Impact of Interstitial Changes on Radiation Pneumonitis After Stereotactic Body Radiation Therapy for Lung Cancer

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Abstract. *Aim: The aim of the present study was to evaluate the impact of interstitial changes (IC) on radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for lung cancer. Patients and Methods: We analyzed 260 consecutive patients with primary lung cancer treated with SBRT. According to the presence or absence of IC on the pre-treatment computed tomography, patients were divided into two groups: an IC group (n=18) and a non-IC group (n=242). Results: RP of grade 2 or more was observed in 9 (50.0%) and 14 (6.7%) patients in the IC and non-IC group, respectively. All three patients with grade 5 RP were in the IC group. As indicated by multivariate analysis, the presence of IC was the only significant predictive factor of RP of grade 2 or more. Conclusion: The presence of IC was a significant indicator of grade 2 or more RP after SBRT for patients with lung cancer.*

Stereotactic body radiation therapy (SBRT) has been widely used to safely treat primary or metastatic lung tumors (1-6). Radiation pneumonitis (RP) is one of the most important toxicities of SBRT. The reported rates of RP of grade 2 or more after SBRT range from 3% to 28% (1, 4, 7-10), and cases of grade 5 RP have also been reported in a small number of patients (3, 8, 10).

Pulmonary interstitial changes (IC) are occasionally observed on the pre-treatment, thin-slice computed tomography (CT) scans of patients with lung cancer without clinical symptoms or diagnostic confirmation of interstitial pneumonia (IP). Severe IP is a contraindication for radiotherapy since radiotherapy can result in acute exacerbation of IP (11). The incidence of RP after SBRT for lung cancer patients with IC is not known. In addition, the influence of clinical and treatment factors on the incidence of RP after SBRT in patients with IC remains unknown. The purpose of the study was to evaluate the impact of IC on RP after SBRT for lung cancer.

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Key Words: Radiation pneumonitis, stereotactic radiation therapy, interstitial changes.

Patients and Methods

Patient's and tumor characteristics. Between April 2003 and April 2012, we selected 260 consecutive patients with primary lung cancer treated with SBRT at Kyushu University Hospital, Fukuoka, Japan. Patients who had received irradiation to the lung in the preceding 2 years were excluded. The 260 patients consisted of 164 male and 96 female patients. The median age was 77 years (range=51-92 years). The clinical T stage was T1a in 104, T1b in 92, and T2a in 64 patients. The histological types of lung cancer were squamous cell carcinoma in 46, adenocarcinoma in 77, large cell carcinoma in three, bronchioloalveolar carcinoma in two, small cell carcinoma in two, non-small cell carcinoma not otherwise specified in nine, and unknown in 121.

Evaluation of IC. A board-certified radiologist evaluated the pre-treatment thin-slice CT (≤2 mm slice thickness) to categorize patients into the IC group and non-IC group. We defined distribution along the subpleural region or bronchovascular bundle, reticular opacity, honeycombing, traction bronchiectasis, and ground-glass opacity as the CT findings of IC. According to the presence or absence of IC, patients were divided into two groups: an IC group (n=18) and a non-IC group (n=242). The clinical factors of these two groups are shown in Table I. The pretreatment Krebs von den Lungen-6 (KL-6) value of the IC group was significantly higher than that of the non-IC group as evidenced by the Mann-Whitney *U*-test.

Stereotactic body radiation therapy. The SBRT technique has been described previously (12). All patients were fixed with a Body Cast System composed of a thermoplastic body cast, a vacuum pillow, arm and leg support, and a carbon plate (Engineering Systems Co.,

Table I. *Comparison of clinical factors and treatment parameters between the IC and non-IC groups.*

	IC group (n=18)	Non-IC group (n=242)	*p*-Value
Gender (Male:female)	16:2	148:94	0.011*
Median age (range), years	75 (60-85)	77 (51-92)	0.477†
PS (0-1:2-3)	14:4	204:38	0.486*
Median (range) dose, Gy	48 (48-48)	48 (40-60)	0.700†
CRP (mg/dl), mean±SD	0.8±1.3	0.3±0.7	<0.001†
LDH (U/l), mean±SD	211±72	195±37.8	0.363†
KL-6 (U/ml) , mean±SD	630±432	297±165	<0.001†
Lung V5 (%), mean±SD	18.6±5.2	18.5±6.3	0.612†
Lung V10 (%), mean±SD	12.5±3.6	11.8±4.4	0.306†
Lung V20 (%), mean±SD	6.0±1.9	6.1±2.6	0.698†
Mean lung dose (Gy), mean±SD	4.0±1.0	4.0±1.3	0.571†

IC, Interstitial change; PS, Performance status; CRP, C-reactive protein; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; Lung Vx, lung volume receiving ≥x Gy. *According to χ^2-test, between the IC and non-IC group. †According to Mann–Whitney U test, between the IC and non-IC group.

