Biomarkers of radioresistance in lung cancer: Current insights and future directions (Review)

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Received June 17, 2025; Accepted October 29, 2025

DOI: 10.3892/mmr.2026.13914

Abstract. Radiotherapy (RT) remains a cornerstone of lung cancer (LC) management, serving as either a definitive treatment or an adjuvant modality following surgical resection. Nevertheless, a major challenge for radiation oncologists is the emergence of radioresistance, whether intrinsic or acquired, which contributes to therapeutic failure, tumor recurrence, metastasis and ultimately to increased patient mortality. Radioresistance is a multifactorial process driven by genetic and epigenetic alterations that dysregulate key signal transduction pathways, enabling cancer cells to survive and adapt under radiotherapeutic stress. A deeper understanding of the molecular mechanisms underlying radioresistance is therefore essential to identify robust biomarkers for patient stratification, prognostication and therapeutic targeting. Such insights could enable individualized treatment strategies within the framework of precision oncology and inform the development of novel radiosensitization approaches to overcome resistance in LC. The present review synthesized current evidence on molecular biomarkers associated with RT resistance in LC.

Contents

1. Introduction

Lung cancer (LC) is the most prevalent malignancy worldwide, affecting individuals of all sexes, with ~2.5 million new cases diagnosed in 2022. It remains the leading cause of cancer-related mortality, accounting for >1.8 million deaths globally in the same year (1). Despite notable advances in treatment, the overall 5-year survival rate remains poor, not exceeding 17% (2). LC is broadly classified into non-small cell LC (NSCLC), which represents ~80% of cases and small-cell

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Abbreviations: ANGPTL4, angiopoietin-like 4 protein; *ATG16L2*, autophagy related 16 like 2 gene; CA-IX, carbonic anhydrase IX; COMP, cartilage oligomeric matrix protein; CSC, cancer stem cell; ctDNA, circulating tumor DNA; ERCC1, excision repair cross-complementation; FASN, fatty acid synthase; FBLN5, fibulin-5; FLOT1, flotillin-1; FBXO22, F-box protein 22; FN1, fibronectin 1; *FOLR3*, folate receptor-3; GRP78, glucose-regulated protein 78; HIF-1α, hypoxia-inducible factor 1α; HSP70, heat shock protein 70; HSPB1, heat shock protein β-1; *iASPP*, inhibitor of apoptosis-stimulating protein of p53; ICAM-1, intercellular adhesion molecule 1; *KEAP1*, Kelch-like ECH-associated protein 1; KLC4, kinesin light chain 4; LIG4, DNA ligase 4; lncRNA, long noncoding RNA; LSCC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; *NFE2L2*, nuclear factor erythroid 2-related factor-2; NOMO2, nodal modulator 2; NSCLC, non-small cell lung cancer; OPN, osteopontin; PAI-2, plasminogen activator inhibitor-2; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PKP2, plakophilin 2; PLOD3, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3; RASA2, Ras p21 protein activator; RT, radiotherapy; SNP, single nucleotide polymorphism; THBS1, thrombospondin 1; VIM, vimentin; *XRCC1*, X-ray repair cross-complementing protein 1

Key words: lung cancer, biomarkers, radioresistance, RT

LC, which accounts for the remaining 20%. According to the 2015 World Health Organization classification (3), NSCLC is further subdivided into three major histological subtypes: Lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LSCC) and large cell carcinoma (3).

The pathogenesis of LC is complex, involving both genetic susceptibility and environmental exposure. In addition, its development is driven by dysregulated oncogenes and tumor suppressor genes (4), contributing to the highly aggressive nature of lung tumors and the frequent occurrence of metastases at diagnosis (5).

Management of LC typically involves a multimodal approach that includes surgery, radiotherapy (RT), chemotherapy and immunotherapy. RT, used either as a stand-alone modality or in combination with systemic therapies, is a cornerstone of LC treatment (6). Of patients with LC, ~77% are estimated to have a clinically justified indication for RT during their disease course (7). However, the lung is one of the most radiosensitive organs, rendering it highly susceptible to radiation-induced toxicity (8). Advances in imaging, dose delivery and treatment planning have enabled more precise targeting of tumor tissue, reducing exposure of surrounding healthy tissue and broadening therapeutic possibilities. This evolution toward adaptive RT allows for the delivery of higher doses while minimizing side effects (9).

Despite these technological improvements, radioresistance remains a major obstacle in LC management (10). Clinical outcomes are often unsatisfactory due to intrinsic or acquired resistance, leading to local recurrence and metastasis (11). Radioresistance is particularly problematic in NSCLC, where only a subset of patients achieve a durable response to RT (12). Furthermore, radioresistant tumor cells actively promote metastasis and recurrence following treatment (13).

The biological basis of radioresistance is multifaceted, involving aberrant DNA damage response, dysregulated cell-cycle checkpoints, impaired apoptosis, altered autophagy, genetic mutations and disrupted signaling pathways (14). Resistance can be classified as intrinsic, where tumors are refractory to initial therapy, or acquired, developing after repeated radiation fractions during treatment (15).

Genomic and molecular biomarker research offers the potential to guide RT decisions and identify radiosensitization strategies (16). Biomarkers such as genetic polymorphisms, gene expression signatures and protein expression profiles can provide crucial insights into tumor biology and predict differential responses to RT (17). In radiation oncology, these biomarkers enable stratification of patients, inform treatment intensity and help spare patients unnecessary toxicity, thereby improving outcomes and quality of life (18-20).

The present review summarized key molecular biomarkers with potential clinical utility in radiation oncology, emphasizing their role in optimizing LC management and enabling precision medicine approaches.

2. Predictive biomarkers in radiation-based personalized medicine for LC

Advances in molecular technologies have transformed cancer management, including in LC, by enabling faster and more precise diagnostic and therapeutic interventions. Genomic sequencing, whether whole-genome, whole-exome or targeted, has been instrumental in advancing precision medicine (21).

According to the U.S. National Institutes of Health, precision medicine is defined as an approach to disease prevention and treatment that accounts for interindividual variability in genes, environment and lifestyle (22). In the context of radiation oncology, the identification of genetic signatures that predict prognosis and/or response to RT offers substantial clinical value. Such biomarkers could inform the personalization of fractionation schedules, optimization of radiation doses and integration, or deliberate avoidance, of systemic therapies. Together, these strategies hold the potential to enhance therapeutic efficacy while mitigating the toxicities associated with conventional anticancer regimens (23).

Genetic biomarkers. Individual variability in RT outcomes is largely attributable to the intrinsic genetic landscape of the tumor (Fig. 1). Compelling evidence has indicated that multiple DNA repair genes modulate the cellular response to RT (24), consistent with the fact that the primary cytotoxic effect of ionizing radiation is the induction of DNA double-strand breaks (25). Genetic variations in radiosensitivity-associated genes contribute to molecular heterogeneity at specific genomic loci, ultimately influencing key cellular processes, including the extent of DNA damage sustained and the efficiency of DNA repair pathways (26).

Mutations associated with radiation resistance. In NSCLC, *KRAS* mutations have been strongly linked to radioresistance (27). Accumulating evidence has indicated that *KRAS*-mutant NSCLC constitutes a heterogeneous group characterized by diverse, tumor-specific mechanisms of resistance (28,29). Consistent with this complexity, a study using heterotopic NSCLC xenograft models has shown that co-mutation of *KRAS* and *TP53* is associated with reduced local tumor control following standard RT regimens. This co-mutation may therefore serve as a predictive biomarker for patient stratification, informing dose escalation strategies or the addition of molecular agents targeting the EGFR signaling pathway. More broadly, these findings underscore the need for biomarker-driven clinical trials that integrate comprehensive genomic profiling with clinically relevant endpoints to refine and personalize RT strategies (30).

The predictive value of EGFR mutations remains controversial. In patients with *EGFR*-mutant stage III adenocarcinoma, concurrent chemoradiation improved local control but was paradoxically associated with shorter progression-free survival (PFS) compared with *EGFR* wild-type patients, primarily due to relapse or distant metastasis (31). Conversely, another study reported improved local control following chemoradiation in patients with *EGFR*-mutant, locally advanced nonsquamous NSCLC (32). These discordant results may reflect differences in patient demographics, smoking status (which influences tumor biology), RT dose and fractionation schemes, sequencing or concurrency of chemotherapy, or the criteria used to define treatment response and failure. Such variability highlights the need for standardized methodologies and better stratified studies to clarify the true predictive value of *EGFR* mutations in RT outcomes.

