Risk Factors for Radiation Pneumonitis in Lung Cancer Patients with Subclinical Interstitial Lung Disease after Thoracic Radiation Therapy

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Abstract

Background: Previous studies have found that patients with subclinical interstitial lung disease (ILD) are more susceptible to developing radiation pneumonitis (RP) after thoracic radiation therapy. The present study aimed to evaluate the incidence of and risk factors for RP after thoracic intensity-modulated radiation therapy (IMRT) in lung cancer patients with subclinical ILD.

Methods: We retrospectively analyzed lung cancer patients with subclinical ILD who were treated with thoracic IMRT with a prescribed dose of ≥50 Gy in our institutions between January 2016 and December 2017.

Results: A total of 87 consecutive lung cancer patients with subclinical ILD were selected for the study. The cumulative incidence of grades ≥2 and ≥3 RP at one year was 51.0% and 20.9%, respectively. In the multivariate analysis, the mean lung dose (MLD) ≥12Gy was a significant risk factor for grade ≥2 RP (p = 0.049). Chemotherapy with gemcitabine in the past、V5≥50%、and subclinical ILD involving ≥25% of lung volume were significantly associated with grade ≥3 RP (p = 0.046, p = 0.040, and p = 0.024, respectively).

Conclusion: MLD is a significant risk factor for grade ≥2 RP. Lung cancer patients who have received chemotherapy with gemcitabine in the past, V5, and those with subclinical ILD involving ≥25% of lung volume have an increased risk of grade ≥3 RP in lung cancer patients with subclinical ILD.

Introduction

Radiation pneumonitis (RP) is a common complication of radiotherapy in lung cancers. Studies have shown that the incidence of symptomatic RP is approximately 15%–40% [1]. Previous studies have demonstrated that dose-volume histogram (DVH)-based dosimetric parameters, including V20 (percentage of lung volume receiving ≥20 Gy), the mean lung dose (MLD), treatment factors (e.g., sequential/concurrent chemotherapy schedules), tumor factors (e.g., tumor size, tumor located in the lower lung), and patient factors (e.g., poor pulmonary function, concomitant disease), are predictive markers for RP [2,3,4,5,6,7,8,9].

Subclinical interstitial lung disease (ILD) has a higher incidence in patients with lung cancer than in the general population [10]. Previous studies found that patients with subclinical ILD were more susceptible to developing RP after thoracic radiation therapy (TRT) [10,11,12,13,14,15,16].

To date, studies on the correlation between subclinical ILD and RP have been limited. Moreover, there is no report on the incidence of and risk factors for radiation pneumonitis (RP) in a population of lung cancer patients with subclinical ILD after intensity-modulated radiated therapy (IMRT). Consequently, this single-institution study was conducted to determine the incidence of and risk factors for RP after IMRT in lung cancer patients with subclinical ILD.

Materials And Methods

Patients

Lung cancer patients with subclinical ILD who were treated with thoracic IMRT in our institutions between January 2016 and December 2017 were retrospectively analyzed. The inclusion criteria were as follows: (1) patients diagnosed with lung cancer by histology or cytology; (2) interstitial lung changes on high-resolution CT (HRCT) images before radiotherapy and chemotherapy; (3) Karnofsky performance status scale ≥ 70 and ability to endure IMRT at a total dose of the equivalent dose in 2.0 Gy/(fraction per day) (EQD2) ≥50 Gy; (4) age ≥18 years; (5) no other serious medical conditions; (6) RT with concurrent or sequential chemotherapy; (7) no TRT received previously; (8) thoracic CT images available for evaluation before and after TRT; and (9) follow-up time of more than six months for patients without RP. TRT terminated due to non-radiotherapy-related complications for more than seven days was excluded.

Radiotherapy

All patients underwent a planning CT scan and were immobilized in a supine position with their arms raised in a customized vacuum-lock mold. Simulation CT images were taken in 0.5 cm increments over the region of interest. Treatment planning was performed with an ADAC Pinnacle™ (Philips Medical Systems) system. Treatment consisted of 6 or 10 MV photon thoracic IMRT using a Siemens Artiste (Oncology Care Systems, Siemens Medical Solutions, CA, USA) digital linear accelerator. The gross tumor volume (GTV) was defined as the volume of a primary tumor and metastatic lymph nodes. The clinical target volume (CTV) was typically a 0.6–0.8cm expansion of the GTV. The CTV of prophylactic postoperative radiotherapy was determined based on postoperative pathology, including the bronchial stump, ipsilateral hilar, and drainage area of tumor-positive lymph nodes. The planning target volume (PTV) was defined by adding margins at the discretion of radiation oncologists (typically 0.5–1.0 cm, depending on respiratory motion and patient fixation). The goal was to deliver the prescription dose to at least 95% of the PTV, while meeting normal tissue constraints. The total dose was ≥50.0 Gy, which was generally delivered at 2.0–3.0 Gy/(fraction per day), five fractions per week. If the lung dose exceeded the safety range, the total dose was reduced as appropriate. Informed consent was obtained from all patients prior to radiotherapy. Ethical approval was obtained from the Ethical Review Committee of Tongji University Affiliated Shanghai Pulmonary Hospital, China.

