to glioblastoma cells.⁸⁰ This study demonstrated that combining this targeted nanoparticle delivery system with temozolomide (TMZ) and radiotherapy significantly inhibited tumor growth and prolonged survival in a murine glioblastoma model. Histological analyses further revealed reduced tumor vascularization and enhanced radiosensitization. While this approach effectively addressed the challenge of BBB penetration, its reliance on gold nanoparticles, which may exhibit long-term bioaccumulation, necessitates exploring biodegradable alternatives for clinical translation.⁸⁰

Building on the implementation of gold nanoparticles, multifunctional magnetic nanoparticles conjugated

with cetuximab were employed to target EGFRvIII-overexpressing glioblastoma cells.¹⁰³ These nanoparticles provided dual functionality as MRI contrast agents and radiosensitizers. When used with ionizing radiation (IR), they significantly enhanced radiosensitivity by increasing DNA double-strand breaks and reactive oxygen species (ROS) formation. The *in vivo* results showed a marked increase in survival among treated mice, emphasizing the therapeutic potential of combining imaging, targeting, and radiosensitization. However, the study highlights the need for optimizing delivery methods, as convection-enhanced delivery (CED) is invasive and may limit broader clinical applications.¹⁰³

A novel nanoplatforms incorporating gold and superparamagnetic iron oxide nanoparticles (SPIOs) targeted PD-L1 expression in tumors to enhance therapeutic efficacy further.⁸² This platform improved imaging with superior T2-weighted MRI contrast and served as a radiosensitizer by increasing ROS production and inhibiting DNA damage repair. Beyond radiosensitivity, the platform exhibited immunomodulatory properties by shifting the tumor microenvironment from immunosuppressive to immunoreactive through TAM polarization and PD-L1/PD-1 pathway blockade. Adding these immune-modulating effects highlights a critical advancement, bridging the gap between localized radiotherapy and systemic immune responses. Despite its promising results, further studies are needed to explore the long-term effects of immune activation and potential off-target impacts in heterogeneous tumor microenvironments.⁸²

Lastly, a study addressing the depth-dependent effectiveness of gold nanoparticles under clinically relevant megavoltage (MV) radiation beams revealed significant radiosensitization in prostate cancer models.⁸³ The nanoparticles, functionalized with PSMA-targeting antibodies, demonstrated active targeting verified through confocal microscopy and transmission electron microscopy (TEM). The therapeutic efficacy was depth-dependent, with increased radiosensitization ratios observed at greater depths due to enhanced low-energy photon interactions. Monte Carlo (MC) microdosimetry and the local effect model (LEM) accurately predicted survival fractions, providing robust evidence for the clinical feasibility of gold nanoparticle-assisted radiotherapy. However, the variability in radiosensitization across depths underscores the need for patient-specific treatment planning and developing nanoparticles capable of maintaining consistent efficacy under diverse clinical conditions.⁸³

Collectively, these studies illustrate the transformative potential of combining monoclonal antibodies with nanoparticles in radiotherapy. They address critical challenges such as BBB penetration, imaging-guided therapy, and immune modulation while demonstrating

depth-dependent adaptability. Future efforts should focus on improving delivery methods, minimizing long-term toxicity, and tailoring treatment strategies to patient-specific tumor characteristics to maximize clinical translation, future. This integrated approach enhances therapeutic efficacy and opens new avenues for combining radiotherapy with emerging immunotherapies, paving the way for more personalized and effective cancer treatments.

Bacteria

Integrating of mAbs with anaerobic bacteria as radiosensitizers represents a groundbreaking approach to overcoming challenges in treating hypoxic tumors, which are often resistant to conventional therapies. Recent studies by JingBo Wu's team⁸⁵ have provided a compelling foundation for understanding how *Bifidobacterium infantis* (Bi), in conjunction with its specific mAb, can enhance radiotherapy efficacy and modulate the tumor microenvironment. These studies offer complementary perspectives, addressing this innovative strategy's mechanistic and therapeutic dimensions.^{76,85}

In the study by Yang et al,⁸⁵ the authors explored the combination of Bi-mAb and radiotherapy in a Lewis lung carcinoma mouse model. This research leveraged advanced imaging techniques, including 18F-FDG and 18F-FMISO PET/CT, to monitor tumor metabolism and hypoxia. The results demonstrated that the combination therapy significantly reduced tumor hypoxia and glucose metabolism, as evidenced by decreased uptake of FDG and FMISO in the treated group.⁸⁵ Additionally, immunohistochemical analyses revealed a reduction in key markers such as HIF-1 α , Glut-1, and Ki-67, indicating suppressed hypoxic signaling and tumor proliferation. Conversely, increased levels of γ -H2AX and TNF- α suggested enhanced DNA damage and a pro-inflammatory response. Tumor growth was significantly slowed, and survival times were markedly prolonged, highlighting the potential of this approach to overcome the limitations of conventional radiosensitizers, which often suffer from poor specificity and significant side effects. However, this study primarily focused on a single tumor model and lacked long-term evaluations, limiting its of its finding's broader applicability.⁸⁵

Building on these results, Wang et al (Table S1) (Fig. 3) expanded the therapeutic framework by incorporating immune checkpoint inhibitors (α PD-1) into the Bi-mAb and radiotherapy regimen.⁷⁶ This quadruple therapy addressed limitations in the earlier study, particularly the lack of a robust abscopal effect. Using 4T1 breast and CT26 colon cancer models, the authors demonstrated that Bi-mAb alleviated tumor hypoxia and transformed the tumor microenvironment, converting "cold" tumors into "hot" ones. This localized inflammation, induced by Bi colonization and the transient "infection" it caused, activated innate immune responses, including

