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Optimal dose-volume histogram thresholds for radiation pneumonitis prevention in lung cancer patients receiving immunotherapy

Yechen Ma[1†], Ziyang Feng[1†], Hao Zhou[2], Xuewen Liu[1*] and Zewen Song[1,2*]

Abstract

Objectives To evaluate the incidence of symptomatic radiation pneumonitis (RP) in lung cancer patients receiving immunotherapy and radiotherapy.

Materials and methods We retrospectively analyzed 389 lung cancer patients who underwent thoracic radiotherapy with/without immunotherapy at the Third Xiangya Hospital (January 2015-September 2024). Propensity score matching (PSM) was employed to compare RP incidence. Univariate, multivariate, and stepwise regression analyses were conducted to identify predictors of grade ≥ 2 RP.

Results Symptomatic RP occurred in 30.33% (118/389) and 7.46% (29/389) of patients for grades ≥ 2 and ≥ 3, respectively. Patients receiving concurrent immunotherapy-radiotherapy demonstrated a significantly lower incidence of grade ≥ 2 RP compared to other treatment groups ($p < 0.05$). Multivariable analysis revealed no significant association between immunotherapy administration and RP risk. Lung V20 (≤ 20% vs. > 20%) emerged as a critical predictor: grade ≥ 2 RP incidence was 4.05–8.73% with V20 ≤ 20%, versus 53.8–65.5% when V20 exceeded 20%.

Conclusions Immunotherapy did not raise the risk of grade ≥ 2 RP. Maintaining lung V20 ≤ 20% may serve as an optimal dosimetric threshold for RP prevention in patients undergoing combined-modality therapy.

Clinical trial number Not applicable.

Keywords Radiation pneumonitis, Lung cancer, Immunotherapy, Radiotherapy

Introduction

As the leading cause of cancer-related mortality globally, lung cancer's aggressive nature necessitates innovative therapeutic approaches. Traditionally dominated by surgery, chemotherapy, and radiotherapy, the treatment landscape has evolved with the advent of immune checkpoint inhibitors [1–5], which have demonstrated remarkable efficacy in enhancing the body's immune response against cancer cells. For instance, the phase III PACIFIC and GEMSTONE-301 trials established durvalumab or sugemalimab as a standard consolidation therapy for stage III NSCLC patients received definitive chemoradiotherapy (CRT) [6, 7]. Additionally, patients with

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oligo-metastatic lung disease can gain advantages from the strategic integration of radiotherapy into their systemic treatment regimen [8]. Local ablative approaches including RT are also the main therapeutic strategies for lung patients with oligo-progressive disease or oligo-residual disease [9, 10].

However, the concomitant use of radiotherapy and immunotherapy has raised critical concerns regarding the toxicity profiles associated with radiation exposure, particularly the risk of radiation pneumonitis (RP) [11, 12]. Radiation pneumonitis is characterized by inflammation of lung tissue following radiotherapy, with an incidence that varies greatly depending on individual patient factors, treatment regimens, and the technique applied in radiation delivery. This condition not only diminishes patients' quality of life but can also limit the feasibility of subsequent treatments, thus presenting a significant barrier in the multidisciplinary management of lung cancer. The emergence of immunotherapy has complicated this scenario, as studies have indicated that immune modulation may alter the dynamics of radiation-induced lung injury. Findings from the PACIFIC-R study revealed that 17.9% of stage III NSCLC patients received durvalumab after CRT experienced pneumonitis or interstitial lung disease (ILD), and 9.5% patients discontinued ICI treatment due to the above-mentioned adverse events [13]. Consequently, the interplay between radiotherapy and immune checkpoint inhibitors necessitates a comprehensive understanding of how various dosimetric parameters contribute to the risk of RP.

Dose and Volume Histogram (DVH) parameters serve as essential metrics in radiation oncology, providing crucial information on the distribution of radiation dose to both the target tissue and surrounding critical structures. Understanding the optimal thresholds for these DVH parameters may offer clinicians the ability to mitigate the risk of RP while preserving the efficacy of radiotherapy in this innovative treatment model. Existing literature has proposed various dose thresholds associated with RP; however, a standardized approach that accounts for the unique challenges posed by immunotherapy is warranted [14–16].

The goal of this paper is to explore the optimal threshold of DVH parameters for the prevention of RP in patients receiving combined modality therapy for lung cancer in the era of immunotherapy. Through a retrospective analysis of 389 lung cancer patients who underwent chest radiotherapy (with or without immunotherapy), we found that the DVH parameters, rather than immunotherapy itself, were associated with the incidence of symptomatic RP. Moreover, a V20 threshold of less than 20% may serve as an optimal criterion for managing the risk of grade ≥ 2 RP in the era of immunotherapy. Our findings are expected to provide critical insights that could inform clinical decision-making and serve as a reference for future clinical research initiatives.

