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Hypofractionated Proton Beam Therapy for cT1-2N0M0 Non-small Cell Lung Cancer Patients With Interstitial Lung Disease

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Abstract. *Background/Aim: To evaluate the outcomes of proton beam therapy (PBT) for early-stage non-small cell lung cancer (NSCLC) in patients with interstitial lung disease (ILD). Patients and Methods: Between 2002 and 2017, 110 patients receiving hypofractionated PBT for cT1-2N0M0 NSCLC were reviewed. Results: Of the 110 patients, 17 were diagnosed with ILD. The median follow-up period was 37.8 months. No significant difference in the 1-year cumulative rate of grade ≥2 pneumonitis was observed between patients with and those without ILD (17.6% vs. 14.1%, p=0.708). The lung doses were significantly lower in patients with than in those without ILD among patients without grade ≥2 pneumonitis. There were no significant differences in overall survival or local recurrence-free rates according to the presence of ILD. Conclusion: PBT appears to be a feasible and effective treatment for cT1-2N0M0 NSCLC in patients with ILD, but the lung dose should be strictly reduced.*

Stereotactic body radiation therapy (SBRT) is a standard treatment for medically inoperable patients with stage I non-small cell lung cancer (NSCLC) as well as patients who refuse to undergo surgery. The 3-year rates of local control and overall survival after SBRT range from 73% to 97% and from 59% to 83%, respectively (1-3). The incidence of grade ≥2 radiation pneumonitis, an important toxicity associated with thoracic radiotherapy (RT), was 5-10% following SBRT among patients with stage I NSCLC (4). However, the risk of developing pneumonitis is particularly high in patients with interstitial lung disease (ILD), and the incidences of grade ≥2 and ≥3 pneumonitis after SBRT were 18-55% and 10-38%, respectively, in patients with interstitial changes on CT images or with ILD (5-8). Therefore, ILD is considered a relative contraindication for SBRT.

The radiation dose and irradiated volume of the lung are associated with the development of severe pneumonitis after SBRT more frequently in patients with ILD than in those without. Although few studies have analyzed the correlations between dosimetric parameters of the lung and the development of pneumonitis after SBRT in patients with ILD, those that have reported that the lung volume receiving doses of ≥5 Gy (V5), ≥10 Gy (V10), or ≥20 Gy (V20) and the mean lung dose (MLD) were predictive of the development of pneumonitis (7, 8). In lung cancer treatment, proton beam therapy (PBT) has the advantage of reducing the irradiated volume and dose to surrounding normal tissue compared with SBRT, because appropriate dose distributions can be achieved using limited irradiation fields (9-13). Therefore, PBT might reduce the risk of severe pneumonitis and provide a treatment option for early-stage NSCLC in patients with ILD. Only one study has evaluated the clinical outcome of hypofractionated PBT for lung tumors in patients with idiopathic pulmonary fibrosis (14). Thus, we conducted

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Key Words: Proton beam therapy, interstitial lung disease, non-small cell lung cancer.

Table I. *Patients, tumor, and treatment characteristics*.

Characteristic	All patients	ILD (–)	ILD (+)	*p*-Value
n	110	93	17	
Age (years), median (range)	76 (52-88)	75 (52-88)	79 (64-88)	0.056
Gender				
Male	86	70	16	0.084
Female	24	23	1	
PS				
0	61	54	7	0.55
1	40	32	8	
2	8	6	2	
3	1	1	0	
Smoking history				
Never	16	14	2	0.43
Ever/Current	71	56	15	
Unknown	23	23	0	
Serum KL-6 (U/ml), median (range)	277 (127-1,711)	253 (127-1,711)	391 (159-962)	0.013
Pulmonary fibrosis score				
1			11	
2			3	
3			3	
Operability				
Operable	56	49	7	0.38
Inoperable	54	44	10	
Histology				
SqCC	24	20	4	0.35
Adenocarcinoma	44	40	4	
NSCLC, NOS	6	4	2	
Unknown	36	29	7	
UICC 7th T-stage				
T1a	38	32	6	0.95
T1b	35	30	5	
T2a	33	28	5	
T2b	4	3	1	
CTV (ml), median (range)	18.2 (2.1-107.8)	17.9 (2.1-107.8)	18.5 (5.8-62.5)	0.66
Tumor location				
Upper lobe	58	50	8	0.87
Middle lobe	11	9	2	
Lower lobe	41	34	7	
Total dose (RBE)				
66 Gy in 10 fractions	77	63	14	0.23
72.6 Gy in 22 fractions	33	30	3	