Chemotherapy

The concurrent chemotherapy regimen consisted of platinum combined with pemetrexed, paclitaxel, docetaxel, vinorelbine, or etoposide. Patients that were older in age, Stage IV, had poor pulmonary function, anemia, abnormal liver and renal function, and exhibited progression after first-line chemotherapy was given single-agent concurrent chemotherapy or sequential chemoradiotherapy. Chemotherapy was generally performed in 4–6 cycles every 3–4 weeks.

Diagnosis of subclinical ILD

Lung cancer patients with subclinical ILD detected with high-resolution CT (HRCT) images who were treated with thoracic IMRT in our institutions between January 2016 and December 2017 were analyzed. Diagnosis of subclinical ILD was based on pretreatment HRCT images with an axial slice thickness of 0.1 cm in a lung window. Reticular abnormalities, traction bronchiectasis, bilateral independent ground-glass abnormalities, honeycombing, and nonemphysematous cysts were considered to be indicative of subclinical ILD [17,18,19]. The diagnosis of subclinical ILD and the CT scans were evaluated independently by a radiologist and two physicians specializing in pulmonology.

Follow-up

Patients were reevaluated at 1–2 months post treatment and subsequently every three months. The endpoint was the incidence of grade ≥2 RP. Adverse events were graded using the Common Terminology Criteria for Adverse Events Version 4.0.

Statistical analysis

Correlations between RP and the risk factors were analyzed using Chi-square or Student's t-test for univariate analysis. Receiver operating characteristic curves were generated to determine the optimal cut-off value of continuous variable. Logistic regression analysis was performed to evaluate the correlations between RP and the risk factors using multivariate analysis. The cumulative incidence of RP was estimated using the Kaplan-Meier method, and differences between the groups were assessed using a log-rank test. Statistical analysis was performed using IBM SPSS software 22.0 for Mac. A p value less than 0.05 was considered to be statistically significant.

Results

From January 2016 to December 2017, a total of 87 consecutive lung cancer patients with subclinical ILD, aged 48 to 86 years with a median age of 67 years, were enrolled in the study. The tumor stage was determined according to the 8th edition of the Union for International Cancer Control TNM staging system for lung cancer. None of the patients had been diagnosed with interstitial lung disease clinically or via lung biopsy prior to receiving chemotherapy or radiotherapy. None of the patients had received treatment with any of the currently available medicines for ILD. Seventy-six patients had received chemotherapy prior to radiotherapy. The median duration of chemotherapy was two cycles (range, 0–6 cycles). Two patients had previously received epidermal growth factor receptor tyrosine kinase inhibitor. The characteristics of the patients are shown in Table 1.

Table 1 Characteristics of the patients

Factors	N（%）
Gender	
Male	81（93.1）
Female	6（6.9）
Age（years）	
<70	57（65.5）
≥70	30（34.5）
Pathological types	
NSCLC	57（65.5）
Adenocarcinoma	17（19.5）
Squamous cell carcinoma	24（27.6）
Large cell carcinoma	1（1.1）
Unclassified NSCLC	15（17.2）
SCLC	30（34.5）
Tumor stage	
I	2（2.3）
IIIA	24（27.6）
IIIB	37（42.5）
IIIC	3（3.4）
IV	10（11.5）
Postoperative	11（12.6）
Chemotherapy	
Concurrent	19（21.8）
Sequential	68（78.2）

NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer

Table 2 Characteristics of patients who discontinued radiotherapy

No.	Age (years)/Gender	Smoking history (pack-years)	Pathological type/tumor stage	Treatment modality	Induction chemotherapy regimen	Radiotherapy dose (Gy/fraction)	Percentage of lung volume affected in subclinical ILD	Grade of RP
1	68/Male	40	Squamous cell carcinoma/IIIB	RT	Cisplatin+gemcitabine	44.0/22	≥25%	4
2	77/Male	50	Squamous cell carcinoma/IIIB	RT	Carboplatin+gemcitabine	49.5/22	≥25%	5
3	67/Male	No	Squamous cell carcinoma/postoperative stump recurrence	RT	Cisplatin+gemcitabine	24.0/12	<25%	2
4	63/Male	80	Adenocarcinoma/IIIB	RT	Cisplatin+gemcitabine	58.0/29	<25%	3
5	65/Male	40	NSCLC/IIIB	RT	Cisplatin+vinorelbine	38.0/19	<25%	4
6	69/Male	50	Squamous cell carcinoma/IIIB	RT	Carboplatin+gemcitabine	38.0/19	≥25%	5
7	52/Male	60	Adenocarcinoma/IIIB	RT	Cisplatin+pemetrexed	30.0/15	<25%	2
8	67/Male	No	SCLC/IIIB	RT	Carboplatin+etoposide	40.0/20	<25%	2

RP, radiation pneumonitis; ILD, interstitial lung disease; RT, radiation therapy; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer

The median follow-up time was 13.4 months (range, 1.2–33.6 months). RP was observed in 19 (21.8%), 27 (31.0%), 10 (11.5%), three (3.4%), and five (5.7%) patients with grades 1, 2, 3, 4, and 5 RP, respectively. Radiotherapy was discontinued in eight patients because grade ≥2 RP occurred during radiotherapy. Characteristics of the patients for whom radiotherapy was discontinued are shown in Table 2. Five patients developed grade 5 RP; their characteristics are shown in Table 3.

Table 3 Characteristics of patients with grade 5 RP

No.	Age (years)/Gender	Smoking history (pack-years)	Pathological types/Tumor stage	Treatment modality	Concurrent chemotherapy regimen	Induction chemotherapy regimen	Radiotherapy dose (Gy/fraction)
1	59/Male	20	Adenocarcinoma/postoperative recurrence	CCRT	Cisplatin+pemetrexed	Cisplatin+gemcitabine	60.0/30
2	77/Male	50	Squamous cell carcinoma/IIIB	RT	None	Carboplatin+gemcitabine	49.5/22
3	69/Male	50	Squamous cell carcinoma/IIIB	RT	None	Carboplatin+gemcitabine	38.0/19
4	71/Male	60	SCLC/IIIA	CCRT	Cisplatin+ etoposide	Cisplatin+etoposide	60.0/30
5	62/Male	30	Squamous cell carcinoma/postoperative recurrence	CCRT	Carboplatin+paclitaxel	None	60.0/30

RP, radiation pneumonitis; MLD, mean lung dose; ILD, interstitial lung disease; RT, radiation therapy; CCRT, concurrent chemoradiotherapy; SCLC, small-cell lung cancer

The cumulative incidence of grades ≥2 and 3 RP at one year was 51.0% and 20.9%, respectively. Although the percentage of lung volume affected in subclinical ILD did not significantly increase the cumulative incidence of grade ≥2 RP (69.4%vs.47.7%, $p = 0.085$,Fig. 1A.), the cumulative incidence of grade ≥3 RP was significantly higher in patients with subclinical ILD involving ≥25% of lung volume than those with <25% involvement of lung volume (46.1% vs. 16.3%, $p = 0.004$, Fig. 1B.). Chemotherapy with gemcitabine before radiotherapy did not significantly affect the cumulative incidence of grade ≥2 RP (53.2% vs. 49.4%, $p = 0.524$, Fig. 1C.), but the cumulative incidence of grade ≥3 RP was significantly higher in patients who had received chemotherapy with gemcitabine in the past than those who had not (32.3% vs. 13.3%, $p = 0.023$, Fig. 1D.).

Table 4 Correlation between factors and RP by univariate analysis

Factors	Grade ≥2 RP（N=45）				Grade ≥3 RP（N=18）			
	Grade <2 RP	Grade ≥2 RP	χ2/T	*p* value	Grade <3 RP	Grade ≥3 RP	χ2/T	*p* value
Gender			1.843	0.175			0.600	0.439
Male	37	44			63	18		
Female	5	1			6	0		
Age (years)			1.291	0.256			0.195	0.659
<70	25	32			46	11		
≥70	17	13			23	7		
Smoking history			1.931	0.165			0.470	0.493
No	15	10			21	4		
Yes	27	35			48	14		
Pathological type			0.448	0.503			1.510	0.219
NSCLC	29	28			43	14		
SCLC	13	17			26	4		
Tumor stage			6.433	0.092			1.457	0.692
I	2	0			2	0		
III	28	36			51	13		
IV	4	6			7	3		
Postoperative	8	3			9	2		
Tumor location			4.094	0.043			2.419	0.120
Upper lobe	32	25			48	9		
Middle or lower lobe	10	20			21	9		
Chemotherapy with gemcitabine in the past			0.033	0.856			4.627	0.031
No	26	27			46	7		
Yes	16	18			23	11		
Concurrent chemotherapy			2.156	0.142			0.076	0.782
No	30	38			53	15		
Yes	12	7			16	3		
Distribution of subclinical ILD			1.190	0.275			2.000	0.157
Lateral	7	4			11	0		
Bilateral	35	41			58	18		
Morphology of subclinical ILD			0.712	0.399			2.208	0.137
No honeycombing	34	33			56	11		
Honeycombing	8	12			13	7		
Percentage of lung volume affected in subclinical ILD			1.876	0.171			4.353	0.037
<25%	38	36			62	12		
≥25%	4	9			7	6		
Pulmonary emphysema			0.196	0.658			0.082	0.775
No	6	8			12	2		
Yes	36	37			57	16		
Total dose (Gy)			0.044	0.834			0.878	0.349
EQD2<60.0	13	13			19	7		
EQD2≥60.0	29	32			50	11		