Materials and methods

Patient selection

This retrospective real-world study adhered to the Declaration of Helsinki and received approval from the Institutional Ethics Board of the Third Xiangya Hospital of Central South University (Ethical approval number: E 24524) as well as the Xiangxi Autonomous Prefecture People's Hospital (Ethical approval number: ECLCKY2024037). The patient cohort consisted of lung cancer patients who underwent radiation therapy (RT), with or without immunotherapy, between January 2015 and September 2023. The inclusion criteria included: (1) histologically confirmed diagnosis of lung cancer; (2) availability of dosimetric data pertaining to the conducted RT; (3) a minimum follow-up duration of six months; (4) access to at least one baseline chest computed tomography (CT) scan and one follow-up lung CT scan within six months post-RT; (5) receipt of daily radiation fractions ranging from 1.8 to 2.2 Gy, culminating in a total delivered dose of at least 50 Gy. The exclusion criteria were: (1) histologically unconfirmed lung cancer; (2) receipt of hypofractionated RT or stereotactic body radiation therapy (SBRT); (3) inability to assess RP due to complications such as significant hydrothorax or obstructive pneumonia; (4) previous history of thoracic radiotherapy (TRT); (5) having more than one TRT within a six-month span (For patients receiving multiple TRT sessions with intervals greater than six months, only the initial TRT was assessed in this study).

Treatments

All patients underwent intensity-modulated radiation therapy (IMRT). To minimize respiratory motion artifacts, patients typically underwent pre-CT simulation breathing training (15–20 min) to practice diaphragmatic breathing, followed by immobilization in a supine position using a thermoplastic mask. For tumors with significant respiratory motion, fluoroscopy-guided motion assessment and adaptive gating were employed, as routinely done in clinical practice. The generally used prescribed doses were: planning gross target volume (PGTV): 60–66 Gy, planning target volume (PTV): 50–54 Gy. Dose coverage aimed for 95% of the PTV receiving the prescribed dose. Normal tissue constraints adhered to widely accepted guidelines: Lungs: V20 < 30%, mean dose < 20 Gy. Esophagus: Dmax < 64 Gy, V60 < 10 cc. Heart: V20 < 30%, V30 < 40%. Spinal cord: Dmax < 45 Gy (ideally < 40 Gy). Chemotherapy and immunotherapy were administered at the discretion of the treating physicians, guided by the package insert, specific clinical scenarios, and cancer treatment guidelines.

Follow-up evaluations, though not standardized, typically involved a CT scan one month post-RT, followed by assessments every three months.

Data collection

Clinical data were extracted from the hospital information system (HIS) and included demographics such as age, sex, smoking history, pathological details, TNM stage (classified according to the 8th edition of the American Joint Committee on Cancer staging system; patients diagnosed prior to 2017 were re-staged according to this system), Eastern Cooperative Oncology Group (ECOG) performance status, complications, and systemic treatment regimens. Information regarding the administered radiation dose, the volume of the PGTV and PTV, mean lung dose (MLD), and lung V5/20 (where Vx is the percentage of lung volume receiving a dose exceeding x Gy) was obtained from the Eclipse treatment planning system (TPS) (Varian Medical Systems, Palo Alto, CA). The most recent survival follow-up was conducted on May 10, 2024. Patients lost to follow-up were recorded as such in the HIS with their last known survival status.

Evaluation of RP

The diagnosis of RP was based on the identification of diffuse lung abnormalities that were confined to or predominantly limited to the radiation field, as observed on CT scans, in conjunction with patient-reported symptoms. A multidisciplinary team, comprising at least one respiratory physician, radiologist, and senior oncologist, evaluated and excluded pneumonitis attributable to other potential causes, including infections and immunotherapy. The severity of RP was assessed following the Radiation Therapy Oncology Group (RTOG) scoring system.

