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Computed tomography patterns and clinical outcomes of radiation pneumonitis in non–small-cell lung cancer patients

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Abstract

Background: Radiation pneumonitis (RP) is not an uncommon complication in lung cancer patients undergoing radiation therapy (RT) and symptomatic RP can affect their quality of life.

Purpose: To investigate the CT findings of RP in non–small cell lung cancer (NSCLC) patients and their relationship with clinical outcomes.

Materials and methods: We reviewed data from 240 NSCLC patients who underwent RT between 2014 and 2022. CT findings of RP were evaluated for parenchymal abnormalities and distribution, which were then classified into three patterns: localized pneumonia (LP), cryptogenic organizing pneumonia (COP), and acute interstitial pneumonia (AIP). Clinical outcomes of RP were evaluated based on Common Terminology Criteria for Adverse Events (CTCAE) grade.

Results: Of the 153 patients, 135 developed RP. The most common pattern was LP ($n = 78$), followed by COP ($n = 30$) and AIP ($n = 25$). Among the three CT patterns, CTCAE grade and days between the start of RT and the onset of RP (RT-RP days) were statistically significantly different ($p < 0.05$). The patients with AIP patterns exhibited higher CTCAE grade, and fewer RT-RP days compared to those with non-AIP patterns ($p < 0.05$). In these patients, lung-to-lung metastasis and underlying interstitial lung abnormality were observed more frequently ($p < 0.05$). Underlying pulmonary fibrosis, the AIP pattern, and higher CT extent scores were more frequently observed in higher CTCAE grade group ($p < 0.001$). In multiple regression analysis, age, bilateral distribution, RT-RP days, and CT extent score ≥3 were independent predicting factors for higher CTCAE grade.

Conclusions: RP in NSCLC patients can be classified into LP, COP, and AIP patterns and they exhibit different severities in clinical outcomes.

Keywords

radiation therapy, radiation pneumonitis, lung cancer, computed tomography

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Introduction

Radiation therapy (RT) is essential and has increased in frequency in the treatment of patients with lung cancer. It is used as a primary treatment in non–small-cell lung cancer (NSCLC) patients with unresectable disease or in cases where surgical indications are poor, where it is either combined with platinum-based chemotherapy or immunotherapy or used alone.[1,2]

Radiation pneumonitis (RP) is one of the serious adverse events (AEs) seen in patients with lung cancer treatment. More advanced RT techniques have been developed to conform the radiation dose to the tumor, with sparing of adjacent normal tissues. However, adverse effects are still common because the normal tissue surrounding the target cannot be entirely spared.[3–5]

The imaging findings of RP display a spectrum ranging from scarce patchy lesions to extensive lesions, often with well-defined area of consolidation within the irradiation field as localized pneumonia pattern. In some cases, RP occurs beyond the irradiated field, and histologically it may manifest as organizing pneumonia. This organizing pneumonia pattern appears as migratory opacities outside of the radiation fields. And is believed to be immunologically mediated. Rarely, ground glass opacities (GGOs) or consolidation is seen in early phase, while some septal thickening over these opacities may occur later and cause a "crazy paving" occupying the extensive lung as acute interstitial pneumonia.[6,7]

Symptomatic RP can affect quality of life in lung cancer patients and occurs in up to 37% of patients receiving concurrent chemo-radiation therapy (CCRT). Follow-up computed tomography (CT) shows varying degrees of lung parenchymal changes in the majority of patients after RT.[8–10] Therefore, it is important to differentiate RP with clinically significant symptoms that require further management. To our knowledge, there have not been many reports on the analysis of specific CT findings and patterns of RP correlated with clinical outcomes. The purpose of this study was to investigate the CT findings of RP in NSCLC patients and their relationship with clinical outcomes based on CT pattern.

Materials and methods

Study population

Institutional review board approval was obtained for this retrospective study, and the need for informed consent was waived. We retrospectively reviewed the medical records of 240 consecutive patients who were diagnosed with NSCLC and received RT as a curative treatment between January 2014 and December 2022. We excluded 87 patients for the following reasons: absence of CT scans after RT (n = 35), incomplete RT (n = 21), surgery after RT (n = 14), and follow-up loss (n = 17). Of the 153 enrolled patients, 135 developed RP. We reviewed their medical records to collect demographic information (age, sex, and smoking history); the results of pulmonary function test (PFT); histologic types of lung cancer; and implementation of additional treatments including adjuvant chemotherapy, chemo-immunotherapy, and tyrosine kinase inhibitor (TKI) therapy.

Radiation therapy method

We planned to deliver 60–66 Gy via convention fraction radiotherapy using a linear accelerator in concomitant chemo-radiotherapy patients and 30 Gy in those receiving palliative treatment. All plans were based on 2.5- or 5-mm CT scan images obtained in the treatment position before radiotherapy. The gross tumor volume (GTV) was defined as the combination of the primary tumor and all lymph nodes considered pathological on pre-treatment CT. All plans were normalized to the prescribed dose covering 90% of the planning target volume using the Eclipse treatment planning system ver. 13.0 (Varian Medical Systems, Palo Alto, CA, USA). The plans were optimized for the True Beam linear accelerator (linac) (Varian Medical Systems, Palo Alto, CA, USA) and Clinac iX (Varian Medical Systems, Palo Alto, CA, USA). Patient positioning during treatment was verified with daily onboard kilovoltage imaging and weekly onboard cone-beam CT imaging. The RT techniques, GTV, total radiation dose, mean lung dose (MLD), and lung volume receiving ≥20 Gy (V20) were assessed in the patients.

CT scan acquisition and interpretation

CT scans were acquired using a multidetector CT system (Somatom Sensation 64, dual-source Somatom definition Flash 128, or dual-source Somatom Force 192 multidetector CT system; Siemens Medical Solutions, Erlangen, Germany) with or without intravenous administration of contrast medium before and after RT. All CT scans were obtained using the following parameters: detector collimation, 1.25 or 0.625 mm; field of view, 36 cm; 80–120 kVp; 90–150 mA; tube rotation time, 0.5 s; pitch, 1.2; and reconstruction interval, 1–2.5 mm. CT data were reconstructed using a high spatial-frequency algorithm for lung window images and a soft-tissue algorithm for mediastinal window images.

We first reviewed the pre-RT CT scans and evaluated the CT features related to lung cancer, including tumor size (T stage); the presence of mediastinal metastatic lymph nodes (N stage); lung-to-lung metastasis; and underlying lung diseases such as emphysema or bronchiectasis, pulmonary fibrosis, and interstitial lung abnormality (ILA).