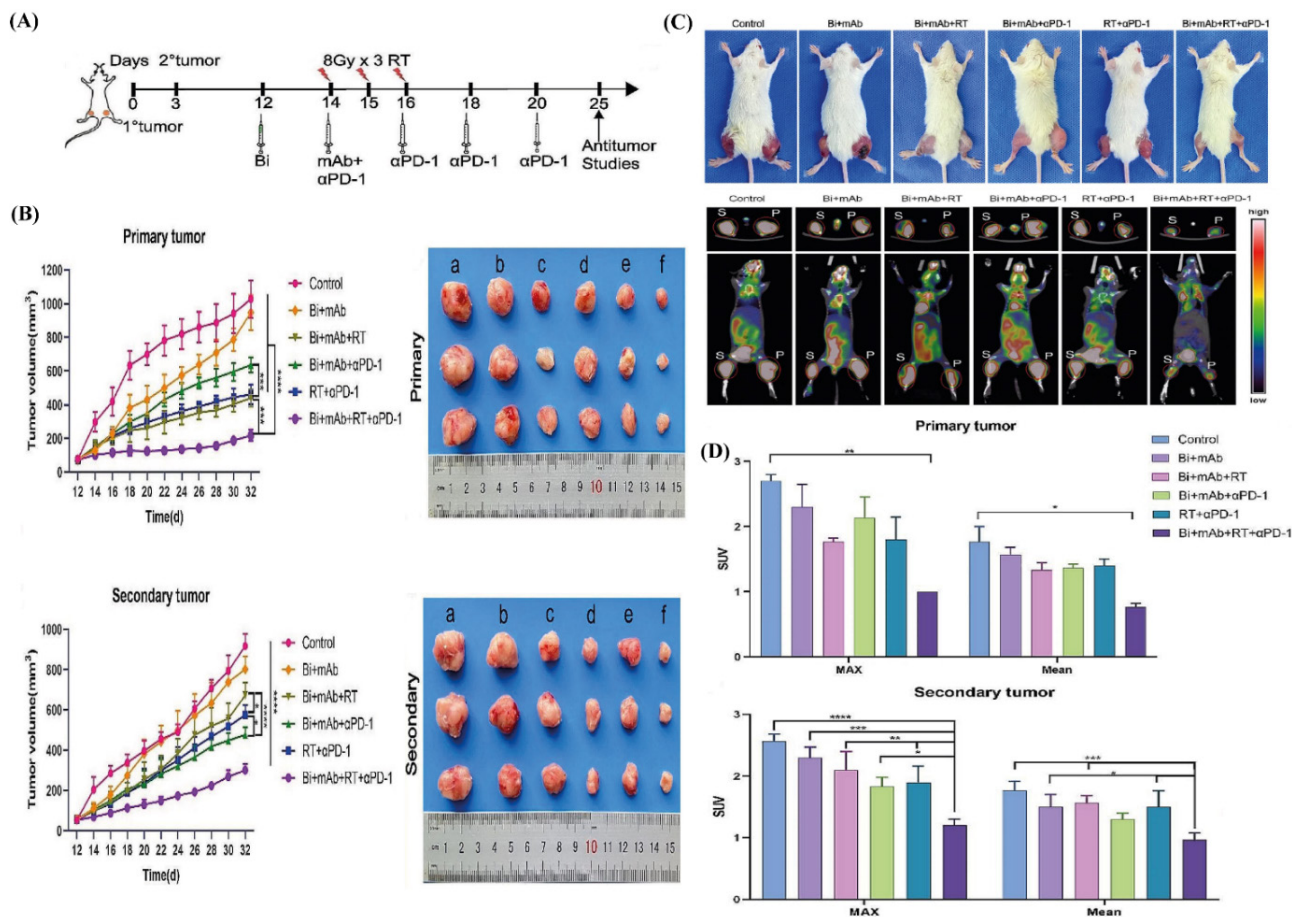


Fig. 3. Antibody Targeting of Anaerobic Bacteria Enhances Radiotherapy and Triggers Abscopal Responses in Cold Tumors. (A) Schematic of the 4T1 tumor model: localized radiotherapy was applied to primary tumors (1°), while secondary tumors (2°) remained untreated to assess systemic abscopal effects. (B) Tumor growth curves for six treatment groups demonstrate the strongest inhibition in the quadruple therapy group (Bi + mAb + RT + αPD-1), confirmed by tumor images at day 25. (C) Representative ^{18}F -FDG PET/CT scans show reduced metabolic activity following combination therapy. (D) Quantification of SUVmax and SUVmean in both tumor sites shows significantly decreased uptake in treated groups. Together, these findings indicate that combining bacterial targeting with radiotherapy and immune checkpoint blockade enhances both local and systemic anti-tumor responses. Abbreviations: Bi, anaerobic bacteria; αPD-1, anti-programmed cell death protein 1 antibody; ^{18}F -FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; SUV, standardized uptake value. This figure is reproduced from⁷⁶ under the CC BY license.

complement activation and ADCC.⁷⁶ The therapy synergistically stimulated adaptive immune responses, amplified systemic antitumor immunity, and prolonged survival in mice, combined with αPD-1 and radiotherapy. As illustrated in Fig. 3, the study evaluated the therapeutic efficacy using primary (irradiated) and secondary (non-irradiated) tumors to assess the abscopal effect. Tumor growth curves (Fig. 3b) demonstrated significantly reduced tumor sizes, especially in the quadruple therapy group. PET/CT imaging (Fig. 3c) further revealed tumor metabolic suppression, corroborated by quantitative SUV analysis (Fig. 3d). Immune profiling (Fig. 3e) showed increased CD4+ and CD8+ T cell infiltration, highlighting robust immune activation. Additionally, the study highlighted the ability of PET/CT imaging to visualize the dynamic changes in tumor metabolism and hypoxia, reinforcing the translational potential of this approach.⁷⁶

its complexity and the absence of clinical validation. The lack of detailed mechanistic insights into how Bi-

mAb modulates the interplay between hypoxia and immune responses leaves room for further investigation. Moreover, both studies relied heavily on preclinical models, which may not fully capture the complexities of human tumors.⁷⁶

These studies illustrate the potential of using Bi-mAb as a dual-function agent for radiosensitization and immune modulation. Addressing hypoxia and leveraging immune mechanisms, provide a multifaceted strategy for enhancing radiotherapy outcomes. Future research should aim to validate these findings in diverse tumor models and clinical settings while exploring strategies to simplify the therapeutic regimen for practical application. This innovative paradigm holds promise for improving localized tumor control and offers a pathway to systemic antitumor responses, particularly for metastatic cancers.^{76,85,115}

From a clinical perspective, bacteria-based micro-robotic systems, such as Bi-mAb, offer several unique

advantages, including tumor-targeting specificity, modulation of the tumor microenvironment, and the potential to synergize with existing immunotherapies and radiotherapy.^{76,85} Their ability to thrive in hypoxic cores of tumors gives them a distinct edge over conventional delivery systems. However, significant challenges remain before clinical translation can be realized. These include concerns regarding biosafety, potential immunogenicity, reproducibility of bacterial colonization across patients, and regulatory hurdles associated with using of genetically modified organisms or live bacteria.^{76,85} Moreover, the complexity of multi-component therapies like Bi-mAb + RT + αPD-1 may limit scalability and clinical implementation without further simplification. Therefore, while the therapeutic potential of bacteria-based systems is considerable, advancing toward clinical application will require robust safety evaluations, standardized manufacturing protocols, and early-phase clinical trials to establish efficacy and safety in human patients.^{76,85}