ILD: Interstitial lung disease; PS: performance status; KL-6: Krebs von den Lungen-6; UICC: Union for International Cancer Control; SqCC: squamous cell carcinoma; NSCLC: non-small cell lung cancer; NOS: not otherwise specified; CTV: clinical target volume; RBE: relative biological effectiveness.

an institutional retrospective study to assess the safety and efficacy of PBT for early-stage NSCLC in patients with ILD.

Patients and Methods

Patients. The present study was approved by the institutional review board at University of Tsukuba Hospital (approval no. H30-303). Between April 2002 and December 2017, 135 consecutive patients with cT1-2N0M0 NSCLC, according to the 7th version of the Union for International Cancer Control TNM classification (15), were treated with passive-scattering PBT at our institution. Twenty-five patients were excluded for the following reasons: no evaluable pretreatment computed tomography (CT) images of the lung (n=21), less than 6 months of follow-up (n=3), and insufficient data obtained from the dose–volume histogram (DVH) in the treatment planning system (n=1). The remaining 110 patients were included in this analysis.

Evaluation of interstitial lung disease. A board-certified diagnostic radiologist (S.H.) reviewed the pretreatment CT images of the lung and determined the presence or absence of ILD according to the idiopathic pulmonary fibrosis clinical practice guidelines of the American Thoracic Society (16). If a patient had ILD, the pulmonary

fibrosis score (PFS), as proposed by Kazerooni *et al*. (17), was used as the maximum score of the lobe in the whole lung.

Proton beam therapy. For treatment planning, CT images were obtained at 2.5- or 5.0-mm intervals in the treatment position using a respiratory-gated system during the end-expiratory phase. The patient's body was immobilized using a custom-shaped body cast (ESFORM, Engineering System Co., Matsumoto, Japan). Passive-scattering PBT plans were made using the VQA version 1.7 or 2.0 (Hitachi, Tokyo, Japan). PBT was delivered during the end-expiratory phase with 155-250 MeV protons generated using a synchrotron accelerator. Prior to each treatment, the patient's position was confirmed by fluoroscopy.

The clinical target volume (CTV) included the primary tumor, and planning target volume (PTV) comprised the CTV plus a 5- to 8-mm margin in all directions. In general, two to three ports in the optimal direction were used, and an aperture margin of 5-10 mm (an additional 5-mm margin in the caudal direction to compensate for respiratory motion) was set to cover the entire PTV by enlarging the multi-leaf collimator and adjusting the range shifter. For patients with a high risk of developing radiation pneumonitis, those with ILD comorbidity, those with extremely low pulmonary function (*e.g.*, forced expiratory volume in 1 s ≤700 ml), and those receiving long-term oxygen therapy, the minimum PTV and aperture margins (*e.g.*, 5 mm) were used to reduce the irradiated volume of the lung as much as possible. The following two treatment protocols were used depending on the tumor location: 66.0 Gy [relative biological effectiveness (RBE)] in 10 fractions for peripherally located tumors and 72.6 Gy (RBE) in 22 fractions for centrally located tumors.

