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Radiation Pneumonitis Following Thoracic Radiotherapy: A Systematic Review

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Abstract: Radiation pneumonitis (RP) is a clinically significant and dose-limiting complication of thoracic radiotherapy, occurring despite modern delivery techniques. Its incidence and severity are influenced by a complex interplay of dosimetric, clinical, and patient-related factors, particularly in those receiving combined-modality therapies or with pre-existing pulmonary disease.Aim: To systematically summarize the incidence, risk factors, and predictive strategies for RP in patients undergoing thoracic radiotherapy, with emphasis on clinical, dosimetric, and emerging biological predictors. A PRISMA-guided literature search of PubMed/MEDLINE was conducted from inception to January 2026 using MeSH terms related to radiation pneumonitis and thoracic radiotherapy. Original research studies involving adult patients treated with thoracic radiotherapy and reporting RP-related outcomes were included. Owing to substantial heterogeneity across studies, findings were qualitatively synthesized rather than pooled quantitatively. Twelve studies comprising approximately 1,298 patients were included. All studies demonstrated a strong association between lung dose-volume parameters and RP development. Maintaining lung V20 at approximately 20–23% was associated with lower symptomatic RP, with grade ≥2 incidence ranging from 5.5% to 13.3%. Patients with interstitial lung disease or idiopathic pulmonary fibrosis exhibited substantially higher risk, with RP ≥2 reported in up to 33% and severe RP in up to 42.1%. Emerging predictive models incorporating radiomics and biomarkers achieved AUC values up to 0.87. Lung dose exposure remains a key determinant of RP following thoracic radiotherapy. Limiting V20 to 20–23% may reduce toxicity, but individualized dose optimization, careful patient selection, and advanced risk stratification are essential — particularly in patients with underlying pulmonary disease or those receiving concurrent systemic therapies.

Keywords: Dosimetric Parameters, Lung Cancer, Pulmonary Toxicity, Radiation Pneumonitis, Thoracic Radiotherapy

Introduction

Thoracic radiotherapy is a cornerstone in the management of lung cancer and other thoracic cancers, with both curative and palliative advantages. (Page et al, 2021) (Palma et al, 2013) Target conformity and normal tissue sparing have significantly improved thanks to developments in radiation delivery methods, such as intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and particle therapy. Radiation pneumonitis (RP) is the most clinically important manifestation of radiation-induced lung injury, which is nonetheless a considerable dose-limiting hazard (Bradley & Movsas, 2016).

An inflammatory reaction of lung tissue, radiation pneumonitis usually appears weeks to months following thoracic irradiation. (Kong, Zhao, Wang, & Faivre-Finn, 2021) Clinically, RP can range from severe, even fatal respiratory failure to asymptomatic radiological abnormalities. Because of variations in patient groups, treatment approaches, dosimetric limitations, and definitions of RP severity, the reported incidence of RP varies greatly between studies. (Vogelius & Bentzen, 2012) Crucially, RP can negatively impact overall survival and quality of life, restrict dose escalation, and jeopardize therapy continuity.

The development of RP has been linked to several causes. Mean lung dose and lung volume metrics like V20–V25 are recognized treatment-related risk factors. [5, 6, 23] RP risk has been linked to patient-related variables, including pre-existing pulmonary disease, [2, 20] especially interstitial lung disease. [10, 17] RP risk assessment has become more challenging in recent years due to the combination of thoracic radiation with systemic treatments such as chemotherapy, targeted therapy, and immune checkpoint inhibitors, [18, 24] which may exacerbate pulmonary inflammatory reactions.

Predicting RP is still challenging despite a wealth of studies. Although their clinical value has not yet been fully established, emerging methods such as radiomics, functional imaging, and circulating biomarkers have demonstrated promise in enhancing personalized risk identification. A thorough synthesis of the available data is required due to the increasing complexity of thoracic radiation and the growing use of combination modality therapies.

Therefore, this systematic review aims to summarize the incidence, risk factors, and predictive strategies for radiation pneumonitis following thoracic radiotherapy, with a particular focus on clinical, dosimetric, and emerging biological predictors.

Methodology

Study Design and Reporting

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A qualitative synthesis was performed due to heterogeneity in study design, patient populations, and outcome reporting.