Molecular targets in radiosensitization

Epidermal growth factor receptor (EGFR) and its family members

EGFR

The EGFR plays a crucial role in cellular proliferation, survival, and repair mechanisms, making it a significant

target in cancer therapy.^{116,117} Overexpression or mutation of EGFR, such as EGFRvIII, is often associated with tumor aggressiveness and resistance to standard treatments, including radiotherapy.¹¹⁸ Monoclonal antibodies targeting EGFR, like cetuximab and panitumumab, have been explored as potential radiosensitizers to enhance the therapeutic efficacy of radiotherapy. However, their success has varied across tumor types and settings, reflecting promise and challenges (Fig. 4).¹¹⁸

EGFR contributes to radioresistance by activating downstream signaling pathways, including the PI3K/AKT and MAPK pathways, which promote DNA repair, cell survival, and anti-apoptotic responses post-irradiation.¹¹⁹ By blocking EGFR signaling, monoclonal antibodies can theoretically enhance radiosensitivity by impeding these repair and survival mechanisms, increasing DNA damage, and inducing apoptosis.¹²⁰

Recent studies highlight the potential of EGFR-targeted approaches. For example, in glioblastoma, cetuximab bioconjugated to iron oxide nanoparticles (IONPs) significantly enhanced radiosensitivity when combined with ionizing radiation.¹⁰³ The radiosensitivity enhancement was attributed to increased DNA double-strand breaks and elevated ROS levels, culminating in greater tumor cell death and prolonged survival in animal models. These findings underline the promise of EGFR

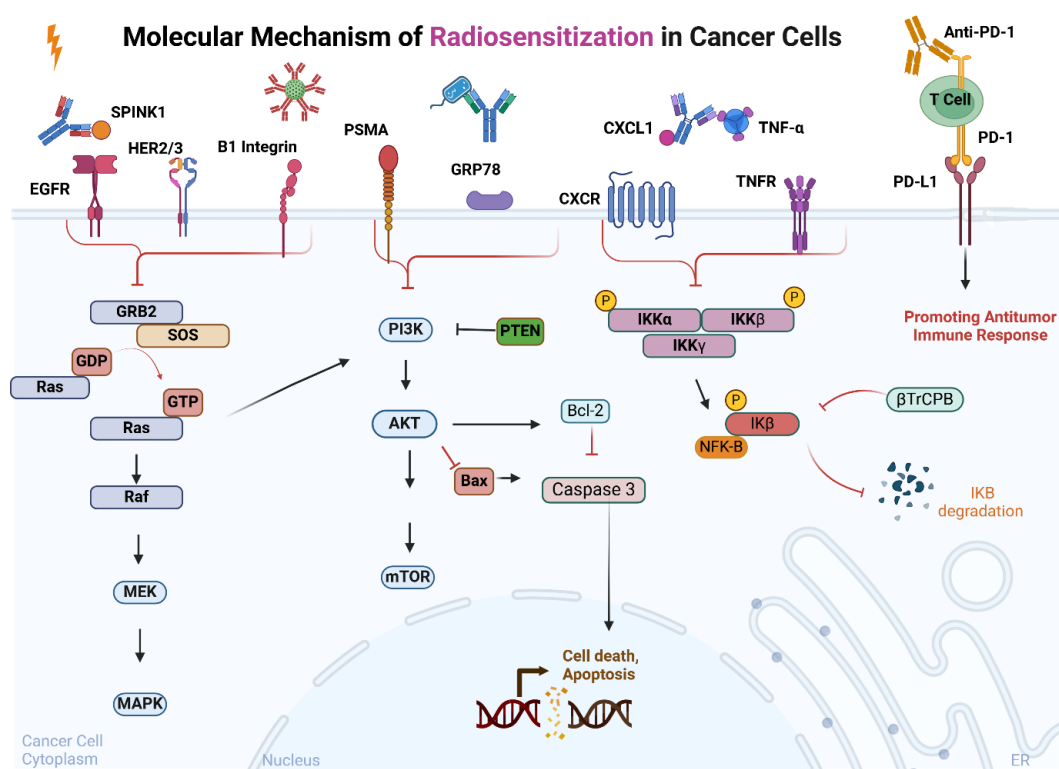


Fig. 4. Molecular Mechanism of Radiosensitization in Cancer Cells. A schematic representation of radiosensitization mechanisms in cancer cells, emphasizing the role of therapeutic antibodies. These antibodies block key signaling pathways, such as PI3K/AKT/mTOR, MAPK, and NF-κB, targeting molecules like PSMA, GRP78, CXCL1, and TNF-α. This inhibition leads to reduced cell survival and increased activation of apoptotic pathways (e.g., Bax, Caspase 3). Additionally, anti-PD-1 therapy enhances the antitumor immune response, further contributing to radiosensitization and tumor control. Created with BioRender.com.

inhibition in improving radiotherapy outcomes.¹⁰³

Despite the encouraging articles, some articles have shown its drawbacks. A study by Guster and her colleagues,¹⁰⁵ demonstrated that cetuximab failed to radiosensitize HPV-positive HNSCC cell lines.¹⁰⁵ This ineffectiveness may be attributed to the distinct biological characteristics of HPV-positive tumors, where alternative pathways such as PARP and Chk1 signaling may dominate in mediating radioresistance. This highlights the need for tailored approaches based on tumor biology. Exploring combination therapies, such as PARP and Chk1 inhibition alongside EGFR targeting, could address these limitations and enhance therapeutic efficacy.¹⁰⁵

In a clinical trial setting, the radiosensitizing potential of panitumumab in locally advanced rectal cancer (LARC). Although some pathological tumor regression was observed, the complete pCR rate remained modest.⁷¹ The study revealed dynamic changes in plasma levels of EGFR ligands during treatment, suggesting potential biomarker-driven strategies for patient stratification. However, the trial's inability to meet its primary endpoint indicates that EGFR inhibition alone may not suffice in specific contexts and underscores the complexity of integrating such therapies into routine clinical practice.⁷¹

The inconsistent outcomes from these studies underscore the necessity for more precise patient selection and a deeper understanding of EGFR's role in specific cancer subtypes. Strategies such as combination therapies, advanced drug delivery systems (e.g., nanoparticle-based approaches), and biomarker-driven patient stratification could enhance the clinical utility of EGFR-targeted radiosensitizers.^{71,103,105}

In conclusion, while EGFR-targeting monoclonal antibodies show potential as radiosensitizers, their efficacy is context-dependent and influenced by tumor-specific biology. Ongoing research into combinatorial approaches and adaptive clinical trial designs will be pivotal in maximizing their therapeutic benefits.