Factors	Grade ≥2 RP（N=45）				Grade ≥3 RP（N=18）			
	Grade <2 RP	Grade ≥2 RP	χ2/T	*p* value	Grade <3 RP	Grade ≥3 RP	χ2/T	*p* value
Single fraction dose			0.049	0.826			0.000	1.000
2.0Gy	38	39			61	16		
>2.0Gy,≤3.0Gy	4	6			8	2		
FVC%	89.53 ± 14.50	92.15 ± 25.83	−0.481	0.632	89.93 ± 22.58	94.53 ± 17.75	−0.723	0.472
FEV1/ FVC (%)	74.71 ± 9.05	74.05 ± 9.89	0.277	0.782	74.57 ± 8.52	73.56 ± 12.40	0.359	0.720
MLD (Gy)	11.52 ± 3.36	12.97 ± 2.45	−2.307	0.024	12.00 ± 3.15	13.29 ± 2.11	−1.636	0.106
V5 (%)	46.07 ± 12.51	48.24 ± 9.54	−0.914	0.363	46.19 ± 11.69	51.06 ± 7.25	−1.679	0.097
V10 (%)	33.14 ± 9.84	35.00 ± 7.20	−1.010	0.316	33.68 ± 9.26	35.72 ± 5.04	−1.253	0.216
V20 (%)	20.62 ± 6.88	21.89 ± 4.46	−1.014	0.314	21.10 ± 6.14	21.94 ± 4.05	−0.551	0.583
V30 (%)	14.24 ± 5.64	16.07 ± 4.08	−1.741	0.085	14.91 ± 5.12	16.22 ± 4.22	−0.999	0.321

RP, radiation pneumonitis; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; FVC%, percentage forced vital capacity; EQD2, equivalent dose in 2.0 Gy/(fraction per day); MLD, mean lung dose; V5, percentage of lung volume receiving ≥5 Gy; V10, percentage of lung volume receiving ≥10 Gy; V20, percentage of lung volume receiving ≥20 Gy; V30, percentage of lung volume receiving ≥30 Gy

Table 4 shows the correlations between the risk factors and RP. In the univariate analysis, tumor location (upper lobe vs. middle or lower lobe) and MLD were associated with grade ≥2 RP ($p = 0.043$ and $p = 0.024$, respectively). The risk of grade ≥3 RP was higher in patients who had received chemotherapy with gemcitabine in the past and subclinical ILD involving ≥25% of lung volume ($p = 0.031$ and $p = 0.037$, respectively).

In the multivariate analysis, MLD≥12.0Gy was a significant risk factor for grade ≥2 RP (p = 0.049). Having received chemotherapy with gemcitabine in the past, V5≥50%, and subclinical ILD involving ≥25% of lung volume were significantly associated with grade ≥3 RP ($p = 0.046$, $p = 0.040$, and $p = 0.024$, respectively). The results of the binary logistic regression analysis for RP are shown in Table 5.

Table 5 Correlation between risk factors and RP using binary logistic regression analysis

Factors	Grade ≥2 RP			Grade ≥3 RP		
	Odds ratio (OR)	95% CI	*p* value	OR	95% CI	*p* value
MLD (≥12.0Gy vs. <12.0Gy)	2.480	1.006–6.113	0.049	-	-	-
Tumor located in lower lobe	2.311	0.898–5.943	0.082	-	-	-
Chemotherapy with gemcitabine in the past	-	-	-	3.209	1.018–10.113	0.046
V5（≥50%vs.<50%）	-	-	-	3.429	1.056–11.140	0.040
Percentage of lung volume affected in subclinical ILD ≥25%	-	-	-	4.861	1.237–19.104	0.024