Findings of follow-up CT scans after RT were evaluated jointly by two radiologists with 30 and 16 years of experience in thoracic CT interpretation, respectively, who reached their conclusions by consensus. The CT findings were assessed for parenchymal abnormalities, including GGOs with reticulation, consolidation, air–bronchogram, traction bronchiectasis, necrosis or cavity formation, pleural effusion, and progression of underlying pulmonary fibrosis or ILA. The laterality (unilateral and bilateral) and distribution of lung parenchymal abnormalities (focal, multifocal, and diffuse) were also evaluated.

The extent of pneumonitis was scored in terms of upper, middle, and lower lungs using a six-point scale (0:none, 1: 1%–5%, 2:6%–25%, 3:26%–50%, 4:51%–75%, 5:76%–100%) according to the methods used in previous studies.[9,11,12]

Parenchymal abnormalities were classified into three patterns—localized pneumonia (LP), cryptogenic organizing pneumonia (COP), and acute interstitial pneumonia (AIP)—with partial reference to the American Thoracic Society/European Respiratory Society international multidisciplinary classification of interstitial pneumonia described previously.[13] Lesions were classified as LP pattern when lung abnormalities of consolidation with or without GGO showed localized distribution around the lung cancer (Figure 1). They were categorized as COP pattern when abnormalities of consolidation with or without GGO showed multifocal distribution along the subpleural or bronchovascular bundles (Figure 2). Finally, lesions were considered to have an AIP pattern when abnormalities demonstrated areas of consolidation with or without GGO, showing patchy and extensive distribution without zonal predominance (Figure 3). In cases with at least two distinct CT patterns, the predominant pattern was chosen. Finally, when lung abnormalities did not fit into any of the three categories, the lesions were considered unclassifiable.

Clinical outcomes of patients

The clinical outcome after RT was evaluated based on CTCAE grade, steroid treatment, hospitalization, and death. The CTCAE grades were as follows: grade1 (asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated); grade2 (minimal, local, or noninvasive intervention indicated; limits on age-appropriate instrumental activities of daily living [ADL]); grade3 (severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated,

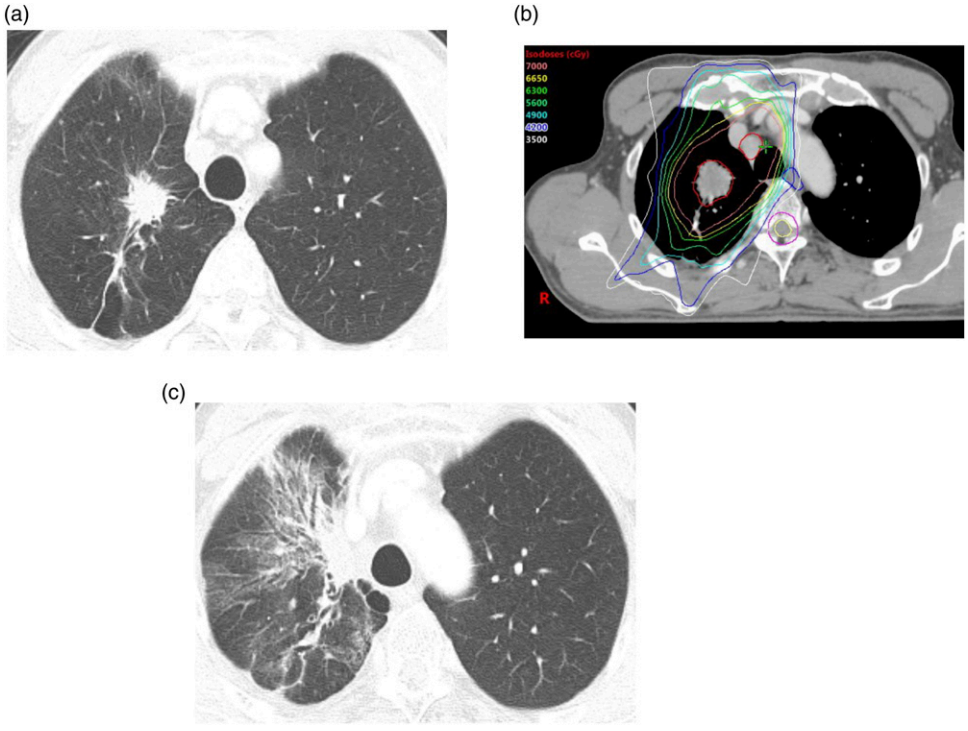

Figure 1. Radiation pneumonitis presenting localized pneumonia pattern in a 55-year-old male patient who was diagnosed with lung adenocarcinoma. The GTV, RT dose, MLD, and Lung V20 were 47.1 cm^3, 7000 mGy, 1478.6 mGy, and 22.9%. On the clinical follow up, he had no significant symptom related to RP (CTCAE grade 1). (a) Pre-RT CT shows a mass with spiculated margin confirmed with lung cancer in the right upper lobe. (b) Isodose multiplanar image for IMRT (c) Chest CT scan 5 months after RT shows that the primary lesion has decreased in size and there is development of peribronchial GGO and consolidation with traction bronchiectasis localized in the right upper lobe with decreased volume.