HER2 and HER3

HER2 (human epidermal growth factor receptor 2) and HER3 (human epidermal growth factor receptor 3) are critical members of the EGFR family, playing pivotal roles in tumor growth, survival, and resistance to therapies, including radiotherapy.¹²¹ These receptors, often overexpressed or dysregulated in various cancers such as breast and cervical cancers, have emerged as potential targets for enhancing radiosensitivity.¹²² Their involvement in key signaling pathways such as PI3K/AKT and MAPK contributes to tumor progression and radioresistance.¹²² Modulate their activity through monoclonal antibodies or ADCs has demonstrated promise in improving radiotherapy outcomes.

HER2 is known to drive aggressive tumor behavior and resistance to radiation through its role in DNA damage repair and cell survival pathways. Targeting HER2

with ADCs, such as trastuzumab emtansine (T-DM1), has shown enhanced radiosensitization by restricting cytotoxic agents specifically to HER2-expressing cells, minimizing off-target effects.^{88, 98} Moreover, preclinical studies have demonstrated that trastuzumab conjugated with cytotoxic agents like monomethyl auristatin F (MMAF) effectively radiosensitizes HER2-positive tumor cells while reducing toxicity to normal tissues.⁸⁸

Although lacking intrinsic kinase activity, HER3 heterodimerizes with other EGFR family members, particularly HER2, to activate downstream signaling pathways. This interaction promotes cell survival and proliferation, contributing to radiation resistance. Dual targeting of HER2 and HER3, as explored with antibodies like MEHD7945A, has demonstrated synergistic effects with ionizing radiation, enhancing tumor control through increased DNA damage and apoptosis.⁸⁹

The therapeutic potential of HER2 and HER3 targeting in radiosensitization underscores the importance of integrating molecularly guided therapies with radiotherapy, paving the way for precision oncology approaches.⁸⁹

SPINK1

Serine protease inhibitor Kazal type I (SPINK1) has recently emerged as a critical player in tumor biology, particularly in modulating radiosensitivity. Its expression is tightly regulated under hypoxic conditions, a hallmark of the tumor microenvironment contributing to radioresistance. Hypoxia-induced SPINK1 expression occurs at the transcriptional level through a HIF-dependent pathway, underscoring its role in adapting to oxygen-deprived conditions within tumors.⁶⁹

SPINK1 demonstrates a dual role in tumor survival and progression under radiotherapeutic stress. Secreted SPINK1 proteins enhance the radioresistance of cancer cells, even in normoxic environments, by leveraging pathways dependent on EGFR and nuclear factor erythroid 2-related factor 2 (Nrf2). This paracrine mechanism protects hypoxic and relatively oxygenated tumor cells from radiation-induced damage. Furthermore, SPINK1 secretion has been linked to accelerated tumor regrowth post-radiotherapy, presenting a significant barrier to effective cancer treatment.⁶⁹

Interestingly, therapeutic interventions targeting SPINK1 have shown promise. Using neutralizing antibodies against SPINK1 exhibits a radiosensitizing effect, making it a compelling candidate for combination therapies. Additionally, SPINK1's presence in plasma offers potential as a biomarker for tumor hypoxia, enabling personalized radiotherapy approaches aimed at overcoming hypoxia-associated resistance.⁶⁹

In summary, SPINK1 is a marker of hypoxia and a facilitator of tumor radioresistance through its paracrine effects and signaling pathway activation (Fig. 5). Its inhibition may enhance the efficacy of radiotherapy