RP, radiation pneumonitis; MLD, mean lung dose; V5, percentage of lung volume receiving ≥5Gy; ILD, interstitial lung disease; CI, confidence interval

Discussions

Previous studies have demonstrated a 4%–11% prevalence of subclinical ILD in high-risk populations undergoing CT screening for lung cancer [20]. A few studies found that the incidence rate of grade ≥2 RP and grade ≥3 RP was significantly higher in patients with subclinical ILD than in those without after stereotactic body radiotherapy (SBRT) [11,20]. Yamaguchi et al [21] reported that although subclinical ILD showed no significant correlation with grade ≥2 RP, three patients with extensive bilateral RP had subclinical ILD prior to receiving radiotherapy. Several studies have also found a significantly higher incidence of RP after 3-dimensional conformal radiotherapy (3D-CRT) in lung cancer patients with subclinical ILD [10,12]. Two of three patients with grade 5 RP had subclinical ILD in multiple lobes [10].

Data on the correlation between subclinical ILD and RP in patients after IMRT are limited. Our previous study revealed that subclinical ILD was a risk factor for grade ≥3 RP in patients with small-cell lung cancer after TRT [13]. In this single-institution retrospectively study, the cumulative incidence of grade ≥2 RP was 51.7%, and that of grade ≥3 RP was 20.7% in lung cancer patients with subclinical ILD after IMRT. The incidence of grade ≥2 RP in this study was consistent with that reported by previous studies, and the rate of grade ≥3 RP in this study was lower than that reported previously for patients with subclinical ILD following 3D-CRT [10,12]. Sanuki et al [22] found the rate of grade ≥3 RP increased from 3% to 26% for patients with subclinical ILD. Niska JR et al [23]

presented 2 cases of fatal RP in patients with limited subclinical ILD. Individuals with subclinical ILD were at higher risk of RP [16]. Recently, a study reported that proton therapy might be helpful for reducing acute and fatal complications in non-small-cell lung cancer (NSCLC) patients with idiopathic pulmonary fibrosis [24].

Although an association between preexisting subclinical ILD and RP has been reported, little is known about the relationship between RP and the CT radiological features of subclinical ILD. Some studies have graded subclinical ILD to evaluate its severity. However, there is no consensus on the definition of subclinical ILD grading. Washko's scoring criteria is commonly used [10,20,21,25,26]. Glick et al [20] reported that Washko's score was associated with grade ≥2 RP in a univariate analysis; however, there was no statistical difference in a multivariate analysis. Another study found that cases that exhibited honeycombing had a high fatality potential due to severe RP after SBRT [27]. In this study, we explored the correlations between the distribution, morphology, percentage of lung volume affected in subclinical ILD, and RP. Only the percentage of lung volume affected in subclinical ILD when it ≥25% was revealed to be significantly associated with the risk of grade ≥3 RP. It is simpler to evaluate the severity of subclinical ILD by indirectly measuring the percentage of lung volume affected based on pretreatment HRCT images than by using the scoring criteria, which makes it easier to identify individuals who have a high risk of RP.

Dosimetric parameters are closely correlated to RP incidence. In our study, we found that MLD is a significant risk factor for grade ≥2 RP, V5≥50% have an increased risk of grade ≥3 RP. Previous studies also found that MLD was a predictor of RP in patients with subclinical ILD after SBRT and 3D-CRT [12,20,21]. A retrospective analysis reported V5 was significantly associated with the occurrence of RP grade progression after Carbon-ion radiotherapy for NSCLC with interstitial lung disease [28]. In addition, Onishi et al [29] found that V20 ≥10% is a major risk factor for severe RP in stage I NSCLC patients with subclinical ILD. In the present study, no correlation was observed between the incidence of RP and V20. The main reason for this may be that we strictly controlled the limits of V20. Other studies have also found no correlation between dosimetric parameters and RP in patients with subclinical ILD after 3D-CRT, SBRT and IMRT [10,13,30].

Gemcitabine is a first-line chemotherapy drug that is commonly used in advanced NSCLC. Some studies have reported the pulmonary toxicity of gemcitabine. Concurrent radiotherapy and gemcitabine after induction with gemcitabine and carboplatin significantly increased the incidence of grade ≥3 RP up to 31.6% [3]. In 2010, the Quantitative Analyses of Normal Tissue Effects in the Clinic group indicated that gemcitabine is associated with a higher risk of pulmonary toxicity when used concurrently with thoracic RT [2]. Leprieur et al [7] found that induction chemotherapy with gemcitabine before radiotherapy was associated with a high incidence of RP.

