Radiation pneumonitis in patients with lung and mediastinal tumours: a retrospective study of risk factors focused on pulmonary emphysema

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Objectives: To evaluate the impact of pulmonary emphysema (PE) on the incidence and severity of radiation pneumonitis (RP) in patients with lung and mediastinal tumours.

Methods: 92 patients were enrolled. Involved-field radiation therapy (non-small cell carcinoma or mediastinal tumours in 69 patients; median 70 Gy) and accelerated hyperfractionation (limited disease small cell carcinoma in 23 patients; median 45 Gy) were performed. Common Terminology Criteria for Adverse Events v.3.0 was used to evaluate RP and the relationship with the percentage of pulmonary volume irradiated to >20 Gy (V20) and PE. PE was diagnosed by the presence of low-attenuation areas (LAAs) on CT scans and was classified into Grades 0–4 according to the extent of the LAAs.

Results: The median follow-up time was 16 months. The 6-month cumulative incidence of RP at Grade 3 or greater was 7.7% and 34.1% in patients with a V20 of <25% and ≥25%, respectively ($p=0.017$). In patients with PE Grades 0, 1, 2 and 3 or greater, the incidence of RP was 16.5%, 9.1%, 8.6% and 54.0%, respectively. As the PE Grade increased, the incidence of RP also increased significantly.

Conclusion: The incidence and severity of RP are significantly higher in patients with a high V20 value as well as in those with severe PE.

Received 24 June 2010
Revised 4 November 2010
Accepted 8 November 2010

DOI: 10.1259/bjr/32629867

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Radiology

There has been an increase worldwide, as well as in Japan, of the prevalence of chronic obstructive pulmonary disease (COPD). It has been estimated that at least 8.6% of Japanese adults (aged >40 years) have this disease [1]. As the population ages, the incidence of COPD is expected to increase. Pulmonary emphysema (PE) is a subtype of COPD, and is defined pathologically as a group of diseases that demonstrate anatomical alterations in the lung characterised by enlargement of air spaces distal to the terminal bronchiole and accompanied by destructive changes of the alveolar walls [2]. PE is the most common subtype of COPD in Japanese patients [3]. Smoking is a common risk factor shared by patients with lung cancer and those with COPD. In patients with lung cancer who also have COPD, surgery frequently cannot be performed because of low cardiopulmonary reserve [4]. Thus, radiation therapy (RT) has been increasingly used for these patients to preserve pulmonary function.

Radiation pneumonitis (RP) is one of the most significant complications for patients with lung cancer and especially for those who also have COPD. There is some consensus about the association of a few dosimetric factors and the

incidence and severity of RP [5–8]. However, although COPD is considered as one of the risk factors of RP, very few investigations have included cases of clinically assessed COPD in their correlations with RP [9–11]. Moreover, the relationship between the incidence and severity of RP and with PE has not been clearly determined.

The purpose of this study was to evaluate the association of PE with the incidence and severity of RP in patients with lung and mediastinal tumours.

Materials and methods

Patients' demographics

In this study, 92 patients with lung and mediastinal tumours who had received definitive RT at Kagawa University from 2004 to 2009 were enrolled. Patients' demographics, such as age, sex, histology, stage and Eastern Cooperative Oncology Group (ECOG) performance status (PS), are summarised in Table 1. All patients were staged by 18-fluorodeoxyglucose-positron emission tomography (FDG-PET).

Treatment procedure of radiation therapy

Three-dimensional conformal RT (3D-CRT) was used for treatment planning in all patients. CT scanning

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This work was partially presented at the 51st Annual Meeting of ASTRO (American Society for Therapeutic Radiology and Oncology), Chicago, IL, 1–5 November 2009.

