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Risk Factors for Radiation Pneumonitis in Patients Receiving Thoracic VMAT and Immune Checkpoint Inhibitors

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Abstract: *We systematically evaluated risk factors for radiation pneumonitis (RP) in patients receiving combined thoracic volumetric modulated arc therapy (VMAT) and immune checkpoint inhibitors (ICIs), aiming to identify clinically safe radiation dose thresholds in the modern immunotherapy era. Patients treated with thoracic VMAT and ICIs between August 2020 and June 2025 were retrospectively analyzed. To ensure dosimetric consistency, all lung volumes were recontoured by a single radiation oncologist according to the Radiation Therapy Oncology Group (RTOG) 1106 protocol. Clinical and dosimetric variables—including mean lung dose (MLD) and lung volumes receiving ≥ 5 Gy (V5) through≥ 40 Gy (V40)—were evaluated using univariate and multivariate logistic regression analyses. Optimal dose thresholds were determined using receiver operating characteristic (ROC) curve analysis and the Youden index. Of 93 patients, the overall incidence of RP was 60.2%, with grade 3 events occurring in 14.1% of patients. A history of chronic obstructive pulmonary disease (COPD) was the only significant clinical risk factor, associated with a 75.6% incidence of RP ($p = 0.004$). Multivariate analysis identified MLD, V5, V20, V30, and V40 as independent predictors of RP (all $p < 0.05$). Integrating COPD history with dosimetric parameters significantly improved predictive accuracy (AUC > 0.7) compared with single-variable models. Based on the Youden index, recommended safety thresholds were MLD < 10.7 Gy, V5 < 35.0%, V20 < 21.8%, V30 < 6.7%, and V40 < 4.6%. Combined VMAT-ICI therapy shows high RP incidence, requiring stricter dosimetric constraints and risk stratification incorporating COPD history with optimized dose-volume parameters for safety.*

Keywords: *Radiation therapy; Immunotherapy; Lung cancer; Radiation pneumonitis; Risk factors; Volumetric modulated arc therapy; Chronic obstructive pulmonary disease*

1. Introduction

Immune checkpoint inhibitors (ICIs), particularly those targeting the programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1) axis, have revolutionized the treatment of metastatic and locally advanced malignancies, including lung cancer. Building on this progress, emerging evidence suggests that combining ICIs with thoracic radiotherapy (TRT) can synergistically enhance antitumor immunity by inducing immunogenic cell death and increasing T-cell infiltration[1].

However, ICIs can induce immune-related adverse events (irAEs), with ICI-associated pneumonitis representing a potentially fatal complication in non-small cell lung cancer (NSCLC)[2,3]. The combination of ICIs with TRT may further exacerbate the risk of radiation pneumonitis (RP), posing a significant clinical challenge[4-7]. Traditionally, dosimetric parameters such as lung volume receiving ≥5 Gy (V5)[8] and ≥20 Gy (V20)[9, 10], and mean lung dose (MLD)[9] have been reliable predictors of RP. However, these benchmarks were established before the advent of ICI therapy and were primarily derived from studies using three-dimensional conformal radiation therapy (3D-CRT) or static intensity-modulated radiation therapy (IMRT). In recent years, volumetric modulated arc therapy (VMAT) has been widely adopted because of its shorter treatment time compared with conventional IMRT and its ability to deliver highly conformal doses while minimizing irradiation of normal organs[11]. However, no study has specifically investigated RP outcomes in patients receiving combined VMAT and ICIs. Consequently, the predictive value of traditional dosimetric parameters in this modern treatment context remains unclear.

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Several studies have examined RP risk factors in combined ICI-TRT therapy, yet substantial inconsistencies persist, particularly regarding dose-volume parameters. Wang et al. identified tumor location, ICI-radiotherapy interval, and multiple pulmonary dose metrics–including MLD and V10 through V40–as independent predictors of symptomatic pneumonitis[12]. A multi-institutional analysis by Bi et al. confirmed that tumor location and MLD were independently associated with RP[13]. In contrast, a retrospective study by Inoue et al. focused on durvalumab consolidation therapy and found no significant associations between pneumonitis incidence and V20 or other clinical variables such as age, smoking history, or lesion location[14]. These discrepancies may arise from patient- heterogeneity and variations in radiotherapy delivery. Despite standardized protocols, interobserver and interinstitutional variability in lung contouring remains substantial. Additionally, differences in radiation fractionation–particularly conventional versus hypofractionated regimens–create distinct dose-time patterns that further complicate the identification of universal RP risk factors.