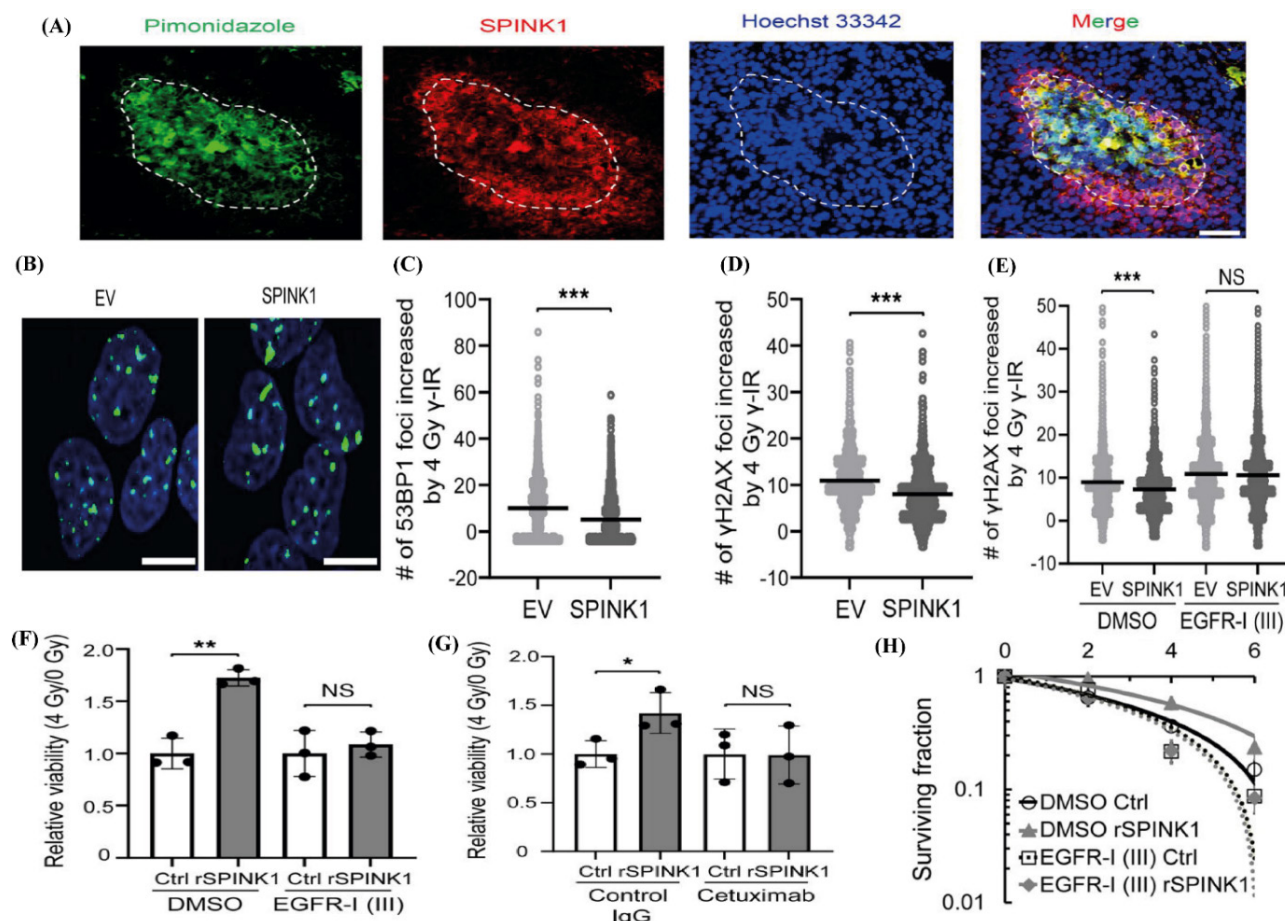


Fig. 5. SPINK1 as a Plasma Biomarker for Tumor Hypoxia and a Radiosensitization Target. (A) Immunofluorescence staining of HeLa tumor xenografts showing SPINK1 (red) in hypoxic areas marked by pimonidazole (green). Blue: counterstaining with Hoechst 33342. The dotted line indicates the outer edge of pimonidazole-positive regions. Scale bar: 50 μ m. (B) SPINK1 overexpression in DU145/EGFP-53BP1-M cells reduces DSBs after irradiation (0 or 4 Gy), shown by EGFP-53BP1 foci (green). (C–E) Quantification of EGFP-53BP1 and γ H2AX foci confirms that SPINK1 reduces irradiation-induced DSBs, and this effect is reversed by EGFR inhibition. (F–G) Cell viability assays reveal that rSPINK1 promotes cancer cell survival after radiation, while EGFR inhibition or cetuximab treatment restores radiosensitivity. (H) Clonogenic assay confirms that SPINK1's protective effect is EGFR-dependent. These findings suggest that SPINK1 promotes EGFR-dependent radioresistance in cancer cells, highlighting its potential as a therapeutic target and supporting the use of monoclonal antibodies like cetuximab to restore radiosensitivity. Abbreviations: EV, empty vector; EGFR-I III, EGFR inhibitor. This figure is reproduced from⁶⁹ under the CC BY license.

and provide a path toward improved cancer treatment outcomes.⁶⁹

Key signaling pathways in radiosensitization

Radiosensitization is a promising approach to enhance the therapeutic efficacy of radiotherapy, especially in targeting critical molecular pathways (Fig. 4). Among these, downstream signaling pathways, cytokine-related pathways, and cancer-specific pathways play pivotal roles in modulating tumor radiosensitivity.

PI3K/AKT and NF- κ B/MAPK

The PI3K/AKT pathway has been extensively studied for its role in promoting tumor survival and resistance to radiotherapy.¹²³ In a study investigating erlotinib-induced radiosensitization in lung adenocarcinoma cells, the blockade of the c-MET-PI3K-AKT pathway significantly enhanced the radiosensitizing effect of erlotinib. Combined treatment with erlotinib and radiation increased apoptosis and reduced colony formation, while

inhibition of c-MET further decreased the activation of PI3K and AKT, demonstrating the pathway's central role in radioprotection.¹⁰⁴

The NF- κ B and MAPK pathways are also crucial in radiation-induced cellular responses, including inflammation, survival, and proliferation.¹²⁴ Their inhibition has been implicated in reducing tumor resilience to radiotherapy, though specific monoclonal antibodies targeting these pathways warrant further exploration for enhanced clinical outcomes.¹²⁴

CXCL1 and TNF- α

CXCL1 signaling contributes to tumor invasion, angiogenesis, and resistance to radiotherapy. A study on bladder cancer revealed that selective inhibition of HDAC6 suppressed radiation-induced CXCL1 expression, effectively reducing tumor migration and malignancy. This suggests that targeting CXCL1 can enhance radiosensitization while mitigating radiation-induced oncogenic signaling.⁷⁸

TNF- α , a key pro-inflammatory cytokine, has been identified as a critical mediator of apoptosis in radiosensitization. The novel SMAC-mimetic Debio 1143 significantly enhanced radiosensitivity in HNSCC models by activating caspase-3 and increasing TNF- α expression. Neutralizing TNF- α or inhibiting caspase activity reversed this effect, confirming their synergistic role in enhancing tumor cell death under radiotherapy.¹⁰¹

PSMA

In prostate cancer, the prostate-specific membrane antigen (PSMA) is a valuable target for radiosensitization. PSMA-targeted gold nanoparticles (PSMA-AuNPs) demonstrated significant radiosensitization under clinical megavoltage radiation beams. The efficacy increased with tumor depth, attributed to enhanced low-energy photon interactions, which boosted dose enhancement ratios. Monte Carlo-based microdosimetry confirmed the distribution and cytoplasmic localization of PSMA-AuNPs, highlighting their potential in depth-dependent radiosensitization strategies.⁸³

These findings underscore the significance of targeting key signaling, cytokine-related pathways, and cancer-specific markers like PSMA in advancing radiosensitization. Integrating molecular insights with targeted monoclonal antibody therapies could revolutionize radiotherapy by overcoming tumor resistance and improving patient outcomes.

Surface proteins

$\beta 1$ Integrin

$\beta 1$ integrin is pivotal in mediating cancer cell interactions with the extracellular matrix (ECM), facilitating survival and therapy resistance.^{125, 126} Multiple studies highlight its significance in repairing radiation-induced DNA double-strand breaks (DSBs) through classical non-homologous end joining (NHEJ). Targeting $\beta 1$ integrin with monoclonal antibodies, such as AIIB2, impairs the repair of radiogenic DSBs, reduces the expression of DNA repair proteins (e.g., Ku70 and Rad50), and enhances radiosensitivity. These effects are evident in HNSCC models, both in vitro and in vivo.⁹⁷

Furthermore, $\beta 1$ integrin inhibition demonstrates robust radiosensitizing effects in pancreatic ductal adenocarcinoma (PDAC) by disrupting kinase activity and impairing ECM-mediated resistance. This effect extends to therapy-naïve and radioresistant cell lines, suggesting its potential to address tumor heterogeneity and improve patient survival. Additionally, combined inhibition of $\beta 1$ integrin and other targets, such as EGFR or PARP, amplifies radiosensitization, indicating its suitability for synergistic treatment approaches.^{70,94}