Parallel clinical trials have explored combining targeted therapies with RT to improve outcomes in *EGFR*-mutant NSCLC. Notably, the phase II trial NCT03667820 evaluated

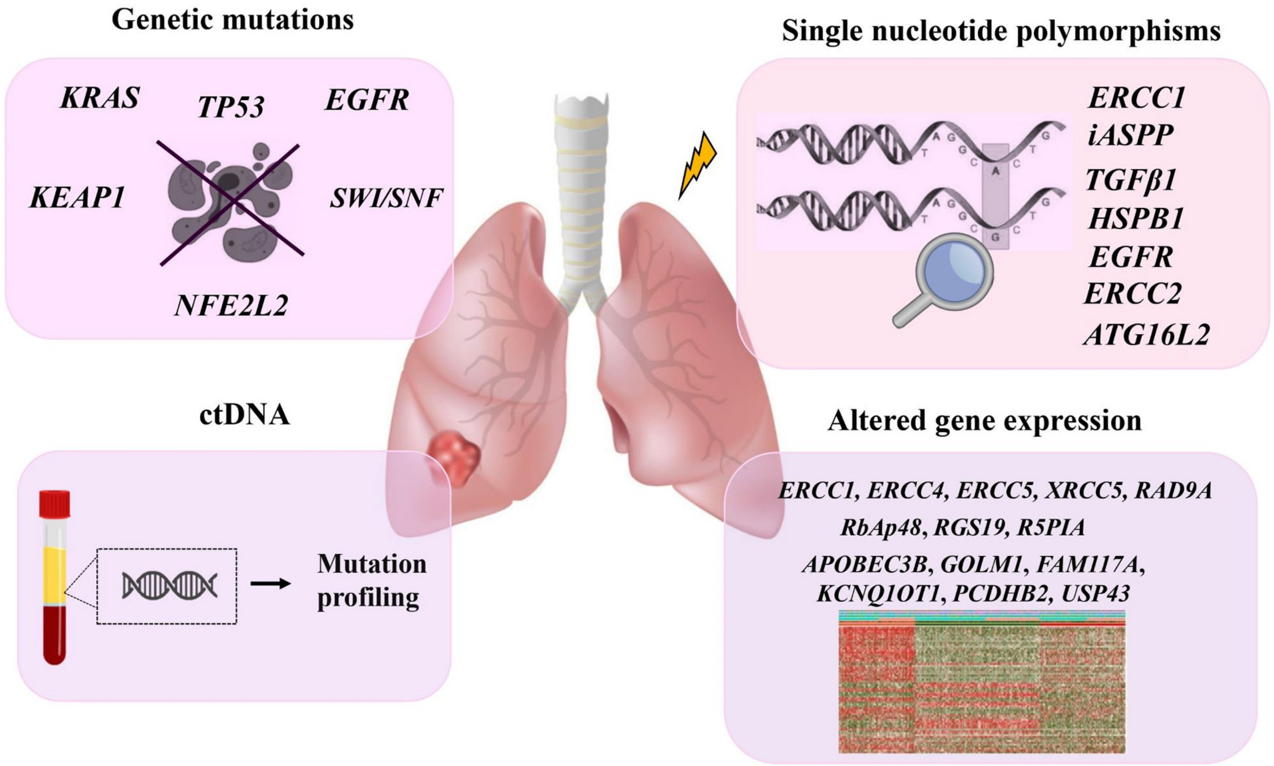

Figure 1. Overview of genetic biomarkers implicated in lung cancer radioresistance. ctDNA, circulating tumor DNA.

osimertinib with consolidative RT for residual lesions in advanced *EGFR*-mutant NSCLC. Among the 42 patients enrolled, 76% of whom received stereotactic RT, the combination yielded a PFS of 32.3 months and an OS of 45 months, with a favorable safety profile. These results suggest that integrating third-generation tyrosine kinase inhibitors with local RT may prolong disease control, offering a viable alternative to more intensive first-line regimens for this patient subgroup (33). Collectively, these data illustrate how *EGFR* mutations serve not only as potential predictors of radioresistance but also as guides for incorporating targeted therapies into combined-modality treatment strategies.

Additional mutations have also been implicated in radioresistance. Binkley *et al* (34) demonstrated that mutations in Kelch-like ECH-associated protein 1 (*KEAP1*) and nuclear factor erythroid 2-related factor 2 (*NFE2L2*) are predictive of radioresistance and are associated with high rates of local recurrence in localized NSCLC. Notably, this resistance could be mitigated with CB-839, a small-molecule glutaminase inhibitor that potentiates radiation-induced DNA damage by reducing the free-radical scavenging capacity of cancer cells. Furthermore, sequencing of peripheral blood samples has revealed that mutations in the *SWI/SNF* chromatin-remodeling complex may serve as stratification biomarkers, as they are enriched in RT-sensitive patient cohorts (35). Table I provides an overview of the key mutations associated with differential radiosensitivity in lung cancer.

Single nucleotide polymorphisms (SNPs). SNPs have been extensively investigated for their potential role in modulating radiosensitivity (Table II). Variants in excision repair cross-complementation (*ERCC*)*1* and inhibitor of apoptosis-stimulating protein of p53 (*iASPP*), both key mediators of DNA repair, have been associated with differential responses to chemotherapy and combined chemoradiation in patients with NSCLC (36). Certain *iASPP* polymorphisms may result in decreased protein levels, leading to activation of ASPP1 and ASPP2 and enhanced p53-mediated apoptosis, thereby sensitizing tumors to RT (37). A combined SNP signature involving *ERCC2* rs238406 and *ERCC1* rs11615 has also been notably associated with radiosensitivity in LC (38), consistent with the pivotal role of these genes in the nucleotide excision repair pathway (39).

Additional polymorphisms in DNA repair genes, including X-ray repair cross-complementing protein *XRCC1* (rs25487), *XRCC2* (rs3218556) and *XPD* (rs13181), have been linked to RT response and OS in NSCLC. Notably, the *XRCC1* rs25487 CC genotype and *XRCC2* rs3218556 AG/AA genotypes were more frequently observed among responders than non-responders (40). These findings highlight the potential utility of these SNPs as predictive biomarkers for stratifying patients probably to benefit from RT.

Polymorphisms in the promoter region of *TGFβ1* have also been associated with increased radiosensitivity (41), suggesting their clinical potential as predictive markers for favorable RT response. Similarly, heat shock protein β-1 rs2868371 polymorphisms have been shown to influence treatment outcomes: In U.S. patients with NSCLC, the CC genotype was associated with poor OS following RT or chemotherapy (42), whereas in a Chinese cohort, the C allele was linked to increased radiosensitivity and improved survival, probably due to reduced Hsp27 expression and impaired DNA repair capacity (43). These discrepancies underscore the influence of genetic background, ethnic differences in allele frequencies and clinical heterogeneity (such as treatment regimens and disease stage) on study outcomes (42).

Table I. Effect of genetic mutations on outcomes of lung cancer radiotherapy.

First author/s, year	Marker	Material	Cohort (size)	Result	Conclusion	(Refs.)
Gurtner *et al*, 2020	*KRAS/TP53*	Tissue	NA	Higher radioresistance	Radioresistant	(30)
Tanaka *et al*, 2015	*EGFR*	Blood	Unresectable stage III adenocarcinoma (n=104)	Poor PFS, metastasis relapse	Radioresistant	(31)
Lim *et al*, 2017	*EGFR*	Tissue	Stage III nonsquamous NSCLC (n=102)	Higher local control, and a longer duration before progression within the irradiated field	Radiosensitive	(32)
Gurtner *et al*, 2020	*KRAS/TP53*	Tissue	NA	Higher radioresistance	Radioresistant	(30)
Binkley *et al*, 2020	*KEAP1/NFE2L2*	Tissue	Localized NSCLC (n=232)	High of rates of local recurrence	Radioresistant	(34)
Zhang *et al*, 2024	*SWI/SNF*	Blood	NSCLC (n=13)	Improved RT response	Radiosensitive	(35)

KEAP1, kelch-like ECH-associated protein 1; NFE2L2, nuclear factor erythroid 2-related factor-2; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RT, radiotherapy.

Butkiewicz *et al* (44) reported that *EGFR* polymorphisms associated with increased gene expression and aberrant protein activity may predict clinical outcomes following DNA-damaging treatments. Specifically, *EGFR* rs2227983 GG and rs712829 TT genotypes were associated with tumor recurrence and acted as independent predictors of poor prognosis, while rs712830 CC genotype was associated with increased mortality risk. Given the established link between *EGFR* upregulation, reduced RT response and shortened survival (45), these findings support the utility of *EGFR* genotyping as both a prognostic tool and a predictor of radioresistance. Incorporating *EGFR* polymorphism screening into clinical practice could refine risk stratification and guide therapeutic decision-making.

Moreover, SNPs in autophagy-related genes have emerged as promising predictive biomarkers. For example, the autophagy related 16 like 2 gene rs10898880 CC homozygous variant has been reported to be associated with improved local recurrence-free survival, PFS and OS (46).

