MicroRNAs: Novel clinical biomarkers for cancer radiotherapy (Review)

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Abstract. MicroRNAs (miRNAs/miRs) have attracted increasing attention as biomarkers and therapeutic agents for cancer treatment, particularly in the context of radiotherapy. Originally identified >30 years ago, miRNAs are short, non-coding RNA molecules that regulate gene expression by binding to target mRNAs. Their involvement in physiological processes such as cell cycle regulation, DNA repair, apoptosis and signal transduction makes them essential for modulating cancer cell responses to therapeutic interventions. Recent research has explained the dual role of miRNAs in tumorigenesis. Some miRNAs function as oncogenes, promoting tumor growth and resistance to treatment, while others act as tumor suppressors, enhancing radiosensitivity and promoting apoptosis in cancer cells. Because of their stability, specificity and presence in bodily fluids, miRNAs are promising non-invasive biomarkers for the diagnosis, prognosis and monitoring of therapeutic responses in cancer. Furthermore, miRNAs such as miR-144, miR-200c and let-7 have demonstrated potential in guiding radiotherapy for breast, prostate, lung and other cancers, modulating treatment outcomes by enhancing radiosensitivity or contributing to radioresistance. Despite the early challenges of miRNA-based therapies, advancements in miRNA delivery systems, including TargomiR- and liposome-based approaches, offer promising avenues for clinical applications. The present review highlights the role of miRNAs as biomarkers and modulators in cancer radiotherapy and discusses ongoing research on miRNA delivery mechanisms to improve therapeutic outcomes. Future studies are needed to address the challenges of miRNA pleiotropy and safety in clinical applications, to advance miRNA-based interventions in precision oncology, and to enhance the efficacy of radiotherapy across various cancer types.

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Contents

1. Introduction

Since the discovery of microRNAs (miRNAs) in *Caenorhabditis elegans* 30 years ago, numerous studies have been conducted in the field of microRNAs. When miRNAs were first elucidated, research has focused on the structure and formation of small non-coding RNA molecules of about 20 to 25 nucleotides and how they bound to 3'-untranslated regions (UTRs) of mRNA to inhibit its expression. After two decades, research has shifted to the efficacy and therapeutic use of miRNAs. Further research is being conducted to use miRNAs as markers to guide cancer therapy. Although the clinical data are not yet clear, current research aims to apply certain miRNAs as specific markers for therapeutic results to clinically regulate miRNA levels to obtain more positive results (1,2). Nevertheless, several studies have reported that miRNAs can act as either oncogenes (oncomiRs) or tumor suppressors during tumorigenesis. miR-21, a well-known oncomiR, promotes tumor growth by inhibiting PTEN, leading to PI3K/AKT pathway activation and increased survival of various cancer cells, such as lung, breast, and colorectal cancers (3,4). Conversely, miR-34a functions as a tumor suppressor by targeting SIRT1 and BCL2 and inducing apoptosis and cell cycle arrest. Similarly, miR-143 and miR-145 suppress cancer progression by inhibiting KRAS and ERK signaling, thereby reducing the proliferation of colorectal and lung cancers (5). Recent studies on miRNA are mostly dedicated to cancer chemotherapy; thus, in this article, we aim to

discuss the relationship between microRNA and cancer therapy, specifically focusing on how it relates to radiation therapy.

miRNAs, which are short RNA molecules consisting of 20-25 nucleotides, are abundantly present in humans and across a wide range of higher eukaryotes. Canonically, miRNAs are derived from primary miRNAs (pri-miRNAs), which include stem-loop (hairpin) precursors called pre-miRNAs. Upon transcription, pri-miRNAs are precisely cleaved by the Drosha/DGCR8 complex to form pre-miRNAs, which are subsequently transported to the cytoplasm by the Exportin-5/RAN-GTP complex. Once in the cytoplasm, the hairpin structure of the pre-miRNA recruits the Dicer-like complex 1, leading to the formation of the Dicer/TRBP complex, which processes the pre-miRNA into an miRNA duplex by removing its loop structure. The mature miRNA then associates with Argonaute proteins (Ago, specifically AGO2 in humans) to regulate the target mRNA. Recent research has uncovered an alternative pathway that is distinct from the canonical miRNA biogenesis pathway. miRNAs that mature without engaging the traditional complexes can be classified into two groups: Drosha-independent miRNAs, which resemble Dicer substrates, and Dicer-independent miRNAs, which consist of miRNAs with shorter hairpins that are too short to act as Dicer substrates. These noncanonical miRNAs complete their maturation by binding to AGO2. miRNAs have numerous functions, the most well-known of which is gene regulation. The target mRNAs of miRNAs typically have specific sequences in the 3' UTR where miRNAs can bind and suppress translation. However, miRNA binding sites have also been discovered in the 5' UTR and promoter regions, where miRNAs can induce gene silencing or promote transcription, respectively. miRNAs regulate gene expression by binding to mRNA, disrupting ribosomal activity, or forming an miRNA-induced silencing complex (miRISC). Mature miRNAs bind to the 3' UTR of mRNA along with Ago proteins and interact with miRNA response elements (MREs) on the target mRNA. The strength of these interactions determines whether the mRNA will be cleaved, inhibited, or degraded. In many cases, seed sequences, typically the first 2-8 nucleotides at the 5' end of miRNAs, play a crucial role in miRNA-MRE interactions. These interactions recruit other accessory proteins to form miRISCs, which effectively deadenylate or decap the target mRNA. In addition to suppressing gene expression, some miRNAs (up-miRNAs) can upregulate mRNA protein levels through the canonical pathway by directly interacting with AGO2 and FXR1. miRNAs can also modulate gene expression in the nucleus by interacting with promoter-associated long RNAs (6,7). As research on miRNAs expands, their diverse roles and effects continue to be discovered. This review discusses the mechanisms of action of miRNAs in cancer radiotherapy, their potential as biomarkers, and the challenges faced and explores possible ways to improve treatment outcomes, providing guidance for future research directions.

2. miRNA: A double-edged sword in tumorigenesis

The first association between miRNAs and tumorigenesis was identified in studies on chronic lymphocytic leukemia (CLL), in which patients exhibited significantly reduced levels of miR-15-a and miR-16-1 (8). Since their discovery, the role of miRNAs in tumorigenesis has expanded, revealing that miRNAs can act as double-edged swords in cancer development. miRNAs also play a dual role in tumorigenesis by acting as oncogenes (oncomiRs) or tumor suppressors, depending on their target genes and signaling pathways. For instance, miR-21 has been widely recognized as an oncomiR that promotes tumor progression by directly targeting PTEN, leading to hyperactivation of the PI3K/AKT pathway, which enhances cell proliferation and survival (4). Similarly, miR-155 facilitates tumor growth by inhibiting TP53INP1, thereby suppressing apoptotic pathways (9). Additionally, miR-221/222 promotes cell cycle progression by downregulating CDKN1B (p27 Kip1), allowing for unchecked proliferation in various cancers, including gastric and prostate cancers (10). In contrast, tumor-suppressive miRNAs act as critical regulators of apoptosis and cell cycle arrest. miR-15a/16-1, for example, inhibit BCL2, thereby promoting apoptosis and suppressing tumor growth in CLL and lung cancer (11). Similarly, miR-143/145 suppress oncogenic signaling by directly targeting KRAS and ERK, thereby inhibiting cancer cell proliferation in lung and colorectal cancers (12). A particularly significant tumor suppressor, miR-34a, is a well-established downstream target of p53, which induces apoptosis by targeting SIRT1 and BCL2, highlighting its potential role as a radiosensitizer in various cancers (13). These findings underscore the complexity of miRNA-mediated tumorigenesis and demonstrate their potential as therapeutic targets in cancer treatment. Currently, a large number of oncogenic miRNAs have been found, and more discoveries are expected. Advances in experimental techniques such as microarray analysis and western blotting have facilitated the identification of miRNAs that are either upregulated or downregulated in cancer. For instance, miR-143 and miR-145 are frequently deleted in lung cancer, whereas miR-125 and miR-155 may function as either tumor suppressors or oncogenes depending on the cancer type (14,15) (Table I). Additionally, research has shown that polymorphisms and mutations in miRNA target sites can result in the loss or alteration of binding sites and the creation of novel sites, further complicating the function of specific miRNAs in tumorigenesis (14).