GRP78

Glucose-regulated protein 78 (GRP78) is overexpressed in several aggressive cancers, including NSCLC and glioblastoma multiforme (GBM). GRP78 is implicated

in radioresistance by regulating the PI3K/Akt/mTOR pathway. Anti-GRP78 antibodies have demonstrated significant antitumor activity by reducing proliferation, enhancing apoptosis, and suppressing PI3K/Akt/mTOR signaling in both NSCLC and GBM cell lines. Notably, combining anti-GRP78 antibodies with ionizing radiation (XRT) further delays tumor growth in xenograft models, positioning GRP78 as a promising target for radiosensitization.⁹⁶

Immune-related pathways: PDL1 in radiosensitization

Programmed death ligand-1 (PD-L1) plays a pivotal role in modulating the immune response in the tumor microenvironment, and recent studies have demonstrated its potential in radiosensitization.¹²⁷ PD-L1, through its interaction with the PD-1 receptor on T cells, contributes to immune suppression in tumors, allowing them to evade immune surveillance.¹²⁸ However, targeting the PD-1/PD-L1 axis has emerged as a promising strategy to enhance radiotherapy (RT) effectiveness by reversing immune suppression and promoting antitumor immune responses.¹²⁸

Several studies have explored how PD-L1 blockade can synergize with radiotherapy to improve therapeutic outcomes. For instance, in a study by Yin et al⁷⁷ (Table S1), combining PD-1 blockades with radiotherapy and Wee1 inhibition showed enhanced radiosensitivity in hepatoma models. This synergistic effect was attributed to the reactivation of CD8⁺ T cells, which are crucial for effective immune responses. Specifically, anti-PD-1 therapy increased the proliferation of cytotoxic T cells and reduced T cell depletion, ultimately improving the tumor response to radiation.⁷⁷

Similarly, a study by Zhou et al (Table S1) discusses the role of immunoradiotherapy, which combines radiotherapy with immune checkpoint inhibition, including anti-PD-L1 antibodies. This study highlighted that anti-PD-L1 treatment, when combined with ultrasmall polyoxotungstate nanoclusters, not only enhanced local tumor destruction but activated a systemic antitumor immune response, further improving the overall efficacy of radiotherapy. This was achieved by generating oxidative stress in the tumor and simultaneously depleting GSH to activate the immune system, thereby overcoming radiation-induced immunosuppression.⁸⁷

In another study, Azad et al demonstrated that PD-L1 expression in PDAC cells was upregulated after radiotherapy, and blocking PD-L1 enhanced the response to high doses of radiation. This radiosensitizing effect was linked to a reduced immunosuppressive myeloid cell and an increased activated CD8⁺ T cells within the tumor. The combination of RT and anti-PD-L1 therapy significantly improved tumor control, emphasizing the critical role of PD-L1 blockade in enhancing RT outcomes, especially at higher radiation doses.⁹⁵

A case report (Fig. 6) also highlights the clinical benefits of combining anti-PD-1 therapy with radiation in advanced oral cavity cancer. This sequential approach led to significant tumor shrinkage and symptom relief after a period of stable disease on pembrolizumab. Although radiation following PD-1 inhibition can increase PD-L1 expression and generate tumor-specific antigens, which may improve the efficacy of checkpoint inhibitors, careful timing and sequencing are crucial to avoid increased toxicity.⁷²

Ongoing clinical investigations further support the synergistic potential of combining immunotherapy with radiation. For instance, several clinical trials are currently evaluating the efficacy and safety of combining checkpoint inhibitors with radiotherapy in HNSCC, such as a phase Ib study of cetuximab, ipilimumab, and intensity-modulated radiation therapy (IMRT) in stage III–IVa HPV-positive oropharyngeal SCC (NCT01935921), and a phase II study comparing concurrent versus sequential administration of pembrolizumab, cisplatin, and IMRT in stage III–IVb HNSCC (NCT0277385). These trials underscore the growing clinical interest in harnessing the immunomodulatory effects of radiation in combination with immune checkpoint blockade.⁷²

Lastly, Zhai et al investigated PD-L1-targeted nanoplateforms (Table S1), combining gold nanoparticles and superparamagnetic iron oxide nanoparticles

(antiPD-L1-SPIOs@PLGA@Au), which was found to enhance radiosensitivity. This platform blocked the PD-L1/PD-1 axis and reversed the immunosuppressive microenvironment caused by tumor-associated macrophages (TAMs). The nanoplatform, combined with radiation, increased reactive oxygen species (ROS) production, attenuated DNA repair, and promoted tumor-associated macrophage polarization towards an M1 phenotype, thus activating the anti-tumor immune response.⁸²

In summary, targeting PD-L1 with radiotherapy has shown promising results in enhancing radiosensitization. The blockade of PD-L1 helps reverse immune suppression in the tumor microenvironment, activates cytotoxic T cells, and enhances the overall immune response, making it a valuable strategy for improving radiotherapy efficacy.

Challenges, emerging alternatives, and future perspectives

Challenges

Despite their immense potential, mAbs face several significant challenges in serving as effective radiosensitizers. These challenges stem from biological, pharmacological, and technical limitations, as demonstrated by various studies.

One major challenge is the inability of mAbs to cross the BBB, which severely limits their application in treating