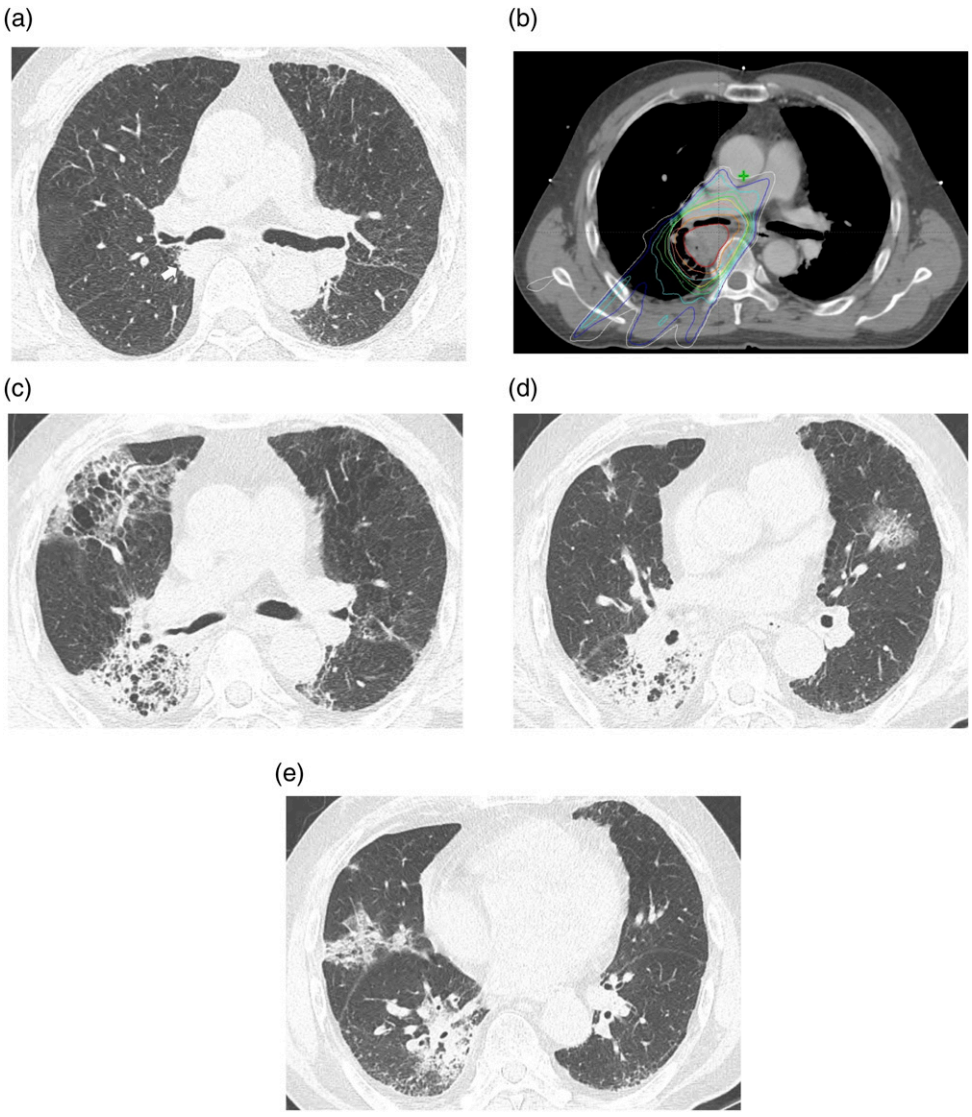

Figure 2. Radiation pneumonitis presenting cryptogenic organizing pneumonia pattern in a 71-year-old male patient who was diagnosed with lung adenocarcinoma. The GTV, RT dose, MLD, and Lung V20 were 39 cm^3, 7000 mGy, 1295.9 mGy, and 23.1%. At the clinical follow up, he had symptoms of dyspnea (CTCAE grade 3). (a) Pre-RT CT shows the primary lung cancer (arrow) in the prevertebral area of the right lower lobe and underlying diffuse emphysema in both lungs. (b) Isodose multiplanar image for IMRT (c)–(e) Chest CT scans 5 months after RT show that the primary lesion has decreased in size and there is development of multifocal peribronchial and subpleural GGO and consolidation in both lungs.

disabling, limits on performing self-care ADLs); grade4 (life-threatening consequences, urgent intervention indicated); and grade5 (death related to AEs) according to CTCAE, version 5.0.[14]

Statistical analysis

Statistical analyses were conducted using SPSS (version 28; IBM Corp., Armonk, NY, USA). Data were summarized and displayed as mean ± standard deviation (SD) or the median for continuous variables and as number of individuals plus the percentage in each group for categorical variables. Statistical comparisons were conducted between two groups using the Mann–Whitney *U* test, Pearson's chi-square test and Fisher's exact test to assess differences in demographic data, RT data, pre- and post-RT CT findings, and clinical outcomes. Correlations between variables and 3 CT pattern were evaluated using the Kruskal–Wallis test with post hoc analysis (Tukey's test) to establish segment-by-segment differences. Logistic regression analysis was employed to identify factors related to AIP pattern and high CTCAE grade. In all statistical analyses, $p < 0.05$ was considered statistically significant.

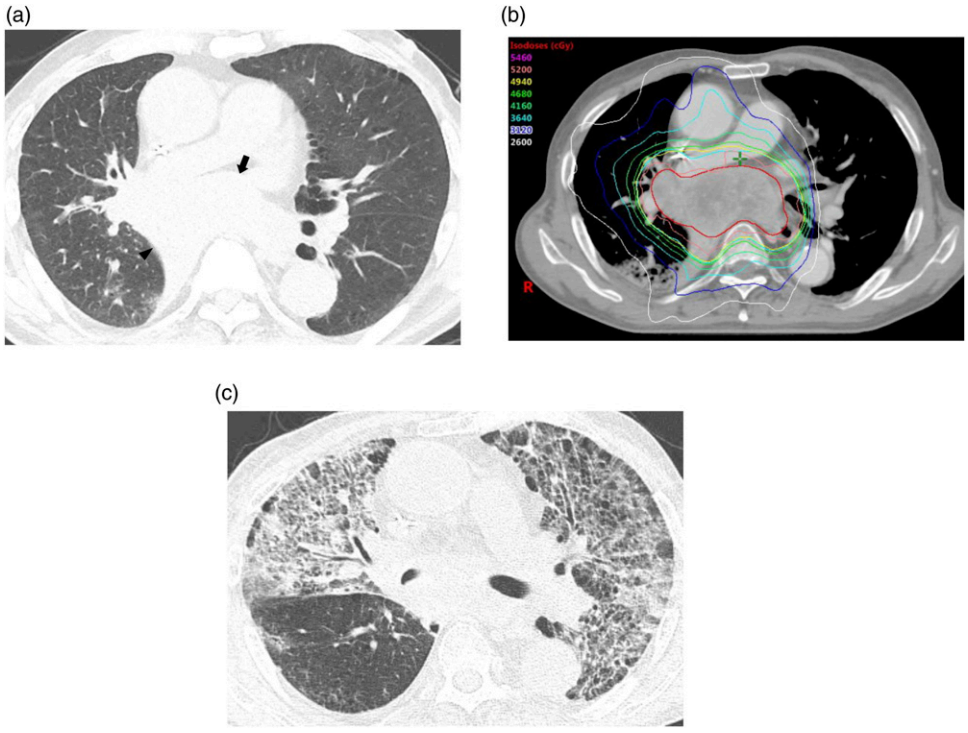

Figure 3. Radiation pneumonitis presenting acute interstitial pneumonia pattern in a 69-year-old male patient who was diagnosed with lung squamous cell carcinoma. The GTV, RT dose, MLD, and Lung V20 were 176.6 cm^3, 5200 mGy, 1532.6 mGy, and 29.6%. At the clinical follow up, he had symptoms of dyspnea and cough (CTCAE grade 3). (a) Pre-RT CT shows a large primary lung cancer (arrow) with mediastinal invasion in central portion of the right lower lobe, accompanied by complete atelectasis of the right lower lobe (arrowhead). Underlying emphysema is noted. (b) Isodose multiplanar image for IMRT (c) Chest CT scan 50 days after RT shows that the primary lesion has decreased in size and there is development of diffuse GGO with interstitial thickening in both lungs. The expansion of the right lower lobe is also noted with no evidence of parenchymal infiltration.