Matsumoto, Japan). CT scans were performed at 2- mm intervals on the day of planning and on the first treatment day for verification of the setup. Treatment planning was performed using a 3D RTP machine (Eclipse: Varian Medical Systems, Palo Alto, CA, USA). The gross tumor volume (GTV) was identified on relevant lung setting CT images. The internal target volume (ITV) was chosen individually according to the internal respiratory motion. When the range of respiratory tumor motion was 1 cm or more, irradiation was performed during breath-holding using a visual feedback-guided breath-holding system (13). The planning target volume (PTV) margin was 5 mm in all directions. Seven to eight multi-leaf-collimator (MLC)-shaped non-coplanar static ports of 4 or 6 MV X-rays were selected. The prescribed dose was 48 Gy in four fractions at the isocenter. There were no significant differences of the dosimetric parameters of the lung between the IC and non-IC groups (Table I). No patients received chemotherapy before or after SBRT.

Evaluation. The grade of RP was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (14). The cumulative incidence of RP and the overall survival (OS) were calculated by the Kaplan–Meier method. Predictive factors of RP were evaluated by univariate and multivariate analyses for the whole patient cohort and for the IC group. The evaluated factors were age, sex, presence of IC (IC or non-IC group), pretreatment C-reactive protein (CRP), lactate dehydrogenase (LDH), and KL-6 levels, lung volume receiving ≥5 Gy (V5), V10, and V20, and the mean lung dose (MLD). Statistical significance was calculated using the log-rank test and the Cox proportional hazards model in univariate and multivariate analysis, respectively. A value of $p<0.05$ was considered statistically significant.

Results

The median follow-up was 26.0 months (range=2.7-104.6 months). Nine and 14 patients developed grade 2 or more RP in the IC and non-IC groups, respectively. The incidence of RP is shown in Table II. The cumulative incidence of grade 2 or more RP at 6 months were 44.4% and 4.1% in the IC and non-IC groups, respectively (Figure 1). The incidence of grade 2 or more RP in the IC group was significantly higher than that of the non-IC group. OS rates at 2 years in the IC and non-IC groups were 49.6% and 86.7%, respectively (Figure 2). The OS of the non-IC group was significantly longer than that of the IC group.

Table II. *Incidence of radiation pneumonitis (RP).*

RP grade	IC group (n=18)	Non-IC group (n=242)	Total (n=260)
Grade 2	2 (11.1%)	11 (4.5%)	13 (5.0%)
Grade 3	3 (16.7%)	3 (1.2%)	6 (2.3%)
Grade 4	1 (5.6%)	0 (0 %)	1 (0.4%)
Grade 5	3 (16.7%)	0 (0 %)	3 (1.2%)
Grade ≥2	9 (50.0%)	14 (6.7%)	23 (8.8%)

IC, Interstitial change.

Tables III and IV show the results of analyses of predictive factors of RP of grade 2 or more for the whole patient cohort and for the IC group, respectively. In all cases, the predictive factors were presence of IC, KL-6, lung V5, V10, V20, and MLD by univariate analysis, while the presence of IC was the only predictive factor by multivariate analysis. In the IC group, KL-6, lung V5 and V10, and MLD were significant predictive factors by univariate analysis.

In the IC group, the cumulative incidence of grade 2 or more RP at 6 months was 83.3% and 25.0% in patients with a KL-6 level ≥600 and <600 U/ml, respectively. The incidence of grade 2 or more RP in patients of the IC group with a KL-6 level ≥600 U/ml was significantly higher than that in patients with KL-6 <600 U/ml ($p=0.017$), however, there were no significant differences in OS between these patients in the IC group (data not shown).

In the IC group, three patients developed grade 5 RP and died at 2.7, 4.3 and 8.5 months after SBRT, respectively. In all three patients, KL-6 was greater than 600 U/ml, and lung V5 was greater than 18%. Even in the IC group, patients with a KL-6 level of <600 U/ml did not develop grade 4 or more RP. On the other hand, none of the seven patients with a KL-6 level of ≥600 U/ml in the non-IC group experienced grade 2 or more RP.