3. miRNA: A potent biomarker

miRNAs are attractive candidates for biomarkers because of several important characteristics, such as their high specificity, accessibility, and sensitivity (16). First, miRNAs are highly tissue-specific, with many tissues exhibiting dominant miRNAs that influence cell lineage and tissue fate (17). Second, miRNAs are easily accessible and extractable owing to their stable circulation in the body. RNase activity and degradation are inhibited by its interaction with Argonaute proteins. Even extreme conditions such as heat or cold have minimal impact on miRNA levels. This stability enables the detection of miRNAs in various extracellular fluids; in humans, miRNAs can be reliably detected in 12 different body fluids, including blood, urine, and saliva. Recent technological advancements have reduced the time and cost associated with miRNA detection, allowing the efficient detection both

Table I. Commonalities and differences of miRNAs in regulating radiotherapy responses.

miRNA	Cancer type	Function	Target gene/pathway	Commonalities	Differences
miR-144	Breast cancer	Increases radioresistance	Inhibits radiation-induced apoptosis	Regulated after irradiation; involved in radiation response	Promotes resistance, enhances tumor survival
miR-95	Prostate and breast cancer	Increases radioresistance	Suppresses SGPP1 → Activates S1P-PI3K-AKT	Upregulated post-irradiation; activates survival pathways	Functions across multiple cancer types; variable downstream effects
miR-126	NSCLC	Increases radiosensitivity	Inhibits the PI3K-Akt pathway	Promotes apoptosis; modulates post-irradiation survival	Enhances sensitivity, improves treatment efficacy
miR-451	NSCLC	Increases radiosensitivity	Activates PTEN	Induces cell death; regulates PI3K-AKT-related signaling	Sensitizes via a PTEN-dependent mechanism
miR-128-b	NSCLC	Modulates sensitivity	Suppresses EGFR	Regulates growth signaling; may influence radiation response	Indirect radiosensitivity effect via EGFR
miR-21	Multiple (lung, breast and CRC)	Increases radioresistance	Suppresses PTEN → Activates PI3K/AKT	OncomiR; post-radiation up-regulation enhances resistance	Dual role in tumorigenesis and radioresistance
miR-155	Multiple	Oncogenic, anti-apoptotic	Inhibits TP53INP1	Promotes tumor survival; involved in apoptosis suppression	Radioresponse role less direct; impacts apoptotic signaling
miR-221/222	Gastric and prostate cancer	Promotes proliferation	Downregulates CDKN1B (p27 Kip1)	Enhances cell cycle progression	Primarily cell cycle regulators, indirect radiation modulators
miR-15a/16-1	CLL and lung cancer	Increases radiosensitivity	Inhibits BCL2 → promotes apoptosis	Tumor suppressors; pro-apoptotic	Sensitize tumors by restoring apoptotic response
miR-34a	Multiple	Increases radiosensitivity	Inhibits SIRT1 and BCL2; activates p53 downstream	Enhances apoptosis; p53-regulated	Well-studied radiosensitizer across cancer types
let-7	Multiple	Tumor suppressor	Broad oncogene repression; enhanced by KSRP	Upregulated post-radiation via the ATM-KSRP pathway	Suppresses oncogenes such as RAS and Myc

ATM, ataxia-telangiectasia mutated; CDKN1B, cyclin dependent kinase inhibitor 1B; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; KSRP, KH-type splicing regulatory protein; miR/miRNA, microRNA; NSCLC, non-small cell lung cancer; S1P, sphingosine-1-phosphate; SGPP1, sphingosine-1-phosphate phosphatase 1; SIRT1, sirtuin 1.

on-chip and off-chip using point-of-care devices (18). The sensitivity of miRNAs is evident in their variable levels during disease progression and in response to therapy. For example, miR-21 upregulation in breast cancer is associated with tumorigenesis, and its elevated levels vary according to cancer stage and genomic subtype (19). These features make miRNAs valuable for non-invasive diagnostics, disease progression prognosis, guiding treatment, and evaluating therapeutic responses and clinical outcomes. Since 2008, miRNAs have been recognized as significant tumor biomarkers, with their first notable application being the detection of diffuse B-cell lymphoma in patient serum (20). Following this discovery, the use of miRNAs as biomarkers has been proposed for various human diseases (21-23). In cancer research, the clinical correlation between miRNA levels and cancer severity, as well as treatment outcomes, continues to increase. Recent studies have explored the potential of miRNAs as immunotherapeutic agents, although further investigation is required because of their pleiotropic functions (1).

4. Radiotherapy and miRNA

Radiation-induced miRNA expression. Ionizing radiation affects intracellular expression of miRNAs in various ways. Several studies have demonstrated the upregulation and downregulation of miRNAs following radiation exposure. For instance, in baboons, miR-212 exhibited 48- to 77-fold upregulation after 2.5 and 5 Gy irradiation, whereas miR-342-3p showed 10-fold downregulation (24,25). Similarly, radiation-induced miRNA regulation has been observed in clinical settings such as radiotherapy. In patients with breast cancer, radiotherapy results in a significant increase in miR-34a levels compared to non-treated or chemotherapy-treated patients (26), whereas miR-29a-3p and miR-150-5p levels gradually decrease with increasing doses of radiotherapy (27). These findings suggest that miRNA expression is influenced by radiation, with expression levels varying according to radiation dosage, cell type, and disease context. The regulation of miRNA expression following radiation exposure remains a complex and evolving field of research. Current research suggests that ionizing radiation alters miRNA expression through multiple mechanisms, including activation of the DNA damage response, modulation of the miRNA biogenesis machinery, and induction of epigenetic modifications. First, ionizing radiation induces the ataxia-telangiectasia mutated (ATM) kinase and activates p53, which, in turn, upregulates key miRNAs involved in apoptosis and DNA repair, including miR-34a and miR-16 (28). ATM-mediated phosphorylation of KH-type splicing regulatory protein (KSRP) enhances the processing of precursor miRNAs, such as let-7, increasing their levels post-radiation (29). Secondly, radiation influences the miRNA biogenesis machinery by modulating Drosha and Dicer, the key enzymes responsible for miRNA maturation. Studies have shown that Exportin-5, which transports precursor miRNAs to the cytoplasm, may also be affected by radiation-induced stress responses, further altering miRNA profiles (30). Finally, radiation-induced histone modifications and DNA methylation contribute to long-term changes in miRNA expression. For instance, radiation exposure has been linked to miR-21 upregulation, which enhances radioresistance by suppressing PTEN and activating PI3K/AKT signaling (31). Understanding these mechanisms will provide valuable insight into how miRNA regulation can be leveraged to enhance radiosensitivity in cancer therapies. However, the precise mechanisms by which ionizing radiation regulates miRNA expression remain largely unknown. Ongoing research is aimed at elucidating these mechanisms and improving our understanding of the interaction between radiation and miRNA regulation.