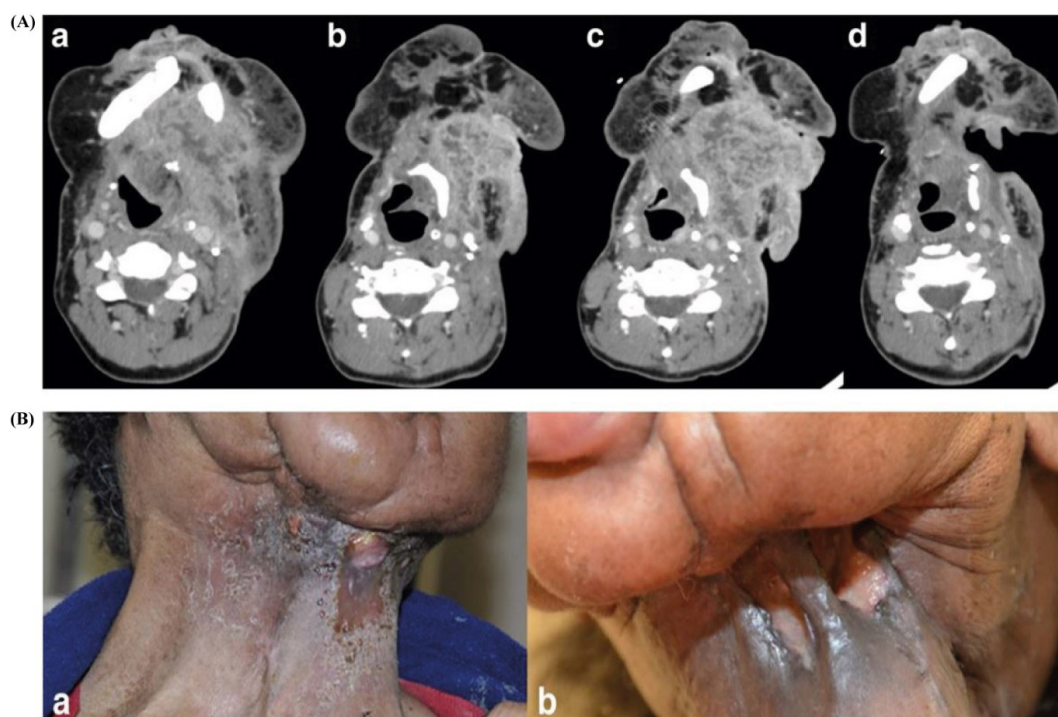


Fig. 6. PD1/PD-L1 inhibition as a potential radiosensitizer in head and neck squamous cell carcinoma: a case report. (A) Change in largest dimensions of neck mass on CT scans over the treatment period. **a)** Prior to pembrolizumab. 8.8×5.9 cm. **b)** Best response to pembrolizumab. 6×4 cm. **c)** Progression on pembrolizumab. 7.1×7.2 cm. **d)** Post radiation 5.9×3.4 cm. **(B)** Appearance of neck mass post pembrolizumab and radiation therapy. **a)** Local tumor control was achieved after six cycles of pembrolizumab monotherapy. **b)** Bleeding from the tumor mass resolved completely after subsequent radiation therapy, highlighting the combined therapeutic effect. This figure is reproduced from Nagasaka et al⁷² under the CC BY license.

brain malignancies like glioblastoma. Glioblastoma is notoriously challenging to treat due to its highly invasive nature and resistance to conventional therapies. In a study, researchers attempted to overcome this limitation by combining radiosensitizer nanoparticles coated with insulin and tumor-targeting antibodies (cetuximab). While this approach showed promise in a mouse model, effectively reducing tumor growth and improving survival, it highlights the inherent barrier posed by the BBB.^{80,129} Without innovative delivery methods, such as nanoparticles, the therapeutic potential of mAbs in brain cancers remains restricted.

Several studies have shown that not all mAbs function effectively as radiosensitizers. Despite reducing microvessel density and metastasis in some cases, for instance Song et al (Table S1) reported that the anti-PDGFR α antibody 1E10Fc failed to significantly enhance the radiosensitivity of soft tissue sarcoma (STS) models.⁹³ This lack of efficacy raises questions about the mechanisms underlying radiosensitization and suggests several possibilities for why specific mAbs may not succeed:

One important factor is the tumor microenvironment. Tumors often exhibit high interstitial pressure and poor vascularization, which can impair the adequate penetration of therapeutic antibodies. As a result, even when the antibodies are present systemically, their concentration within the tumor may be insufficient to achieve effective radiosensitization.

Another contributing factor is variability in target expression. The therapeutic efficacy of monoclonal antibodies largely depends on the expression level of their target antigen. In the case of PDGFR α , heterogeneous or low-level expression across tumor cells can reduce the overall effectiveness of the treatment, limiting its ability to sensitize tumors to radiation.

Additionally, the activation of compensatory signaling pathways by tumor cells represents a major challenge. Even when an mAb successfully binds to its intended target, cancer cells may evade its effects by engaging alternative pathways that maintain survival and proliferation. This adaptability can undermine the radiosensitizing effect of the treatment.

In a study belonging to Guster et al,¹⁰⁵ cetuximab, an EGFR inhibitor, failed to enhance the radiosensitivity of HPV-positive HNSCC cells.¹⁰⁵ This suggests that EGFR inhibition alone may not sufficiently impact the cellular mechanisms involved in radiosensitivity in these specific tumor subtypes.¹⁰⁵ One possible explanation for this underperformance is the complex role of EGFR signaling in the tumor microenvironment, particularly under hypoxic conditions. As demonstrated by Suwa et al⁶⁹ secreted SPINK1 proteins—induced by hypoxia in a HIF-dependent manner—can activate EGFR and its downstream antioxidant pathways (e.g., Nrf2),

promoting radioresistance even in oxygenated tumor regions. This implies that blocking EGFR without addressing hypoxia-induced compensatory mechanisms, such as SPINK1-mediated signaling, may be inadequate to reverse radioresistance. Interestingly, PARP inhibitors, particularly when combined with Chk1 inhibition, demonstrated significant radiosensitization, highlighting the importance of selecting the right molecular targets and combination therapies for effective outcomes.¹⁰⁵

Mignot et al evaluated T-DM1, a HER2-targeted ADC, in HER2-positive breast cancer cell lines. While T-DM1 effectively induced cell death and G2/M cell cycle arrest, it did not act as a radiosensitizer under the experimental conditions.⁸⁶ A potential explanation lies in the intrinsic radioresistance of high HER2-expressing cell lines, which may overshadow the radiosensitizing effects of T-DM1. Additionally, the in vitro nature of the study might not fully replicate the complex in vivo tumor environment where T-DM1 could potentially exhibit better radiosensitizing properties.⁸⁶

Emerging alternatives

The emergence of alternative technologies, such as aptamers, nanobodies, engineered proteins, and other innovative approaches, poses significant challenges to the widespread use of mAbs.¹³⁰⁻¹³³ Aptamers, short nucleic acid sequences that bind to specific targets, offer distinct advantages, including ease of chemical synthesis at lower costs with greater reproducibility, reduced immunogenicity that minimizes the risk of eliciting immune responses, and superior tumor penetration due to their smaller size, which enhances their potential for radiosensitization.^{130,134-136} Similarly, nanobodies, derived from camelid antibodies, are smaller and more stable than traditional mAbs, allowing them to access difficult-to-reach targets, penetrate tissues more effectively, and retain high binding affinities even under harsh conditions.¹³⁴

Engineered proteins, such as DARPins and scaffold proteins, broaden the spectrum of alternatives by offering exceptional stability, precise target binding, and ease of production, making them versatile for therapeutic applications. With their minimal size and straightforward synthesis, Short peptides are gaining traction in specific therapies, providing efficient targeting capabilities, particularly in radiosensitization.^{137,138} Additionally, oncolytic viruses selectively infect and destroy tumor cells, act as direct antitumor agents, and stimulate the immune system to target residual cancer cells, offering a multifaceted therapeutic approach.¹³⁹ RNA-based therapeutics, including siRNA and mRNA technologies, also present promising alternatives by enabling precise gene modulation and protein expression, making them powerful tools for immunotherapy and tumor radiosensitization.¹⁴⁰⁻¹⁴³

These advancements collectively highlight the dynamic

evolution of alternatives to mAbs, reflecting ongoing efforts to optimize therapeutic outcomes across diverse medical applications.