Discussion

In the present study, the incidence of grade 2 or more RP was significantly higher in the IC group than the non-IC group, and all three patients with grade 5 RP were from the IC group. A high incidence of RP after thoracic radiotherapy for patients

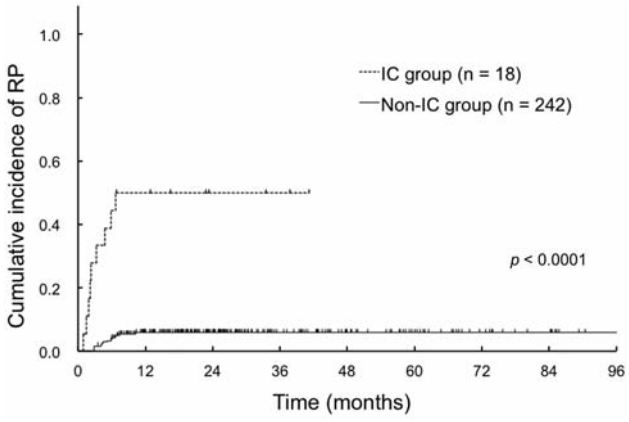

Figure 1. *Comparison of the cumulative incidence of radiation pneumonitis (RP) between the interstitial changes (IC) group and non-IC group by the Kaplan–Meier method. The incidence of grade 2 or more RP of the IC group was significantly higher than that of the non-IC group.*

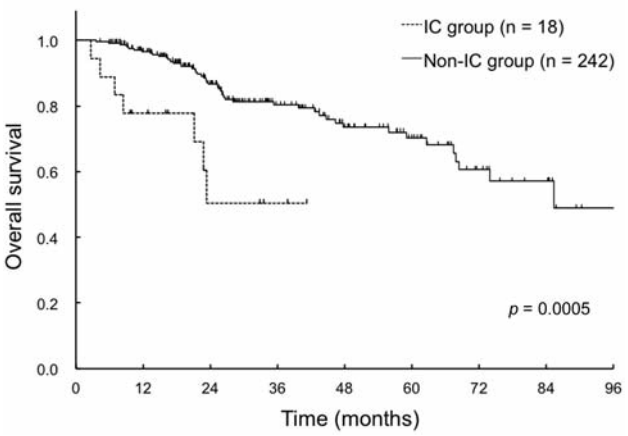

Figure 2. *Overall survival (OS) of the interstitial changes (IC) and non-IC group. The 2-year OS rates of the IC and non-IC groups 49.6% were 86.7%, respectively. The OS of the non-IC group was significantly longer than that of the IC group.*

with IC has been described in a few previous reports (15-18). Yamaguchi *et al*. described that grade 2-5 RP was observed in three (19%) out of 16 patients with sub-clinical interstitial lung disease (ILD) treated with SBRT for primary and metastatic lung cancer. Although sub-clinical ILD was not found to be a significant factor for grade 2 or more RP or clinical outcomes in their study, all three patients with extensive RP beyond the irradiated field had sub-clinical ILD. Therefore, they concluded that uncommon extensive RP can occur in patients with subclinical ILD (17). Yamashita *et al*. evaluated the incidence and the risk factors for grade 4-5 RP in 117 patients with primary and metastatic lung cancer after SBRT. The 1-year cumulative incidence of grade 4-5 RP was 57% in 13 patients with IC, and IC was found to be a significant risk factor for grade 4-5 RP (15). Sanuki *et al*. evaluated the association of IC with RP for 106 patients treated with conventional thoracic radiotherapy of 40 Gy or more for lung cancer or thymic tumors, and the incidence of grade 3 or more RP was significantly increased from 3% (2/79) to 26% (7/27) (16). Therefore, severe and potentially fatal RP may occur on SBRT for patients with IC on the pretreatment CT.

It has been well-established that there is a dose–response relationship between the incidence of RP after SBRT and dosimetric factors such as lung V5, V20, or MLD (7, 9, 19-21). Ong *et al*. described that the contralateral lung V5 was the best predictor of grade 2 or more RP in 18 patients with lung tumors and PTV exceeding 80 cm3 after SBRT using volumetric-modulated arc therapy (21). Barriger *et al*. reported that high MLD (≥4 Gy) and lung V20 (≥4%) were significant risk factors of grade 2 or more RP in 143 patients with lung cancer treated by SBRT (19). It is still controversial which of these dosimetric parameters is the better predictor. Following a univariate analysis in the present study, all lung parameters were found to be significant risk factors of grade 2 or more RP in the whole patient group, but lung V20 was not significantly related to the incidence of RP grade or more in the IC group. Yamashita *et al*. reported that the incidence of RP was not related to lung V20 or V40 in 117 patients with IC, but they did not evaluate lung V5, V10, or MLD (15). Patients with IC are thought to be a risk for IP, because IC is one of the major criteria of idiopathic pulmonary fibrosis. Therefore, it is speculated that patients with IC may develop RP on exposure to low-dose radiation more easily than patients without IC. Based on the present findings, it may be advisable to reduce both the low-dose and the high-dose irradiation areas in order to reduce the risk of RP in patients with IC. However, a further prospective study will be required to confirm this, since the present study was somewhat limited by its retrospective nature and the small number of patients with IC.