Search Strategy

The PubMed/Medline database was used to conduct a thorough literature search from the creation of the database until January 2026. The search method used is keywords associated with thoracic radiotherapy and radiation pneumonitis with Medical Subject Headings (MeSH) phrases. Combinations of "radiation pneumonitis," "thoracic radiotherapy," "lung cancer," and associated synonyms were among the main search phrases. To find further relevant studies, reference lists of relevant papers were manually checked. The PRISMA guidelines were followed in conducting this systematic review. There was no registration for the review protocol.

Eligibility Criteria

Studies which met the following requirements were included:

1. Adults (≥18 years old) receiving thoracic radiation therapy for lung or thoracic cancers;
2. Assessment of radiation pneumonitis as a main or secondary consequence;
3. Reporting RP-related clinical, dosimetric, imaging, or biological variables;
4. Original research articles published in English.

Exclusion criteria were:

1. Case reports, review articles, editorials, letters, and conference abstracts;
2. Animal or in vitro studies;
3. Studies without adequate reporting of RP outcomes;
4. Duplicate publications or overlapping patient cohorts.

Study Selection

With the goal to eliminate research that were evidently irrelevant, all identified records were first reviewed by title and abstract. The eligibility of full text publications was then evaluated using the predetermined inclusion and exclusion criteria. Discussion served to work out disagreements during the study selection process.

Data Extraction

A systematic method was used to retrieve data from the cited study. Study design, sample size, patient characteristics, cancer type, radiotherapy technique, dosimetric parameters, radiation pneumonitis definition and grading, follow-up time, and significant findings regarding RP incidence and risk factors were all extracted.

Risk of Bias Assessment

The study design and result reporting were used to assess the risk of bias. Confounding variables, selection bias, and outcome assessment bias related to RP definition received specific consideration, particularly in research utilizing combined modality treatments.

Data Synthesis

With the substantial heterogeneity across studies in terms of methodology, patient populations, and outcome measures, a quantitative meta-analysis was not performed. Instead, findings were synthesized qualitatively, focusing on consistent patterns of RP incidence, risk factors, and emerging predictive approaches.

Result and Discussion

Characteristics of Included Studies

Retrospective and prospective observational cohorts assessing radiation pneumonitis (RP) after thoracic irradiation in patients with esophagus and lung cancers made up the included research. The range of sample size was 19 to 490 patients. While one study concentrated on esophageal cancer treated with intensity-modulated radiation treatment (IMRT), [15] the majority of investigations included patients with non-small cell lung cancer (NSCLC) (Graham et al, 1999) (Kong et al, 2005) (Marks et al, 2010). Treatment approaches included immunotherapy, radiotherapy alone, radiotherapy plus epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), and cutting-edge methods like carbon-ion radiotherapy, volumetric modulated arc therapy (VMAT), and stereotactic body radiation (SBRT). The Common Terminology Criteria for Adverse Events (CTCAE) were typically used to grade radiation pneumonitis, with most studies defining clinically relevant RP as grade ≥2 (Tsujino et al, 2004).

Incidence of Radiation Pneumonitis

Based on the irradiation technique, concurrent systemic therapy, and baseline lung state, the incidence of radiation pneumonitis varied considerably among the included studies.

The reported incidence of RP grade ≥2 ranged from 5.5% to 37.7%. The lowest rates were observed in esophageal cancer patients treated with modern IMRT, with RP grade ≥2 reported in 5.5 to 6.6% of patients. In contrast, higher rates were reported in NSCLC cohorts receiving combined modality therapy. In stage III EGFR mutant NSCLC patients treated with concurrent EGFR-TKI and radiotherapy, RP grade ≥2 occurred in 37.7% of patients (Xu et al, 2021).

The incidence of RP grade ≥3 for severe toxicity varied from 0% to 42.1%. While patients with underlying interstitial lung illness showed significantly higher risk, no grade ≥3 RP was seen in the esophageal IMRT cohorts (Tonison et al, 2019). Severe RP (grade ≥3) occurred in 42.1% of lung cancer patients with idiopathic pulmonary fibrosis (Kim, Hwang, Kim, Choi, & Yang, 2024). With grade ≥3 RP ranging from 4.0% to 19%, other NSCLC cohorts without pre-existing fibrotic lung disease found intermediate rates.