We systematically evaluated RP risk factors in patients receiving combined thoracic VMAT and ICIs and identified clinically safe radiation dose thresholds. To ensure data consistency and diagnostic accuracy, RP was defined using unified criteria and adjudicated by a multidisciplinary team. All lung volumes were recontoured by a single radiation oncologist according to the Radiation Therapy Oncology Group (RTOG) 1106 protocol to minimize interobserver variability in dosimetric analysis.

2. Materials and Methods

2.1 Patients and Treatments

We retrospectively reviewed patients treated with thoracic VMAT and ICIs at our institution between August 2020 and June 2025. Inclusion criteria were: (1) pathologically or cytologically confirmed primary or metastatic lung cancer; (2) receipt of at least one cycle of ICIs either before TRT or as consolidation therapy after TRT; and (3) an interval between TRT and ICI treatment not exceeding 1 month. Exclusion criteria included a history of autoimmune disease, prior TRT, treatment with hypofractionated radiotherapy or stereotactic body radiotherapy (SBRT), or missing follow-up data or post-TRT CT scans.

Medical, radiological, and radiotherapy records were reviewed to collect clinical variables, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, cancer type, history of chronic obstructive pulmonary disease (COPD), and prior treatments. Sequential treatment was defined as an interval exceeding 7 days between TRT and ICI administration. To ensure dosimetric consistency, a single radiation oncologist recontoured all lung volumes on planning CT images according to the RTOG 1106 protocol. Dosimetric parameters–including planning target volume (PTV), MLD, V5, V20, V30, and V40–were extracted from the MOSAIQ system. Lung dosimetric parameters were calculated after excluding the gross tumor volume (GTV) from the total lung volume.

This study was approved by the Ethics Committee of Meishan City People's Hospital. The requirement for informed consent was waived due to the retrospective design, and all analysis was conducted in accordance with the Declaration of Helsinki.

2.2 Pneumonitis Assessment

RP was diagnosed by a multidisciplinary team comprising oncologists, radiologists, and pulmonologists. Diagnosis was based on CT findings demonstrating diffuse lung abnormalities or fibrosis confined to, or predominantly within, the radiation field, in conjunction with compatible clinical symptoms. Patients with alternative causes, including infection, disease progression, or checkpoint inhibitor-induced pneumonitis, were excluded. RP severity was graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Grade 1 RP was defined as radiographic evidence without documented therapeutic intervention. Grade 2 RP was established based on medical records, indicating the necessity for symptomatic treatment. Grades 3 and 4 RP were defined by severe cough or dyspnea at rest requiring supplemental oxygen or mechanical ventilation, respectively. Grade 5 RP was defined as RP-related mortality.

2.3 Statistical Analysis

Descriptive statistics were used to summarize patient characteristics, tumor features, and treatment details. Binary logistic regression analyses were conducted to evaluate the associations between clinical

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and dosimetric variables and the risk of RP. To assess potential multicollinearity among the dosimetric parameters (MLD, V5, V20, V30, and V40), Spearman's rank correlation analysis was performed, considering correlation coefficients of > 0.7 as indicative of high collinearity. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability of identified risk factors for RP. The bootstrap method was applied to assess internal validity. The Youden index was used to assess RP risk and determine recommended thresholds. The time interval from the initiation of TRT to RP diagnosis and the cumulative incidence of pneumonitis were estimated using the Kaplan–Meier method and compared using the log-rank test. Patients who did not develop RP were censored at 6 months. All statistical analyses were performed using IBM SPSS Statistics software (v. 27.0; Armonk, NY, USA). All statistical tests were two-tailed, with a significance threshold of $p < 0.05$.