Follow-up procedures and statistical analysis. Post-treatment evaluation was performed every 2-3 months during the first year and every 3-6 months thereafter. The follow-up examinations included physical examinations, blood tests, chest X-rays, and CT or positron emission tomography/CT. Local recurrence at the primary tumor site was defined as an increase in tumor size on serial CT scans, significant positive accumulation on positron emission tomography/CT, or histological confirmation. Treatment-related toxicities including pneumonitis were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Overall survival (OS), recurrence-free survival (RFS), and local recurrence-free (LRF) rates and the cumulative rate of pneumonitis were calculated from the first day of PBT to the date of the event or the last follow-up using the Kaplan–Meier method. Differences between survival curves were assessed using the log-rank test. Student's *t*-test was used to compare background clinical factors between two groups. Dosimetric parameters of the lung obtained from DVHs were compared between groups using the Mann–Whitney *U*-test, and cut-off values of these parameters for predicting the development of grade ≥2 pneumonitis were calculated using receiver operating characteristic analysis. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using JMP version 13 (SAS institute, Cary, NC, USA).

Results

Patient and treatment characteristics. The patient, tumor, and treatment characteristics are shown in Table I. The patients comprised 86 men (78.1%), and the median age was 76 years (range=52-88 years). NSCLC was confirmed histologically in 74 patients (67.2%). The clinical T stages were T1a (n=38; 34.6%), T1b (n=35; 31.8%), T2a (n=33; 30.0%), and T2b (n=4; 3.6%). Total doses of 66.0 Gy (RBE) in 10 fractions and 72.6 Gy (RBE) in 22 fractions were prescribed to 77 and 33 tumors, respectively. The median follow-up period was 37.8 months (range=2.1-176.9 months) in all patients and 43.1 months (range=6.3-176.9 months) in the surviving patients.

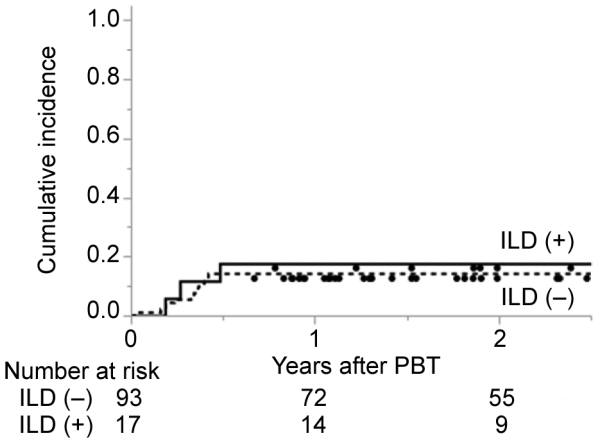

Figure 1. *Cumulative rates of grade ≥2 pneumonitis after proton beam therapy (PBT). Straight and dashed lines show the cumulative rates of grade ≥2 pneumonitis in patients with and those without interstitial lung disease (ILD), respectively.*

Of the 110 patients, 17 had ILD on pretreatment CT images. Among them, PFSs of 1, 2, and 3 were observed in 11, 3, and 3 patients, respectively, but no patient had a PFS ≥4. There were no significant differences in the patient, tumor, or treatment factors between the patients with and those without ILD, except for the serum level of Krebs von den Lungen-6, which was lower in the patients without ILD.

Pneumonitis and dose–volume histogram parameters of the lung. Grade 2 and 3 pneumonitis was observed in 10 (9.1%) and 6 (5.4%) patients, respectively, but no grade 4 or 5 pneumonitis was found. The incidences of grade 2 and 3 pneumonitis were 11.7% and 5.8% in patients with ILD and 8.6% and 5.4% in those without ILD, respectively. The 1-year cumulative rate of grade ≥2 pneumonitis in all patients was 14.6% [confidence interval (CI)=9.1-22.6], and there was no significant difference in this rate between patients with and those without ILD (17.6% *vs*. 14.1%, p=0.708) (Figure 1). Details regarding the pneumonitis cases are shown in Table II. For patients with ILD, grade ≥2 pneumonitis developed in one (7.1%) of 14 patients with a PFS of 1 or 2 and in two (66.6%) of three patients with a PFS of 3.