Table 1. Patients' demographics

Characteristic (N = 92)		No. of patients
Age		55–93 (median 73)
Sex	Male	78 (84.8%)
	Female	14 (15.2%)
Smoking history by sex ^a	Male	62 (67.4%)
	Female	3 (1.3%)
Histologies	Non-small cell carcinoma	64 (69.6%)
	Small cell carcinoma (LD)	23 (25%)
	Mediastinal tumour	5 (5.4%)
Stage (non-small cell carcinoma)	I (a/b)	2 (1/1)
	II (a/b)	8 (0/8)
	III (a/b)	46 (15/31)
	IV	8
Stage (small cell carcinoma)	II (a/b)	3 (1/2)
Stage (mediastinal tumour) ^b	III (a/b)	20 (12/8)
	III	2
	IV (a/b)	3 (0/3)
PS ^c	0	73 (79.3%)
	1	15 (16.3%)
	2	2 (2.2%)
	3	2 (2.2%)

LD, limited disease.

^aSmoking history by sex, known smoking history in 65 patients.^bStage (mediastinal tumour), Masaoka stage.^cPS, Eastern Cooperative Oncology Group performance status.

(Asteion; Toshiba Medical System, Tokyo, Japan) was performed by long-time scan (3 s per scan) to calculate the internal target volume (ITV) of the patients who were treated under free breathing. CT volume data were transferred to a 3D treatment planning system (Focus Xio; ELEKTA, Stockholm, Sweden). A physician delineated the target volume on the axial CT slices. The primary tumour and lymph nodes that were >1.0 cm in short axis or PET positive were delineated as the gross target volume (GTV) or ITV. The positive lymph nodes were diagnosed in consultation with the nuclear medicine physician [12].

RT for patients with non-small cell lung cancer (NSCLC) and mediastinal tumours was performed by involved field (IF). A clinical target volume (CTV) margin of 5 mm was usually added to the GTV (or ITV) according to the pathology. RT for patients with small cell lung cancer (SCLC) was performed by large fields, including elective nodal regions for CTV. A planning target volume (PTV) margin of 10 mm was usually added, including reproducibility of respiratory motion and set-up error to the CTV.

The prescribed dose was calculated with a heterogeneous dose calculation algorithm (Clarkson method). Conventional fractionation was used (2–3 Gy fr⁻¹, median 2 Gy fr⁻¹), and the total prescribed dose ranged from 54 to 80 Gy (median 70 Gy) for patients with NSCLC and mediastinal tumours (n=69). Accelerated hyperfractionation was used (45 Gy 30 fr⁻¹, twice per day) for 16 patients with SCLC. Conventional fractionation was used (1.8 Gy or 2 Gy fr⁻¹, median 1.8 Gy fr⁻¹), and the total prescribed dose ranged from 50 to 60 Gy (median 52.8 Gy)

in seven patients with SCLC. Treatment was delivered using 10 MV photons of the linear accelerator (Primus; Siemens, Erlangen, Germany).

Chemotherapy

73 patients (79.3%) were administered chemotherapy; of these, 10 were given chemotherapy sequentially and 63 concurrently. The basic regimen for patients with NSCLC and mediastinal tumours was a concurrent administration of carboplatin (CBDCA) [area under the blood concentration time curve (AUC)=5–6] + docetaxel 60 mg m⁻² for 1 or 2 cycles (35 patients). Five patients received CBDCA (AUC=5–6) + docetaxel 60 mg m⁻² over one–three cycles sequentially. Four patients received a weekly low-dose cisplatin (CDDP) regimen and two patients received a daily tegafur, gimeracil, oteracil potassium (TS-1) regimen concurrently. Four patients received bronchial arterial infusion sequentially. 19 patients did not undergo chemotherapy because of the presence of various co-morbidities and/or advanced age. The basic regimen for patients with SCLC was CDDP 80 mg m⁻² or CBDCA (AUC=5) + etoposide (VP-16) 100 mg m⁻² × 3 for three or four cycles concurrently (21 patients). One patient received a weekly low-dose CDDP regimen concurrently, and one patient received CBDCA (AUC=5–6) + irinotecan (CPT-11) 60 mg m⁻² × 3 for three sequential cycles. Basically, adjuvant chemotherapy was not given, although nine patients received only tegafur-uracil (UFT) or TS-1 300 mg body⁻¹ day⁻¹ or TS-1 100–120 mg body⁻¹ day⁻¹.