Although the mechanistic foundation of miRNA regulation by radiation remains unclear, efforts have been made to explore how radiation influences miRNA biogenesis and how radiation-induced miRNAs affect cellular responses to radiation. Proposed mechanisms linking the radiation response to enhanced miRNA biogenesis include increased processing of pri-miRNAs via KSRP following phosphorylation by the DNA damage sensor protein ATM as well as the activation of pri-miRNA transcription driven by the DNA damage-stabilized transcription factor p53 (32,33).

miRNA regulation of radiotherapy response. Tumor radiosensitivity is a critical determinant of radiotherapy outcomes and miRNAs play a significant role in modulating various aspects of tumor radiosensitivity by regulating key cellular processes such as cell cycle arrest, DNA damage repair, cell death, and radiation-related signal transduction (34). miRNAs can hinder the production of proteins that are crucial for recognizing DNA damage. They can also interfere with signaling pathways and cell cycle arrest mechanisms, thereby initiating repair processes. This can lead to a diminished DNA repair capacity and increased radiosensitivity. For instance, miR-24 and miR-451 suppress the expression of DNA damage sensor proteins H2AX and ATM, respectively (35,36). Both miRNAs influence cell cycle progression during stress responses. miR-421 targets ATM, impairing S-phase cell cycle arrest, whereas miR-24 regulates cell cycle proteins, such as cyclins A and E, as well as the retinoblastoma protein. miRNAs can also directly target DNA repair pathways. For example, miR-210 represses RAD52, a protein involved in homologous recombination, whereas miR-101 regulates DNA-PK kinase, which is crucial for nonhomologous end joining (37,38). Moreover, miRNAs can modulate the downstream signaling pathways involved in the radiation response, which ultimately influences cell survival or death. This includes pathways such as PI3K/AKT, nuclear factor-kappa B, mitogen-activated protein kinase, and transforming growth factor-beta. For instance, a suppressive effect of miR-221 and miR-222 on the AKT pathway by targeting the upstream tumor suppressor PTEN has been observed in gastric carcinoma cells, where they promote increased cell death and radiosensitivity (39). Since miR-210, which was previously discussed, is hyperactivated in hypoxic environments and controls tumor survival, it is especially notable that miRNAs may potentially influence external stimuli like radiation (33,38,40). Given that radiotherapy consistently involves radiation exposure, albeit at varying doses, it is reasonable to conclude that miRNAs are important determinants of the tumor response to radiotherapy (Table II).

Table II. miRNAs that are upregulated or downregulated by radiation.

First author/s, year	Cancer	miRNA	Up/down	Target	Reaction to radiation	(Refs.)
Yu *et al*, 2015; Buffa *et al*, 2011	Breast	miR-144	Up	Caspase-3/caspase-7	Resistant	(41,42)
Lin *et al*, 2013; Song *et al*, 2015		miR-200c	Up	KRAS	Sensitive	(43,44)
Pajic *et al*, 2018		miR-139-5p	Up	ROS defense mechanisms	Sensitive	(47)
Xue *et al*, 2015	Prostate	miR-145	Up	DNMT3b	Sensitive	(49)
Huang *et al*, 2013; Xi *et al*, 2019		miR-95	Up	SGPP1	Resistant	(50,51)
Ni *et al*, 2017; Sang *et al*, 2019		miR-9	Up	MEKK3	Sensitive	(52,53)
Xin *et al*, 2016		miR-22	Up	ATP citrate lyase	Sensitive	(55)
Xu *et al*, 2016		miR-30a	Up	TP53INP1	Sensitive	(54)
Li *et al*, 2011		miR-106b	Down	P21	Resistant	(56)
Mao *et al*, 2016		miR-449a	Up	c-Myc	Sensitive	(57)
Ni *et al*, 2017; Wagner *et al*, 2014		miR-521	Down	CSA	Sensitive	(52,58)
Wagner *et al*, 2014		let-7	Up	RAS/c-Myc/HMG/AR	Sensitive	(58)
Li *et al*, 2022		miR-34a	Up	P53/MET/BCL-2/SIRT1	Sensitive	(59)
Wang *et al*, 2011	Lung	miR-126	Up	PI3K-Akt	Sensitive	(66)
Tian *et al*, 2016		miR-451	Up	PTEN	Sensitive	(67)
Li and Wang, 2019		miR-128b	Up	EGFR	Sensitive	(68)
Liu *et al*, 2018; Zhao *et al*, 2018		miR-let-7a	Up	Cyclin D1	Sensitive	(69,70)
Fu *et al*, 2016; Zheng *et al*, 2018		miR-495	Up	TCF4	Sensitive	(71,72)
Wang *et al*, 2017; Rahman *et al*, 2014		miR-15b	Down	P53	Resistant	(74,75)
Gu *et al*, 2021		miR-22	Down (NSCLC)	SIRT1/FGFR1	Sensitive	(76)
Jiang *et al*, 2019		miR-22	Up (SCLC)	WRNIP1	Sensitive	(77)
Sagar, 2021; Yin *et al*, 2019		miR-106b	Down	BTG3	Resistant	(78,79)
Baumgartner *et al*, 2018; Zaporozhchenko *et al*, 2016		miR-19b	Down	EGFR	Resistant	(80,81)
Ma *et al*, 2014; Wang *et al*, 2022		miR-21	Down	PTEN	Resistant	(82,83)
Li *et al*, 2020		miR-17-5p	Down	TBP2	Resistant	(84)
Zheng *et al*, 2015	Nasopharyngeal	miR-9	Up	Glutathione	Resistant	(91)
He *et al*, 2014	Gastric	miR-300	Down	BCL2L11/GAS2/CASP8AP2 APAF1/DLC1/TP53/CASPS2 CASPS7/CASPS9/CASPS10 BCL2L11/CCNK	Sensitive	(99)

Table II. Continued.

First author/s, year	Cancer	miRNA	Up/down	Target	Reaction to radiation	(Refs.)
		miR-642	Down	KLF4/NASP/TP53/CDK10 CHFR/ING4/GRB2/TP53BP1 XPA/MRE11A/PRELD1	Sensitive	
Li *et al*, 2021	Brain	miR-144-3p	Up	c-Met	Sensitive	(100)
Devara *et al*, 2023		miR-502-5p	Up	CCND1/DNMT3b	Sensitive	(102)
Yang *et al*, 2020		miR-4262	Down	PTEN	Sensitive	(101)
Yang *et al*, 2020		miR-302d-3p	Down	TMBIM6	Sensitive	(101)
Gao *et al*, 2022	Cervix	miR-630	Up	p53	Resistant	(114)
Ghafouri-Fard *et al*, 2021		miR-1246	Up		Resistant	(115)
Guz *et al*, 2022		miR-1290	Up		Resistant	(116)

miR/miRNA, microRNA; NSCLC, non-small cell lung cancer; ROS, reactive oxygen species; SCLC, small cell lung cancer.

5. Cancer miRNA response in radiotherapy

Breast cancer. The functions of miRNAs in radiotherapy vary significantly depending on the type of cancer, with miRNAs being either upregulated or downregulated to act as oncogenes or tumor suppressors. In breast cancer, miR-144 is upregulated following radiotherapy and contributes to radiation resistance by inhibiting radiation-induced apoptosis in cancer cells. A study analyzing 207 early invasive breast cancer samples with a 10-year follow-up validated these findings using over 1,000 cases and identified key miRNAs associated with radiotherapy resistance (41). Yu *et al* (41) demonstrated that miR-144 inhibits caspase-3 and caspase-7, preventing these caspases from initiating radiation-induced apoptosis. Consistent with this finding, miR-144 overexpression has been associated with poor prognosis in patients with breast cancer (42). In contrast, miR-200c has been identified as a radiosensitizing miRNA in breast cancer radiotherapy, enhancing ionizing radiation-induced double-stranded breaks and apoptosis by directly inhibiting KRAS in breast cancer cell lines. Notably, the expression of miR-200c increases in a dose-dependent manner upon radiation exposure, and its overexpression varies depending on the type of breast cancer (43,44). Another key miRNA is let-7d, and although it did not exhibit changes in expression levels during radiotherapy, it plays a critical role in sensitizing triple-negative breast cancer stem cells to radiation by repressing their self-renewal capacity. The combination of radiotherapy and let-7d significantly inhibited tumor growth by targeting the cyclin D1/Akt1/Wnt1 signaling pathway, which is crucial for breast cancer treatment (45,46). Additionally, miR-139-5p expression was significantly increased in patients undergoing radiotherapy who experienced favorable clinical outcomes, including no relapse or death. Research has demonstrated that miR-139-5p plays a key role in enhancing radiosensitivity by inhibiting DNA repair and reactive oxygen species defense mechanisms, ultimately inducing apoptosis in irradiated breast cancer cells (47).