Future perspectives

Future research should focus on several key areas to address the current challenges in utilizing mAbs as radiosensitizers:

- A. *Innovative delivery systems*: The limited ability of mAbs to cross biological barriers, such as the BBB, necessitates the development of advanced delivery mechanisms.¹⁴⁴ Combining mAbs with nanoparticles or other carriers could significantly enhance their penetration and targeting efficiency.¹⁴⁵ For example, gold nanoparticles have shown promise in enhancing the transport of therapeutic agents, including antibodies, into hard-to-reach tumor sites, making this a vital avenue for research.¹⁴⁶
- B. *Combination therapies*: Tumor resistance remains a significant obstacle to effective radiosensitization. Exploring combination therapies that synergize mAbs with other agents, such as PARP or Chk1 inhibitors, could improve outcomes.¹⁴⁷ Such combinations could disrupt compensatory pathways and enhance tumor radiosensitivity, particularly in intrinsically resistant tumor subtypes.^{147,148}
- C. *Target validation*: Identifying and validating new molecular targets is essential for overcoming heterogeneity in tumor response.¹⁴⁹⁻¹⁵¹ Future studies should focus on discovering targets more universally expressed or critical to radiosensitivity. This approach could help expand the applicability of mAbs across diverse cancer types and improve treatment outcomes.¹⁴⁹
- D. *Integration of alternatives*: Evaluating novel modalities such as aptamers as replacements or complements to mAbs may offer cost-effective and concrete alternatives for radiosensitization.^{152,153} Aptamers, with their smaller size and high specificity, could address some limitations of mAbs, including production costs and tumor penetration challenges.¹⁵²
- E. *Exploiting tumor hypoxia*: Hypoxia in the tumor microenvironment is a significant barrier to effective cancer treatment. Recent studies have demonstrated the potential of utilizing *Bifidobacterium infantis* engineered to target hypoxic tumor regions. Specific antibodies against *B. infantis* were developed, allowing the selective eradication of hypoxic tumor areas.^{76,85} This innovative approach underscores the potential of leveraging hypoxia for targeted therapy, a promising direction for future research (Fig. 3).^{76,85}
- F. *Immunochemoradiotherapy integration*: The combination of immunotherapy, chemotherapy, and radiotherapy—termed immunochemoradiotherapy—holds significant

promise.^{154,155} This approach integrates mAbs into multimodal treatment strategies, enhancing therapeutic efficacy while addressing the limitations of single-modality treatments. For instance, combining mAbs with chemotherapeutic agents and radiation could simultaneously target multiple aspects of tumor biology, creating a more comprehensive and practical treatment framework.^{154,156-158}

By addressing these areas, future research can overcome the limitations of mAbs as radiosensitizers and realize their full therapeutic potential. These advancements would offer more effective and personalized cancer treatment options, significantly improving patient outcomes.

Conclusion

mAbs have revolutionized cancer therapy by offering targeted, effective treatments with reduced systemic toxicity compared to traditional approaches.¹⁵⁹ Their ability to selectively bind specific antigens on tumor cells and mediate immune responses has established them invaluable tools in oncology.¹⁵⁹ Beyond their standalone therapeutic efficacy, mAbs have demonstrated immense potential in radiosensitization, enhancing tumor sensitivity to radiation while sparing healthy tissues.¹⁶⁰ By targeting pathways like EGFR, HER2, and immune checkpoints like PD-L1, mAbs inhibit tumor growth and synergistically amplify radiotherapy's effect.¹⁶¹

However, despite their success, mAbs as radiosensitizers face notable challenges, including limited penetration into hypoxic tumor microenvironments, variability in target expression, and the inability to cross biological barriers like the blood-brain barrier. Furthermore, the emergence of resistance mechanisms in certain tumors underscores the need for combination therapies and novel delivery strategies. Innovations such as ADCs, bispecific antibodies, and engineered nanoparticles pave the way for more precise and practical applications.¹⁶²

Emerging alternatives, including aptamers, show promise in addressing some limitations of mAbs by offering better tumor penetration and reduced immunogenicity, suggesting a complementary role in future cancer therapies.¹⁶³ Moreover, integrating mAbs with immunotherapy and leveraging their radiosensitizing properties in combination with immune checkpoint inhibitors could redefine treatment paradigms, particularly for resistant and aggressive cancers.¹⁶³

To fully harness the potential of mAbs in radiosensitization, future research must focus on optimizing their delivery, validating new molecular targets, and developing integrative approaches that address tumor heterogeneity and microenvironmental challenges. By overcoming these obstacles, mAbs could significantly enhance the efficacy of radiotherapy, offering personalized, effective treatment options that improve outcomes for cancer patients globally.

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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

Not applicable to this review.

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Supplementary files

Supplementary file 1 contains Table S1.

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Review Highlights

What is the current knowledge?

- Radiotherapy is a cornerstone of cancer treatment but lacks specificity, causing damage to normal tissues.
- Monoclonal antibodies (mAbs) enhance radiosensitivity by targeting cancer cells, improving radiotherapy efficacy while minimizing collateral damage.
- mAbs function through diverse mechanisms, including immune activation, growth factor receptor inhibition, and apoptosis induction.
- Antibody-drug conjugates (ADCs), nanoparticles, and immune checkpoint inhibitors improve radiosensitization.
- Tumor heterogeneity, resistance mechanisms, and delivery barriers remain key challenges in the clinical application of mAbs.

What is new here?

- Provides the first integrated analysis of 20 years of clinical and preclinical data on mAb-based radiosensitization.
- It highlights novel therapeutic combinations that have not been comprehensively reviewed, such as mAbs with HDAC inhibitors and nanoparticles.
- Covers emerging strategies like bacterial vectors, aptamers, nanobodies, and engineered proteins as next-gen radiosensitizers.
- Discusses multimodal therapies, especially immunochemoradiotherapy, as a forward-looking solution to resistance mechanisms.
- Maps key molecular targets to specific antibody-based interventions, offering a practical guide for future therapeutic development.

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