Despite these advances, most studies have examined individual SNPs in isolation. RT response is a multifactorial phenotype shaped by the interplay of multiple genetic variants and environmental exposures. Interactions between genes regulating DNA repair, apoptosis and cell-cycle checkpoints can synergistically influence radiosensitivity, as can gene-environment interactions such as smoking status, comorbidities and baseline clinical characteristics. The lack of integrative, systems-level analyses remains a key limitation in the field. Well-designed studies incorporating polygenic risk models and environmental data are needed to improve prediction accuracy and enable clinically actionable stratification. Furthermore, the underlying mechanisms by which these SNPs influence RT outcomes remain incompletely characterized, limiting their current utility as robust predictive biomarkers. Reliance solely on previously reported functional variants also risks overlooking rare but clinically meaningful SNPs that could inform precision RT strategies.

Altered gene expression. Several approaches have been developed to identify differential gene expression patterns between radiosensitive and radioresistant samples. One widely cited method is the radiosensitivity index, proposed by Torres-Roca *et al* (47), which quantifies intrinsic tumor radiosensitivity by measuring the surviving fraction at 2 Gy. Through gene expression profiling, three genes, *RbAp48*, *RGS19* and *R5PIA*, were identified the expression levels of which were reported to be associated with radiosensitivity, suggesting their potential as predictive biomarkers for patient selection prior to RT (47). Table III summarizes representative studies identifying gene expression signatures that influence radiotherapy response in lung cancer.

Building on these efforts, Peinado-Serrano *et al* (48) used data from The Cancer Genome Atlas LC cohort to establish a six-gene predictive signature (*APOBEC3B*, *GOLM1*, *FAM117A*, *KCNQ1OT1*, *PCDHB2* and *USP43*) associated with OS and PFS. This gene panel displayed differential expression according to irradiation phenotype in both NSCLC cell lines and patients with stage I-III NSCLC treated with RT, supporting its utility for patient stratification and prediction of long-term outcomes. Similarly, an eight-gene risk model (*APOBEC3B*, *DOCK4*, *IER5L*, *LBH*, *LY6K*, *RERG*, *RMDN2* and *TSPAN2*) was found to independently predict prognosis and immune infiltration. Among these, *LBH* has been experimentally validated as a functional biomarker: Its upregulation enhances the radiosensitivity of A549 cells, whereas its silencing restores radioresistance. These findings suggest that *LBH*, as well as multi-gene risk scores, hold promise for prognostic stratification and therapeutic decision-making in NSCLC (49).

Transcriptome sequencing of p53 wild-type A549 and p53-deficient H1299 NSCLC cell lines, along with their radioresistant derivatives (A549IR and H1299IR), has revealed shared molecular signatures associated with radioresistant phenotypes (50). Specifically, seven genes (*ATRNL1*, *CA2*, *CNR1*, *FAM189A1*, *GFRA1*, *RASGRP1* and *RGL3*) were upregulated, whereas nine genes (*ADGRF1*, *EPHA7*, *LOX*,

Table II. SNPs associated with radiotherapy outcomes in lung cancer.

First author/s, year	Marker	dbSNP ID	Cohort (size)	Clinical relevance	Pathway	Result	(Refs.)
Su *et al*, 2007	*ERCC1*	rs11615	Advanced NSCLC (stages IIIA-IV) (n=154)	Improved RT response	DNA repair	Radio-sensitizing	(36)
Su *et al*, 2007	*iASPP*	rs3136820	Advanced NSCLC (stages IIIA-IV) (n=154)	Improved RT response	DNA repair	Radio-sensitizing	(36)
Kelsey *et al*, 2012	*TGFβ1*	rs1800469	Lung cancer (n=39)	Higher radiation sensitivity	DNA repair	Radio-sensitizing	(41)
Xu *et al*, 2012	*HSPB1*	rs2868371	NSCLC (n=224)	Poor OS	Cellular stress response	Radioresistant	(42)
Jin *et al*, 2015	*ERCC1*	rs11615	All stage-III NSCLC (n=92)	Improved RT response	DNA repair	Radio-sensitizing	(38)
Jin *et al*, 2015	*ERCC2*	rs238406	All stage-III NSCLC (n=92)	Improved RT response	DNA repair	Radio-sensitizing	(38)
Wen *et al*, 2018	*ATG16L2*	rs10898880 CC	NSCLC (n=393)	Improved local recurrence-free survival, PFS and OS	Autophagy	Radio-sensitizing	(46)
Yang and Liu, 2020	*XRCC1*	rs25487	NSCLC (n=486)	Improved efficacy and toxicity of RT	DNA repair	Radio-sensitizing	(40)
Yang and Liu, 2020	*XRCC2*	rs3218556	NSCLC (n=486)	Improved efficacy and toxicity of RT	DNA repair	Radio-sensitizing	(40)
Yang and Liu, 2020	*XPD*	rs13181	NSCLC (n=486)	Improved efficacy and toxicity of RT	DNA repair	Radio-sensitizing	(40)
Butkiewicz *et al*, 2021	*EGFR*	rs712830 CC; rs2227983 GG; rs712829 TT	Unresectable NSCLC (n=436)	Worse OS; risk factor for locoregional recurrence	Receptor tyrosine kinase signaling	Radioresistant	(44)

ATG16L2, autophagy related 16 like 2 gene; dbSNP, single nucleotide polymorphism database; *ERCC*, excision repair cross-complementation; *HSPB1*, heat shock protein β-1; *iASPP*, inhibitor of apoptosis-stimulating protein of p53; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SNP, single nucleotide polymorphism; *XRCC2*, X-ray repair cross-complementing protein 2.

LY6G5C, *NSUN7*, *SLC22A31*, *SNAI2*, *TNFRSF11B* and *ZNF233*) were downregulated. These dysregulated pathways represent potential predictive biomarkers and therapeutic targets.

Pathway-level analyses further highlighted activation of the WNT signaling cascade, including WNT ligand biosynthesis, WNT5A-FZD4 internalization and canonical WNT/β-catenin signaling, together with NF-κB pathway upregulation. Radioresistant H1299IR cells exhibited elevated β-catenin levels due to sustained GSK3 activity downstream of AKT, promoting enhanced cellular motility and invasion. These transcriptomic alterations were accompanied by a senescence-associated secretory phenotype, characterized by increased *IL6*, *CXCL8* and *TGFβ2* expression and decreased *NRG1* expression, thereby supporting tumor progression (50).

Other studies have identified additional gene panels with potential clinical relevance. Eight genes (*FOLR3*, *SLC6A11*, *ALPP*, *IGFN1*, *KCNJ12*, *RPS4XP22*, *HIST1H2BH* and *BLACAT1*) have been shown to be associated with RT response in patients with NSCLC (51). Moreover, profiling of drug-tolerant persister cancer cells has yielded a four-gene prognostic risk index (*LYNX1*, *SYNPO*, *GADD45B* and *PDLIM1*), the co-expression network of which was revealed to be notably associated with RT response and OS (52).

Given the established link between autophagy and radioresistance, Gao *et al* (53) developed a three-gene autophagy-related prognostic model (*SHC1*, *NAPSA* and *AURKA*), in which *SHC1* and *AURKA* upregulation, combined with *NAPSA* downregulation, predicted enhanced radioresistance. Furthermore, strong expression of DNA repair genes (*ERCC1*, *ERCC4*, *ERCC5*, *XRCC5*, *RAD9A*, *PRKDC* and the gene encoding DNA-PK), as well as proliferation- and apoptosis-related genes (*MDM2*, *PIM2*, *BCL2* and *PKCZ*), has been observed in radioresistant

Table III. Gene expression signatures associated with radiotherapy response in lung cancer.