CT classification of pulmonary emphysema

PE was diagnosed by the presence of low-attenuation areas (LAAs) on pre-treatment CT scans (the lung window: level, -500 HU; width, 1500 HU) by the radiologists and not by pulmonary function tests. CT examinations of the entire lung were performed using a multislice helical technique at 120 kV, 200 mA, 5-mm slice thickness, pitch 1. In most cases, contiguous 1.0 mm sections encompassed the part of the thorax with high-resolution reconstruction. CT appearance was classified by one of the authors (T.K.) in each patient while referring to the advice and the reports provided by the radiologists in our institution. According to the extent of LAAs in the whole lung fields, the CT findings were classified into the following five Grades: Grade 0, no LAAs; Grade 1, sparse, scattered small LAAs up to 5 mm in diameter; Grade 2, adjacent LAAs up to 10 mm in diameter; Grade 3, LAAs >10 mm that were adjacent to or indistinguishable from each other; and Grade 4, absence of normal lung parenchyma [13]. This optical classification is widely used in CT diagnosis of PE. Figure 1 shows our CT findings according to Grades 1–4.

Follow-up and evaluation

Patients were followed up each month during the first year and every 2–3 months thereafter during the next 2 years after completion of RT. Patients were interviewed monthly to determine the presence or absence of symptoms, and physicians evaluated clinical symptoms with Common Terminology Criteria for Adverse Events

*Grade 0: no LAAs

Figure 1. CT classification of pulmonary emphysema. According to the extent of low-attenuation areas (LAAs) in the lung fields, the CT findings were classified into five grades: Grade 0, no LAAs; Grade 1, sparse, scattered small LAAs up to 5 mm in diameter; Grade 2, adjacent LAAs up to 10 mm in diameter; Grade 3, LAAs >10 mm that were adjacent to or indistinguishable from each other; and Grade 4, absence of normal lung parenchyma.

(CTCAE) v.3.0 during the first year. Recurrence, such as locoregional failure and distant metastasis, was assessed by CT, FDG-PET, MRI and pathology. This study was performed retrospectively, but we evaluated the adverse effects and pre-treatment classifications of PE routinely in clinical examinations, and the RP grading for each patient was finally decided by several radiation oncologists at our institution to maintain consistency of grading.

The follow-up time ranged from 3 to 83 months (median, 16 months). The endpoints were as follows: (1) incidence of RP; (2) the relationship between lung V20 and RP (V20 was defined as the percentage of pulmonary volume irradiated to >20 Gy, and was calculated by lung PTV); and (3) the relationship between PE and RP.

Statistical analysis

Univariate analysis by the Mantel-Haenzel χ^2 or *t*-tests, multivariate analyses by the logistic regression test and the cumulative incidence curves of RP at Grades 2 and 3 or greater by the Kaplan-Meier method were carried out by StatMateIV v.4.01 software (ATMS Co., Ltd., Tokyo, Japan). A *p*-value of <0.05 was considered significant for the log-rank test, univariate analysis and multivariate logistic regression analysis.

Results

Incidence of radiation pneumonitis

Most of the patients (88.0%) were classified as Grade 1 or 2. One patient (aged 84 years, male), who was classified as Grade 5, had interstitial pneumonitis and his V20 was 31%.

The relationship between lung V20 and radiation pneumonitis

Figure 2a,b shows the cumulative incidence curves of RP at Grades 2 and 3 or greater stratified by V20. The 6 month cumulative incidence of RP at Grade 2 or greater was 68.7% (95% confidence interval [CI] 55.6–81.9%) in patients with V20 <25% compared with 84.5% (95% CI, 69.2–99.0%) in patients with V20 ≥25% (*p*=0.0594). The incidence of RP at Grade 3 or greater was 7.7% (95% CI, 0.4–15.1%) in patients with V20 <25% and 34.1% (95% CI, 10.6–57.6%) in patients with V20 ≥25% (*p*=0.017).

The relationship between pulmonary emphysema and radiation pneumonitis

59 of 92 patients (64.1%) were diagnosed with PE. The CT findings of PE were classified into five grades: Grade 0, 33 patients; Grade 1, 23 patients; Grade 2, 25 patients; Grade 3, 10 patients; and Grade 4, 1 patient.