Table 1 The baseline information and disease characteristics of the 389 patients from the third Xiangya hospital enrolled in this study

	Levels	No ICI (*N*=284)	CIR (*N*=68)	IAR (*N*=37)	*p* value
Stage	I-II	17 (6%)	1 (1.5%)	0 (0%)	0.044
	III	179 (63%)	52 (76.5%)	30 (81.1%)	
	IV	88 (31%)	15 (22.1%)	7 (18.9%)	
ECOG	>=2	12 (4.2%)	3 (4.4%)	1 (2.7%)	0.9
	0-1	272 (95.8%)	65 (95.6%)	36 (97.3%)	
Gender	Female	53 (18.7%)	3 (4.4%)	1 (2.7%)	0.001
	Male	231 (81.3%)	65 (95.6%)	36 (97.3%)	
Age	<60	159 (56%)	22 (32.4%)	21 (56.8%)	0.002
	>=60	125 (44%)	46 (67.6%)	16 (43.2%)	
Smoke status	No	109 (38.4%)	17 (25%)	7 (18.9%)	0.014
	Yes	175 (61.6%)	51 (75%)	30 (81.1%)	
Pathology	NSCLC	232 (81.7%)	63 (92.6%)	36 (97.3%)	0.007
	SCLC	52 (18.3%)	5 (7.4%)	1 (2.7%)	
COPD	No	272 (95.8%)	59 (86.8%)	35 (94.6%)	0.018
	Yes	12 (4.2%)	9 (13.2%)	2 (5.4%)	

Statistical analysis

Measurement data underwent normality testing and homogeneity of variance assessment prior to analysis. The analysis of variance (ANOVA) was utilized for comparisons among three groups, while the LSD mean multiple comparison test or Tamhanes' T2 test was employed for inter-group comparisons. Categorical data were analyzed using the Chi-square test, applying the Bonferroni correction for group comparisons. Univariate, multivariate, and stepwise Cox regression analyses were conducted to identify risk factors for RP occurrence, using the autoreg package in R software. Propensity score matching (PSM) was performed via the MatchIt package in R software. Data analysis and graphical representation were executed using the SPSS statistical software package (version 26.0, IBM Corp, Armonk, NY, USA) and R software (version 4.3.3). A p-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

From January 1st, 2015 to September 30th, 2023, 871 lung patients were treated with thoracic IMRT in the Third Xiangya hospital. 482 patients were excluded for analyses. Most of them ($n=343$) were due to follow-up time less than 6 months. Besides, 56 patients without chest CT scan within 6 months after radiation, 65 patients received total actual dose less than 50 Gy, 5 patients without pathological results, 7 patients with complication interfering RP evaluation, and 6 patients received previous TRT in other hospitals were also excluded. The remaining 389 patients were used for analyses of RP, and they were categorized into three subgroups based on the sequence of immunotherapy and radiation, namely *No ICI* (referred to patients not received immunotherapy within 3 months before the start of radiation and 6 months after the end of radiation, $n=284$), *CIR* (concurrent immunotherapy and RT, referred to patients received ICI treatment during radiation or within 3 months before the start of radiation, $n=68$), and *IAR* (immunotherapy after RT, referred to patients received ICI treatment after the end of radiation, $n=37$). Table 1 summarized the baseline information and disease characteristics of these patients. Except the ECOG score, the rest baseline characteristics were not balanced between the subgroups (Table 1).

Further, the DVH parameters were also compared among the three subgroups. As shown in Fig. 1, patients in the *CIR* subgroup exhibited the lowest DVH parameters than those in the rest two subgroups, while no significant differences in these parameters were observed between the *IAR* and *No ICI* subgroups.