3. Results

3.1 Patients and Treatment

We retrospectively analyzed 93 patients with lung cancer treated with a combination of TRT and ICIs. At the data cutoff on November 17, 2025, the median follow-up duration was 16.0 months (95% CI: 14.458-17.542). At that time, 16 patients (17.2%) had died, 41 (44.1%) remained on ICI therapy, and 52 (55.9%) discontinued treatment. Detailed patient and tumor characteristics are summarized in Table 1. The median patient age was 61 years (interquartile range [IQR: 56–68]). The cohort was predominantly male (89.2%), with 96.8% exhibiting an ECOG performance status of 0 or 1 and 72.0% having a smoking history. Histopathological diagnoses included primary lung cancer (92.5%) and metastatic lung cancer (7.5%). Forty patients (43.0 %) had a history of COPD. With respect to immunotherapy, 90.3% of patients received PD-1 inhibitors and 9.7% received PD-L1 inhibitors, with a median of seven cycles (IQR: 3–13). Seventy-six patients (81.7%) received ICI treatment before TRT, and 64 (68.8%) received ICI consolidation after TRT. Additionally, 35.5% underwent concurrent chemoradiotherapy, and 22.6% received concurrent TRT and ICIs with a median interval of 25 days (IQR: 8.5–37). Radiotherapy was administered at dose levels ranging from 1.8 to 3.0 Gy per fraction, with the majority (n=59) receiving 2.0 Gy per fraction. Dosimetric parameters (Table 2) included a median EQD2 of 56.0 Gy (IQR: 49.6–60.0), a median MLD of 9.4 Gy (IQR: 7.3–11.9), and median V5, V20, V30, and V40 values of 32.7% (IQR: 26.8–42.8), 15.8% (IQR: 12.1–21.9), 12.3% (IQR: 8.4–15.5), and 8.6% (IQR:5.5–11.9), respectively. The median PTV was 239.2 cc (IQR: 128.3–335.9).

Table 1. Patient and tumor characteristics.

Characteristic	No. (%) (N=93)
Median age, years (IQR)	61 (56-68)
Sex	
Female	10 (10.8)
Male	83 (89.2)
ECOG PS	
0-1	90 (96.8)
≥2	3 (3.2)
Smoking history	
No	26 (28.0)
Yes	67 (72.0)
Cancer type	
Primary lung cancer	86 (92.5)
Metastatic lung cancer	7 (7.5)
History of COPD	
No	53 (57.0)
Yes	40 (43.0)
ICI type	
PD-L1 inhibitor	9 (9.7)
PD-1 inhibitor	84 (90.3)
Median cycles of ICI (IQR)	7 (3-13)
Tumor location	
Peripheral	25 (26.9)
Central	68 (73.1)

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Median cycles of ICIs before TRT (IQR)	3 (2-5)
Interval between TRT and ICI, days (IQR)	25 (8.5-37)
Antecedent ICI therapy	
No	17 (18.3)
Yes	76 (81.7)
ICI consolidation	
No	29 (31.2)
Yes	64 (68.8)
Concurrent chemoradiotherapy	
No	60 (64.5)
Yes	33 (35.5)
Concurrent ICI	
No	72 (77.4)
Yes	21 (22.6)

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ICI: Immune checkpoint inhibitor; PD-L1: Programmed cell death ligand 1; PD-1, programmed cell death protein 1; TRT, thoracic radiation therapy; COPD, chronic obstructive pulmonary disease. Concurrent treatment was defined as an interval of less than 7 days between TRT and ICIs administration.

Table 2. Thoracic radiotherapy characteristics.

Characteristic	No. (%) (N=93)
Median radiation EQD2, Gy (IQR)	56 (49.6-60)
Median dose/fraction, Gy (IQR)	2.0 (2.0-2.0)
MLD, Gy Median (IQR)	9.4 (7.3-11.9)
V5, % Median (IQR)	32.7 (26.8-42.8)
V20, % Median (IQR)	15.8 (12.1-21.9)
V30, % Median (IQR)	12.3 (8.4-15.5)
V40, % Median (IQR)	8.6 (5.5-11.9)
Median PTV, cc (IQR)	239.2 (128.3-335.9)

IQR, interquartile range; EQD2: Equivalent Dose in 2 Gy/f; MLD, mean lung dose; V5, volume receiving > 5 Gy; V20, volume receiving > 20 Gy; V30, volume receiving > 30 Gy; V40, volume receiving > 40 Gy; PTV, planning target volume.