First author/s, year	Gene expression signature	Method of detection	Regulation	Result	(Refs.)
Torres-Roca *et al*, 2005	*RbAp48*, *RGS19* and *R5PIA*	Microarrays, quantitative PCR	Upregulation	Improved RT response	(47)
Guo *et al*, 2005	*ERCC1*, *ERCC4*, *ERCC5*, *XRCC5*, *RAD9A*, *DNA-PK*, *MDM2*, *PIM2*, *BCL2* and *PKCZ*	Microarray analysis	Upregulation	Lower RT efficacy	(54)
Zhao *et al*, 2020	*LYNX1*, *SYNPO*, *GADD45B* and *PDLIM1*	Multiple factor Cox regression model	Upregulation	Tumor resistance and repopulation following RT	(52)
Ma *et al*, 2021	*FOLR3*, *SLC6A11*, *ALPP*, *IGFN1*, *KCNJ12*, *RPS4XP22*, *HIST1H2BH* and *BLACAT1*	WGCNA, LASSO Cox regression analysis	NR	Prediction of prognosis	(51)
Peinado-Serrano *et al*, 2022	*APOBEC3B*, *GOLM1*, *FAM117A*, *KCNQ1OT1*, *PCDHB2* and *USP43*	cDNA microarrays	Upregulation	Prediction of OS and PFS	(48)
Gao *et al*, 2022	*SHC1*, *AURKA* and *NAPSA*	WGCNA, Cox regression analysis, RT-qPCR	SHC1/AURKA: Upregulated; NAPSA: Downregulated	Enhanced radioresistance	(53)
Pustovalova *et al*, 2023	*ATRNL1*, *CA2*, *CNR1*, *FAM189A1*, *GFRA1*, *RASGRP1* and *RGL3*	RNA sequencing	Upregulation	Lower RT efficacy	(50)
Pustovalova *et al*, 2023	*ADGRF1*, *EPHA7*, *LOX*, *LY6G5C*, *NSUN7*, *SLC22A31*, *SNAI2*, *TNFRSF11B* and *ZNF233*	RNA sequencing	Downregulation	Lower RT efficacy	(50)
Pustovalova *et al*, 2023	*CXCL8*, *IL6* and *TGFB2*	RNA sequencing	Upregulation	Lower RT efficacy	(50)
Pustovalova *et al*, 2023	*NRG1*	RNA sequencing	Downregulation	Lower RT efficacy	(50)
Xu *et al*, 2024	*KRT6A*	GEO2R analysis, Kaplan-Meier survival analysis, qPCR, CCK-8 and cell migration assays	Upregulation	Improved OS	(56)
Chen *et al*, 2025	*APOBEC3B*, *DOCK4*, *IER5L*, *LBH*, *LY6K*, *RERG*, *RMDN2* and *TSPAN2*	WGCNA + DEGs LASSO regression, Random survival forest and multivariate Cox regression	Dysregulation	Prediction of prognosis	(49)
Chen *et al*, 2025	*LBH*	*In vitro* validation	Upregulation	Increased radiosensitivity	(49)
Li *et al*, 2025	*ADAMTS3*, *FADS2* and *RTBDN*	RNA sequencing, DEGs analysis	Dysregulation	Prediction of RT outcome	(55)
Li *et al*, 2025	*FADS2*	RNA sequencing, DEGs analysis + *in vitro* validation	Upregulation	Higher radioresistance	(55)

CCK-8, Cell Counting Kit-8; DEG, differentially expressed gene; OS, overall survival; PFS, progression-free survival; RT-qPCR, reverse transcription-quantitative PCR; RT, radiotherapy; WGCNA, weighted gene co-expression network analysis; NR, not reported.

A549 cells compared with the more radiosensitive NCI-H446 line, reinforcing their potential as biomarkers for treatment stratification and combination therapy development (54).

Emerging evidence has also implicated metabolic pathways in modulating RT response. A recent study identified a three-gene lactate metabolism-related risk model (*ADAMTS3*, *FADS2* and *RTBDN*) capable of distinguishing radiosensitive from radioresistant patients, with *FADS2* emerging as a key predictive biomarker. Further mechanistic validation linked this signature to DNA repair modulation and tumor immune response, highlighting lactate metabolism as a promising source of novel biomarkers for precision RT (55).

Finally, keratin 6A (*KRT6A*) expression has been associated with improved OS in patients with LC. Functional experiments have shown that *KRT6A* downregulation reduces proliferation and invasion *in vitro*, suggesting that while *KRT6A* may not directly mediate radioresistance, it could serve as a valuable prognostic marker and potential therapeutic target (56).

Despite these advances, translating radiosensitivity gene-expression signatures from preclinical models to clinical practice remains challenging. Cell lines offer a controlled platform for dissecting radiation response independent of clinical confounders, but they lack microenvironmental, stromal and immune interactions, realistic dose-rate effects and intratumoral heterogeneity. Therefore, validation in physiologically relevant models, such as patient-derived xenografts (PDXs), organoids and prospective clinical cohorts, remains essential before these signatures can be reliably implemented in routine clinical decision-making.

Circulating tumor DNA (ctDNA). ctDNA represents a fraction of cell-free DNA released from tumor cells through necrosis, apoptosis, macrophage-mediated clearance or direct secretion (57). LC exhibits marked intratumoral heterogeneity, both spatially, across primary and metastatic sites and temporally, as molecular characteristics evolve during disease progression. Consequently, liquid biopsy offers a practical and minimally invasive strategy for quantifying ctDNA levels in the bloodstream, providing a dynamic snapshot of tumor burden, stage and treatment response.

This approach holds particular value in radiation oncology, as ctDNA measurement enables real-time monitoring of therapeutic efficacy, detection of resistance emergence and surveillance of disease progression during RT (58). Changes in ctDNA kinetics during treatment closely mirror the cytotoxic effects of ionizing radiation and tumor cell death, positioning ctDNA as a promising biomarker of radiation response (59).

Recent evidence has demonstrated that a decline in ctDNA levels during RT in patients with NSCLC is associated with a reduction in tumor burden and may serve as an early predictor of treatment response, even in cases where complete ctDNA clearance is not achieved (35). These findings support the integration of ctDNA monitoring into clinical practice to guide adaptive RT strategies and enable timely treatment modifications.

Proteomic biomarkers. Using a proteomics approach combining two-dimensional electrophoresis and matrix-assisted laser desorption ionization-time of flight mass spectrometry, Yun *et al* (60) identified several proteins with notably increased expression in radioresistant H460 cancer stem cell (CSC) lines compared with radiosensitive parental H460 cells. These candidate biomarkers included fatty acid synthase, vimentin, glucose-regulated protein 78, plasminogen activator inhibitor-2, nodal modulator 2, kinesin light chain 4 and procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (PLOD3) (Fig. 2). Their upregulation may serve as predictive indicators of RT response, enable pre-treatment identification of radioresistant tumors and represent promising therapeutic targets to overcome resistance. Table IV summarizes proteomic biomarkers identified in multiple studies that are associated with radioresistance in lung cancer.

CSCs, a subpopulation within tumors with self-renewal, differentiation and tumor-initiating capacity, have been shown to be intrinsically more resistant to both irradiation and systemic therapies than non-CSCs (61). This property may contribute to post-RT recurrence and metastasis, highlighting the need for innovative RT strategies aimed specifically at eradicating CSCs (60).

Hypoxia-related biomarkers. Hypoxia is a well-recognized driver of radioresistance. In NSCLC, serial measurements of serum hypoxia-inducible factor 1α (HIF-1α) before and after chemoradiotherapy have revealed notable decreases during treatment, associated with tumor shrinkage. These findings suggest that HIF-1α could serve as a dynamic biomarker for monitoring tumor response (62).

Angiopoietin-like 4 protein (ANGPTL4) has also been implicated in NSCLC radioresistance. Under hypoxic conditions, ANGPTL4 upregulation suppresses ferroptosis by upregulating antioxidant proteins, thereby enhancing tumor cell survival after irradiation. Furthermore, ANGPTL4 is enriched in exosomes secreted by hypoxic tumor cells, which transfer radioresistance signals to neighboring normoxic cells through indirect ferroptosis inhibition. These findings position ANGPTL4 as both a predictive biomarker and a potential therapeutic target to enhance radiosensitivity (63).

Other hypoxia-induced molecules include osteopontin (OPN) and heat shock protein 70 (HSP70). Elevated pre-RT plasma OPN levels have been associated with poor OS, whereas post-treatment reductions in HSP70 within 4-6 weeks are associated with tumor regression. Notably, patients with relatively high post-RT HSP70 levels demonstrate improved treatment responses, probably reflecting an immunostimulatory effect of extracellular HSP70 released from dying tumor cells (64). Together, these results support the combined assessment of OPN and HSP70 as predictive and dynamic biomarkers of treatment response.

Additional hypoxia-related biomarkers, VEGF and carbonic anhydrase IX, have been linked to poor OS, with their expression associated with adverse clinical features such as weight loss, reduced lung function and larger tumor size. These markers may help identify highly hypoxic, aggressive tumors, supporting their integration into multi-center validation studies and personalized treatment planning (65).

Plasma and cytokine biomarkers. Incorporation of blood-based biomarkers into prognostic models has been shown to notably improve survival prediction in NSCLC. Among a panel of eight analytes, serum CEA and IL-6 have been identified as independent predictors of poor outcomes (66). Similarly, cytokine profiling of patients undergoing chemoradiotherapy has revealed that elevated post-treatment levels of IL-13, TNF-α, IL-8, CXCL5 and CXCL3, together with reduced levels of intercellular adhesion molecule 1 (ICAM-1), IFN-γ and soluble programmed cell death ligand 1 (PD-L1), are associated with improved objective response. Combinations such as IL-8 with ICAM-1 or soluble PD-L1 with TNF-α may further enhance predictive accuracy and IL-8/ICAM-1 levels