Figure 3a,b shows cumulative incidence curves of RP at Grades 2 and 3 or greater stratified by different PE grades. The 6 month cumulative incidences of RP at Grade 2 or greater were: 63.9% (95% CI, 42.6–85.2%) in patients with PE Grade 0; 76.7% (95% CI, 58.0–95.4%) in patients with PE Grade 1; 82.2% (95% CI, 64.9–99.4%) in patients with PE Grade 2; and 90.1% (95% CI, 73.9–100%) in patients with PE Grade 3 or greater. At RP Grade 3 or greater they were: 16.5% (95% CI, 0–35.1%) in patients with PE Grade 0; 9.1% (95% CI, 0–26.1%) in patients with PE Grade 1; 8.6% (95% CI, 0–20.0%) in patients with PE Grade 2; and 54.0% (95% CI, 19.6–88.4%) in patients with PE Grade 3 or greater. As the PE grade increased, the incidence of RP also increased significantly (PE Grade 3 or greater *vs* Grades 0, 1, 2: *p*=0.0058, *p*=0.1027 and *p*=0.0394, respectively, in patients with RP Grade 2 or greater; for PE Grade 3 or greater *vs* Grades 0, 1, 2: *p*=0.0021, *p*=0.002 and *p*=0.0043, respectively, in patients with RP Grade 3 or greater). We performed univariate and multivariate analyses for several patient- and treatment-related factors to assess the risk of Grades 2 and 3 or greater RP (Tables 2 and 3). The factors analysed were PS, PE grade, age, sex, smoking history, forced expiratory volume in 1 s (FEV₁), location of primary tumour, chemotherapy, total radiation dose, and lung V20. In univariate analysis, no significant associations were noted in the study of factors related to RP Grade 2 or Greater. For RP Grade 3 or greater, PE was the only factor that showed a significant association (*p*=0.0003). According to multivariate analysis of the same factors using logistic regression analysis, PE and total irradiation dose were significantly associated with the incidence of RP of Grade 3 or greater (*p*=0.0136 in PE, and *p*=0.0354 in total radiation dose). No association was noted for any of the factors related to RP of Grade 2 or greater.

Discussion

A close correlation has been reported by many investigators between the incidence and severity of RP and several dosimetric factors, such as the V20 value of lung and mean lung dose, in patients treated with RT for

Figure 2. The cumulative incidence curves of radiation pneumonitis (RP) stratified by V20. (a) RP at Grade 2 or greater; (b) RP at Grade 3 or greater.

lung tumours [5–8]. Tsujino et al [6] reported that the 6 month cumulative incidence of RP at Grade 2 or greater was 14% in patients with $V20 \leq 25\%$ and 63% in patients with $V20 > 25\%$ after concurrent chemoradiation therapy. They also concluded that the incidence and grade of RP were significantly related to the V20 value. In this study, we also found that the incidence of RP at Grade 2, and especially at Grade 3 or greater, increased significantly in patients with $V20 \geq 25\%$.

Additionally, we described the relationship between the incidence and severity of RP and PE in this study. PE is considered as one of the risk factors of RP, and therefore RT tends to be avoided for lung cancer patients who have severe PE [9–11]. Lee et al [14] surveyed radiation oncologists regarding their recommendations for treatment (chemoradiation, RT alone, chemotherapy

alone or no therapy) for hypothetical patients with stage IIIB NSCLC who varied by age (55 vs 80 years) and comorbid illness (none, moderate or severe COPD). They learned that most radiation oncologists would not recommend any radiation in patients with severe COPD, regardless of age, because of the potential pulmonary toxicity. Rancati et al [9] analysed 84 patients with SCLC or NSCLC, irradiated at >40 Gy (median, 61.6 Gy; range, 42.3–75.4 Gy, 1.8 Gy daily fractions), and reported that the actual incidences of RP at 6 and 12 months were $11.4 \pm 6.3\%$ and $15.7 \pm 10.3\%$ in patients without COPD, and $24.8 \pm 13.2\%$ and $29.8 \pm 19.2\%$ in patients with COPD. They concluded that the presence of COPD was associated with a higher risk of RP. Moreover, according to guidelines produced by the American College of Chest Physicians [15], a patient

Figure 3. The cumulative incidence curves of radiation pneumonitis (RP) stratified by pulmonary emphysema (PE) grade. (a) RP at Grade 2 or Greater; (b) RP at Grade 3 or greater.