Results

The overall results of demographics, clinical characteristics, pre-RT CT findings, and RT techniques of the patients with RP are summarized in Table 1.

The mean number of days between the start of RT and the onset of RP (RT-RP days) on CT scan was 160.5 (SD, 99.7; range, 8–658) days. The CT findings and extent of RP are summarized in Table 2. The CT findings were classified into three patterns. The most common pattern was LP (57.8%, 78 patients), followed by COP (22.2%, 30 patients) and AIP (18.5%, 25 patients). In two patients, the CT findings were unclassifiable.

CTCAE grade was grade 1 in 61 patients (45.9%), grade 2 in 27 (20.3%), grade 3 in 32 (24.1%), grade 4 in 12 (9.0%), and grade 5 in one (0.7%). Fifty-four patients (40.6%) underwent steroid treatment. There were 45 patients (33.8%) who required hospitalization, and their mean hospital stay length was 19.7 (SD, 19.7; range, 1–173) days. A total of 13 patients died, and the mean duration between the onset of RP and death was 22.7 (SD, 19.1; range, 5–18) days. Of 133 patients with RP, 88 (66%) were CTCAE grade ≤2 and 45 (34%) were CTCAE grade ≥3. Comparisons of the clinical characteristics, RT techniques, and CT patterns of RP between the higher and lower CTCAE grade groups are demonstrated in Table 3. Underlying pulmonary fibrosis was more frequent in the CTCAE grade ≥3 group ($p < 0.001$). The AIP pattern was also more frequent in the CTCAE grade ≥3 group, accounting for 44% (20/45 patients) compared to just 0.6% (5/88 patients) in the CTCAE grade ≤2 group ($p < 0.001$). Conversely, the LP and COP patterns were more frequent in the CTCAE grade ≤2 group ($p < 0.001$). Patients with a CT extent score ≥3 points were more common in the CTCAE grade ≥3 group ($p < 0.001$). There was a significant difference in mean RT-RP days between the two groups ($p < 0.001$).

Table 4 summarizes the clinical characteristics, RT techniques, and outcomes in each RP CT pattern group. Significant differences were observed among the three CT patterns in terms of GTV ($p = 0.016$), CTCAE grade ($p < 0.001$), RT-RP days ($p = 0.002$), hospitalization ($p < 0.001$), and steroid treatment ($p < 0.001$). For the RP patients with the AIP pattern, lung-to-lung metastasis ($p = 0.026$) and ILA on pre-RT CT scan ($p = 0.019$) were more frequently observed. Additionally, these patients exhibited

Table 1. Demographics, clinical characteristics, pre-CT findings, and radiation therapy techniques of patients with radiation pneumonitis.

Characteristics		Patients with RP (n = 135)
Age, mean, (range)		67.3 (43–88) year-old
Gender		
Male (%)		121 (89.6)
Female (%)		14 (10.4)
Smoking status		
Never smoker		12 (8.9)
Former/current smoker (%)		123 (91.1)
Mean pack-year, year	41.1	
Pulmonary function test		
Mean FEV_1/FVC, %		67.3 (± 7.9)
Mean FEV_1, L		2.1 (± 0.6)
Mean FVC, L		3.2 (± 0.8)
Histologic type of lung cancer		
Squamous cell carcinoma (%)		89 (65.9)
Adenocarcinoma (%)		44 (32.6)
NSCLC not otherwise specified (%)		1 (0.75)
Adenosquamous carcinoma (%)		1 (0.75)
Additional treatment		
Chemotherapy (%)		125 (92.6)
Chemo-immunotherapy (%)		21 (15.6)
TKI therapy (%)		2 (0.01)
Pre-RT CT		
Tumor size, mean ± SD, (range)		50.1 ± 20.1 (3–104) cm
T stage (%)	1	16 (11.9)
	2	28 (20.7)
	3	20 (14.8)
	4	71 (52.6)
N stage (%)	0	16 (11.9)
	1	34 (25.2)
	2	55 (40.7)
	3	30 (22.2)
Lung-to-lung metastasis		15 (11.1)
Underlying pulmonary disease		
Emphysema or bronchiectasis		50 (37.0)
ILA		19 (14.1)
Pulmonary fibrosis		7 (5.2)
Radiation therapy technique		
GTV, mean, median (range)		127.5, 106.9 (6.3–487.4) cm^3
Radiation dose, mean, median (range)		6142.4, 6600.0 (3000.0–7000.0) mGy
MLD, mean, median (range)		1433.3, 1458.7 (364.8–2267.5) mGy
Lung V20, mean, median (range)		24.3, 24.6 (1.1–44.8) %

RP, radiation pneumonitis; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; RT, radiation therapy; CT, computed tomography; SD, standard deviation; ILA, interstitial lung abnormality GTV, gross tumor volume; MLD, mean lung dose; Lung V20, volume of normal lung receiving 20 Gy.

higher GTV ($p = 0.006$), CTCAE grade ($p < 0.001$), and rate of hospitalization ($p < 0.001$) and steroid treatment ($p < 0.001$) as well as fewer RT-RP days ($p = 0.017$) compared to the patients with non-AIP patterns. When comparing the LP and COP patterns, patients with the LP pattern had lower CTCAE grade ($p < 0.001$), lower rate of hospitalization ($p = 0.003$) and steroid treatment ($p = 0.002$), and more RT-RP days ($p = 0.010$).

Regarding the extent of RP (Table 5), underlying pulmonary fibrosis onpre-RT CT scans ($p = 0.013$) was frequently observed in patients with a CT extent score ≥3 points. They also had higher GTV ($p = 0.022$), RT dose ($p = 0.011$), MLD ($p = 0.049$), V20 ($p = 0.014$), CTCAE grade ($p < 0.001$), and rate of hospitalization ($p < 0.001$) and steroid treatment ($p < 0.001$) as well as fewer RT-RP days ($p = 0.031$) compared to patients with a CT extent score ≤2 points. In logistic regression analysis, age ($p = 0.016$, odds ratio [OR] = 1.050 [95% confidence interval (CI), 0.025–0.073]), bilateral distribution ($p = 0.002$, OR = 9.219 [95% CI, 1.512–2.930]), RT-RP days ($p = 0.003$, OR = 0.992 [95% CI, −0.011 to −0.005]), AIP pattern ($p < 0.001$, OR = 13.280 [95% CI, 2.036–3.136]), and CT extent score ≥3 points ($p < 0.001$, OR = 15.750 [95% CI, 2.304–3.210) were associated with CTCAE grade ≥3. In multiple regression analysis, age ($p = 0.018$, OR = 1.091 [95% CI, 0.050–0.124]), bilateral distribution ($p = 0.010$, OR = 6.538 [95% CI, 1.146–2.610]), RT-RP days ($p = 0.027$, OR = 0.991 [95% CI, −0.013 to −0.005]), and CT extent score ≥3 points ($p < 0.001$, OR = 10.259 [95% CI, 1.702–2.954]) were independent predicting factors for higher CTCAE grade. In logistic regression analysis with pre-RT CT and RT factors, lung-to-lung-metastasis ($p = 0.033$, OR = 3.474 [95% CI, 0.661–1.829]), underlying ILA

Table 2. CT findings of radiation pneumonitis.