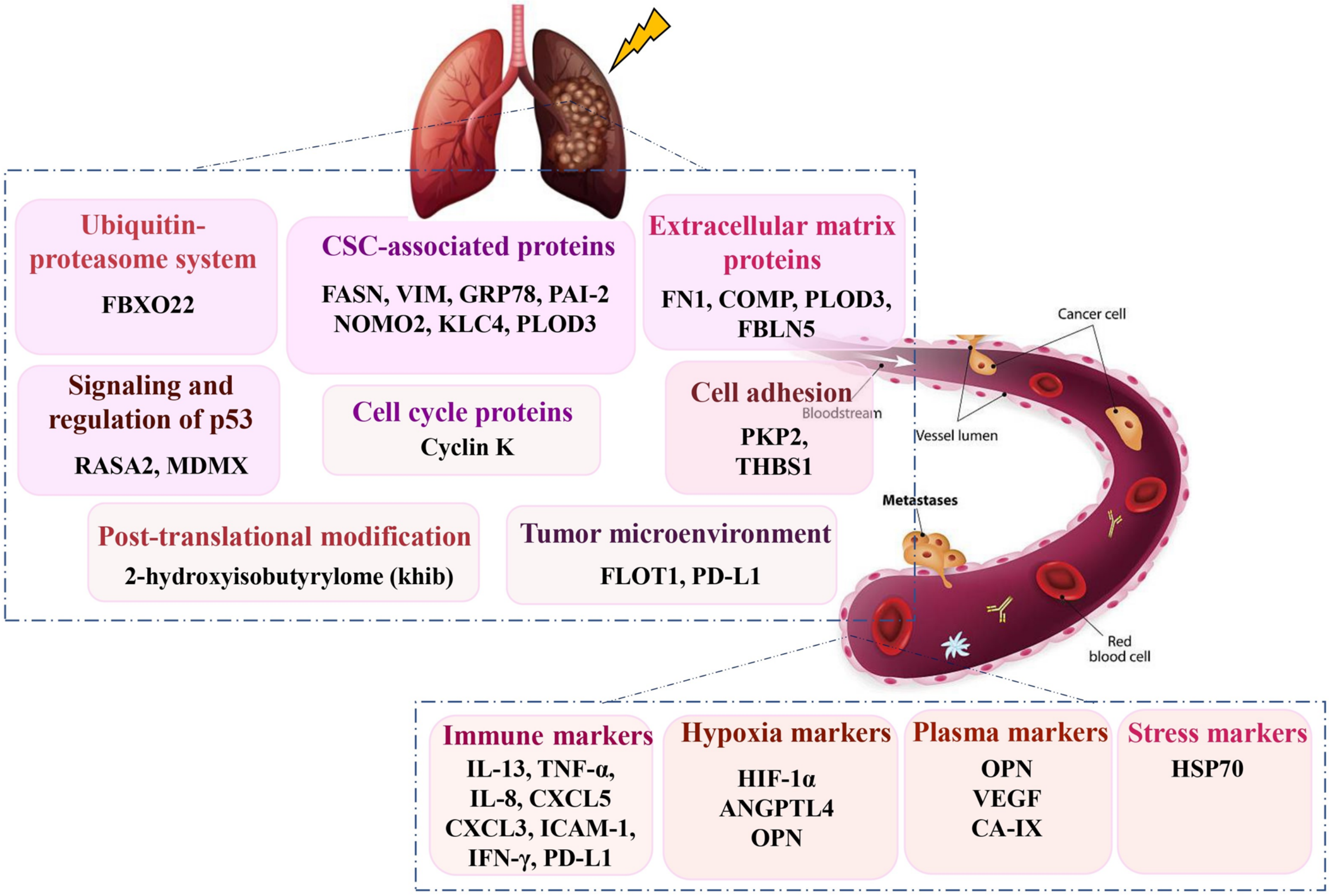

Figure 2. Summary of proteomic biomarkers associated with lung cancer radioresistance. FBXO22, F-box protein 22; CSC, cancer stem cell; FASN, fatty acid synthase; VIM, vimentin; GRP78, glucose-regulated protein 78; PAI-2, plasminogen activator inhibitor-2; NOMO2, nodal modulator 2; KLC4, kinesin light chain 4; PLOD3, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3; FN1, fibronectin 1; COMP, cartilage oligomeric matrix protein; FBLN5, fibulin-5; RASA2, Ras p21 protein activator; PKP2, plakophilin 2; THBS1, thrombospondin 1; FLOT1, flotillin-1; PD-L1, programmed cell death ligand 1; HIF-1α, hypoxia-inducible factor 1α; ANGPTL4, angiopoietin-like 4 protein; OPN, osteopontin; CA IX, carbonic anhydrase IX; HSP, heat shock protein.

are associated with PFS (67). These findings highlight plasma cytokines as valuable tools for stratifying patients and optimizing RT strategies.

Proteomic and molecular biomarkers. Proteomic profiling of H460 LC cells pre- and post-irradiation has identified fibronectin 1 and thrombospondin 1 as key contributors to radioresistance and poor outcomes (68). Yao *et al* (69) demonstrated that cyclin K may stabilize β-catenin and promote G_2/M checkpoint activation, thereby enabling DNA repair and survival. By contrast, silencing cyclin K increased radiosensitivity *in vitro* and *in vivo* by abrogating this checkpoint, suggesting cyclin K as both a predictive biomarker and therapeutic target.

Cheng *et al* (70) reported that PRMT1-mediated methylation of plakophilin 2 (PKP2) can recruit ubiquitin-specific protease 7, which stabilizes DNA ligase 4 and enhances non-homologous end-joining repair. Pharmacological inhibition of PRMT1 has been shown to disrupt this axis and sensitize NSCLC cells to RT, supporting PKP2 as a novel predictive biomarker and therapeutic target. Similarly, knockdown of PLOD3 triggers ER stress and caspase-3-mediated apoptosis, thereby enhancing radiosensitivity (71).

Ras p21 protein activator, a Ras GTPase-activating protein, has been demonstrated to promote p53 phosphorylation and proteasomal degradation, leading to reduced apoptosis and increased radioresistance. Its expression is associated with poor RT response, underscoring its value as a biomarker and target for therapeutic intervention (72). Upregulation of F-box protein 22 (FBXO22) activates the FOXM1/Rad51 axis to promote homologous recombination repair, whereas its inhibition, particularly with the small molecule deguelin, restores radiosensitivity (73). Conversely, high expression of MDMX has been shown to be associated with enhanced response to RT and longer OS, implicating it as a favorable biomarker in LUAD and LSCC (74).

Cartilage oligomeric matrix protein, an extracellular matrix protein, promotes NSCLC proliferation and invasion following irradiation, indicating its potential as a biomarker for identifying patients likely to benefit from intensified treatment or combination therapy (75).

Tumor microenvironment (TME)-associated biomarkers. The TME serves a critical role in RT response. High stromal expression of fibulin-5 (FBLN5) in cancer-associated fibroblasts (CAFs) activates Src-STAT3 signaling, inhibits ferroptosis and promotes post-irradiation tumor survival. Clinically, elevated FBLN5 levels are associated with poor RT outcomes, supporting its role as a predictive biomarker (76). Similarly, flotillin-1 (FLOT1) upregulates PD-L1 and promotes epithelial-mesenchymal transition (EMT), enhancing cell

Table IV. Proteomic profiles associated with RT response in lung cancer.

First author/s, year	Marker	Method of detection	Cohort (size)	Regulation	Clinical significance	Pathways	Result	(Refs.)
Dehing-Oberije *et al*, 2011	CEA, IL-6	ELISA	NSCLC (n=158)	Upregulation	Lower probability of survival	CEA: Cell adhesion; IL-6: JAK/STAT signaling	Radioresistance	(66)
Ostheimer *et al*, 2014	VEGF, CA-IX	ELISA	Advanced NSCLC (n=55)	Upregulation	Poor OS	Hypoxia	Radioresistance	(65)
Ostheimer *et al*, 2014	OPN	ELISA	Advanced NSCLC (n=55)	Upregulation	Poor OS	Hypoxia	Radioresistance	(65)
Yun *et al*, 2016	FASN, VIM, GRP78, PAI-2, NOMO2, KLC4 and PLOD3	2D electrophoresis, MALDI-TOF mass spectrometry, western blotting	Human H460, A549 and H1299 NSCLC cells	Upregulation	Lower RT response	Regulation of cell death, cancer and stem cell proliferation, differentiation and morphogenesis	Radioresistance	(60)
Ostheimer *et al*, 2017	OPN	ELISA	Advanced NSCLC at M0 (n=44)	Upregulation	Poor OS	Hypoxia	Radioresistance	(64)
Ostheimer *et al*, 2017	HSP70	ELISA	Advanced NSCLC at M0 (n=44)	Upregulation	Poor OS	Tumor protection from stress-induced programmed cell death	Radioresistance	(64)
Afsar and Uysal, 2019	HIF-1α	ELISA	Locally advanced NSCLC (n=80)	Downregulation	Improved RT response	Response of cells to hypoxia	Radiosensitivity	(62)
Baek *et al*, 2019	PLOD3	Western blotting	H460 and A549 cancer cell lines	Upregulation	Poor 5-year survival	Regulating apoptosis	Radioresistance	(71)
Yao *et al*, 2020	Cyclin K	IHC	A549 and H460 cell lines	Upregulation	Poor OS	Tumorigenesis via positive modulation of β-catenin/cyclin D1	Radioresistance	(69)
Sui *et al*, 2021	IL-8	U-PLEX assay	Locally advanced inoperable/unresectable NSCLC (n=31)	Upregulation	Improved response after RT	Regulating angiogenesis	Radiosensitivity	(67)
Sui *et al*, 2021	TNF-α	U-PLEX assay	Locally advanced inoperable/unresectable NSCLC (n=31)	Upregulation	Improved response after RT	Antitumor immune response	Radiosensitivity	(67)
Sui *et al*, 2021	PD-L1, ICAM-1	Luminex assay	Locally advanced inoperable/unresectable NSCLC (n=31)	Downregulation	Improved response After RT	T-cell dysfunction, inflammatory process and tumor metastasis	Radiosensitivity	(67)

Table IV. Continued.