Serum KL-6 is one of the most reliable biomarkers for ILD (22, 23). Previous studies reported that KL-6 is increased in RP and would help to predict the occurrence of severe RP (16, 24, 25). Yamashita *et al*. evaluated 117 patients with primary and metastatic lung cancer who were treated with SBRT and reported that a correlation was found between the incidence of grade 4-5 RP and higher serum KL-6 levels (≥500 U/ml) (15). In the present study, the pretreatment serum KL-6 level was a significant predictive factor of grade 2 or more RP by univariate analysis. In particular, of the 13 patients with IC and high serum KL-6 levels (≥600 U/ml), three (23%) died of RP.

Table III. *Predictive factors of radiation pneumonitis (RP) of grade 2 or more in the whole patient group.*

Factor	n	RP incidence at 6 months	*p*-Value	
			Univariate	Multivariate
Gender				
Male	164	8.0%	0.495	
Female	96	5.2%		
Age (years)				
<77	124	8.9%	0.175	
≥77	136	5.2%		
Group				
Non-IC	242	4.2%	<0.0001	<0.0001
IC	18	44.4%		
PS				
0-1	218	7.4%	0.676	
2-3	42	4.8%		
CRP (mg/dl)				
<0.1	126	3.2%	0.064	
≥0.1	134	10.5%		
LDH (U/l)				
<200	151	6.6%	0.837	
≥200	101	7.4%		
KL-6 (U/ml)				
<600	187	4.3%	<0.001	0.198
≥600	13	38.5%		
Lung V5 (%)				
<18.0	122	2.5%	0.011	0.187
≥18.0	138	10.9%		
Lung V10 (%)				
<12.0	140	2.9%	0.005	0.869
≥12.0	120	11.7%		
Lung V20 (%)				
<6.0	142	3.5%	0.013	0.252
≥6.0	118	11.0%		
MLD (Gy)				
<4.0	135	2.2%	0.009	0.690
≥4.0	125	12.0%		

PS, Performance status; CRP, C-reactive protein; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; Lung Vx, lung volume receiving ≥x Gy; MLD, mean lung dose.

Table IV. *Predictive factors of radiation pneumonitis (RP) of grade 2 or more in the IC group.*

Factor	n	RP incidence at 6-months	*p*-Value
Gender			
Male	16	43.8%	0.732
Female	2	50.0%	
Age (years)			
<77	11	63.6%	0.143
≥77	7	14.3%	
PS			
0-1	14	50.0%	0.338
2-3	4	25.0%	
CRP (mg/dL)			
<0.4	10	40.0%	0.952
≥0.4	8	50.0%	
LDH (U/l)			
<200	9	33.3%	0.572
≥200	9	55.6%	
KL-6 (U/ml)			
<600	12	25.0%	0.017
≥600	6	83.5%	
Lung V5 (%)			
<18.0	6	0.0%	0.041
≥18.0	12	66.7%	
Lung V10 (%)			
<12.0	8	12.5%	0.038
≥12.0	10	70.0%	
Lung V20 (%)			
<6.0	8	25.0%	0.210
≥6.0	10	60.0%	
MLD (Gy)			
<4.0	8	12.5%	0.038
≥4.0	10	70.0%	

PS, Performance status; CRP, C-reactive protein; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; Lung Vx, lung volume receiving ≥ x Gy; MLD, mean lung dose.

Therefore, we strongly recommend avoiding SBRT for patients with IC and high levels of KL-6. However, even in patients with IC with a low KL-6 level and low lung dosimetric indices, the indication for SBRT remains unclear.

Conclusion

The presence of IC on a pre-treatment CT was an indicator of grade 2 or more RP and poor prognosis after SBRT for patients with lung cancer. SBRT should not be performed for patients with lung cancer with IC and pretreatment KL-6 level of ≥600 U/ml.

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