Table 2. Univariate and multivariate analyses of factors related to Grade 2 or greater radiation pneumonitis

Factor		No. of Grade 2 or greater RP (total)	p-Value	
			Univariate ^c	Multivariate ^d
PS	0–1	56 (87)	0.4754	0.4033
	≥2	4 (5)		
PE	Grade 0–2	50 (81)	0.0566	0.1245
	Grade ≥3	10 (11)		
Age	<75 y.o.	39 (59)	0.8118	0.503
	≥75 y.o.	21 (33)		
Sex	M	51 (78)	0.9366	0.4955
	F	9 (14)		
Smoking history ^a	+	45 (65)	0.0667	0.1264
	–	11 (23)		
FEV ₁	<1.0 l	6 (9)	0.8646	0.7755
	≥1.0 l	44 (69)		
Location of primary tumour ^b	Upper	41 (65)	0.4104	0.7907
	Middle/lower	16 (22)		
Chemotherapy	Concurrent	44 (63)	0.1699	0.2272
	Sequential/none	16 (29)		
Total irradiation dose	<60 Gy	14 (22)	0.8583	0.7539
	≥60 Gy	46 (70)		
Lung V20	<25%	35 (58)	0.2000	0.3317
	≥25%	25 (34)		

F, female; FEV₁, forced expiratory volume in 1 s (unknown in 14 patients); M, male; PE, pulmonary emphysema; PS, performance status; RP, radiation pneumonitis; y.o., years old.

^aSmoking history, unknown in four patients.

^bLocation of primary tumour, five patients with mediastinal tumour were excluded.

^cUnivariate, univariate analysis by the Mantel-Haenzel χ^2 or *t*-tests.

^dMultivariate, multivariate logistic regression analysis.

with FEV₁ <1 l s⁻¹ is unlikely to withstand definitive therapy. However, the relationship between the incidence and severity of RP to PE lacks clarity, and there are no good prospective data demonstrating that an attempt

at definitive RT would indeed be detrimental in patients with severe COPD including PE.

We previously reported the relationship between RP and PE in 18 patients with PE who were treated by

Table 3. Univariate and multivariate analyses of factors related to Grade 3 or greater radiation pneumonitis

Factor		No. of Grade 3 or greater RP (total)	p-Value	
			Univariate ^c	Multivariate ^d
PS	0–1	10 (87)	0.5686	0.5288
	≥2	1 (5)		
PE	Grade 0–2	6 (81)	0.0003	0.0136
	Grade ≥3	5 (11)		
Age	<75 y.o.	6 (59)	0.4799	0.247
	≥75 y.o.	5 (33)		
Sex	M	9 (78)	0.7705	0.4761
	F	2 (14)		
Smoking history ^a	+	8 (65)	0.5833	0.5669
	–	2 (23)		
FEV ₁	<1.0 l	1 (9)	0.9310	0.9151
	≥1.0 l	8 (69)		
Location of primary tumour ^b	Upper	6 (65)	0.1341	0.6612
	Middle/lower	5 (22)		
Chemotherapy	Concurrent	7 (63)	0.7126	0.6013
	Sequential/none	4 (29)		
Total irradiation dose	<60 Gy	5 (22)	0.0743	0.0354
	≥60 Gy	6 (70)		
Lung V20	<25%	4 (58)	0.0507	0.4276
	≥25%	7 (34)		

F, female; FEV₁, forced expiratory volume in 1 s (unknown in 14 patients); M, male; PE, pulmonary emphysema; PS, performance status; RP, radiation pneumonitis; y.o., years old.

^aSmoking history, unknown in four patients.

^bLocation of primary tumour, five patients with mediastinal tumour were excluded.

^cUnivariate, univariate analysis by the Mantel-Haenzel χ^2 or *t*-tests.