CT findings	No. Of patients (%)
Parenchymal abnormalities	
GGO with reticulation	131 (98.5)
Consolidation	114 (85.7)
Air-bronchogram	96 (72.2)
Traction bronchiectasis	82 (61.7)
Additional findings	
Pleural effusion	49 (36.8)
Necrosis or cavity formation	9 (6.8)
Progression of ILA or pulmonary fibrosis	[a]13/26
Distribution	
Bilateral	45 (33.8)
Focal	78 (58.6)
Multifocal	34 (25.6)
Diffuse	29 (21.8)
Classification of CT patterns	
LP	78 (57.8)
COP	30 (22.2)
AIP	25 (18.5)
Unclassified	2 (1.5)
CT extent score	
1	32 (24.1)
2	50 (37.6)
3	26 (19.5)
4	16 (12.0)
5	9 (6.8)

CT, Computed tomography; No, number; GGO, ground-glass opacity; ILA, interstitial lung abnormality; LP, localized pneumonia; COP, cryptogenic organizing pneumonia; AIP, acute interstitial pneumonia.
[a]On the pre-RT CT, 26 patients presented ILA or pulmonary fibrosis, of whom 13 patients further progressed after RT.

(p = 0.024, OR = 3.429 [95% CI, 0.685–1.779]), GTV (p = 0.009, OR = 1.005 [95% CI, 0.003–0.007]), and RT-RP days (p = 0.040, OR = 0.993, [95% CI, −0.004 to −0.010]) were associated with the AIP pattern of RP. In multiple regression analysis, lung-to-lung metastasis (p = 0.078, OR = 1.779 [95% CI, 0.008–0.288]) and underlying ILA (p = 0.012, OR = 2.541 [95% CI, 0.144–0.33]) were independent predicting factors for the AIP pattern of RP.

Discussion

Radiation-induced lung injury can manifest with a broad spectrum of clinical symptoms, from asymptomatic cases to those with life-threatening acute respiratory distress syndrome. Clinically severe symptomatic RP has been reported at rates of approximately 2%–5%. In such cases, immediate supportive treatment with corticosteroids is imperative.[9,15–17]

CTCAE version 5.0, which we applied, is the most common grading system and is applicable not only for grading RP, but also for standardizing the classification of adverse effects by drugs used in cancer therapy.[14] In our study, of a total of 219 patients who completed RT, approximately 20% (45 patients) developed RP of CTCAE grade ≥3. Notably, RP occurred at a higher frequency in our work than in previous studies. This discrepancy may be attributed to concomitant administration of anti-cancer drugs including chemotherapy or chemo-immunotherapy in all patients, and the patient cohort was selected by retrospectively collecting individuals who had detailed medical records.

The incidence of radiation injury is directly correlated with lung radiation dose and the total volume of irradiated lung tissue.[18,19] Notable factors related to RT include irradiation techniques, total RT dose, fractionation, and the volume of irradiated lung.[10,18,20–22] In our study, patients with a CT extent score ≥3 points exhibited higher GTV, RT dose, MLD, and V20 compared to those patients with a CT extent score ≤2 points.

Several patient-related factors, including age, performance status, smoking history, and underlying pulmonary condition, have been implicated in the development of RP.[23,24] In our study, all patients underwent additional treatment with chemotherapy, chemo-immunotherapy, or TKI, and we could not identify the influence of the additional cancer therapy itself or significant differences according to the treatment regimen. However, age was one of the significant predicting factors for higher CTCAE grade. Additionally, underlying pulmonary fibrosis (p = 0.013) was frequently observed in patients with a CT extent score ≥3 points. The presence of underlying interstitial lung disease (ILD) is also a significant risk factor for any grade and fatal RP.[25–29] In our study, patients with pulmonary fibrosis on pre-RT CT scans presented with subpleural GGO, reticulation, and traction bronchiectasis with or without honeycombing which corresponds to a probable UIP or UIP pattern.[30] Although limited ILD rarely leads to fatal RP, caution remains necessary during RT, and severe and extensive ILD may contraindicate RT.[31–33]

In our study, ILA cases were defined separately. Notably, although ILA was not a direct risk factor for a high RP grade, it was a risk factor for the AIP pattern of RP. Seven of 19 patients who presented with an ILA later developed AIP pattern RP. ILA do not refer to a specific disease itself, but rather to abnormal imaging findings incidentally found on CT. It is known that it can progress to clinical significant ILD and is associated with increased mortality.[34–36] ILA are known to be associated with increased mortality in both general population and smokers, and have also reported to be correlated with increased cancer-related mortality. The cause of this increase in mortality has not yet been clearly defined. However, some studies have suggested a correlation between ILA and the risk of diffuse lung damage related to cancer treatment in patients receiving thoracic RT, systemic chemotherapy, targeted therapy, or immunotherapy. Particularly, ILA has been reported as one of the risk

Table 3. Clinical characteristics, radiation therapy techniques, and CT findings of radiation pneumonitis in terms of CTCAE grades.