First author/s, year	Marker	Method of detection	Cohort (size)	Regulation	Clinical significance	Pathways	Result	(Refs.)
Cheng *et al*, 2021	PKP2	CRISPR/Cas9 library screen	A549 cells	Upregulation	Poor OS and postprogression survival	PKP2 positively regulates β-catenin stability to induce transcription of LIG4, involved in non-homologous end-joining-mediated repair	Radioresistance	(70)
Zhang *et al*, 2022	ANGPTL4	RT-qPCR, western blotting	*In vivo* and *in vitro* experiments	Upregulation	Worse radio-therapeutic outcome	Inhibition of ferroptosis	Radioresistance	(63)
Li *et al*, 2022	FN1, THBS1	Tandem Mass Tagbased quantitative proteomic analysis	H460 cells	Upregulation	Low survival rates migration	Adhesion and	Radioresistance	(68)
Wang *et al*, 2023	FLOT1	Western blotting	A549 and H520 cell lines	Upregulation	Higher radioresistance	Positive regulation of PD-L1	Radioresistance	(77)
Li *et al*, 2024	RASA2	IHC	Stage IIIa and IVa LUAD (n=205)	Upregulation	Poor response to RT	Regulating apoptosis	Radioresistance	(72)
Chen *et al*, 2024	FBXO22	Western blotting	Lung cancer cell lines	Upregulation	Higher radioresistance	Activation of the FOXM1/Rad51 axis and DNA repair	Radioresistance	(73)
Ji *et al*, 2025	MDMX	IHC	LUAD and LSCC tissues	Upregulation	Increased radiosensitivity	Regulation of P53-mediated autophagy	Radiosensitivity	(74)
Reno *et al*, 2025	COMP	RT-qPCR, proteomics (LC-MS/MS)	A549, NCI-H1975 and NCI-H1437 cell lines	Upregulation	Increased proliferation, invasion, migration and viability after irradiation	Oxidative phosphorylation and drug resistance	Radioresistance	(75)
Zhang *et al*, 2025	FBLN5	Spatial, transcriptomics single-cell RNA-sequencing	NSCLC (n=105), *in vitro* CAF models	Upregulation	Poor response to RT	pathways Src-STAT3 pathway, suppression of ferroptosis	Radioresistance	(76)

ANGPTL4, angiopoietin-like 4 protein; CAF, cancer-associated fibroblast; CA-IX, carbonic anhydrase IX; COMP, cartilage oligomeric matrix protein; FASN, fatty acid synthase; FBLN5, fibulin-5; FLOT1, flotillin-1; FBXO22, F-box protein 22; FN1, Fibronectin 1; GRP78, glucose-regulated protein 78; HIF-1α, hypoxia-inducible factor 1α; HSP70, heat shock protein 70; ICAM-1, intercellular adhesion molecule 1; IHC, immunohistochemistry; KLC4, kinesin light chain 4; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LIG4, DNA ligase 4; LUAD, lung adenocarcinoma; MALDI-TOF, matrix-assisted laser desorption ionization-time of flight; NOMO2, nodal modulator 2; NSCLC, non-small cell lung cancer; OPN, osteopontin; OS, overall survival; PAI-2, activator inhibitor-2; PD-L1, programmed cell death ligand 1; PKP2, plakophilin 2; PLOD3, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3; RASA2, Ras p21 protein activator; RT, radiotherapy; RT-qPCR, reverse transcription-quantitative PCR; THBS1, thrombospondin 1; VIM, vimentin.

motility and DNA damage tolerance. FLOT1 inhibition sensitizes cells to RT, activates the STING pathway and enhances CD8$^+$ T-cell recruitment through chemokine secretion (77).

In a large retrospective study of 328 patients with stage III NSCLC treated with concurrent chemoradiation and durvalumab, high PD-L1 expression (TPS ≥90%) and elevated tumor mutational burden were associated with prolonged disease control, supporting their use for patient stratification prior to RT and immunotherapy (78).

Multi-omics and inflammatory biomarkers. A prior multi-omics analysis comparing parental A549 cells and their radioresistant derivatives has revealed >900 differentially expressed genes and ~700 proteins, including >30,000 sites of lysine 2-hydroxyisobutyrylation (khib). Notably, EGFR was shown to be both upregulated and highly khib-modified in radioresistant cells, suggesting that khib-regulated EGFR may represent a novel mechanism of radioresistance and a therapeutic vulnerability (79). Fig. 2 provides a comprehensive summary of proteomic biomarkers associated with lung cancer radioresistance.

Finally, systemic inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, derived NLR and systemic immune-inflammation index have shown prognostic and predictive value in locally advanced NSCLC. Low values of these markers have been shown to be independently associated with improved PFS, OS and locoregional control and to be linked to increased radiosensitivity (80). These metrics are inexpensive, widely accessible and may complement molecular biomarkers in patient stratification and treatment planning.

Epigenetic biomarkers. Epigenetic regulation serves a pivotal role in shaping the response to irradiation in LC. Radiosensitive and radioresistant NSCLC cell lines display distinct methylation signatures, underscoring the involvement of epigenetic mechanisms in radioresponse. Genome-wide analysis of CpG methylation patterns has revealed that several key regulators of radiosensitivity are epigenetically controlled by CpG methylation (81). Notably, the presence of an unmethylated promoter in the insulin-like growth factor-binding protein-3 gene has been associated with poor RT response and unfavorable clinical outcomes in patients receiving adjuvant chemoradiotherapy (82). Furthermore, radiation-induced changes in DNA methylation vary in a tissue-specific and dose-dependent manner, highlighting the complexity of epigenetic modulation in RT response (83).

(miRNAs/miRs) as biomarkers of RT response. miRNAs are short (~22 nucleotides) non-coding RNAs that post-transcriptionally regulate gene expression by binding to complementary sequences on target mRNAs (84). Their notable stability in tissues, plasma and other biofluids makes them attractive candidates for minimally invasive biomarkers (85). Numerous differentially expressed miRNAs have been implicated in LC radiosensitivity (Fig. 3).

For example, miR-214 is upregulated in radioresistant NSCLC cells, where it enhances radioresistance and inhibits RT-induced apoptosis (86). Similarly, miR-410 promotes EMT and radioresistance by augmenting DNA damage repair capacity, suggesting its potential as a therapeutic target (87). Serum levels of miR-130a, miR-191 and miR-25 have been shown to be increased following 2-4 Gy irradiation in patients with NSCLC, and are associated with heightened invasiveness of A549 cells *in vitro* and in xenograft models, thus supporting their potential role as biomarkers of RT-induced metastasis (88). Elevated exosomal miR-96 has been associated with vascular invasion and poor OS, indicating its prognostic value for radioresistant NSCLC (20).

Plasma miRNA signatures also hold promise for stratifying patients. Hsa-miR-302e, hsa-miR-98-5p, hsa-miR-613 and hsa-miR-495-3p have all been linked to radiosensitivity in NSCLC (89), while miR-18a-5p levels have been associated with treatment response and could be used to categorize patients into radiosensitive or radioresistant subgroups (90). Zhang and Hu (91) identified miR-148a as a candidate biomarker of radioresistance, whereas miR-26b-5p was found to be notably downregulated in LUAD tissues, serum and radioresistant cell lines. Upregulation of miR-26b-5p increases radiosensitivity in both parental LUAD cells and radiation-resistant LUAD cells (A549R) by promoting DNA damage and apoptosis, partly through direct inhibition of activating transcription factor-2. Notably, exosomal transfer of miR-26b-5p from A549 cells to resistant cells may restore radiosensitivity, underscoring its value as a non-invasive predictive marker (92).

Serum exosomal miR-378 has emerged as a clinically relevant biomarker; its levels are notably decreased after RT and high baseline expression is associated with poor OS, making it an independent prognostic factor (93). Similarly, miR-148a, a tumor suppressor, is downregulated in radioresistant patients but upregulated following RT in radiosensitive ones. Its upregulation inhibits proliferation, migration and invasion by targeting SOS2, thereby improving radiosensitivity and serving as a potential marker for both prediction and monitoring of RT response (91).

Long non-coding RNAs (lncRNAs) and radioresistance. LncRNAs (>200 nucleotides) have emerged as key regulators of carcinogenesis, immune modulation, apoptosis and therapy response (94). Several lncRNAs have been implicated in RT outcomes in NSCLC, making them promising prognostic and predictive markers (Fig. 3).