The DVH parameters of the lung according to the presence of ILD and pneumonitis are shown in Table III. Among the

Table II. *Details of the pneumonitis cases according to the presence of interstitial lung disease.*

Pneumonitis	All (n=110)	ILD (–) (n=93)	ILD (+)		
			PFS 1 (n=11)	PFS 2 (n=3)	PFS 3 (n=3)
Grade 0, 1	94 (85.5%)	80 (86.0%)	10 (90.9%)	3 (100%)	1 (33.3%)
Grade 2	10 (9.1%)	8 (8.6%)	1 (9.1%)	0 (0%)	1 (33.3%)
Grade 3	6 (5.4%)	5 (5.4%)	0 (0%)	0 (0%)	1 (33.3%)
Grade 4, 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

ILD: Interstitial lung disease; PFS: pulmonary fibrosis score.

Table III. *Parameters from lung dose–volume histograms according to the presence of interstitial lung disease and pneumonitis.*

DVH parameter	Pneumonitis	ILD (–) (n=93)	ILD (+) (n=17)	*p*-Value
V5, median (range)	All	11.2% (4.5-31.8%)	8.0% (4.5-20.9%)	0.011
	Grade ≤1	10.8% (4.5-31.8%)	7.7% (4.5-20.9%)	0.016
	Grade ≥2	14.5% (6.5-31.5%)	11.2% (7.2-12.3%)	0.200
	p-Value	0.064	0.377	
V10, median (range)	All	10.0% (3.9-29.2%)	7.1% (3.9-18.2%)	0.009
	Grade ≤1	9.5% (3.9-29.0%)	6.7% (3.9-18.2%)	0.017
	Grade ≥2	12.3% (5.8-29.2%)	8.7% (6.0-11.3%)	0.178
	p-Value	0.066	0.412	
V20, median (range)	All	8.0% (2.7-25.9%)	5.9% (3.0-13.3%)	0.012
	Grade ≤1	7.7% (2.7-24.6%)	5.5% (3.0-13.3%)	0.021
	Grade ≥2	10.0% (4.8-25.9%)	7.2% (4.4-9.7%)	0.157
	p-Value	0.055	0.412	
MLD, median (range)	All	4.0 Gy (1.4-15.9 Gy)	3.1 Gy (1.5-7.6 Gy)	0.015
	Grade ≤1	3.9 Gy (1.4-13.0 Gy)	2.9 Gy (1.5-7.6 Gy)	0.028
	Grade ≥2	5.1 Gy (2.5-15.9 Gy)	4.3 Gy (2.3-4.3 Gy)	0.121
	p-Value	0.051	0.283	

DVH: Dose-volume histogram; ILD: interstitial lung disease; V5: lung volume receiving a dose of ≥5 Gy; V10: lung volume receiving a dose of ≥10 Gy; V20: lung volume receiving a dose of ≥20 Gy; MLD: mean lung dose.

patients without ILD, the median lung V5, V10, and V20 and the MLD were higher, with marginal significance, in patients who developed grade ≥2 pneumonitis compared with grade ≤1 pneumonitis (14.5% *vs.* 10.8%, p=0.064; 12.3% *vs.* 9.5%, p=0.066; 10.0% *vs.* 7.7%, p=0.055; and 5.1 *vs.* 3.9 Gy, p=0.051). On the other hand, a similar tendency was not found among the patients with ILD. In patients with grade ≤1 pneumonitis, the lung V5, V10, and V20 and the MLD were significantly lower in patients with than those without ILD (7.7% *vs.* 10.8%, p=0.016; 6.7% *vs.* 9.5%, p=0.017; 5.5% *vs.* 7.7%, p=0.021; and 2.9 *vs.* 3.9 Gy, p=0.028), but there were no significant differences according to the presence of ILD in patients with grade ≥2 pneumonitis. Figure 2 shows the cut-off values of the lung V5, V10, and V20 and MLD for predicting the development of grade ≥2 pneumonitis, determined using receiver operating characteristic curves.