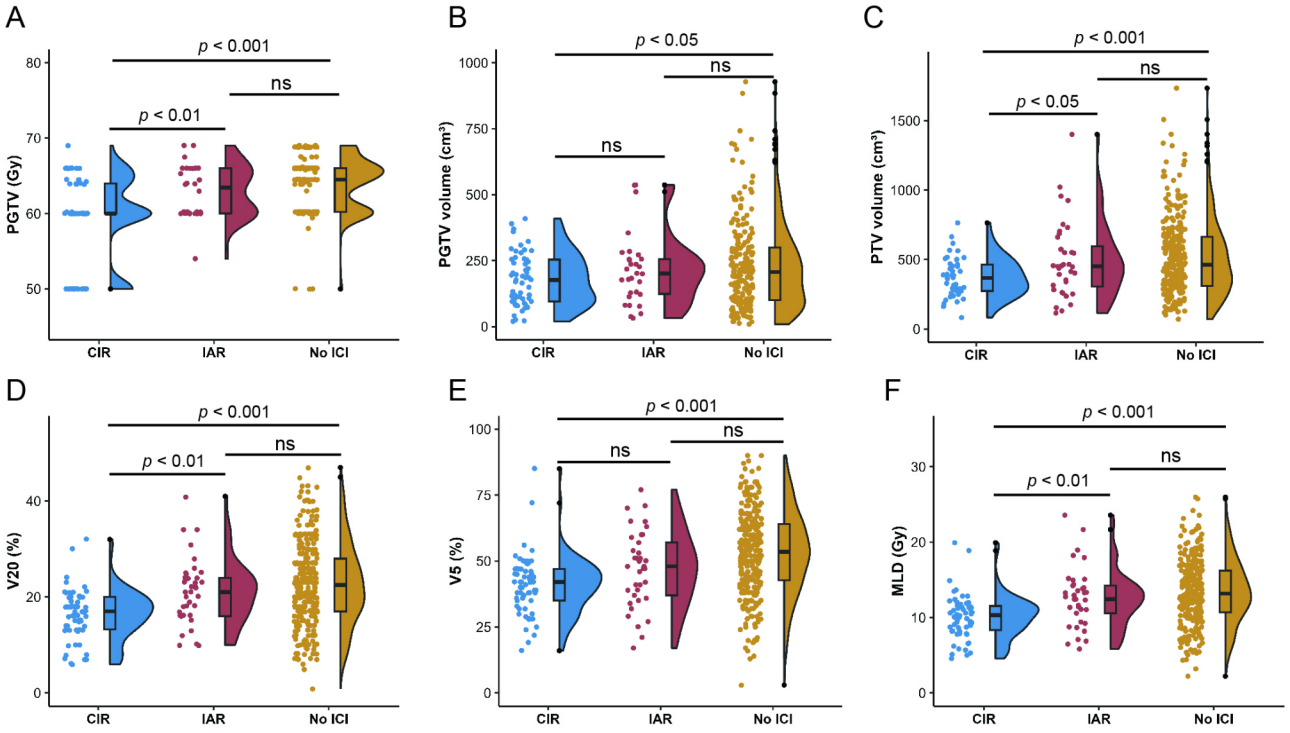

Fig. 1 Comparison of DVH parameters among the three subgroups. (**A**-**F**) The box and dot plot showing the value of PGTV (**A**), PGTV volume (**B**), PTV volume (**C**), V20 (**D**), V5 (**E**), and MLD (**F**) in patients from the *CIR*, *IAR*, and *No ICI* subgroups. Ns represented no significance

Table 2 The incidence of grade ≥ 2 RP in the three subgroups

Group	Total	< 2 RP (%)	≥ 2 RP (%)	χ^2 test	
				χ^2 value	*p* value
No ICI	284	188 (66.2%)	96 (33.8%)	9.553	0.008
CIR	68	58 (85.3%)	10 (14.7%)#		
IAR	37	25 (67.6%)	12 (32.4%)		

represents significant difference existed between the CIR and No ICI subgroups

Table 3 The incidence of grade ≥ 3 RP in the three subgroups

Group	Total	< 3 RP (%)	≥ 3 RP (%)	χ^2 test	
				χ^2 value	*p* value
No ICI	284	259 (91.2%)	25 (8.8%)	2.659	0.258
CIR	62	66 (97.1%)	2 (2.9%)		
IAR	37	35 (94.6%)	2 (5.4%)		

Incidence of RP

In total, 30.33% (118/389) and 7.46% (29/389) patients experienced grade ≥ 2 and grade ≥ 3 RP, respectively. Table 2 displayed the incidence of grade ≥ 2 RP in the three subgroups. 33.8% patients in the *No ICI* subgroup, 14.7% patients in the *CIR* subgroup, and 32.4% patients in the *IAR* subgroup experienced grade ≥ 2 RP, respectively. There was statistically significant difference among the three subgroups (Table 2, $\chi^2 = 9.553$, $p = 0.008$). No difference in the incidence of grade ≥ 2 RP was observed between *No ICI* and *IAR* subgroups ($p > 0.05$), but the incidence of grade ≥ 2 RP in the *CIR* subgroup was significantly lower than that in the *No ICI* subgroup ($p < 0.05$). As shown in Table 3, 8.8% patients in the *No ICI* subgroup, 2.9% patients in the *CIR* subgroup, and 5.4% patients in the *IAR* subgroup experienced grade ≥ 3 RP, respectively. There were no statistically significant differences among the three subgroups or between any two subgroups ($p > 0.05$).