LINC01224 expression has been associated with RT response, suggesting its potential as a prognostic indicator (95). Song *et al* (96) identified a four-lncRNA signature (CASC19, LINC01977, LINC02471 and MAGI2-AS3) that was shown to be associated with radiological response and could accurately predict patient prognosis.

HNF1A-AS1, a lncRNA upregulated in NSCLC, contributes to advanced disease stages and radioresistance by sponging miR-92a-3p, which results in MAP2K4 upregulation and JNK pathway activation. Silencing HNF1A-AS1 has been reported to reduce proliferation, induce apoptosis and notably sensitize NSCLC cells to RT, positioning the HNF1A-AS1/miR-92a-3p/MAP2K4 axis as a potential biomarker and therapeutic target (97).

Notably, male patients with NSCLC exhibit a unique pattern of radiosensitivity linked to Y-chromosome loss (LOY) and dysregulation of Y-linked lncRNAs. Linc-SPRY3-2/3/4 transcripts are dose-dependently induced after irradiation in radiosensitive cell lines but absent in LOY radioresistant lines. These transcripts interact with IGF2BP3 to destabilize

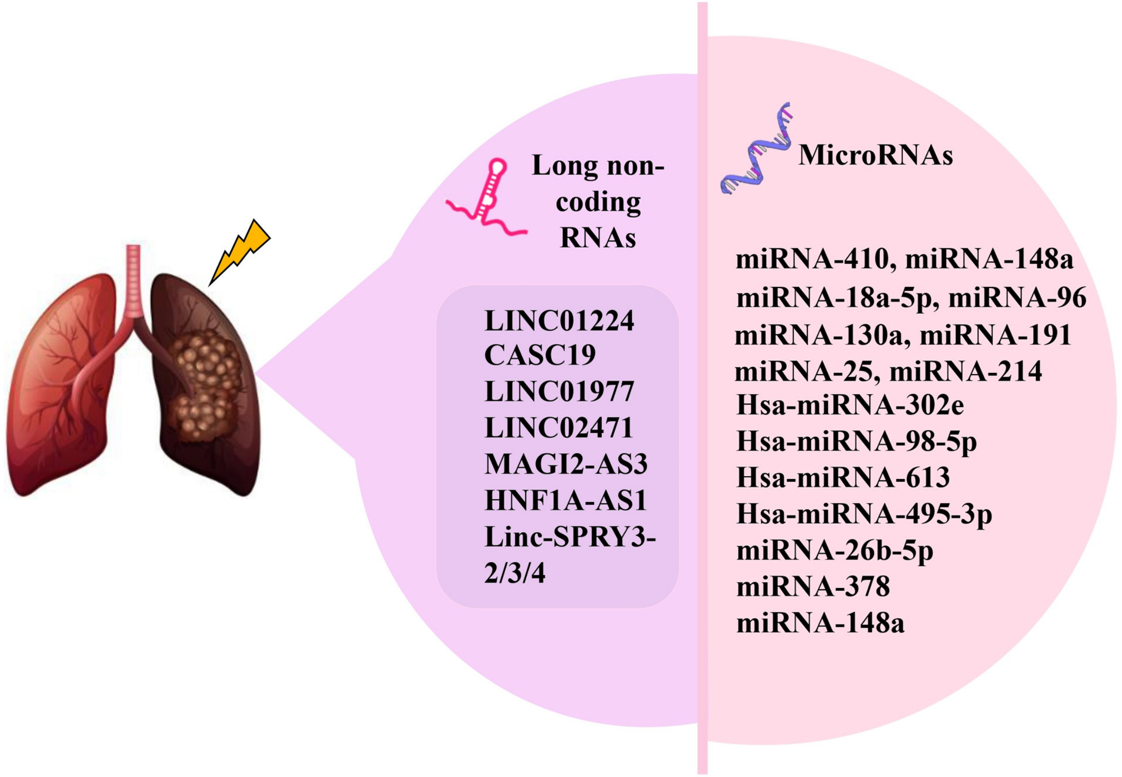

Figure 3. Summary of miRNA and long non-coding RNA biomarkers associated with lung cancer radioresistance. miRNA/miR, microRNA.

oncogenic mRNAs, including HMGA2 and c-MYC, thereby promoting apoptosis. Loss of linc-SPRY3-2/3/4 or LOY is associated with poorer OS, suggesting a male-specific biomarker signature for predicting radiosensitivity (98).

Fig. 4 provides an integrated overview of the key genetic, epigenetic, circulating and proteomic biomarkers that have been implicated in LC radioresistance, highlighting their potential roles in patient stratification and personalized RT strategies. The figure provides an overview of the main molecular biomarkers implicated in LC radioresistance and their associated pathways. It includes genetic alterations (such as *EGFR*, *KRAS*, *TP53*, *KEAP1* and *NFE2L2*), DNA repair factors (Cyclin K, PRMT1 and FBXO22), non-coding RNAs (miRNAs and lncRNAs) and CSC markers. Contributors to the TME, such as hypoxia, stromal CAFs and key signaling pathways (HIF-1α, VEGF, PD-L1) are also shown. Collectively, these biomarkers and pathways interact to promote tumor survival, treatment resistance and disease progression, underscoring potential targets for improving RT outcomes.

3. Limitations and perspectives

Over the past decade, cancer management has evolved considerably at both conceptual and methodological levels, propelled by advances in molecular biology and technological innovation. Modern RT techniques have achieved marked improvements in tumor targeting and sparing of adjacent healthy tissue; however, these technological refinements alone are insufficient to overcome the biological complexity underlying tumor resistance to ionizing radiation. A major unmet need is the ability to predict which patients will derive durable benefit from RT and which are probably to experience treatment failure due to intrinsic or acquired radioresistance.

At present, no predictive biomarkers for RT response in LC have been validated for routine clinical use within an evidence-based framework. Most reported candidates have emerged from *in vitro* studies or small-scale clinical cohorts, often with limited statistical power and population-specific applicability. To translate these findings into clinical practice, several key challenges must be addressed (Fig. 5): i) Lack of biomarker convergence and validation. Most studies focus on individual biomarkers or small panels of molecular targets, frequently chosen based on the specific research interests or preliminary data of a group. Consequently, few biomarkers have been independently validated across multiple studies, limiting reproducibility and comparability. This highlights the need for collaborative, multicenter efforts and integrative approaches to evaluate promising candidates in larger, diverse patient populations using standardized protocols.

ii) Biological complexity of radioresistance. Radioresistance arises from the interplay of multiple pathways, including DNA damage repair, oxidative stress responses, hypoxia signaling, tumor-stroma interactions and immune modulation. A single biomarker is unlikely to capture this complexity or accurately predict RT outcomes. Multivariable models integrating several molecular and cellular determinants are likely to offer greater predictive accuracy and clinical utility, facilitating improved patient selection and personalized treatment strategies.

iii) Integration of multi-omics and artificial intelligence (AI). Incorporating multidimensional data, including genomic, transcriptomic, epigenetic, proteomic, imaging and clinical