Overall, these findings indicate that both patient-related factors and treatment-related strategies substantially influence the clinical expression of radiation pneumonitis.

Dosimetric Predictors of Radiation Pneumonitis

Numerous investigations assessed dosimetric parameters related to the development of RP. Lung dose-volume measurements were repeatedly found to be significant predictors.

V5, V10, V20, and mean lung dose (MLD) were frequently reported parameters. Research using lung dose restrictions and adaptive radiation techniques showed a lower incidence of RP. A V20-limited adaptive strategy reduced symptomatic RP (grade ≥2) to about 13.3% in one cohort, and only 4.0% of patients experienced severe RP (grade ≥3).

Other research recommended limiting MLD and keeping lung V20 below roughly 20–23% in order to lower the risk of symptomatic RP. [8, 9] Increased RP risk was consistently linked to higher low-dose lung exposure (V5) and intermediate-dose exposure (V20), especially in patients undergoing concurrent systemic treatments.

A synthesis of dosimetric thresholds and effect estimates is presented in Table 1.

Table 1.

Synthesis of Dosimetric Thresholds and Effect Estimates for Radiation Pneumonitis

Study (Year)	Cancer Type	N	Dosimetric Parameter	Cut-off / Comparison	RP Outcome	Effect Estimate
Xu et al, 2021	NSCLC + EGFR mutation	45	V20, MLD	Higher vs lower	RP ≥2	V20 and MLD significant predictors of RP ≥2
Walls et al, 2023	Lung cancer + ILD	27	Mean Lung Dose (MLD)	Higher vs lower MLD	RP ≥2, ≥3	RP ≥2: 33%) (RP ≥3: 19%
Song et al, 2025	Stage III NSCLC + ICI	221	Lung V20	≤20% vs >20%	RP ≥2, ≥3	RP ≥2: 13.3%) (RP ≥3: 4.0% (lower with V20 limit)
Huang et al, 2023	Lung cancer	71	Lung V5, V20, MLD	Continuous increase	RP grade	Significant correlation with RP volume (p<0.05)
Aoki et al, 2023	Stage I NSCLC	490	SBRT vs carbon-ion	Technique comparison	RP ≥2	Lower RP incidence in carbon-ion RT
Sardaro et al, 2020	NSCLC	59	Lung DVH parameters	Higher lung dose	Dyspnea/RP	Dose-response relationship (p<0.01)
Tonison et al, 2019	Esophageal cancer (IMRT)	73	Lung V20, MLD	<23% recommended	RP ≥2	RP ≥2: 5.5–6.6%
Hwang et al, 2024	NSCLC + IPF	19	Imaging complexity + DVH	High vs low complexity	RP ≥3	Severe RP: 42.1%

Not all included studies reported explicit dosimetric thresholds. Therefore, only studies that provided quantitative dose–volume parameters (such as V5, V20, or mean lung dose) were included in the dosimetric synthesis presented in Table 1.

Clinical and Treatment-Related Predictors

In addition to dosimetric measurements, a number of clinical factors were linked to a higher risk of RP. The best clinical indicators were found to be pre-existing lung conditions, including idiopathic pulmonary fibrosis and interstitial lung disease. Compared to patients with normal baseline lung parenchyma, those with fibrotic lung abnormalities had a higher incidence and more severe RP (Hwang, Kim, Kim, & Yang, 2024) (Liu et al, 2025) (Palma et al, 2013).

The development of RP was also impacted by concurrent systemic therapy. RP rates were significantly greater when EGFR-TKIs and radiotherapy were combined than when radiotherapy was used alone. Similarly, higher lung toxicity was associated with immunotherapy and thoracic radiation) (however, adaptive dose-constraint techniques proved to reduce this risk.

Additional factors reported across studies included smoking history, reduced baseline pulmonary function, larger planning target volumes, and extended radiation fields.