Since the baseline characteristics and DVH parameters were not well balanced among the three subgroups (Table 1; Fig. 1). PSM method was manipulated before comparison between any two subgroups. When only the disease characteristics were controlled between the *CIR* and *IAR* subgroups (supplementary Table 1), A higher percentage of patients in the IAR subgroup occurred grade ≥ 2 RP (32.4%) than that of patients in the CIR subgroup (9.4%, $p = 0.043$). Patients in the *IAR* subgroup also exhibited significantly larger PTV volume ($p = 0.033$) and higher PGTV dose ($p = 0.001$), V20 ($p < 0.001$), V5 ($p = 0.014$), and MLD ($p < 0.001$). However, when both the disease characteristics and DVH parameters were well balanced between the two subgroups, no difference in the incidence of grade ≥ 2 RP or grade ≥ 3 RP was observed (25.0% vs. 21.7%, supplementary Table 2). Similarly, when both the disease characteristics and DVH parameters were controlled between the *CIR* and *No ICI* subgroups, no difference in the incidence of grade ≥ 2 RP or grade ≥ 3 RP was observed (supplementary Table 3). However, significantly higher percentage of patients had grade ≥ 2 RP

in the *No ICI* subgroup when only the baseline characteristics were balanced (27.9% vs. 12.7%, $p = 0.032$, supplementary Table 4).

Optimal threshold of DVH parameters for the prevention of symptomatic RP.

The above analyses suggested that immunotherapy did not add extra risk to the incidence of grade ≥ 2 or grade ≥ 3 RP, and grade ≥ 2 RP was tightly correlated with DVH parameters. V20, V5, and MLD were key parameters for the prediction of incidence of RP [15–17]. These parameters had a highly positive correlation in the whole cohort or in 105 patients received both immunotherapy and RT (the *CIR* and *IAR* subgroups, renamed as the immuno-RT cohort) (Fig. 2A and B).

To explore the pivotal factor and its corresponding threshold associated with the incidence of grade ≥ 2 RP in the immuno-RT subgroup, stepwise logistic regression and receiver operating characteristic curve (ROC) analyses were conducted in these 105 patients. Univariate regression analyses suggested that PTV volume ($p = 0.012$), PTV ($p = 0.025$), PGTV ($p = 0.003$), V20 ($p < 0.001$), V5 ($p < 0.001$), and MLD ($p < 0.001$) were all risk factors for the incidence of grade ≥ 2 RP (Table 4). Among these parameters, V20 was found to be the paramount factor associated with occurrence of grade ≥ 2 RP (Table 4). Although the cutoff value of V20 for the incidence of grade ≥ 2 RP was 20.50% (Fig. 2C, AUC = 0.884), V20 ≤ 20% might be more feasible for the convenience of clinical application. As shown in Figs. 2D and 4.05% (3/74) patients with V20 ≤ 20% in the immuno-RT subgroup experienced grade ≥ 2 RP, however, the ratio was up to 65.5% for those with V20 > 20% ($p < 0.001$). Considering immunotherapy did not add risk to the incidence of RP, the incidence of grade ≥ 2 RP in the *No ICI* subgroup stratified by V20 at 20% was also evaluated. Similarly, 8.73% of them with V20 ≤ 20% experienced symptomatic RP, and the ratio was 53.8% when the V20 was greater than 20% ($p < 0.001$). Further, 103 lung patients received TRT in the Xiangxi Autonomous Prefecture People's Hospital were used as a validating cohort, and their baseline characteristics and DVH parameters were displayed in the supplementary Table 5. As shown in Fig. 2D, the incidence of grade ≥ 2 RP in this cohort divided by V20 at 20% were 7.14% vs. 55.74% ($p < 0.001$).

Discussion

Research from bed to bench demonstrates that synergetic effects exist in the combination of immunotherapy and RT [18–22]. Consolidation with ICIs after definitive chemo-radiotherapy is the standard treatment for unresectable, stage III NSCLC patients [6, 7]. CCRT followed by immunotherapy consolidation had also been explored in limited-disease small-cell lung cancer (LD-SCLC) [23]. In addition, lung patients at advanced stage could benefit from TCT when they have oligo-metastatic, oligo-progressive or oligo-residual diseases in the lung during ICIs treatment [8–10]. Thus, the combination of immunotherapy and TRT is inevitable for lung patients.