		CTCAE ≤2 (n = 88)	CTCAE ≥3 (n = 45)	p value
Age (range), year		66.3 ± 8.1 (43–86)	69.3 ± 7.1 (50–88)	0.055
Sex				
Male		78	41	0.772
Female		10	4	
Pulmonary function test				
FEV_1 (range), L		3.23 ± 0.74 (1.82–4.67)	2.93 ± 0.76 (0.99–4.21)	0.061
FVC (range), L		2.18 ± 0.63 (0.73–3.48)	1.89 ± 0.57 (0.63–2.92)	0.089
FEV_1/FVC (range), %		66.26 ± 10.51, (38–90)	64.79 ± 13.01 (32–87)	0.728
Pre-RT CT				
T stage	1	11	5	0.934
	2	19	9	
	3	12	8	
	4	46	23	
T size (range), cm		48.1 ± 19.7 (3–104)	51.6 ± 19.0 (18–101)	0.370
N stage	0	9	7	0.327
	1	24	9	
	2	39	16	
	3	16	13	
Lung-to-lung metastasis		8	7	0.265
Emphysema/ Bronchiectasis		22	16	0.202
Fibrosis		0	7	<0.001
ILA		9	9	0.119
Radiation therapy				
GTV (range), cm^3		121.1 ± 102.5 (6.3–487.4)	142.6 ± 106.0 (10.6–466.4)	0.178
RT dose (range), mGy		6164.8 ± 958.3 (3000–7000)	5925.3 ± 1148.3 (3000–7000)	0.200
MLD (range), mGy		1451.5 ± 385.3 (364.8–2215.9)	1500.5 ± 402.5 (526.4–2267.5)	0.479
V20 (range), mGy		24.7 ± 7.8 (1.1–43.2)	26.0 ± 8.5 (6.8–44.8)	0.401
CT extent score				
≤2		72	10	<0.001
≥3		16	35	
CT pattern of RP				
LP		65	13	<0.001
COP		18	12	
AIP		5	20	
RT-RP days (range)		179.3 ± 110.9 (8–658)	124.8 ± 61.3 (40–354)	<0.001

Data are mean ± standard deviation or n values.
CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; RT, radiation therapy; ILA, interstitial lung abnormality; GTV, gross tumor volume; MLD, mean lung dose; Lung V20, volume of normal lung receiving 20 Gy; RP, radiation pneumonitis; LP, localized pneumonia; COP, cryptogenic organizing pneumonia; AIP, acute interstitial pneumonia; RT-RP days, days between the start of radiation therapy and the onset of radiation pneumonitis.

factors of severe RP in the patients who underwent thoracic RT for lung cancer.[37–40] Subclinical ILA can progress to significant lung damage and is associated with increased mortality in patients with undergoing thoracic RT. It is important to recognize ILA during the pretreatment evaluation of the patients with lung cancer.

In the previous study, Thomas et al. classified the CT findings of RP into AIP, COP, non-specific interstitial pneumonia, and hypersensitivity pneumonia patterns, and compared the AIP pattern and other patterns. In their research, both focal and multifocal pneumonitis were classified as COP pattern and patients showing NSIP and HP patterns were only included in small numbers.[9] In comparison with their study, we classified the CT findings of RP differently. Specifically, focal lesions within RT fields were separately classified into the LP pattern, known as typical RP finding. Multifocal lesions beyond the RT fields were categorized into COP pattern, bilateral diffuse lesions as AIP pattern, and some as unclassified patterns. We then compared these three main patterns.

Table 4. Clinical characteristics, radiation therapy techniques, and outcomes of radiation pneumonitis in terms of CT patterns.

		LP (n = 78)	COP (n = 30)	AIP (n = 25)	p value
Age (range) year		66.7 ± 7.6 (43-83)	69.6 ± 8.6 (46-86)	66.6 ± 7.5 (55-88)	0.135
Sex					
Male		69	27	23	0.877
Female		9	3	2	
Pulmonary function test					
FEV_1 (range) L		3.17 ± 0.77 (0.99–4.67)	3.2 ± 0.81 (1.96–4.66)	3.17 ± 0.68 (2.01–4.39)	0.995
FVC (range) L		2.07 ± 0.62 (0.63–3.37)	2.11 ± 0.64 (1.05–3.33)	2.17 ± 0.60 (1.22–3.48)	0.813
FEV_1/FVC (range) %		65.21 ± 10.94 (38–90)	65.97 ± 11.39 (39–84)	68.16 ± 9.25 (44–80)	0.432
Pre-RT CT					
T stage	1	10	6	0	0.244
	2	19	4	5	
	3	9	6	5	
	4	40	14	15	
T size (range) cm		48.5 ± 19.6 (3–104)	47.9 ± 21.7 (17–99)	53.4 ± 16.0 (28–87)	0.512
N stage	0	12	3	1	0.256
	1	20	7	6	
	2	33	14	8	
	3	13	6	10	
Lung-to-lung metastasis		6	3	6	0.078
Emphysema/ Bronchiectasis		21	8	9	0.659
Fibrosis		2	3	2	0.239
ILA		7	4	7	0.053
Radiation therapy					
GTV (range) cm^3		110.8 ± 91.7 (6.3–487.4)	131.4 ± 110.7 (14.8–441.9)	179.8 ± 116.7 (46.5–466.4)	0.016
RT dose (range) mGy		6191.0 ± 889.2 (3000–7000)	6193.3 ± 934.4 (3000–7000)	5617.6 ± 1395.4 (3000–7000)	0.154
MLD (range) mGy		1423.8 ± 364.5 (474.2–2066.9)	1589.0 ± 354.1 (737.3–2215.9)	1461.0 ± 485.6 (364.8–2267.5)	0.156
V20 (range) mGy		24.2 ± 7.4 (4.6–39.2)	27.0 ± 6.7 (11.4–37.2)	25.7 ± 11.0 (1.1–44.8)	0.182
CTCAE					
≤2		65	18	5	<0.001
≥3		13	12	20	
RT-RP days (range)		183.8 ± 111.9 (8–658)	131.2 ± 71.6 (40–321)	124.1 ± 67.7 (25–354)	0.002
Hospitalization		13	13	19	<0.001
Admission days (range)		13.3 ± 12.8 (3–52)	19.2 ± 13.1 (4–40)	24.5 ± 37.3 (1–173)	0.280
Steroid treatment		18	16	20	<0.001

Data are mean ± standard deviation or n values.
CT, computed tomography; LP, localized pneumonia; COP, cryptogenic organizing pneumonia; AIP, acute interstitial pneumonia; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; RT, radiation therapy; ILA, interstitial lung abnormality; GTV, gross tumor volume; MLD, mean lung dose; Lung V20, volume of normal lung receiving 20 Gy; CTCAE, Common Terminology Criteria for Adverse Events; RP, radiation pneumonitis; RT-RP days, days between the start of radiation therapy and the onset of radiation pneumonitis.

The LP pattern was most common in our study, present in 78 patients (57.8%). Among them, 65 patients had CTCAE grade ≤2 and 13 patients had CTCAE grade ≥3. Meanwhile, 30 patients (23%) exhibited the COP pattern. Unlike the typical RP pattern, the COP pattern presents with multifocal subpleural and peribronchial opacities beyond the radiation fields. This effect is believed to result not only from a direct cytotoxic effect of the irradiation but also from indirect effects of immunological hypothesis.[41] In our study, patients with the COP pattern had higher CTCAE grade (p < 0.001), rate of hospitalization (p = 0.003) and steroid treatment (p = 0.002), and fewer RT-RP days (p = 0.01) compared to patients with the LP pattern. Although these patients had higher grade of clinical symptoms, the follow-up CT scans of some showed that the parenchymal opacities were partially migratory or transient. This suggests that the parenchymal infiltration of the COP pattern may be attributed to a temporary immune response rather than the result of permanent damage.