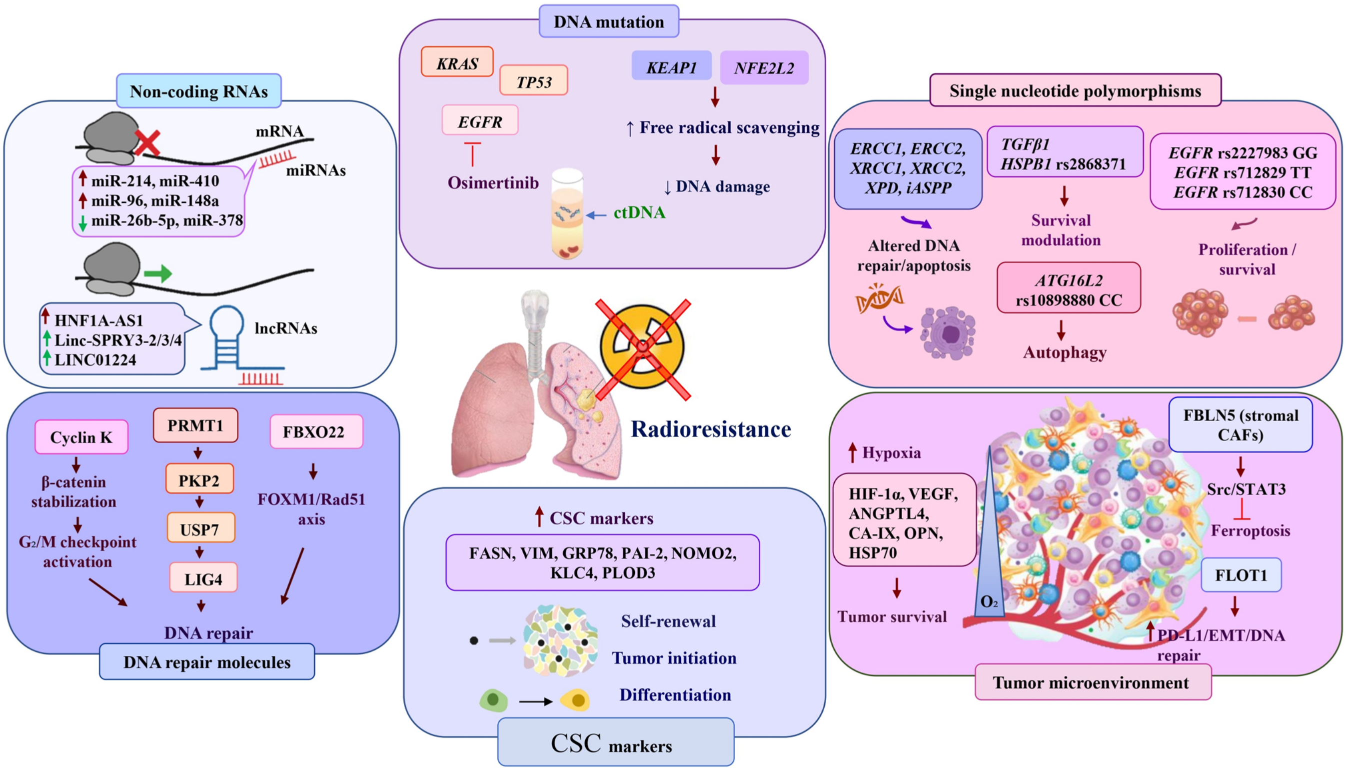

Figure 4. Key molecular biomarkers and associated pathways contributing to radioresistance in lung cancer. CAFs, cancer-associated fibroblasts; CSC, cancer stem cell; ctDNA, circulating tumor DNA; EMT, epithelial-mesenchymal transition; lncRNA, long non-coding RNA; miRNA/miR, microRNA.

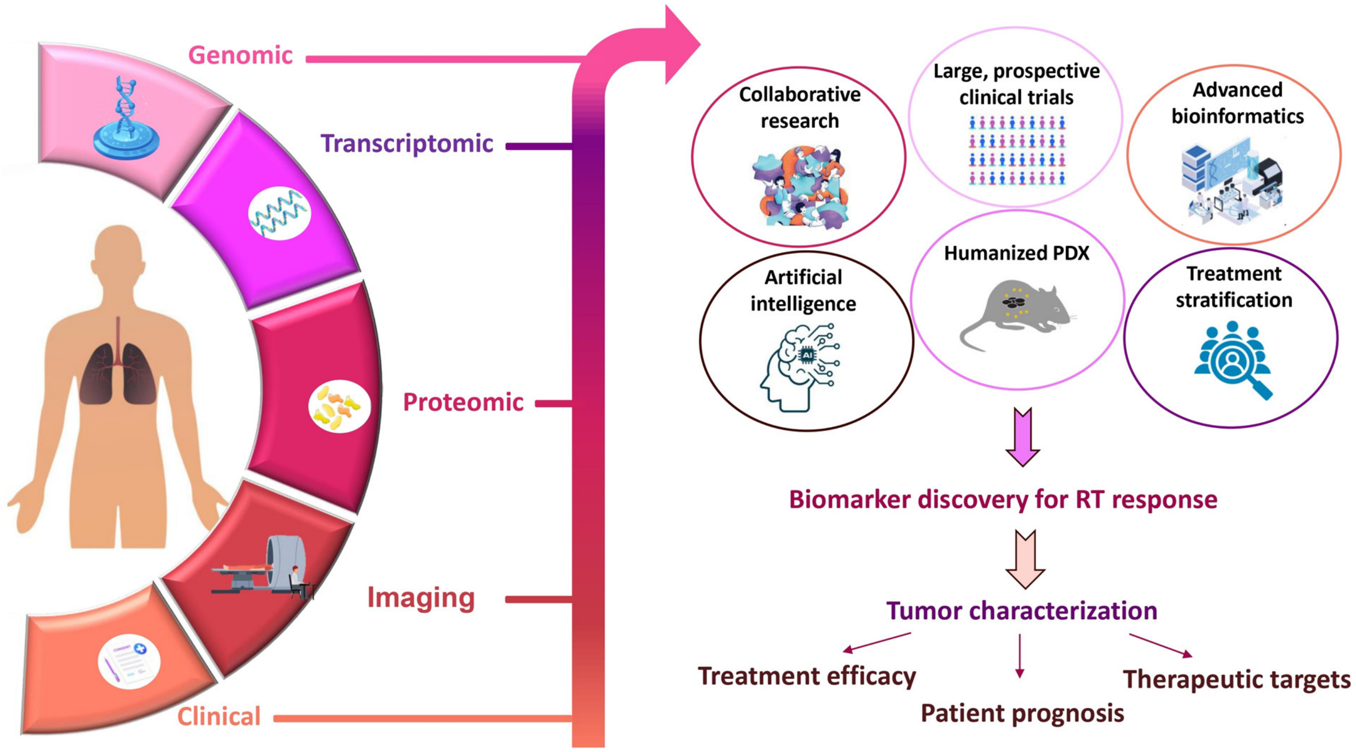

Figure 5. Strategies and prospects to advance personalized RT. PDX, patient-derived xenograft; RT, radiotherapy.

information, offers the opportunity to build robust predictive models that reflect the full biological heterogeneity of lung tumors. Machine learning and AI-driven analytical pipelines can extract complex patterns from these data, enabling high-performance prediction models that inform adaptive RT and precision oncology approaches.

iv) Need for representative preclinical models. Mechanistic insights and biomarker discovery rely heavily on preclinical models. PDXs, especially those generated from radioresistant tumors, are valuable tools for predicting RT efficacy and conducting 'co-clinical' studies. However, current models have limitations, including replacement of human stroma with murine stroma and the requirement for immunodeficient hosts, which prevents assessment of immune-mediated effects. Development of humanized PDX models that retain tumor-immune interactions will be critical for advancing translational research (99).

v) Influence of concurrent treatments. A number of biomarker studies are confounded by concomitant chemotherapy, particularly platinum-based regimens, making it difficult to distinguish radiosensitivity-specific effects from combined chemoradiotherapy responses. Stratifying patients by treatment regimen or conducting analyses in RT-only cohorts will be necessary to identify these contributions and avoid false-positive associations.

vi) Variability in experimental design and methodology. Differences in sample collection, preparation, analytical techniques and statistical approaches notably limit reproducibility and generalizability across studies. Establishing standardized operating procedures and consensus criteria for biomarker studies is imperative. Future research should prioritize large, prospective trials with pre-specified biomarker endpoints, multicenter validation and integration of bioinformatics pipelines capable of harmonizing multi-omics and clinical data.

In summary, while the discovery of biomarkers of radioresistance in LC remains in an early phase, the convergence of molecular biology, high-throughput technologies and AI-driven analytics is promising. Overcoming current methodological and translational challenges will be critical to accelerating the development and clinical implementation of robust, reproducible biomarkers. Ultimately, such efforts will enable precision RT strategies that optimize therapeutic efficacy, minimize toxicity and improve survival outcomes for patients with LC.

4. Conclusion

Cancer cell resistance to ionizing radiation remains a critical obstacle in the management of LC. This resistance is highly patient-dependent, either arising from intrinsic genetic predispositions or developing as an adaptive response during treatment, ultimately contributing to therapeutic failure. Innate and acquired radioresistance both engage multiple molecular pathways and reveal a broad spectrum of candidate biomarkers that could guide precision medicine approaches. Incorporating such biomarkers into clinical workflows would enable radiation oncologists to identify patients most likely to benefit from RT, tailor radiation dose and fractionation schemes and integrate radiosensitizing agents to enhance therapeutic efficacy.

Although substantial progress has been made in characterizing biomarkers of radioresistance, their translation into routine clinical practice is still limited. Independent validation in large, prospective cohorts and robust meta-analyses are urgently needed to confirm their predictive and prognostic utility.

Advances in multi-omics technologies have greatly expanded the understanding of the genomic, transcriptomic and epigenetic alterations that underlie radioresistance, paving the way for individualized treatment strategies. Ongoing research continues to explore tumor heterogeneity and the integration of biomarker data into predictive models, with the ultimate goal of enabling truly personalized, adaptive RT that improves survival outcomes and quality of life for patients with LC.

Acknowledgements

Not applicable.

Funding

The publication has been prepared within the framework of the project funded by Mohammed VI Polytechnic University and OCP Foundation (TNI 2024 program). The authors would like to thank The Centre National pour la Recherche Scientifique et Technique (CNRST) of Morocco for funding Attouahri Fatima Zohra's 'PhD-ASociate Scholarship-PASS'.

Availability of data and materials

Not applicable.

Authors' contributions

FZA initially began the review and wrote the first draft of the manuscript with the help of IC, MAb, AL and MEMz. MAt, MRT, MO, MEMa, MK, KEn and KEr reviewed, completed and improved the review according to their respective specialties. Data authentication is not applicable. All authors have approved the final 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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