However, RP remains a significant concern for lung cancer patients undergoing treatment, particularly within the context of immunotherapy combined with thoracic radiotherapy. This issue is particularly pronounced in patients with unresectable stage III lung cancer, where the risk of developing RP poses a challenge in treatment optimization. While traditional DVH parameters (e.g., V20, MLD) remain valuable for predicting RP risk in patients treated with chemoradiation alone [24], emerging preclinical and clinical evidence suggests these thresholds may not fully capture the biologic interplay between radiation and immune checkpoint inhibitors (ICIs). A recent murine study demonstrated that concurrent anti-PD-1 therapy exacerbates radiation-induced lung injury (RILI) by amplifying IL-17 A production from γδ T cells, leading to neutrophilic infiltration and heightened pulmonary inflammation, even at radiation doses traditionally considered safe [25]. A body of research also indicated a heightened risk of RP when combining immunotherapy with chest radiotherapy [26]; however, data from various Phase III clinical trials have nuanced this understanding [6, 7]. These trials suggest that, under specific conditions, the use of immunotherapy as maintenance therapy following thoracic radiotherapy does not markedly increase the incidence of RP. Furthermore, evidence from Phase II and III studies has supported the notion that simultaneous administration of immunotherapy alongside chest radiotherapy does not exacerbate the frequency of RP [27, 28]. This observation highlights the potential value of strict compliance with contemporary dose-volume constraints in reducing synergistic toxicity risks. However, critical knowledge gaps persist as both the PACIFIC and GEMSTONE-301 trials notably failed to report comparative DVH parameters between immunotherapy and placebo arms [6, 7], leaving unresolved whether dosimetric disparities influence RP development. Furthermore, the absence of standardized DVH benchmarks for ICI-treated patients underscores the urgency for personalized treatment planning, especially in ICI-radiotherapy combination therapies.

Our study corroborates this emerging consensus, revealing that the parameters derived from DVH metrics, rather than the immunotherapy itself, correlate more closely with the occurrence of symptomatic RP. This finding underscores the need for clinicians to prioritize meticulous DVH analysis, shifting the focus from a simplistic concern over immunotherapy's contribution to RP risk to a more nuanced consideration of the radiogenic factors at play. Such an approach is particularly critical in the immunotherapy era, where optimized treatment