In our study, the AIP pattern of RP was observed in 25 patients (18.5%). We attribute this relatively higher prevalence to the inclusion of a larger number of patients

Table 5. Clinical characteristics, radiation therapy techniques, and outcomes of radiation pneumonitis in terms of CT extent.

		CT extent ≤2 (n = 82)	CT extent ≥3 (n = 51)	p value
Age (range) year		67.1 ± 8.0 (43–86)	67.7 ± 7.9 (50–88)	0.974
Sex				
Male		72	47	0.427
Female		10	4	
Pulmonary function test				
FEV_1 (range) L		3.24 ± 0.73 (0.73–4.67)	3.06 ± 0.81 (0.99–4.66)	0.338
FVC (range) L		2.12 ± 0.64 (1.82–3.48)	2.04 ± 0.61 (0.63–3.16)	0.937
FEV_1/FVC (range) %		65±11.8 (38–90)	67 ± 10.1 (32–64)	0.333
Pre-RT CT				
T stage	1	10	6	0.784
	2	18	10	
	3	14	6	
	4	40	29	
T size (range) cm		49.3 ± 20.1 (3–104)	49.3 ± 18.6 (10–87)	0.849
N stage	0	11	5	0.085
	1	23	10	
	2	36	19	
	3	12	17	
Lung to lung metastasis		5	10	0.023
Emphysema/ Bronchiectasis		22	16	0.693
Fibrosis		1	6	0.013
ILA		8	10	0.106
Radiation therapy				
GTV (cm^3)		110.7 ± 90.3 (6.3–441.9)	156.9 ± 117.8 (10.6–487.4)	0.022
RT dose (mGy)		6267.1 ± 851.4 (3000–7000)	5789.0 ± 1214.2 (3000–7000)	0.011
MLD (mGy)		1425.2 ± 358.9 (474.2–2215.9)	1537.0 ± 431.0 (364.8–2267.5)	0.049
V20 (%)		24.0 ± 7.1 (4.6–39.2)	26.9 ± 9.2 (1.1–44.8)	0.014
CTCAE				
≤2		72	16	<0.001
≥3		10	35	
RT-RP days (range)		173.7 ± 109.0 (8–658)	139.8 ± 80.8 (25–429)	0.031
Hospitalization		12	33	<0.001
Admission days (range)		16.6 ± 16.2 (3–52)	20.8 ± 29.0 (1–173)	0.298
Steroid treatment		19	51	<0.001

Data are mean ± standard deviation or n values.
CT, computed tomography; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; RT, radiation therapy; ILA, interstitial lung abnormality; GTV, gross tumor volume; MLD, mean lung dose; Lung V20, volume of normal lung receiving 20 Gy; CTCAE, Common Terminology Criteria for Adverse Events; RT-RP days, days between the start of radiation therapy and the onset of radiation pneumonitis.

who received additional oncology treatments compared to previous studies, and to the selection of patients with specific medical records. Additional treatments such as chemotherapy are known risk factors increasing lung toxic effects in the patients undergoing RT.[6] In recent, lung injury has become increasingly important as the application of immunotherapy expands because prior chest RT is a potential factor that increases the risk of immune check-point inhibitor pneumonitis.[42] Recent trends show an increasing number of lung cancer patients receiving CCRT and immunotherapy, raising concerns about the potential increase in the occurrence of the AIP pattern of RP. In logistic regression analysis, a higher extent score and AIP pattern of RP were associated with a higher CTCAE grade, showing a high odds ratio. Several previous studies have described the imaging findings of high-grade and lethal RP as extensive consolidation and GGO in both lungs, along with reticular opacities and traction bronchiectasis.[43,44] Several theories have been suggested to explain the pathogenesis of RP beyond the irradiated lung to the opposite side: 1) blockage of lymphatic channels, hindering egress of alveolar macrophages; 2) errors in dosimetry or placement of ports,

scattered radiation, or a sensitizing effect of concomitant infection; and 3) individual hyperreactivity.[45,46] It has been suggested that hypersensitivity immune reaction may be mediated by lymphocytes.[46,47] It has also been reported that radiation results in increased regional lymphocytes, and this phenomenon is not confined to the irradiated lung but is also visible in the opposite lung.[48] We found that lung-to-lung metastasis, underlying ILA, GTV, and fewer RT-RP days were associated with the AIP pattern of RP. In patients with lung-to-lung metastasis or high GTV, the extended RT fields may lead to the development of an extensive radiation effect and hypersensitivity reaction.

This study has several limitations, including its retrospective nature and that patients were treated in a single institution. Additionally, there were fewer patients with AIP and COP patterns than with the LP pattern. The disproportionate numbers of the different CT patterns might exaggerate or reduce the differences between them. Furthermore, we did not analyze the serial follow-up CT findings. The CT scans we analyzed were performed at the time of symptom presentation or routine follow-up. Some AIP patterns seen on CT scans might have progressed from COP or LP patterns, and some COP patterns may have improved and transitioned to LP patterns. Lastly, we did not assess statistical inter-reader variability between the two radiologists who had different periods of experience. However, each reader interpreted the CT patterns independently before discussing their views and came to a collective agreement. This approach would allow for a more nuanced understanding of inter-reader agreement. A study focusing on more specific CT findings, including serial changes in RP patients, should be conducted with a prospective study design.

In conclusion, CT findings of RP in NSCLC patients can be classified into LP, COP, and AIP patterns based on the parenchymal abnormality and distribution, and they exhibit different severities of clinical outcomes. The presence of underlying ILD, early development of RP, greater extent of RP, and presence of the AIP pattern may be associated with more severe adverse events. Recognizing the CT pattern of RP and considering factors such as the presence of underlying ILD, the timing of RP development, and the extent of parenchymal infiltration will allow improved prediction of RP clinical prognosis.