In summary, miRNAs such as miR-144, miR-200c, let-7d, and miR-139-5p exhibit distinct roles in modulating the breast cancer response to radiotherapy, either promoting radioresistance or enhancing radiosensitivity. These findings underscore the potential of miRNA-based therapies to improve the efficacy of radiotherapy in patients with breast cancer.

Prostate cancer. Radiotherapy is a conventional treatment option for localized prostate cancer with overall survival rates comparable to those of radical prostatectomies. Several miRNAs have been shown to modulate prostate cancer cell responses to radiation, either by enhancing radiosensitivity or promoting radioresistance (48). miR-145 is upregulated in most prostate cancer cells after 4 h of irradiation. miR-145 suppresses DNMT3b expression by directly targeting the 3' UTR of DNMT3b mRNA, which sensitizes prostate cancer cells to radiation by reducing DNMT3b levels (49). In contrast, miR-95 is upregulated in prostate cancer cells after irradiation and mediates radiotherapy resistance by downregulating SGPP1, a gene that promotes cell death and activates the S1P-PI3K-AKT survival pathway. Elevated miR-95 expression correlates with more aggressive prostate cancer phenotypes and poor prognosis, as demonstrated by next-generation

sequencing and functional validation using prostate cancer cell lines and mouse xenograft models. The study further confirmed SGPP1 as a direct target of miR-95 and identified enhanced cell proliferation and impaired G2-M checkpoint as key mechanisms of resistance (50,51). miR-9, another miRNA upregulated during radiotherapy, inhibits tumor growth by suppressing MEKK3 protein expression (52,53). Additionally, miR-22 and miR-30a are upregulated in irradiated prostate cancer cells and enhance radiosensitivity by modulating ATP citrate lyase and TP53INP1, which influence metastasis and autophagy in prostate cancer (CaP) cells (54,55). Several miRNAs were modulated at 24 h after radiation exposure. miR-106b is downregulated in irradiated prostate cancer cells, and its downregulation is associated with improved prognosis, as it prevents miR-106b from overriding radiation- or therapy-induced p21 activation, thereby preventing radioresistance. Similarly, miR-521, which induces radiosensitivity by inhibiting the DNA repair protein Cockayne syndrome protein A, is downregulated and contributes to radioresistance in CaP cells (56). Conversely, miR-449a is upregulated and enhances radiosensitivity by reducing c-Myc transcription in CaP cells (57). The let-7 family and miR-34a are typically downregulated in prostate cancer but are upregulated in certain radiosensitive CaP cell lines following fractionated radiation exposure (52). Let-7 regulates prostate cell homeostasis by targeting RAS, c-Myc, HMG family proteins and androgen receptors (58). miR-34a inhibits cancer stemness and targets CD44, MET, BCL2, and SIRT1, which interact with p53 to suppress tumorigenesis. Clinically, upregulated miR-34a expression is associated with a better prognosis in patients with prostate cancer (59,60). Another important miRNA in prostate cancer prognosis is miR-200a, whose downregulation has been linked to poor outcomes in prostate cancer (61). Similarly, miR-200b and miR-200c act as tumor suppressors in prostate cancer, and their downregulation leads to chemoresistance and radioresistance in tumor cells (62). Several miRNAs, such as miR-126, miR-20b, miR-203, let-7g, miR-30b, miR-30a, and others, are downregulated in LNCaP prostate cancer cells following irradiation. These miRNAs, which modulate radiosensitivity, were not consistently downregulated across studies and their expression varied depending on radiation dosage and timing (54,63-65).

Despite the increasing number of miRNAs involved in radiotherapy, most studies on prostate cancer have been conducted in vitro. Therefore, further research using animal models and human clinical trials is required to better understand the role of miRNAs in radiation therapy for prostate cancer.

Lung cancer. Radiotherapy is primarily used to treat non-small cell lung cancer (NSCLC), which accounts for approximately 85% of all lung cancers. Many miRNAs are either upregulated or downregulated following radiation exposure, with some contributing to radiosensitivity and radioresistance. Among the miRNAs overexpressed in radiosensitive cancers are miR-126, miR-451, miR-128b, miR-let-7a, and miR-495, whereas miR-15b, miR-22, miR-106b, miR-19b, miR-21, miR-17-5p, and miR-130a are downregulated compared to their levels in radioresistant cancers. miR-126 enhances the sensitivity of NSCLC cells to radiation by regulating the PI3K-Akt pathway. One study analyzed miRNA expression in 30 patients with NSCLC undergoing postoperative radiotherapy and identified 12 differentially expressed miRNAs (66). miR-451 increases radiosensitivity by promoting irradiation-induced apoptosis via the PTEN pathway. In another study, pre-miR-451 was transfected into A549 NSCLC cells and its effects were analyzed using clonogenic assays, apoptosis analyses, and western blotting. Irradiation (0-6 Gy) showed that miR-451 overexpression enhanced apoptosis and increased radiosensitivity via PTEN activation (67). miR-128b acts as a tumor suppressor by suppressing the mRNA expression of epidermal growth factor receptor (EGFR) and subsequently reducing tumor growth. In another study, miR-128-b and EGFR expression were analyzed in 42 NSCLC patient samples using RT-qPCR and immunohistochemistry. A549 lung cancer cells transfected with miR-128-b mimics and inhibitors revealed a negative correlation between miR-128-b and EGFR expression in NSCLC (68). miRNA-let-7a inhibits cell growth by targeting cyclin D1-associated factors, thereby reducing the migration and invasion of tumor cells. Let-7a expression is also positively associated with the efficacy of radiotherapy in patients with lung cancer with brain metastasis (66,69,70). miR-495 functions as a tumor suppressor by inhibiting tumor progression via targeting TCF4 expression and repressing epithelial-mesenchymal transition (EMT) and the Wnt/β-catenin pathway. In radiotherapy, miR-495 reduces the radiation-induced bystander effect, improves patient tolerance to radiotherapy, and enhances clinical outcomes (71-73). Conversely, miR-15b protects cells from radiation-induced stress by promoting p53 phosphorylation and facilitating DNA repair. While this function is oncogenic in NSCLC, it helps protect the surrounding lung cells from the damaging effects of radiation (74,75). Interestingly, miR-22 acts as a tumor suppressor by inhibiting angiogenesis by targeting SIRT1 and FGFR1, but is downregulated in radiosensitive NSCLC (76). In contrast, miR-22 is upregulated in small cell lung cancer (SCLC) during γ-irradiation, where it enhances radiosensitivity by targeting WRNIP1 (77). miR-106b plays a key role in tumor formation by suppressing BTG3 and is associated with resistance to both chemotherapy and radiotherapy (78,79). miR-19b is a critical biomarker in lung cancer and is known to enhance cell proliferation and resistance to apoptosis, drugs, and radiation by modulating EGFR signaling (80,81). miR-21, a well-known miRNA implicated in various cancers, promotes growth, metastasis, and resistance to chemotherapy and radiotherapy in NSCLC by targeting PTEN. Silencing miR-21 expression promotes radiosensitivity in lung cancer (82,83). miR-17-5p negatively regulates TBP2, a tumor suppressor gene, in lung cancer, and its silencing reduces cell viability, invasion, migration, and resistance to therapy (84). One study found that miR-130a plays a complex role, as its upregulation has been associated with low survival rates in patients with NSCLC after radiotherapy, although its exact function remains unclear. While miR-25 and miR-191 are associated with poor survival outcomes, miR-130a is both an oncogene and a tumor suppressor, depending on the context. Low miR-130a expression can lead to poor survival in patients with NSCLC by inhibiting KLF3, a key regulator of lung cancer growth (85,86). Finally, although not downregulated, miR-410 is upregulated in most NSCLC cases and has been found to

promotes radioresistance by binding to PTEN and indirectly activating the PI3K/mTOR pathway, highlighting its role in therapeutic resistance (87).