3.2 Incidence and Prognosis of Radiation Pneumonitis

At the final follow-up, the overall incidence of RP of any grade was 60.2%. Grade 1 RP occurred in 33 patients (35.5%), grade 2 in 10 (10.8%), grade 3 in 6 (6.5%), grade 4 in 5 (5.4%), and grade 5 in 2 (2.2%) patients. Notably, RP incidence was markedly higher among patients with baseline COPD, affecting 31 of 40 individuals in this subgroup (77.5%). The median time to RP onset was 2.8 months (95% CI: 2.20–3.34) following TRT initiation. Clinical outcomes showed that 96.4% (54/56) of patients with RP achieved recovery or clinical stability. However, two patients with a history of COPD in the sequential treatment group developed refractory pneumonitis.

3.3 Risk Factors for Radiation Pneumonitis

Univariate analysis of clinical and treatment-related factors (Table 3) identified a history of COPD as a significant risk factor for RP. Other variables–including age, sex, ECOG performance status, smoking history, cancer type, ICI type and number of cycles, and the timing or sequence of ICIs relative to TRT–were not significantly associated with RP (all $p > 0.05$). Regarding dosimetric factors (Table 4), MLD, V5, V20, V30, and V40 were significantly associated with RP in univariate analyses (all $p < 0.05$), whereas equivalent dose in 2 Gy per fraction (EQD2) and planning target volume (PTV) were not ($p > 0.05$). Spearman's correlation analysis revealed strong intercorrelations among these dosimetric parameters, with correlation coefficients ranging from 0.558 to 0.960 (all $p < 0.001$; Table 5). To avoid multicollinearity, each significant dosimetric parameter was entered individually into multivariate logistic regression models adjusted for COPD history. MLD, V5, V20, V30, and V40 were independent predictors of RP.

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Table 3. Patient and tumor characteristics correlated with radiation pneumonitis.

Characteristic	*p*	OR	95% CI
Age (continuous)	0.946	0.998	0.950-1.049
Sex, n (%)			
Female		[Reference]	
Male	0.488	1.594	0.427-5.942
ECOG PS, n (%)			
0-1		[Reference]	
≥2	0.817	1.333	0.117-15.255
Smoking history, n (%)			
No		[Reference]	
Yes	0.435	1.440	0.576-3.600
Cancer type, n (%)			
Lung	0.533	0.583	0.107-3.176
lung metastasis		[Reference]	
History of COPD, n (%)			
No		[Reference]	
Yes	0.004	3.858	1.541-9.655
ICI type, n (%)			
PD-L1 inhibitor		[Reference]	
PD-1 inhibitor	0.098	0.167	0.020-1.393
Cycles of ICI, (continuous)	0.796	1.007	0.957-1.059
Cycles of ICIs before TRT (continuous)	0.709	0.980	0.879-1.092
Interval between TRT and ICI, days (continuous)	0.715	1.003	0.989-1.016
Concurrent systemic therapy			
No		[Reference]	
Yes	0.291	0.638	0.276-1.470
Antecedent ICI therapy, n (%)			
No		[Reference]	
Yes	0.499	1.441	0.500-4.153
ICI consolidation, n (%)			
No		[Reference]	
Yes	0.806	0.893	0.363-2.199
Concurrent chemoradiotherapy, n (%)			
No		[Reference]	
Yes	0.206	0.572	0.241-1.358
Concurrent ICI			
No		[Reference]	
Yes	0.184	0.514	0.192-1.372

OR odds ratio, CI confidence interval, ECOG: Eastern Cooperative Oncology Group, PS: performance status, COPD: chronic obstructive pulmonary disease, ICI: Immune checkpoint inhibitors, PD-L1: Programmed cell death ligand 1, PD-1: programmed cell death protein 1, TRT: thoracic radiation therapy. Concurrent treatment was defined by an interval of less than 7 days between TRT and ICIs.

Table 4. Thoracic radiotherapy characteristics correlated with radiation pneumonitis.