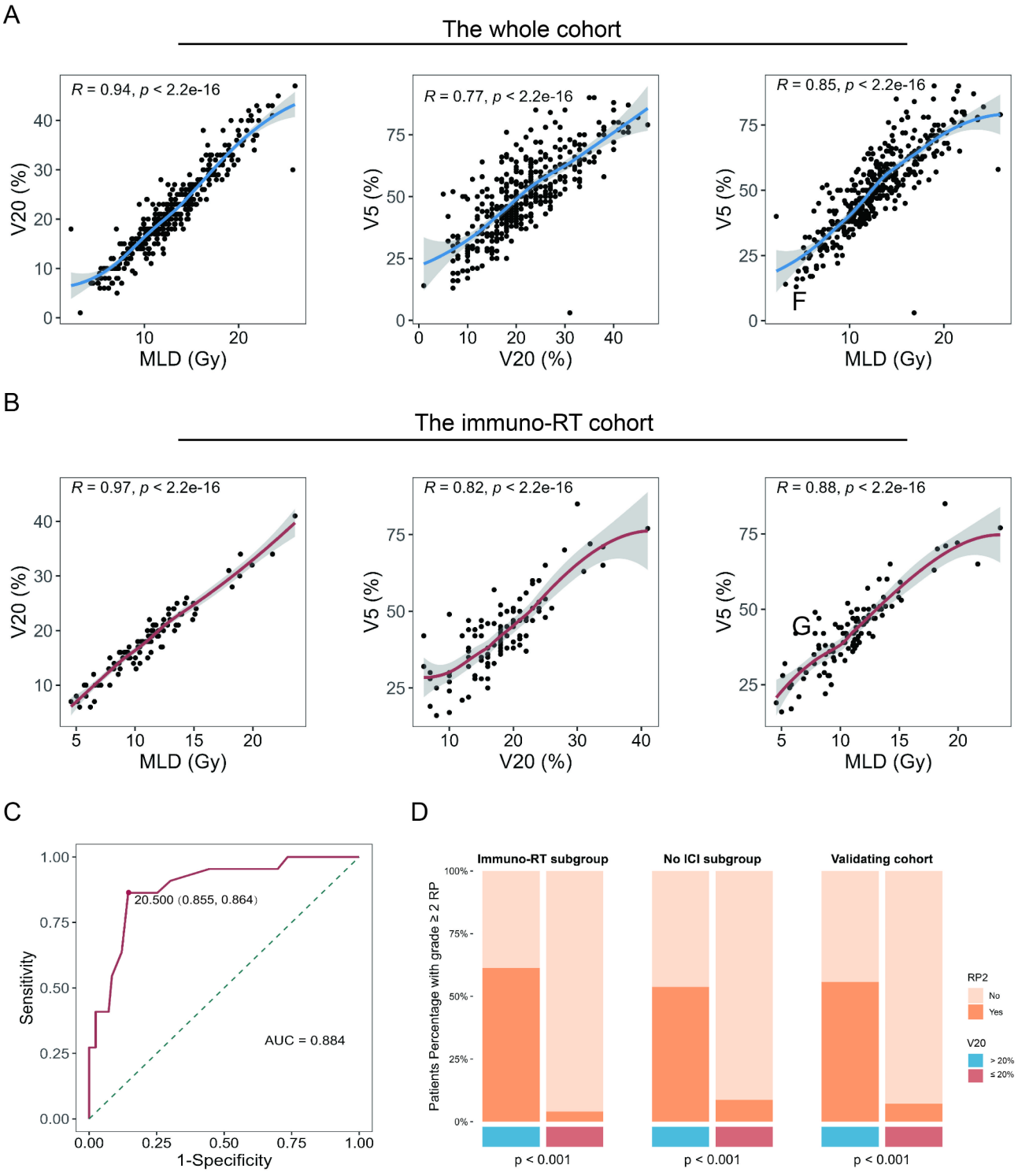

Fig. 2 Identification of optimal threshold of DVH parameters for the prevention of symptomatic RP. (**A**) Correlation analyses between V20, MLD, and V5 in the whole cohort. (**B**) Correlation analyses between V20, MLD, and V5 in the immune-RT cohort. (**C**) Receiver operating characteristic curve (ROC) analysis of V20 in the prediction of grade ≥ 2 RP in the immune-RT cohort. (**D**) Incidence of grade ≥ 2 RP in patients stratified by V20 at 20% in the immune-RT subgroup, No ICI subgroup and the validating cohort

Table 4 Univariate and Stepwise regression analyses of patients with grade ≥ 2 RP in the immuno-RT subgroup

	Levels	No ($n = 83$)	Yes ($n = 22$)	OR (univariable)	OR (multivariable)	OR (stepwise)
Gender	Female	4 (4.8%)	0 (0%)			
	Male	79 (95.2%)	22 (100%)	4358606.84		
				($p = 0.990$)		
Age	<60	33 (39.8%)	10 (45.5%)			
	>=60	50 (60.2%)	12 (54.5%)	0.79		
				($p = 0.629$)		
Stage	I-II	1 (1.2%)	0 (0%)			
	III	66 (79.5%)	16 (72.7%)	1395833.41		
				($p = 0.992$)		
	IV	16 (19.3%)	6 (27.3%)	2159179.81		
				($p = 0.992$)		
Smoke status	No	19 (22.9%)	5 (22.7%)			
	Yes	64 (77.1%)	17 (77.3%)	1.01		
				($p = 0.987$)		
ECOG	>=2	3 (3.6%)	1 (4.5%)			
	0-1	80 (96.4%)	21 (95.5%)	0.79		
				($p = 0.840$)		
Pathology	NSCLC	78 (94%)	21 (95.5%)			
	SCLC	5 (6%)	1 (4.5%)	0.74		
				($p = 0.791$)		
COPD	No	74 (89.2%)	20 (90.9%)			
	Yes	9 (10.8%)	2 (9.1%)	0.82		
				($p = 0.812$)		
PTV volume	Mean ± SD	388.1 ± 203.2	534.7 ± 211.8	1	1	
				($p = 0.012$)	($p = 0.363$)	
PGTV volume	Mean ± SD	182.0 ± 103.1	234.9 ± 138.5	1		
				($p = 0.085$)		
PTV	Mean ± SD	54.0 ± 2.4	55.5 ± 3.4	1.23	1.05	
				($p = 0.025$)	($p = 0.820$)	
PGTV	Mean ± SD	59.9 ± 5.2	64.2 ± 3.2	1.31	1.16	1.2
				($p = 0.003$)	($p = 0.349$)	($p = 0.088$)
V20	Mean ± SD	16.3 ± 4.7	24.8 ± 6.3	1.43	1.25	1.37
				($p < 0.001$)	($p = 0.391$)	($p < 0.001$)
V5	Mean ± SD	39.7 ± 10.0	55.0 ± 13.7	1.13	0.98	
				($p < 0.001$)	($p = 0.779$)	
MLD	Mean ± SD	10.0 ± 2.5	14.9 ± 3.8	1.86	1.18	
				($p < 0.001$)	($p = 0.776$)	

strategies hinge on balancing therapeutic benefits against potential toxicities.