In summary, miRNAs play diverse roles in regulating radiosensitivity and radioresistance in NSCLC, with some acting as tumor suppressors and others as oncogenes. Continued research on miRNA-targeted therapies holds promise for improving the efficacy of radiotherapy in lung cancer treatment.

Nasopharyngeal cancer. Nasopharyngeal cancer (NPC) is predominantly characterized by poorly differentiated and undifferentiated squamous cell carcinomas. Due to the unique anatomical location and locally invasive growth pattern of NPC, surgical intervention is often unsuitable, making radiotherapy the most effective treatment option. Several miRNAs have been implicated in promoting radioresistance in NPC. miR-19b-3p, miR-125b, miR-21, and miR-205 contribute to NPC recurrence by enhancing radiotherapy resistance through the regulation of BCL2 family proteins (88). In contrast, miR-203 is upregulated in radiosensitive NPC, exerting its effect by downregulating IL8/AKT signaling (89). miR-222 is commonly upregulated in NPC cell lines and promotes radioresistance by targeting PTEN (90). Furthermore, miR-9 expression increases following radiation exposure and suppresses apoptosis in NPC cells by modulating glutathione levels (91). In contrast, miR-120 is down-regulated in most NPC cell lines, reducing their sensitivity to radiation. Studies have shown that miR-120 upregulation decreases the survival fraction of NPC cells by targeting PDCD6, inhibiting BCL2, and activating caspase-3 and histone H2AX phosphorylation (92).

Gastric cancer. Although radiotherapy is not typically the first-line treatment for gastric cancer (GC), recent studies have demonstrated its benefits in locally advanced gastric cancer, showing a reduction in both mortality and recurrence compared with surgery alone (93). Several miRNAs have been implicated in the response of gastric cancer to radiotherapy. miR-21, miR-24, miR-421, and miR-605 are upregulated in diffuse-type GC and play oncogenic roles by increasing radioresistance by targeting ATM/ATR/H2AX, thereby impairing DNA damage repair (94). Additionally, miR-192 and miR-215 are naturally upregulated in most GCs, promoting tumorigenesis by activating the Wnt/β-catenin pathway through the targeting of APC, which in turn enhances DNA damage repair (95). In contrast, miR-129-5p functions as a tumor suppressor by inhibiting nucleolar and spindle-associated protein 1 (NUSAP1). The overexpression of NUSAP1 in GC leads to increased radioresistance and enhanced DNA damage repair, resulting in poor patient prognosis (96). Similarly, miR-4537 acts as a tumor suppressor by binding to ZNF587 and suppressing its expression. In GC cells, miR-4537 inhibits cell proliferation while enhancing apoptosis and increasing radiosensitivity (97). miR-4766-5p is another tumor suppressor that is typically downregulated in GC cells, where it inhibits cancer progression by targeting NKAP and inactivating the AKT/mTOR pathway, thereby promoting radiosensitivity in GC (98). In addition, miR-300 and miR-642 function as tumor suppressors by modulating apoptosis and cell cycle regulation. These miRNAs are downregulated in GC cells after radiation, and although their target genes and pathways remain under investigation, they have been shown to increase apoptosis and reduce DNA damage repair in GC cells. Intriguingly, some studies have associated miR-300 and miR-642 with chemoresistance in other tumor cell lines, suggesting that they may serve as promising biomarkers for the treatment, diagnosis, and prognosis of GC (99). In summary, miRNAs play diverse roles in the response to radiotherapy in both nasopharyngeal and gastric cancers, thereby influencing radiosensitivity and resistance. Further research on the roles of specific miRNAs could provide valuable insights for improving the therapeutic outcomes of these cancers.

Brain cancer. Radiotherapy is typically the first-line treatment for brain tumors, particularly localized brain tumors. In response to radiotherapy, 16 miRNAs were found to be downregulated: miR-5687, miR-4766-3p, miR-4690-3p, miR-4262, miR-302d-3p, miR-6752-5p, miR-548ao-5p, miR-4772-3p, miR-485-5p, miR-511-5p, miR-1471, miR-2276-5p, miR-548n, miR-3132, miR-425-3p, miR-4460, miR-4262, and miR-302d-3p. In contrast, 19 miRNAs were upregulated, including miR-7153-3p, miR-609, miR-373-5p, miR-5582-3p, miR-4662a-3p, miR-619-5p, miR-3656, miR-502-5p, miR-6754-3p, miR-4804-3p, miR-3199, miR-4434, miR-3677-5p, miR-4528, miR-4731-5p, miR-144-3p, miR-548x-3p, miR-4795-5p, miR-1276, miR-502-5p, and miR-144-3p (100). miR-4262 has been implicated in promoting cell proliferation and migration in gliomas by targeting large tumor suppressor 1 (101). Similarly, miR-302d-3p enhanced cancer cell proliferation by influencing various biological pathways. Radiotherapy may reduce brain cancer cell proliferation by downregulating miR-4262 and miR-302d-3p, thereby potentially inhibiting tumor growth (101). Although the exact mechanisms underlying the upregulation of miR-502-5p and miR-144-3p in brain tumors remain unclear, both miRNAs have shown tumor-suppressive activity in other cancers. Their expression is associated with a better prognosis in glioblastoma, suggesting that they may act as potential tumor suppressors in brain cancer. Consistently, the upregulation of miR-502-5p and miR-144-3p has been linked to decreased cell proliferation in glioma, further supporting their role as tumor suppressors (100,102).

Cervical cancer. Radiotherapy, often combined with cisplatin, is the first-line treatment for cervical cancer. Numerous proteins involved in radiosensitivity are regulated by miRNAs, and approximately ten miRNAs have been identified as key regulators of radiosensitivity in cervical cancer. Among these, miR-9, miR-21, miR-200a, miR-218, miR-34a, miR-23b, and miR-203 have been shown to enhance radiosensitivity, whereas miR-421, miR-181a, and miR-106b promote radioresistance (103). miR-9 enhances radiosensitivity and inhibits angiogenesis by targeting suppressor of cytokine signaling 5, a key protein involved in cytokine regulation (104). miR-21, a well-studied miRNA in various cancers, functions as a tumor suppressor in cervical cancer by downregulating the RECK signaling pathway and inhibiting cancer growth and migration. However, the role of miR-21 is controversial because it represses PTEN and contributes to drug resistance in cancer cells (105,106). Low expression of miR-200a in cervical

cancer has been linked to pronounced radioresistance, whereas miR-218 and miR-34a enhance radiosensitivity by promoting radiation-induced apoptosis (107-109). miR-23b increases radiosensitivity and chemosensitivity by suppressing the biological progression of cervical cancer through direct targeting of Six1, as well as by modulating EMT and the AKT/mTOR signaling pathway (110,111). miR-203 inhibits cervical cancer cell growth by inducing cell cycle arrest and apoptosis, thereby contributing to its radiosensitizing effects (112). In contrast, miR-421 promotes radioresistance by regulating ATM, a key sensor in the ionizing radiation response, which functions alongside the ATR and BRCA proteins (113). miR-181a and miR-106b contribute to radioresistance by inhibiting immediate early response 3, a regulator of apoptosis (106). Additionally, other miRNAs, such as miR-630, miR-1246, and miR-1290, have been reported to be upregulated in radiation-resistant cervical cancer. The upregulation of these miRNAs after irradiation has been associated with enhanced cancer cell survival, highlighting their potential role in promoting radioresistance (114-116).