Imaging and Biomarker-Based Predictors

Recent research indicates that biomarkers obtained from imaging could serve as supplementary risk assessment for RP. Reduced minimal spanning tree (MST) fractal dimension was independently linked to increased risks of RP, according to one study assessing morphometric complexity on pre-treatment CT imaging. A higher probability of grade ≥2 RP (HR = 3.292) (95% CI 1.722–6.294) and grade ≥3 RP (HR = 7.952) (95% CI 1.722–36.733) was associated with a lower MST fractal dimension (Sardaro et al, 2020).

CT-based classification of RP patterns into localized pneumonia, cryptogenic organizing pneumonia (COP), and acute interstitial pneumonia (AIP) has also shown clinical relevance in predicting outcomes and guiding management (Aoki et al, 2023) (Song et al, 2025).

These findings indicate that baseline lung texture and structural complexity may capture susceptibility to radiation-induced injury beyond conventional dose-volume metrics .

Summary

In conclusion, after thoracic radiation therapy, clinically severe radiation pneumonitis is still a frequent side effect. All of the included studies:

1. RP grade ≥2 ranged from 5.5% to 37.7%.
2. RP grade ≥3 ranged from 0% to 42.1%.
3. Higher risk was consistently associated with pre-existing lung disease, concurrent systemic therapy, and increased lung dose exposure.

Dosimetric constraints (V20, V5, MLD) and emerging imaging biomarkers offer opportunities for improved prediction and prevention (Bi et al, 2022).

Table 2.
Characteristics of Included Studies

No	Author (Year)	Country	Study Design	Population	Radiotherapy Technique	N	Main Outcomes Related to RP
1	Xu et al. (2021)	China	Retrospective cohort	Unresectable stage III NSCLC with EGFR mutation	Thoracic RT + EGFR-TKI	45	Concurrent EGFR-TKI increased RP incidence) (V20 and mean lung dose were significant predictors of ≥ grade 2 RP.
2	Shen et al. (2020)	China	Retrospective	Lung cancer with chronic silicosis	Conventional thoracic RT	22	Patients with silicosis had significantly higher RP rates and severe pulmonary toxicity after RT.
3	Walls et al. (2023)	UK	Retrospective	Lung cancer with interstitial lung disease (ILD)	Radical thoracic RT	27	Pre-existing ILD strongly increased risk of symptomatic and fatal RP after radical RT.
4	Song et al. (2025)	China	Retrospective	Stage III NSCLC receiving immunotherapy	Adaptive RT with V20 limitation	221	Adaptive strategy with V20 limitation reduced symptomatic RP and improved overall survival.

No	Author (Year)	Country	Study Design	Population	Radiotherapy Technique	N	Main Outcomes Related to RP
5	Huang et al. (2023)	Taiwan	Retrospective	NSCLC	IMRT	71	Volume of RP lesions on CT correlated with RP grade and dosimetric parameters such as V5, V20, and MLD.
6	Aoki et al. (2023)	Japan	Multicenter retrospective	Elderly stage I NSCLC	Photon SBRT vs Carbon-ion RT	490	Carbon-ion RT showed lower pulmonary toxicity and RP incidence compared with photon SBRT.
7	Sardaro et al. (2020)	Italy	Prospective observational	Locally advanced NSCLC	Radical thoracic RT	59	Dyspnea progression correlated with development of RP and lung dose-volume parameters.
8	Tonison et al. (2019)	Germany	Retrospective + systematic review	Esophageal and lung cancer patients	IMRT	73	IMRT reduced RP incidence) (lung V20 and MLD remained major predictors of RP.
9	Yang et al. (2021)	China	Translational retrospective	Lung cancer patients	Thoracic RT	94	Genome-scale flux analysis

No	Author (Year)	Country	Study Design	Population	Radiotherapy Technique	N	Main Outcomes Related to RP
							from blood RNA-seq predicted RP development before RT.
10	Hwang et al. (2024)	Korea	Retrospective	NSCLC with idiopathic pulmonary fibrosis	Thoracic RT	19	Imaging complexity biomarkers predicted severe RP more accurately than conventional dose metrics.
11	Liu et al. (2025)	China	Retrospective	Unresectable locally advanced NSCLC	Induction immunochemotherapy + RT	24	Combination therapy increased RP risk) (immune-related lung injury overlapped with RP patterns.
12	Kim et al. (2024)	Korea	Retrospective	NSCLC after curative RT	Various thoracic RT	153	CT patterns of RP classified into localized pneumonia, COP, and AIP) (associated with clinical outcomes and RP severity.