Characteristic	Univariate analysis		Multivariate analysis	
	p	OR (95% CI)	*p*	OR (95% CI)
MLD	0.007	1.002 (1.001-1.003)	0.017	1.002 (1.000-1.003)
V5	0.025	1.049 (1.006-1.094)	0.047	1.047 (1.001-1.095)
V20	0.011	1.093 (1.020-1.171)	0.030	1.084 (1.008-1.166)
V30	0.004	1.133 (1.040-1.234)	0.010	1.126 (1.029-1.231)
V40	0.006	1.148 (1.040- 1.266)	0.010	1.144 (1.032-1.267)
EQD2	0.069	1.048 (0.996-1.102)		
PTV	0.210	1.002 (0.999-1.004)		

OR, odds ratio; CI, confidence interval, EQD2: Equivalent dose in 2 Gy/f; MLD, mean lung dose; V5, volume receiving > 5 Gy; V20, volume receiving > 20 Gy; V30, volume receiving > 30 Gy; V40, volume receiving > 40 Gy; PTV, planning target volume.

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Table 5. Spearman's correlation coefficients between the dosimetric parameters.

Variable	MLD	V5	V20	V30	V40
MLD	1.000	**0.874**	**0.960**	**0.929**	**0.852**
V5	<0.001	1.000	**0.809**	**0.683**	**0.558**
V20	<0.001	<0.001	1.000	**0.938**	**0.797**
V30	<0.001	<0.001	<0.001	1.000	**0.931**
V40	<0.001	<0.001	<0.001	<0.001	1.000

Notes: Values in the upper right triangle (bold) represent Spearman's rank correlation coefficients. Values in the lower left triangle are the corresponding two-tailed *p*-values. All correlations are based on 93 patients. All *p* -values of $p < 0.001$ indicate statistical significance at the 0.01 level (two-tailed). MLD, mean lung dose; V5, volume receiving > 5 Gy; V20, volume receiving > 20 Gy; V30, volume receiving > 30 Gy; V40, volume receiving > 40 Gy.

Predictive performance was evaluated using ROC curve analysis (Figure 1 and Table 6). For individual factors, the area under the curve (AUC) values for MLD, V5, V20, V30, and V40 were 0.659 (95% CI: 0.547–0.772), 0.631 (95% CI: 0.516–0.746), 0.655 (95% CI: 0.542–0.768), 0.662 (95% CI: 0.548–0.775), and 0.661 (95% CI: 0.548–0.774), respectively. The AUC for COPD history was 0.655 (95% CI: 0.542–0.768). Integrating clinical and dosimetric factors significantly improved predictive accuracy; models combining COPD history with MLD (AUC = 0.728, 95% CI: 0.623–0.833), V5 (AUC = 0.715, 95% CI: 0.609–0.821), V20 (AUC = 0.725, 95% CI: 0.620–0.831), V30 (AUC = 0.732, 95% CI: 0.625–0.839), or V40 (AUC = 0.734, 95% CI: 0.627–0.842) outperformed single-variable models. The bootstrap method (1,000 resamples) was applied to evaluate internal validity. Table 7 summarizes the corresponding results.

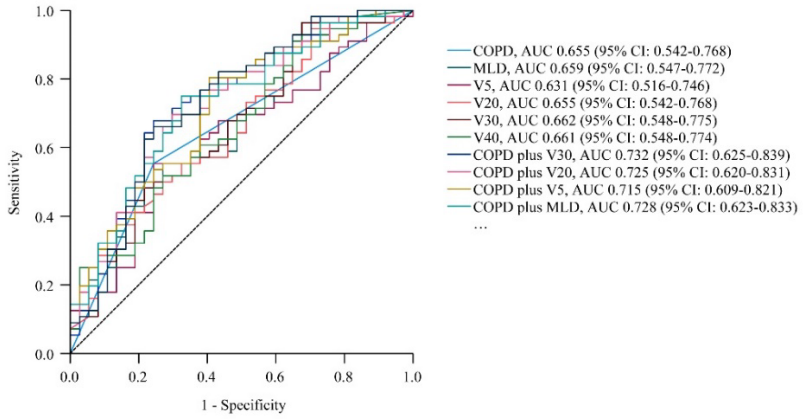

Figure 1. Predictive accuracy of various models. Receiver operating characteristic curves for radiation pneumonitis prediction using chronic obstructive pulmonary disease (COPD) history, mean lung dose (MLD), volume receiving more than 5 Gy (V5), 20 Gy (V20), 30 Gy (V30), and 40 Gy (V40). AUC: area under the curve. Integrating COPD history and dosimetric factors into a unified model significantly improved predictive performance.