6. Clinical use of miRNA in cancer radiotherapy

miRNA-based therapeutics and diagnostics have garnered significant interest owing to their potential for improving cancer treatment outcomes. Their ability to regulate key oncogenic and tumor-suppressive pathways, modulate radiation responses, and serve as reliable biomarkers make them promising candidates for clinical applications. However, several challenges must be addressed before miRNA-based strategies can be widely implemented in the clinical setting. The possible therapeutic uses of miRNAs in radiotherapy are examined in this section with a focus on the main obstacles to their clinical application and treatment.

Challenges in miRNA delivery systems. Despite advancements in miRNA-based therapeutics, clinical translation is hindered by challenges related to the immune response, delivery efficiency, and targeting specificity. Naked miRNA molecules and virus-based delivery vectors can be recognized as foreign agents that trigger immune activation, which may cause systemic toxicity. This issue was evident in a phase I clinical trial of MRX34, a miR-34a mimic, which was halted because of severe immune-related adverse effects (117). To mitigate immunogenicity, researchers have explored chemical modifications, such as 2'-O-methylation and locked nucleic acids, which enhance stability and reduce immune activation. Additionally, exosome-based miRNA delivery systems have shown promise because of their natural biocompatibility and ability to evade immune detection. Early research on miRNA delivery primarily relied on viral vectors; however, their clinical application was limited due to significant safety concerns. Polylactide-co-glycolide (PLGA) particles, widely used for RNA transport, are considered potential miRNA delivery vehicles, but their low efficiency has proven insufficient for clinical application. Among the lipid-based delivery systems, neutral liquid emulsions (NLEs) were initially explored because of their low toxicity; however, their delivery efficiency remains suboptimal (118,119). Currently, safer and more effective delivery methods are being investigated. TargomiR, a delivery system utilizing bacterially derived mini-cells containing miRNA mimics and targeting moieties, has shown encouraging results in mesothelioma and NSCLC. Phase I trials have demonstrated significant suppression of target miRNAs, indicating their potential for cancer treatment. Another promising approach is the use of neutral liposomes, such as 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC), which has been widely used in small interfering RNA (siRNA) delivery. Preclinical studies using DOPC liposomes loaded with miRNA-506 mimics or miRNA-520 demonstrated significant tumor suppression in ovarian cancer models, whereas miR-2000-complexed DOPC liposomes effectively inhibited tumor growth in lung cancer models (118,119). Additionally, targeting specificity remains a significant challenge in miRNA-based therapies to ensure precise delivery to tumor cells while minimizing unintended effects on normal tissues. Ligand-conjugated nanoparticles such as antibody-functionalized liposomes or aptamer-based delivery systems enhance specificity by targeting tumor-associated antigens. Moreover, CRISPR/Cas-mediated miRNA editing offers a precise approach for modulating miRNA activity in cancer cells, thereby reducing systemic toxicity and off-target effects (120). Alternative polymer-based delivery methods have also been investigated. Early research on polyethyleneimines (PEIs) revealed high cytotoxicity and low transfection efficiencies, limiting their clinical use. However, modifications such as polyethylene glycol (PEG) conjugation have significantly improved biocompatibility and delivery efficiency. Similarly, chitosan, a cationic polymer derived from chitin, has been studied as a biocompatible alternative for miRNA delivery with promising results in preclinical models (110).

miRNA as a clinical biomarker and future research. miRNAs have emerged as promising noninvasive biomarkers for cancer detection and prognosis because of their stability in bodily fluids and their disease-specific expression profiles. However, their integration into routine clinical practice requires overcoming the challenges related to the standardization of detection protocols, quality control, and integration with traditional biomarkers. Currently, multiple detection methods, including quantitative real-time PCR, droplet digital PCR, and next-generation sequencing, are used for miRNA profiling. However, variability in sample collection, RNA extraction, and normalization complicates its clinical implementation. Establishing standardized protocols using reference miRNAs, such as miR-16 or let-7a, is crucial for improving reproducibility. Moreover, ensuring quality control and validation is vital, as pre-analytical factors, such as hemolysis in blood samples and RNA degradation, can introduce variability in miRNA measurements. The incorporation of spike-in-control RNAs and stringent quality control procedures can enhance the reliability of miRNA-based diagnostics. Although miRNA profiling alone provides valuable insights, its clinical utility can be amplified through multi-marker integration. For instance, combining miR-21 expression analysis with PSA testing has demonstrated improved accuracy in the diagnosis of prostate cancer (3). Similarly, artificial intelligence-driven models are being developed to analyze miRNA signatures and conventional clinical parameters, thereby fostering precision medicine approaches for personalized cancer treatment. With

Table III. miRNA delivery vehicles under investigation.

First author/s, year	Delivery system	Method	Advantage	Disadvantage	(Refs.)
Dasgupta and Chatterjee, 2021	Viral	RV	Stable gene integration	Toxic,~8 Kb	(118)
Dasgupta and Chatterjee, 2021		LV	Long-term gene expression	Toxic, ~8 Kb	(118)
Dasgupta and Chatterjee, 2021		AD	Less toxic compared with RV/LV; ~38 Kb	Still toxic for clinical use	(118)
Dasgupta and Chatterjee, 2021		AAV	Less toxic compared with RV/LV; ~4.8 Kb, but efficient in transporting miRNA	Still toxic for clinical use	(118)
Pan *et al*, 2012		Bacteriophage based virus-like particles	Low toxicity; effective, can carry miRNA plus ligand	Still under preclinical investigation	(126)
Campani *et al*, 2016	Lipid-based	NLE	Low toxicity	Low effectiveness due to low stability	(127)
Chapoy-Villanueva *et al*, 2015		Neutral DOPC liposome	Low toxicity and high biocompatibility, improved serum stability	Still under preclinical investigation	(128)
Dasgupta and Chatterjee, 2021	Polymeric	PEIs	Low molecular weight PEIs are less toxic	Cytotoxicity/low efficiency	(118)
Alanazi *et al*, 2022		PLGA	Biodegradable (safe)	Low loading of miRNA due to hydrophobicity	(129)
Javanmardi *et al*, 2022		PEG	Superior gene silencing vs. PEI; biocompatible		(130)
Wang *et al*, 2016		PAMAM	Biodegradable; higher transfection efficiency compared with liposome and PLGA; low cytotoxicity	Still under preclinical investigation	(131)
Genedy *et al*, 2022		Chitosan	Biocompatible; cheap; stable	Not stable with miRNA	(132)
Dasgupta and Chatterjee, 2021	Extracellular	Exosomes	Efficient; clinical results already in place	Mass production is difficult; regulation/biogenesis not well known	(118)
Rupaimoole and Slack, 2017; Reid *et al*, 2016	Others	Bacterium-derived nanoparticles (TargomiRs)	Efficient; biodegradable; in phase 1 trial for delivering miRNA		(119,133)
Dasgupta and Chatterjee, 2021; Moncal *et al*, 2019		3D biomaterial scaffold	Effective; inexpensive; high tissue specificity	Still needs further study	(118,134)

AAV, adeno-associated virus; AD, adenovirus; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine; LV, lentiviral; miRNA, microRNA; NLE, neutral lipid emulsion; PAMAM, positively charged synthetic polyadenoamine; PEG, polyethylene glycol; PEIs, polyethyleneimines; PLGA, polylactide-co-glycolide; RV, retroviral; siRNA, small interfering RNA.

Table IV. Clinically important miRNAs influencing radiotherapy.