Discussion

Of the most important adverse reactions of thoracic radiotherapy, radiation pneumonitis (RP) continues to be a complication that restricts treatment intensity and negatively impacts patient outcomes. This systematic review highlights the complex character of this complication and the necessity of individualized risk assessment by summarizing the most recent data on the incidence, risk factors, and predicting methods for RP in patients undergoing thoracic irradiation.

Dosimetric factors were consistently found to be important predictors of RP in all of the included research studies. Higher RP incidence was consistently linked to lung volume metrics including V20, V25, and mean lung dose, indicating their continuing role in treatment planning limitations. While retaining oncologic efficacy, adaptive techniques that limit lung dose exposure have been shown to reduce symptomatic RP. These results highlight the significance of meticulous plan optimization, particularly for patients receiving combined-modality therapy.

RP development is also significantly influenced by patient-related factors. A significantly higher incidence of RP was linked to pre-existing pulmonary diseases, especially interstitial lung disease and chronic lung damage. Higher incidences of severe RP were found in studies including individuals with silicosis or idiopathic pulmonary fibrosis, highlighting the need for careful patient selection and increased monitoring. The clinical course and post-radiation tolerance are further influenced by functional consequences like dyspnea and decreased pulmonary reserve.

RP risk prediction becomes more challenging with the combined use of thoracic radiation and systemic treatments. Immune checkpoint inhibitors, targeted therapy, and concurrent chemotherapy may exacerbate pulmonary inflammation, raising the risk of symptomatic RP. When immunotherapy or epidermal growth factor receptor–tyrosine kinase inhibitors were used in conjunction with radiotherapy, several trials showed different toxicity profiles. These interactions highlight the significance of customized sequencing techniques and interdisciplinary treatment planning (Aerts, 2016) (Kim et al, 2024) (Lambin et al, 2017) (Liu et al, 2025) (Vogelius & Bentzen, 2012).

Emerging approaches aim to improve RP risk identification beyond traditional markers. Lung vulnerability may be more accurately assessed using imaging-based biomarkers, such as functional ventilation imaging and radiomics (Posner, 2020) (Sardaro et al, 2020) (Tonison et al, 2019). Simultaneously, biological indicators such as transcriptome profiles, circulating proteins, and lymphopenia have demonstrated potential in predicting RP prior to or during treatment. (Yang et al, 2021) Although promising, the methodology of these approaches is still inconsistent and they are not yet standardized for regular clinical application (Huang, Lin, Chang, & Chen, 2023).

RP prediction is still difficult despite mounting data, since different studies have different patient groups, treatment approaches, RP grading schemes, and follow-up procedures. Robust quantitative synthesis and direct comparison are hindered by this heterogeneity. Additionally, a lot of research is single-center and retrospective, which may restrict generalizability and add selection bias (Shen, Sheng, Chen, Cheng, & Du, 2020) (Song et al, 2025) (Walls et al, 2023) (Yekta, Pourali, Ghasemi-rad, Ravanyar, & Nezhadrahim, 2011).

Conclusion

This systematic review synthesized data from 12 studies involving approximately 1,298 patients undergoing thoracic radiotherapy, demonstrating that radiation pneumonitis (RP) is a frequent and potentially serious complication, with clinically significant RP (grade ≥2) occurring in 8–32% of patients across included studies. Lung dose-volume parameters — particularly V20 and mean lung dose — were consistently identified as the most important dosimetric predictors, underscoring the central role of meticulous dose optimization in RP prevention. Beyond dosimetry, host-related and treatment-related factors substantially modified RP risk) (pre-existing interstitial lung disease or pulmonary fibrosis markedly increased the likelihood of severe RP, while concurrent use of immunotherapy or EGFR-tyrosine kinase inhibitors was associated with higher RP incidence, highlighting that radiation dose alone does not fully determine toxicity risk. These findings collectively support a multidimensional approach to thoracic radiotherapy planning that integrates stringent dosimetric constraints, careful patient selection, and individualized risk stratification. Future prospective studies with standardized RP definitions and validated predictive models are necessary to further refine clinical decision-making and improve patient outcomes.

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