Table 6. ROC analysis of radiation pneumonitis.

	AUC	*p*	Accuracy (%)	Cutoff Value	Sensitivity	Specificity
COPD	0.655 (95% CI: 0.542–0.768)	0.012	63.4	-	-	-
MLD	0.659 (95% CI: 0.547–0.772)	0.010	63.4	10.7Gy	0.500	0.784
V5	0.631 (95% CI: 0.516–0.746)	0.033	61.3	35.0%	0.554	0.757
V20	0.655 (95% CI: 0.542–0.768)	0.012	63.4	21.8%	0.357	0.892
V30	0.662 (95% CI: 0.548–0.775)	0.009	64.5	6.7%	0.964	0.324
V40	0.661 (95% CI: 0.548–0.774)	0.009	64.5	4.6%	0.911	0.351
COPD plus MLD	0.728 (95% CI: 0.623–0.833)	<0.001	68.8	-	0.750	0.676
COPD plus V5	0.715 (95% CI: 0.609–0.821)	<0.001	72.0	-	0.804	0.595
COPD plus V20	0.725 (95% CI: 0.620–0.831)	<0.001	68.8	-	0.696	0.703
COPD plus V30	0.732 (95% CI: 0.625–0.839)	<0.001	68.8	-	0.679	0.757
COPD plus V40	0.734 (95% CI: 0.627–0.842)	<0.001	71.0	-	0.661	0.757

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ROC, receiver operating characteristic; COPD: chronic obstructive pulmonary disease; MLD, mean lung dose; V5, volume receiving > 5 Gy; V20, volume receiving > 20 Gy; V30, volume receiving > 30 Gy; V40, volume receiving > 40 Gy.

Table 7. Bootstrap validation of the risk factors.

Model	Variables	B	SE	Wald X^2	*p*	95% CI
COPD+ MLD	COPD	1.248	0.097	0.533	0.008	0.409-2.539
	MLD	0.002	0.000	0.001	0.013	0.000-0.004
COPD+ V5	COPD	1.292	0.092	0.531	0.005	0.461-2.566
	V5	0.046	0.002	0.023	0.026	0.004-0.098
COPD+ V20	COPD	1.236	0.102	0.525	0.009	0.407-2.480
	V20	0.081	0.005	0.042	0.032	0.010-0.176
COPD+ V30	COPD	1.270	0.059	0.530	0.005	0.361-2.426
	V30	0.118	0.007	0.047	0.005	0.036-0.225
COPD+ V40	COPD	1.320	0.097	0.542	0.004	0.483-2.670
	V40	0.134	0.009	0.054	0.004	0.046-0.251

COPD: chronic obstructive pulmonary disease; MLD, mean lung dose; V5, volume receiving > 5 Gy; V20, volume receiving > 20 Gy; V30, volume receiving > 30 Gy; V40, volume receiving > 40 Gy.

Based on the Youden index, optimal thresholds were identified as 10.7 Gy for MLD, 35.0% for V5, 21.8% for V20, 6.7% for V30, and 4.6% for V40. Patients exceeding any threshold had a significantly higher 6-month cumulative incidence of RP (Figure 2). Incidence rates below versus above each threshold were 43.3% vs. 70.7% for MLD (p = 0.007); 42.5% vs. 72.5% for V5 (p = 0.001); 49.5% vs. 73.9% for V20 (p = 0.008); 7.7% vs. 63.6% for V30 (p = 0.001); and 23.0% vs. 63.0% for V40 (p = 0.008).