First author/s, year	Cancer	miRNA	Target	Effect on prognosis	(Refs.)
Sun *et al*, 2016; Pajic *et al*, 2018	Breast	Let-7d	Cyclin D1/Akt1/Wnt1	Increases radiosensitivity in triple-negative breast cancer	(46,47)
Guan *et al*, 2019	Prostate	miR-200a	BRD4	Downregulation leads to poor prognosis	(61)
Kozak *et al*, 2020		miR-200b	AR-v7	Downregulation of miR-200b/c both related to chemoresistance and radioresistance	(62)
Kozak *et al*, 2020		miR-200c			(62)
Lv *et al*, 2020; Wei *et al*, 2021	Lung	miR-130a	KLF3	Low expression related to poor prognosis	(85,86)
Lv *et al*, 2020; Wei *et al*, 2021		miR-25; miR-191	MOAP1	miR-25/191 upregulation related to poor prognosis after radiotherapy	(85,86)
Yuan *et al*, 2020		miR-410	PTEN, P13K/mTOR pathway	Upregulated in NSCLC cell lines and promotes radioresistance	(87)
Tian *et al*, 2020	Nasopharyngeal	miR-19b-3p	Bcl-2 gene family proteins	Promotes radiotherapy resistance and recurrence of NPC	(88)
Tian *et al*, 2020		miR-125b/miR-21			(88)
Tian *et al*, 2020		miR-205			(88)
Qu *et al*, 2015		miR-203	IL8/AKT signaling	Upregulated in radiosensitive NPC cell lines	(89)
Wu *et al*, 2018		miR-222	PTEN	Upregulated in NPC cell lines and promotes radioresistance	(90)
Zhang *et al*, 2017		miR-120	PDCD6/Bcl-2	Downregulated in NPC cell lines and decreases radiosensitivity	(92)
Manoel-Caetano *et al*, 2019	Gastric	miR-21/miR-24/ miR-421/miR-605	ATM/ATR/ H2AX/P53	Increase radioresistance/impair proper DNA repair in cancer/promote metastasis and growth	(94)
Deng *et al*, 2020		miR-192/miR-215	APC/Wnt/β□catenin pathway	Promote DNA damage repair/tumorigenesis	(95)
Ge *et al*, 2024		miR-129-5p	NUSAP1	Good prognosis/increases radiosensitivity	(96)
Liu *et al*, 2021		miR-4537	ZNF587	Increases cell apoptosis/radiosensitivity	(97)
Wei *et al*, 2019		miR-4766-5p	NKAP	Increases radiosensitivity	(98)
Wei *et al*, 2019	Cervix	miR-9	SOCS5	Increases radiosensitivity and angiogenesis	(104)
Aguilar-Martinez *et al*, 2024; Masadah *et al*, 2021		miR-21	RECK signaling	Increases radiosensitivity but increases drug resistance	(105,106)
Nilsen *et al*, 2022		miR-200a/b, miR-429	ZEB1, ZEB2, β-catenin, Bcl-2	Poor prognosis due to increased radioresistance	(107)
Yuan *et al*, 2014		miR-218/miR-34a	SLIT2/ROBO1, SIRT1, BCL2	Increases sensitivity to radiation and induces apoptosis	(108)

Table IV. Continued.

First author/s, year	Cancer	miRNA	Target	Effect on prognosis	(Refs.)
Wang *et al*, 2017; Li *et al*, 2019		miR-23b	SIX1, AKT/mTOR	Increases sensitivity to radiation and chemotherapy	(110,111)
Zhao *et al*, 2019		miR-203	FGF2, SOCS3, ABL1	Induces cell cycle arrest and apoptosis	(112)
Mansour *et al*, 2013		miR-421	ATM protein	Poor prognosis/increases radiosensitivity	(113)
Pedroza-Torres *et al*, 2014; Masadah *et al*, 2021		miR-181a/ miR-106b	IER3	Induce radioresistance by regulating apoptosis	(103,106)

miRNA/miR, microRNA; NPC, nasopharyngeal cancer; NSCLC, non-small cell lung cancer.

the evolution of miRNA-based therapeutics and diagnostics, key research directions must be prioritized. Optimization of multifunctional miRNA delivery platforms, integration of tumor-targeting peptides, exosome-based carriers, and CRISPR-based precision editing could enhance therapeutic specificity while minimizing off-target effects. Further advancements in miRNA-based liquid biopsy will facilitate early cancer detection and monitoring. Additionally, research on the stability of miRNAs in body fluids and storage conditions will improve their reliability as diagnostic biomarkers. Leveraging machine learning algorithms trained on large miRNA datasets can enhance diagnostic precision and enable tailored treatment strategies for individual patients. Another promising area of research involves anti-angiogenic miRNAs, which have the potential to improve radiotherapy efficacy by normalizing the tumor vasculature and reducing hypoxia-related resistance. For example, miR-210 regulates angiogenesis through the vascular endothelial growth factor (VEGF) signaling pathway, and its inhibition can restore normal blood vessel function and enhance oxygenation and radiosensitivity in tumors (121-123). Similarly, inhibiting miR-155, which promotes neovascularization by modulating the ELK3 and E2F2 transcription factors, could enhance radiosensitivity and reduce tumor progression (113). miRNA-based interventions have the potential to revolutionize cancer management by addressing these challenges and refining miRNA detection methodologies to ensure greater efficacy and safety in therapeutic and diagnostic applications.

In 2016, the biotechnology company miRNA Therapeutics, now known as Synlogic, discontinued phase 1 clinical trials of the miRNA-34 mimic drug MRX34, intended for cancer treatment, after five patients experienced severe immune reactions resulting in serious adverse events (SAEs). Consequently, the planned phase 2 trials of MRX34 for melanoma were also canceled. Since then, no phase 3 trials have been registered at clinicaltrials.gov, although ongoing reviews and new strategies for utilizing miRNAs as therapeutic agents are in progress. Early studies on miRNA delivery relied primarily on viral vectors. However, as demonstrated by the adverse events mentioned above, viral vectors pose significant safety concerns in clinical use. PLGA particles, which are widely used to transport small RNAs, have been considered as potential miRNA delivery vehicles, but the low efficiency of miRNA loading has proven insufficient for clinical application. Among lipid-based delivery systems, NLEs have been extensively tested because of their low toxicity; however, they are not sufficiently efficient for miRNA delivery. Despite these initial challenges, safer and more effective delivery methods are currently being investigated. One promising technology is TargomiR, a delivery system that uses bacterially derived mini-cells containing miRNA mimics and targeting moieties (antibodies that recognize proteins on target cells). The use of TargomiR has shown encouraging results in mesothelioma and NSCLC, with phase 1 trials demonstrating significant suppression of target miRNAs, suggesting a viable method for treating these cancers (117). Additionally, neutral liposomes such as DOPC are commonly used for siRNA delivery and are currently being tested for miRNA delivery in preclinical studies. For example, DOPC liposomes loaded with miRNA-506 mimics or miRNA-520 were shown to significantly suppress tumor growth in an