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References

1. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2022; 20: 497–530.
2. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: e278S.
3. Bucci MK, Bevan A, Roach M 3rd. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. Ca - Cancer J Clin 2005; 55: 117–134.
4. Haasbeek CJ, Slotman BJ, Senan S. Radiotherapy for lung cancer: clinical impact of recent technical advances. Lung Cancer 2009; 64: 1–8.
5. Chang JY, Cox JD. Improving radiation conformality in the treatment of non-small cell lung cancer. Semin Radiat Oncol 2010; 20: 171–177.
6. Benveniste MF, Gomez D, Carter BW, et al. Recognizing radiation therapy-related complications in the chest. Radiographics 2019; 39: 344–366.
7. Arroyo-Hernandez M, Maldonado F, Lozano-Ruiz F, et al. Radiation-induced lung injury: current evidence. BMC Pulm Med 2021; 21: 9.
8. 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: 444–450.
9. Thomas R, Chen YH, Hatabu H, et al. Radiographic patterns of symptomatic radiation pneumonitis in lung cancer patients: imaging predictors for clinical severity and outcome. Lung Cancer 2020; 145: 132–139.
10. Rodrigues G, Lock M, D'Souza D, et al. Prediction of radiation pneumonitis by dose - volume histogram parameters in lung cancer--a systematic review. Radiother Oncol 2004; 71: 127–138.
11. Nishino M, Hatabu H, Sholl LM, et al. Thoracic complications of precision cancer therapies: a practical guide for radiologists in the new era of cancer care. Radiographics 2017; 37: 1371–1387.
12. Nishino M, Boswell EN, Hatabu H, et al. Drug-related pneumonitis during mammalian target of rapamycin inhibitor therapy: radiographic pattern-based approach in waldenstrom macroglobulinemia as a paradigm. Oncol 2015; 20: 1077–1083.
13. 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.

14. Common Terminology criteria for adverse events (CTCAE) | protocol development | CTEP. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
15. Park YH, Kim JS. Predictors of radiation pneumonitis and pulmonary function changes after concurrent chemo-radiotherapy of non-small cell lung cancer. Radiat Oncol J 2013; 31: 34–40.
16. Zhou Z, Song X, Wu A, et al. Pulmonary emphysema is a risk factor for radiation pneumonitis in NSCLC patients with squamous cell carcinoma after thoracic radiation therapy. Sci Rep 2017; 7: 2748.
17. Fujimoto D, Kato R, Morimoto T, et al. Characteristics and prognostic impact of pneumonitis during systemic anti-cancer therapy in patients with advanced non-small-cell lung cancer. PLoS One 2016; 11: e0168465.
18. Yorke ED, Jackson A, Rosenzweig KE, et al. Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 2002; 54: 329–339.
19. Uno T, Isobe K, Kawakami H, et al. Dose-volume factors predicting radiation pneumonitis in patients receiving salvage radiotherapy for postlobectomy locoregional recurrent non-small-cell lung cancer. Int J Clin Oncol 2006; 11: 55–59.
20. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the nrg oncology rtog 0617 randomized clinical trial. J Clin Oncol 2017; 35: 56–62.
21. Jain V, Berman AT. Radiation pneumonitis: old problem, new tricks. Cancers 2018; 10.
22. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010; 76: 70–76.
23. Vogelius IR, Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. Acta Oncol 2012; 51: 975–983.
24. Bjermer L, Cai Y, Nilsson K, et al. Tobacco smoke exposure suppresses radiation-induced inflammation in the lung: a study of bronchoalveolar lavage and ultrastructural morphology in the rat. Eur Respir J 1993; 6: 1173–1180.
25. 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.
26. 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: 676–686.
27. 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.
28. 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: e219–e226.
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.
30. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a fleischner society white paper. Lancet Respir Med 2018; 6: 138–153.
31. Kashihara T, Nakayama Y, Ito K, et al. Usefulness of simple original interstitial lung abnormality scores for predicting radiation pneumonitis requiring steroidal treatment after definitive radiation therapy for patients with locally advanced non-small cell lung cancer. Adv Radiat Oncol 2021; 6: 100606.
32. Turkkan G, Willems Y, Hendriks LEL, et al. Idiopathic pulmonary fibrosis: current knowledge, future perspectives and its importance in radiation oncology. Radiother Oncol 2021; 155: 269–277.
33. 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: 45–52.
34. Nam BD, Hwang JH. [Update in diagnosis of idiopathic pulmonary fibrosis and interstitial lung abnormality]. Taehan Yongsang Uihakhoe Chi 2021; 82: 770–790.
35. Putman RK, Hatabu H, Araki T, et al. Association between interstitial lung abnormalities and all-cause mortality. JAMA 2016; 315: 672–681.
36. Hatabu H, Hunninghake GM, Lynch DA. Interstitial lung abnormality: recognition and perspectives. Radiology 2019; 291: 1–3.
37. Araki T, Dahlberg SE, Hida T, et al. Interstitial lung abnormality in stage IV non-small cell lung cancer: a validation study for the association with poor clinical outcome. Eur J Radiol Open 2019; 6: 128–131.
38. Liu Y, Zhu Y, Wu R, et al. Stereotactic body radiotherapy for early stage non-small cell lung cancer in patients with subclinical interstitial lung disease. Transl Lung Cancer Res 2020; 9: 2328–2336.
39. 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.
40. Iwasawa T, Okudela K, Takemura T, et al. Computer-aided quantification of pulmonary fibrosis in patients with lung cancer: relationship to disease-free survival. Radiology 2019; 292: 489–498.
41. Crestani B, Kambouchner M, Soler P, et al. Migratory bronchiolitis obliterans organizing pneumonia after unilateral radiation therapy for breast carcinoma. Eur Respir J 1995; 8: 318–321.
42. Nishino M. Imaging of oncologic treatment-related pneumonitis: a focused review on emerging issues of immune checkpoint inhibitor pneumonitis, from the ajr special series on inflammation. AJR Am J Roentgenol 2022; 218: 19–27.

43. Hwang JH, Lee KS, Song KS, et al. Extensive acute lung injury following limited thoracic irradiation: radiologic findings in three patients. J Kor Med Sci 2000; 15: 712–717.
44. Onishi H, Marino K, Yamashita H, et al. Case series of 23 patients who developed fatal radiation pneumonitis after stereotactic body radiotherapy for lung cancer. Technol Cancer Res Treat 2018; 17: 1533033818801323.
45. Roswit B, White DC. Severe radiation injuries of the lung. AJR Am J Roentgenol 1977; 129: 127–136.
46. Gibson PG, Bryant DH, Morgan GW, et al. Radiation-induced lung injury: a hypersensitivity pneumonitis? Ann Intern Med 1988; 109: 288–291.
47. Roberts CM, Foulcher E, Zaunders JJ, et al. Radiation pneumonitis: a possible lymphocyte-mediated hypersensitivity reaction. Ann Intern Med 1993; 118: 696–700.
48. Song SH, Oh YJ, Ha CW, et al. Bilateral diffuse radiation pneumonitis caused by unilateral thoracic irradiation: a case report. J Lung Cancer 2012; 11: 97–101.