^dMultivariate, multivariate logistic regression analysis.

stereotactic body RT (SBRT) [16]. Although there were no significant correlations between the Grade of RP and that of PE, the percentage of PE was significantly lower in patients who were diagnosed with RP Grade 2 or 3 than in patients who were diagnosed with RP Grade 1, and there was little change on CT, such as the absence of an increasing density or scar-like pattern. Several reasons were considered to explain this phenomenon in patients with PE. First, RP and pulmonary fibrosis may be the results of a cytokine cascade that is triggered by irradiation [17, 18]. It could also mean that the amount of normal lung tissue is important for the development of RP and pulmonary fibrosis.

In patients with PE, normal lung tissue seldom exists around the tumour. As PE becomes more advanced, less normal lung tissue remains around the tumour, and results in a decrease in the cytokine cascade. Therefore, RP would not occur frequently, in spite of the concentrated high dose of radiation. Second, as PE progresses, more perfusion defects of the lung would be observed. Even if RP occurs in these regions, which are perfusion defects, RP may not contribute to the loss of respiratory function. Finally, the V20 value in SBRT was generally low compared with that in conventional RT for advanced lung cancer (around 10% or less).

However, in this study, as PE progressed, the incidence and severity of RP increased. This result differed from that of SBRT studies, and did not match the cytokine cascade theory described above. The following possibilities were considered:

- (1) Although the effect of the cytokine cascade may be low in patients with advanced PE, the actual irradiated volume of residual functional lung tissue in this study may be larger than that in SBRT.
- (2) Therefore, patients with advanced PE may intrinsically have a lower pulmonary function and may easily advance to RP Grade 3 (oxygen inhalation is required), even if the actual irradiated volume of residual functional lung tissue is small (if it is as small as in SBRT, this may seldom be problematic).
- (3) Some authors reported that chemotherapy increased the risk of RP, especially when used concurrently [5, 18]. Most of the patients (79.3%) in this study were administered chemotherapy.

According to univariate and multivariate analyses for several patient- and treatment-related factors, PE and total dose (≥ 60 Gy) were significant factors for the development of RP of Grade 3 or greater, and the V20 value was also relatively significant. In particular, PE was the most significant factor in these analyses. There were 5 patients who actually developed pneumonitis of Grade 3 or more out of 11 patients with PE of Grade 3 or more. These results show that PE is one of the independent risk factors for RP. On the other hand, we examined the other factors which were not used in these analyses, such as with or without taxans and histological type, but they were without significance.

We are aware that this study, because of its retrospective nature, suffers from certain deficiencies, and that pulmonary function tests (PFTs) were not considered. PFTs are the first choice for, and definitive method of, COPD diagnosis, and the classification according

to the Global Initiative for Chronic Obstructive Lung Disease criteria may be needed to diagnose COPD correctly. The correlations between RP and COPD, as determined by PFTs, have already been reported [9–11]. However, in this study, PE was not diagnosed by PFTs, but by CT scans. There were two reasons for using CT classification of COPD in this study. Firstly, CT classification gives descriptive information, and is obviously superior to PFTs in that respect, whereas PFTs give quantitative information. Secondly, CT can describe non-functional areas of the lung, which makes it possible to use this functional imaging in treatment planning of RT, especially intensity-modulated radiation therapy to reduce RP in the future. For these reasons, it was considered important to investigate the relationship between the CT classification of PE and RP. Additionally, the grade of PE was also evaluated optically by CT scans, and was lacking in objectivity. A quantitative measurement of LAA by CT scan and a pulmonary perfusion image for evaluation may be needed. In the future, a prospective study will be needed to address the points mentioned above.

To reduce the risk of RP in patients with PE, several authors have reported on functional imaging modalities such as four-dimensional CT [19], single-photon emission CT [20] and functional MRI [21]. For example, Bates et al [21] suggested that reductions in the V20 for functional lung are possible for a subset of patients with locally advanced NSCLC when standard IMRT planning techniques are supplemented by simulated functional lung imaging information to reduce the risk of RP. However, further work will be needed to confirm such reports and to establish their clinical usefulness.

Conclusion

The incidence and severity of RP are significantly higher in patients with a high V20 value as well as in those with severe PE. Functional lung imaging information using several techniques may be useful to reduce the risk of RP in patients with severe COPD.

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