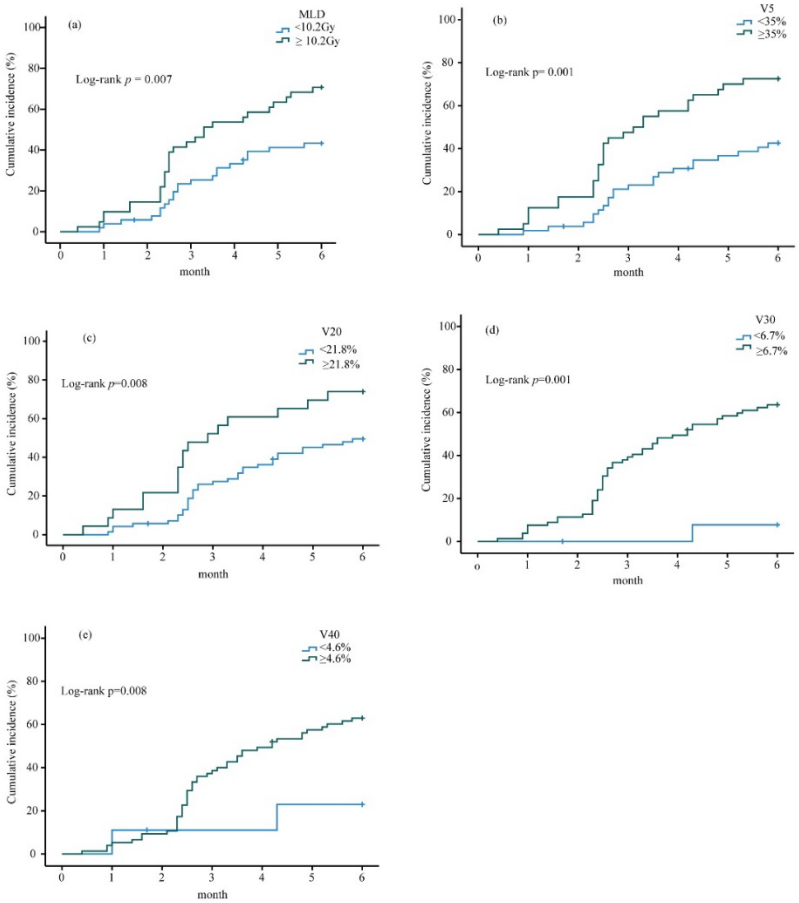

Figure 2. Comparison of 6-month radiation pneumonitis incidence stratified by (a) mean lung dose (MLD); (b) volume receiving more than 5 Gy (V5); (c) volume receiving more than 20 Gy (V20); (d) volume receiving more than 30 Gy (V30); (e) volume receiving more than 40 Gy (V40). Thresholds were determined by receiver operating characteristic curve (ROC) analysis. Radiation pneumonitis incidence below each threshold was significantly lower than above-threshold incidence.

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4. Discussion

The combination of ICIs with TRT has significantly shifted the treatment paradigm for lung cancer[15]; however, the potential for synergistic pulmonary toxicity remains a critical concern. In this study, we observed an overall RP incidence of 60.2%, and both a history of COPD and specific dosimetric parameters (MLD, V5–V40) emerged as independent predictors. These findings underscore that, in the immunotherapy era, RP risk stratification must extend beyond physical dose constraints to incorporate patient-specific clinical vulnerabilities.

Grade 3 or higher RP occurred in 14.1% of patients, consistent with real-world evidence suggesting that TRT-ICI combinations may exacerbate pulmonary toxicity[13, 16-18]. A meta-analysis by Wang et al. reported a pooled pneumonitis incidence of 62% among Asian patients receiving durvalumab consolidation after chemoradiotherapy, comparable to the 63.9% incidence observed in our cohort. In contrast, the PACIFIC trial reported a lower incidence of any-grade pneumonitis (33.9%)[19]. This discrepancy may be attributed to several factors. Subgroup analyses of the PACIFIC trial demonstrated a significantly higher incidence of all-grade pneumonitis among Asian patients compared with Western patients following consolidation immunotherapy after chemoradiotherapy (47.9% vs. 17.6%)[5]. Additionally, the "real-world" nature of our cohort, particularly the high prevalence of COPD (43.0%), likely contributed to the elevated risk. Our analysis identified COPD as the sole significant clinical risk factor, with an RP incidence of 75.6% in affected patients. Furthermore, most patients (90.3%) received PD-1 inhibitors, which have been associated with a higher pneumonitis risk than PD-L1 inhibitors[20]. Despite these risks, the observed incidence of grade ≥3 RP (14%) was comparable to prior reports (4–15%)[6, 13, 16, 18, 21], supporting the clinical feasibility of combined ICI-TRT therapy in Asian populations.