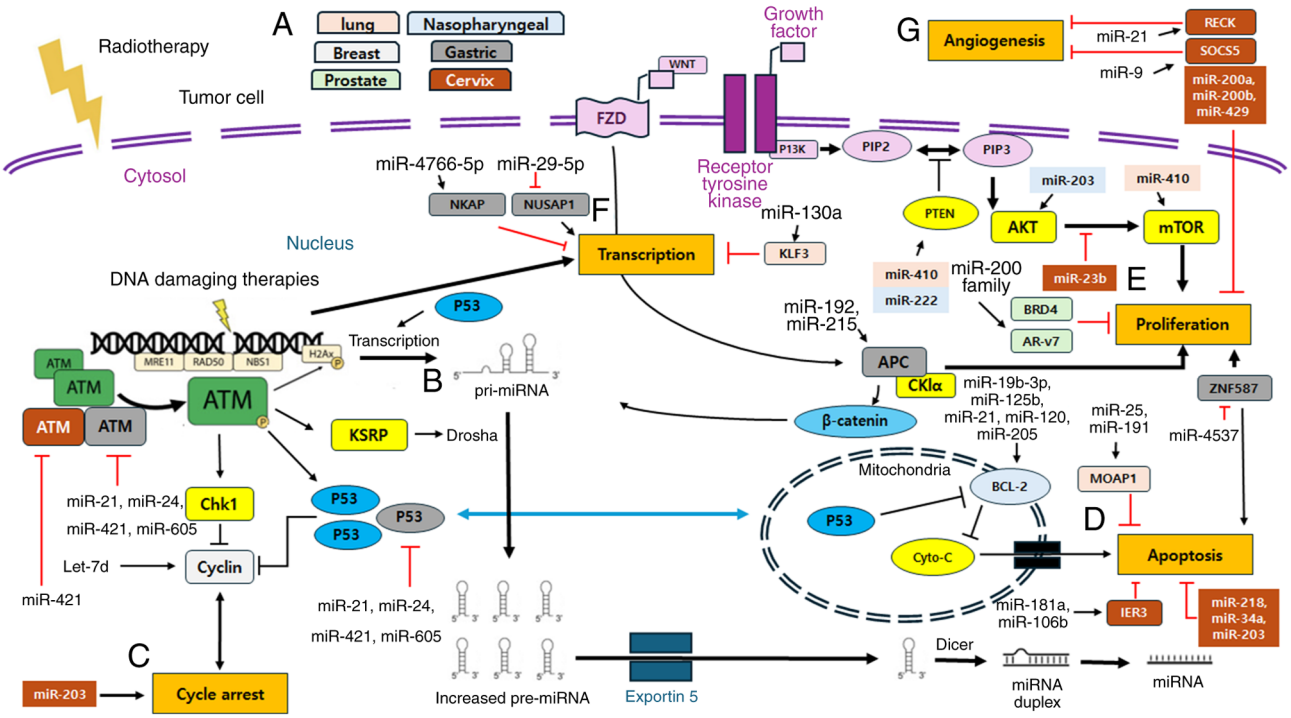

Figure 1. Overview of the interaction of miRNAs and key proteins in response to DNA damage induced by cancer radiotherapy. (A) Proteins and miRNAs are categorized by six distinct colors, each representing a specific cancer type. Highlighted proteins indicate proteins directly modulated by miRNA. Colored miRNAs are miRNAs with an indirect influence on the targets. (B) DNA damage activates the ATM kinase, which subsequently recruits various proteins, including KSRP and P53. These proteins promote the upregulation of pre-miRNAs, accelerating miRNA maturation within the cytoplasm. (C) ATM activation also stimulates CHK1, impairing cyclin function and checkpoint regulation. Cyclins, which are essential for proper cell cycle progression, normally regulate checkpoint activation. However, mutations or upregulation of cyclins in tumor cells can disrupt these checkpoints, leading to abnormal cell cycle progression. (D) This process occurs through the inhibition of the anti-apoptotic gene BCL-2, which normally prevents the release of the mitochondrial heme protein Cyto-c into the cytoplasm. Once released, Cyto-c initiates the intrinsic apoptotic pathway, promoting programmed cell death. (E) The PI3K/AKT pathway, a well-known promoter of cell proliferation, is frequently upregulated in tumor cells due to various mechanisms, leading to uncontrolled tumor growth. The tumor suppressor PTEN acts as a critical antagonist to the PI3K/AKT pathway, maintaining cellular homeostasis. (F) Additionally, miR-4766-5p enhances radiosensitivity in gastric cancer by targeting NKAP, a well-known transcriptional repressor involved in Notch signaling and T cell development. miR-129-5p suppresses radioresistance by inhibiting NUSAP1. However, APC loss-of-function mutations are common in tumor cells, resulting in uncontrolled growth. (G) Several miRNAs directly regulate genes and proteins associated with transcription and angiogenesis, impacting tumor development. miR/miRNA, microRNA; P, phosphorylated.

ovarian cancer orthotopic mouse model. Similarly, DOPC liposomes complexed with miR-2000 effectively inhibited tumor growth in an orthotopic lung cancer model. Polymeric delivery methods such as those utilizing PEIs initially exhibit low transfection efficiencies and high cytotoxicity. However, alternative polymers, such as PEG, have emerged as more favorable miRNA delivery vehicles owing to their improved biocompatibility and lower toxicity. PEG can be covalently fused to PEI to enhance its stability and efficiency. Chitosan, a cationic polymer derived from chitin, has been studied as a biocompatible natural polymer for miRNA delivery (118,119). Ongoing studies are exploring novel delivery systems for miRNA therapeutics, as outlined in Table III.

Although there is great potential for miRNA therapeutics, challenges remain, including the pleiotropic nature of miRNAs and the complexity of their interactions with cellular processes and proteins. These factors underscore the need for further clinical and bioinformatics research to support reliable clinical applications (120). Nevertheless, the development of sophisticated miRNA delivery systems could unlock diverse therapeutic and clinical applications, particularly for enhancing the effectiveness of radiotherapy by increasing the radiosensitivity of cancer cells. The miRNAs listed in Table IV, which are associated with favorable clinical outcomes, emphasize the importance of low toxicity and high specificity in miRNA therapeutics. Moreover, anti-angiogenic miRNAs have the potential to reduce the side effects and increase the effectiveness of radiotherapy. Recent preclinical and clinical trials combining radiotherapy with anti-angiogenic drugs have shown promising results. The enhancement of radiotherapy through these drugs may be attributed to improved tumor oxygenation stemming from the normalization of blood vessels and suppression of angiogenic growth factors typically stimulated by radiotherapy. However, these drugs exhibit unnecessary toxicity and adverse effects in patients, and rapid resistance to current anti-angiogenic therapies is becoming a concern. As alternative strategies to target angiogenesis are required, miRNAs have emerged as potential antiangiogenic agents. For example, miR-210 induces angiogenesis by mediating the VEGF signaling pathway. The inhibition of miR-210 in hypoxic tumors can restore abnormal tumor vasculature, improve oxygenation, and sensitize tumors to radiotherapy (124,125). Similarly, inhibition of miR-155 can enhance radiosensitivity because miR-155 regulates angiogenesis and promotes neovascularization by modulating the transcription of ELK3 and E2F2 (121,122).

7. Conclusion

This study underscores the pivotal role of miRNAs in modulating the cancer cell response to radiotherapy, specifically by regulating key processes such as apoptosis, cell cycle arrest, angiogenesis, and metastasis. These findings suggest that miRNA-based interventions have significant potential to improve radiosensitivity and minimize side effects, particularly by targeting specific miRNAs that influence the radiation response in distinct cancer cell types. This can be achieved by leveraging clinical data and innovative delivery methods to ensure precise targeting of miRNAs to cancer cells during treatment. Development of optimized miRNA delivery systems that address both efficiency and safety concerns is crucial for clinical applications. Recent studies have explored various strategies to achieve this goal, including chemical modifications to enhance stability, non-viral delivery systems for improved targeting, and biocompatible materials to reduce immune responses. By integrating these advanced strategies, miRNA-based therapies can be further optimized to enhance their therapeutic efficacy and clinical translation. Furthermore, we discuss recent advancements in miRNA delivery vehicles, which are progressively enhancing both safety and efficacy (Fig. 1). However, further research is imperative to address unresolved concerns regarding the safety of miRNA applications in patients, which remains a critical barrier to clinical translation. Key safety challenges include immune responses, off-target effects, potential toxicity, and unintended gene regulation, all of which must be thoroughly investigated to ensure the clinical viability of miRNA-based therapies. Overall, miRNAs play a crucial role in the regulation of tumor biology, and their manipulation offers promising new avenues for enhancing the efficacy of radiotherapy. Targeting the molecular mechanisms through which miRNAs regulate radiosensitivity may overcome the current limitations of radiotherapy, ultimately reducing patient suffering and improving cancer treatment outcomes.

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Authors' contributions

JP and JSL designed the review. JP wrote most of the manuscript. JSL edited the manuscript. MEK contributed to the writing and revision of the manuscript during the revision process and performed overall editing. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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