So far, there has been no study that evaluated the safety of chemotherapy with gemcitabine before TRT in patients with ILD or subclinical ILD. In the current study, chemotherapy with gemcitabine before radiotherapy was a significant factor influencing the occurrence of grade ≥3 RP in lung cancer patients with subclinical ILD. Moreover, three of the five patients with grade 5 RP received chemotherapy with gemcitabine before TRT, as had five of the eight patients in whom radiotherapy was discontinued due to the occurrence of grade ≥2 RP. One phase II clinical trial concluded that induction with gemcitabine/carboplatin followed by concurrent paclitaxel/carboplatin with conformal radiation is safe and tolerable [31]. However, this study did not assess whether or not patients had concomitant pulmonary diseases prior to radiotherapy.

In conclusion, MLD is a significant risk factor for grade ≥2 RP, and lung cancer patients who have received chemotherapy with gemcitabine in the past, V5, and those with subclinical ILD involving ≥25% of lung volume have an increased risk of grade ≥3 RP. The dose-volume parameters should be strictly controlled to ensure the safety of radiotherapy. It is recommended that chemotherapy with gemcitabine be avoided prior to radiotherapy in lung cancer patients with subclinical ILD. Radiation oncologists should carefully select treatment options for lung cancer patients with subclinical ILD by considering the clinical characteristics and IMRT-induced benefits and toxicities.

As this was a single-center retrospective study with a small sample size, there is a possibility of confounding factors. A larger, prospective multi-center study is needed to confirm these conclusions.

Abbreviations

RP, radiation pneumonitis; DVH, dose-volume histogram; V20, percentage of lung volume receiving ≥20 Gy; MLD, mean lung dose; ILD, interstitial lung disease; TRT, thoracic radiation therapy; IMRT, intensity-modulated radiated therapy; EQD2, equivalent dose in 2.0 Gy/(fraction per day); GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; HRCT, high-resolution CT; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; RT, radiation therapy；CCRT, concurrent chemoradiotherapy; FVC, forced vital capacity；FEV1, forced expiratory volume in one second；FVC%, percentage forced vital capacity; V5, percentage of lung volume receiving ≥5 Gy; V10, percentage of lung volume receiving ≥10 Gy; V30, percentage of lung volume receiving ≥30 Gy; CI, confidence interval; SBRT, stereotactic body radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Ethical Review Committee of Tongji University Affiliated Shanghai Pulmonary Hospital, China.

Consent for publication

All authors consented to the publication of the manuscript.

Availability of data and materials

Support data is available to interested readers upon reasonable request to corresponding author.

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Authors' contributions

Yaping Xu and Shixiong Liang designed the research, interpreted and discussed the results; Fangjuan Li, Hui Liu, and Hongyu Wu collected the data, analyzed the data, wrote the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare that they have no competing interests.