The median onset time of 2.8 months after TRT initiation aligns with the typical clinical window for classic RP[10]. However, differentiating RP from ICI-induced pneumonitis or "synergistic" pneumonitis remains challenging. In our study, a multidisciplinary team approach was instrumental in confirming diagnoses by evaluating the spatial relationship between CT abnormalities and the radiation field.

Among the clinical factors examined, the history of COPD emerged as a significant risk factor for RP. Pathophysiologically, COPD is characterized by chronic airway inflammation and impaired tissue repair mechanisms[22], which may lower the biological threshold for lung injury when combined with ICI-induced T-cell activation[23]. This observation aligns with previous reports[9,24,25], including a retrospective analysis by Liu et al., which identified chronic lung disease as an independent risk factor for RP[9]. Notably, the occurrence of refractory pneumonitis in patients with COPD in our cohort further suggests that a pre-existing pro-inflammatory microenvironment may exacerbate treatment-induced lung damage.

Our analysis identified MLD, V5, V20, V30, and V40 as independent risk factors for RP. These findings are consistent with previous studies on the dose-volume dependency of RP[12,13,17,26,27]. Wang et al.[12] also reported MLD, V20, V30, and V40 as predictors, along with V10. Similarly, Saito et al.[17] identified V20 and MLD as risk factors for symptomatic pneumonitis after immunotherapy and before TRT. Mechanistically, these dosimetric parameters reflect cumulative dose distribution within the functional pulmonary parenchyma, which may predispose patients to radiation-induced alveolar-capillary endothelial disruption and subsequent proinflammatory signaling cascades. This localized damage may be further amplified by ICI-induced lymphocyte differentiation and cytokine-mediated crosstalk between systemic immune activation and sites of radiation injury[28]. However, the moderate predictive power of these individual dosimetric factors (AUC, 0.631–0.662) underscores the limitations of a purely dose-centric approach. By integrating COPD history with dosimetry, predictive accuracy improved significantly (AUC > 0.7), supporting the concept that ICI-related pulmonary toxicity is not merely a deterministic dose-volume phenomenon, but a stochastic process modulated by baseline clinical vulnerabilities.

Our results indicate that constraining MLD to < 10.7 Gy, V5 to < 35.0%, V20 to < 21.8%, V30 to < 6.7%, and V40 to < 4.6% may help reduce RP risk. The thresholds recommended in our study are substantially lower than those in current guidelines. Previous studies conducted before the immunotherapy era established that dosimetric parameters, particularly V20 and MLD, were associated with severe RP[10, 29]. Consequently, the National Comprehensive Cancer Network (NCCN) guidelines recommend maintaining V20 < 35% and MLD < 20 Gy[30]. These findings highlight the need for stricter dosimetric constraints in the immunotherapy era. Furthermore, the implementation of advanced radiation techniques, including deep inspiratory breath-hold, smaller target margins, image-guided radiation therapy, and proton therapy, is recommended to minimize exposure of normal lung tissue in patients receiving combined ICI and TRT therapy.

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This study had some limitations. First, as a single-center retrospective analysis, the generalizability of our specific dosimetric thresholds requires validation in larger prospective cohorts. Second, the heterogeneity of ICI types and sequencing (concurrent vs. sequential) may have influenced the results. Third, PD-L1 expression status was unavailable for some patients and therefore not included in the analysis. Future research should focus on biological markers that can further refine the identification of high-risk patients when combined with COPD status and dosimetry.

5. Conclusions

This study demonstrated a high incidence of RP (60.2%) in patients receiving combined TRT and ICIs. A history of COPD and specific dose parameters (MLD, V5–V40) are key risk factors. Although traditional dosimetric constraints remain essential, our results demonstrate that clinical factors, particularly COPD, significantly enhance predictive accuracy for RP. The established thresholds provide practical guidance for treatment planning. For patients with identified risk factors, strict dose optimization and careful post-treatment monitoring are necessary to reduce the risk and severity of lung injury.

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