In this work, the incidence of symptomatic RP in lung patients received concurrent RT and immunotherapy was lower than that of patients received sequential RT and immunotherapy or RT without immunotherapy (Table 2, $p = 0.008$). Two reasons might result in the lower ratio of symptomatic RP in the *CIR* subgroup in this study. Firstly, lung patients in the CIR subgroup received significantly lower radiation dose than those in the rest two subgroups (Fig. 1). Secondly, the PTV volume of patients in the *CIR* subgroup was smaller than that of patients in the rest two subgroups (Figs. 1C and 4F). The prior use of immunotherapy alone or with chemotherapy largely contributed to the reduction of PTV volume. A bunch of phase III studies revealed that immunotherapy with or without chemotherapy has a significantly higher objective response rate (ORR) than chemotherapy in advanced lung cancer patients [1, 3, 29–31]. In resectable, stage II-IIIB NSCLC patients, 4 cycles of neoadjuvant pembrolizumab plus chemotherapy led to higher major pathological response (MPR) rate (30.2% vs. 11.0%, $p < 0.0001$) and pathological complete response (pCR) rate (18.1% vs. 4.0%, $p < 0.0001$) than placebo with chemotherapy [32]. RATIONALE-315 study also reported a significantly higher MPR rate (56.2% vs. 15%, placebo group) and pCR rate (40.7% vs. 5.7%, placebo group) in stage II-IIIB NSCLC patients from the neoadjuvant tislelizumab plus chemotherapy group [33]. Consequently, both relative lower radiation dose and reduced PTV volume due to

prior use of ICIs contributed to decreased MLD and V20, and lower incidence of grade ≥ 2 RP in the *CIR* subgroup.

In our exploration of DVH parameters, we discovered that the V20 is critical in mitigating the risk of symptomatic grade ≥ 2 RP. Our data indicated that when V20 is maintained at or below 20%, the incidence of grade ≥ 2 RP ranges from 4.05 to 8.73%. In stark contrast, when the V20 threshold surpasses 20%, this incidence escalates alarmingly to between 53.8% and 65.5%. These findings resonate with earlier analyses emphasizing the predictive capacity of V20 in relation to RP occurrence. Additionally, previous multi-institutional studies highlighted that MLD stands as a pivotal parameter for patients receiving immune checkpoint inhibitors (ICIs) coupled with radiotherapy [17]. In examining the relationship between MLD and RP incidence, an MLD of 11.6 Gy correlates with a 50% risk for grade ≥ 2 RP at an MLD threshold of 14.1 Gy [17]. Notably, our results indicated a strong correlation between MLD and V20 (R^2 = 0.94–0.96), suggesting that both parameters hold equal significance in predicting the onset of RP. This correlation underscores the importance of individualized treatment planning, where both MLD and V20 are carefully managed to avert the onset of RP, allowing for optimized therapeutic outcomes while minimizing toxicity to healthy lung tissue.

Despite the strengths of this study (e.g., application of PSM method, large sample sizes, longer follow-up, and uniform use of IMRT), several limitations must be acknowledged. Firstly, this study was a retrospective one, although PSM method was used to balance baseline characteristics before comparison, biases were still inevitable. Secondly, while COPD was included as a risk factor for RP, critical pulmonary function metrics (e.g., forced expiratory volume in one second [FEV1]) were unavailable for most patients, and the potential influence of other pulmonary comorbidities (e.g., ILD) remains unaddressed, which may compromise the comprehensiveness of our risk model. Thirdly, most patients had no reports of the expression of PD-L1 in this retrospective analysis, and its impact on the incidence of RP and its contribution to the prognosis of stage III NSCLC patients was not evaluated. Additionally, the heterogeneity in immunotherapy subtypes (e.g., PD-1 vs. PD-L1 inhibitors) and administration timing (concurrent vs. sequential) limited our ability to dissect differential dose-volume effects across regimens. Finally, the absence of grade 4–5 RP events restricts conclusions regarding high-grade toxicity thresholds, necessitating validation in larger cohorts with prolonged toxicity surveillance. These limitations underscore the need for prospective studies integrating comprehensive pulmonary function testing, multidimensional biomarker profiling (e.g., PD-L1, IL-17 A), and granular dosimetric analyses to refine risk stratification in the era of combined radiotherapy and immunotherapy. Furthermore, machine learning approaches such as LASSO (least absolute shrinkage and selection operator) regression could be strategically incorporated into future large-scale studies to enhance variable selection robustness.

In conclusion, combining immunotherapy and radiotherapy for lung cancer requires data-driven strategies to minimize complications like RP. Maintaining V20 ≤ 20% proves critical for treatment optimization. As combined therapies advance, systematic analysis of radiotherapy-immunotherapy interactions and patient-specific factors will be essential to refine protocols and improve outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-025-02639-2.

Supplementary Material 1

Author contributions

The study was designed by Xuewen Liu and Zewen Song. Yechen Ma, Ziyang Feng and Hao Zhou collected the data. Zewen Song and Yechen Ma processed data analyses and drafted the manuscript. Zewen Song and Xuewen Liu revised the final manuscript. All authors have read and approved the final manuscript.

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Data availability

The data was available with proper request.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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