References

1. Palma DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys.2013;85(2): 444-450.
2. Marks LB, Bentzen SM, Deasy JO, et al. Radiation Dose Volume Effects in the Lung. Int J Radiat Oncol Biol Phys.2010;76(3Suppl): S70-76.
3. Arrieta O, Gallardo-Rincón D, Villarreal-Garza C, et al. High frequency of radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent radiotherapy and gemcitabine after induction with gemcitabine and carboplatin. J Thorac Oncol. 2009; 4(7): 845-852.
4. Meadors M, Floyd J, Perry MC. Pulmonary toxicity of chemotherapy. Semin Oncol. 2006; 33(1): 98-105.
5. Zhang XJ, Sun JG, Sun J, et al. Prediction of radiation pneumonitis in lung cancer patients: a systematic review. J Cancer Res Clin Oncol.2012;138(12): 2103-2016.
6. Dang J, Li G, Zang S, et al. Risk and predictors for early radiation pneumonitis in patients with stage III non-small cell lung cancer treated with concurrent or sequential chemoradiotherapy. Radiat Oncol.2014;9:172.
7. Leprieur EG, Fernandez D, Chatellier G, et al. Acute radiation pneumonitis after conformational radiotherapy for non-small cell lung cancer: clinical, dosimetric, and associated-treatment risk factors. J Cancer Res Ther. 2013; 9(3): 447-451.
8. Baker R, Han G, Sarangkasiri S, et al. Clinical and dosimetric predictors of radiation pneumonitis in a large series of patients treated with stereotactic body radiation therapy to the lung. Int J Radiat Oncol Biol Phys.2013; 85:190-195.
9. Torre-Bouscoulet L, Muñoz-Montaño WR, Martínez-Briseño D, et al. Abnormal pulmonary function tests predict the development of radiation-induced pneumonitis in advanced non-small cell lung Cancer. Respir Res. 2018; 19: 72.
10. Yamaguchi S, Ohguri T, Matsuki Y, et al. Radiotherapy for thoracic tumors: association between subclinical interstitial lung disease and fatal radiation pneumonitis. Int J Clin Oncol. 2015; 20(1): 45-52.
11. Ueki N, Matsuo Y, Togashi Y, et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung cancer. J Thorac Oncol. 2015; 10: 116-125.
12. Lee YH, Kim YS, Lee SN, et al. Interstitial lung change in pre-radiation therapy computed tomography is a risk factor for severe radiation pneumonitis. Cancer Res Treat. 2015; 47(4): 676-686.
13. Li F, Zhou Z, Wu A, et al. Preexisting radiological interstitial lung abnormalities are a risk factor for severe radiation pneumonitis in patients with small-cell lung cancer after thoracic radiation therapy. Radiat Oncol. 2018; 13: 82.
14. Chen H, Senan S, Nossent EJ, et al. Treatment-related toxicity in patients with early-stage non-small cell lung cancer and co-existing interstitial lung disease: a systematic review. Int J Radiat Oncol Biol Phys. 2017; 98(3): 622-631.
15. Onishi H，Yamashita H，Shioyama Y, et al. Stereotactic Body Radiation Therapy for Patients with Pulmonary Interstitial Change: High Incidence of Fatal Radiation Pneumonitis in a Retrospective Multi-Institutional Study. Cancers (Basel) 2018; 10(8): 257.
16. Goodman CD, Nijman SF, Senan S, et al. A Primer on Interstitial Lung Disease and Thoracic Radiation. J Thorac Oncol. 2020; 15(6): 902-913.
17. Yamashita H, Kobayashi-Shibata S, Terahara A, et al. Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy. Radiat Oncol. 2010; 5: 32.
18. Doyle TJ, Hunninghake GM, Rosas IO. Subclinical interstitial lung disease: why you should care. Am J Respir Crit Care Med. 2012; 185: 1147-1153.
19. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013; 188: 733-748.
20. Glick D, Lyen S, Kandel S, et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival in patients treated with lung stereotactic body radiation therapy (SBRT). Clin Lung Cancer. 2018; 19(2): e219-226.
21. Yamaguchi S, Ohguri T, Ide S, et al. Stereotactic body radiotherapy for lung tumors in patients with subclinical interstitial lung disease: the potential risk of extensive radiation pneumonitis. Lung Cancer. 2013; 82: 260-265.

22. Sanuki N，Ono A，Komatsu E，Kamei N, Akamine S,et al. Association of Computed Tomography-detected Pulmonary Interstitial Changes with Severe Radiation Pneumonitis for Patients Treated with Thoracic Radiotherapy. J Radiat Res.2012;53(1):110-116.
23. Niska JR,Schild SE,Rule WG,Daninels TB,Jett JR.Fatal Radiation Pneumonitis in Patients With Subclinical Interstitial Lung Disease.Clinical lung cancer.2018;19(4):E417-E420.
24. Kim H, Pyo H, Noh JM et al. Preliminary result of definitive radiotherapy in patients with non-small cell lung cancer who have underlying idiopathic pulmonary fibrosis: Comparison between X-ray and proton therapy. Radiat Oncol 2019; 14:19.
25. Bahig H, Filion E, Vu T, et al. Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease. Pract Radiat Oncol. 2016; 6(5): 367-374.
26. Washko GR, Lynch DA, Matsuoka S, et al. Identification of early interstitial lung disease in smokers from the COPDGene Study. Acad Radiol. 2010; 17(1): 48-53.
27. Okubo M, Itonaga T, Saito T, et al. Predicting risk factors for radiation pneumonitis after stereotactic body radiation therapy for primary or metastatic lung tumours. Br J Radiol. 2017; 90(1073): 20160508.
28. Nakajima M, Yamamoto N, Hayashi K, et al. Carbon-ion radiotherapy for non-small cell lung cancer with interstitial lung disease: a retrospective analysis. Radiat Oncol. 2017; 12: 144.
29. Onishi H, Yamashita H, Shioyama Y, et al. Stereotactic body radiation therapy for patients with pulmonary interstitial change: high incidence of fatal radiation pneumonitis in a retrospective multi-institutional study. Cancers. 2018；10(8): 257.
30. Ozawa Y, Abe T, Omae M, et al. Impact of preexisting interstitial lung disease on acute, extensive radiation pneumonitis: retrospective analysis of patients with lung cancer. PLoS One. 2015; 10: e0140437.
31. Bepler G, Dilling TJ, Wagner H, et al. Phase II trial of induction gemcitabine and carboplatin followed by conformal thoracic radiation to 74 Gy with weekly paclitaxel and carboplatin in unresectable stage III non-small cell lung cancer. J Thorac Oncol. 2011; 6(3): 553-558.

Figures

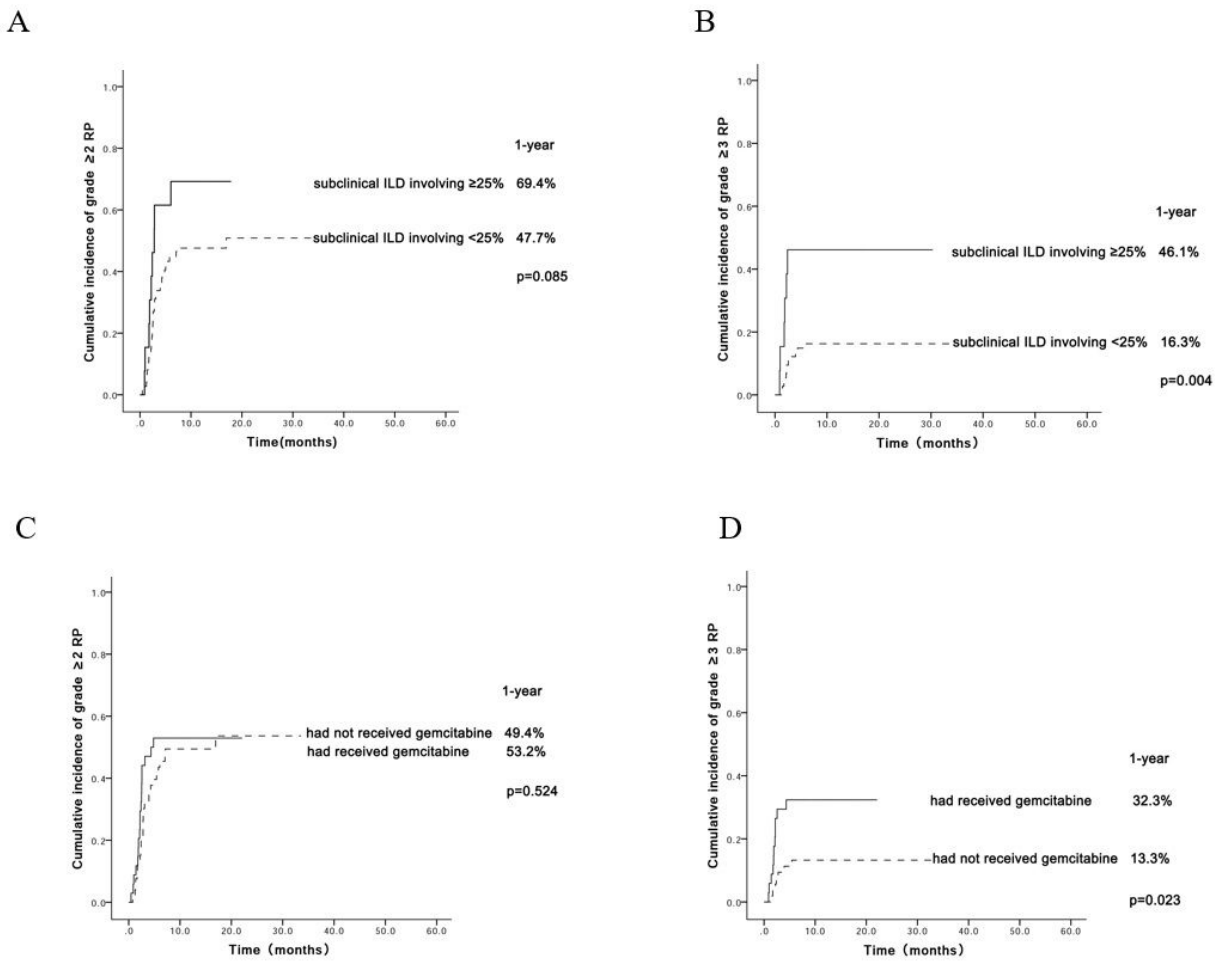

Figure 1

(A) Cumulative incidence of grade ≥2 RP in patients with different involvement volumes of subclinical ILD; (B) Cumulative incidence of grade ≥3 RP in patients with different involvement volumes of subclinical ILD; (C) Cumulative incidence of grade ≥2 RP in patients who had (solid line) or had not (dashed line) received chemotherapy with gemcitabine in the past; (D) Cumulative incidence of grade ≥3 RP in patients who had (solid line) or had not (dashed line) received chemotherapy with gemcitabine in the past