Survival and local control. The 3-year rates of OS, RFS, and LRF of all patients were 78.2% (95%CI=68.8-85.4), 61.9% (95%CI=52.3-70.7), and 88.9% (95% CI=80.5-94.0), respectively. The corresponding rates of the patients with ILD were 72.3% (95%CI=44.8-89.3), 61.6% (95%CI=36.4-81.7), and 85.5% (95%CI=56.7-96.3), respectively, and those of the patients without ILD were 79.3% (95%CI=68.8-87.4), 62.0% (95%CI=51.6-71.5), and 89.6% (95%CI=80.4-94.7), respectively (Figure 3). No significant differences in OS (p=0.077), RFS (p=0.502), or LRF (p=0.220) rates were observed between patients with and those without ILD.

Discussion

SBRT for early-stage lung cancer in patients with ILD can cause severe or fatal pneumonitis. There are several studies so far that have evaluated the outcomes of SBRT for lung tumors in patients with ILD, many of which have been conducted in Japan (5-8, 18-20). As shown in Table IV, the incidences of grade ≥2, ≥3, and 5 pneumonitis after SBRT in patients with ILD were 18.7-55.0%, 10.0-38.8%, and 0-

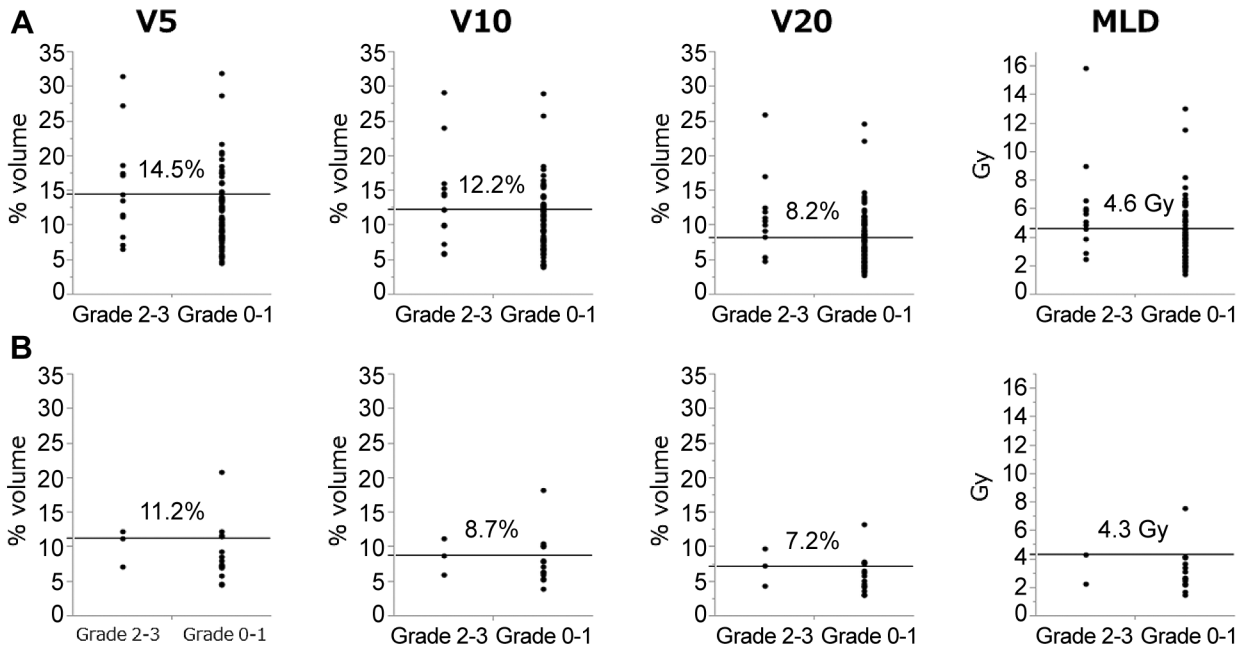

Figure 2. *Dosimetric parameters in patients with and those without grade ≥2 pneumonitis. Horizontal bars show the cut-off values calculated using receiver operating characteristic curves. (A) Patients without ILD and (B) patients with ILD.*

21%, respectively (5-8, 18-20). Because there is an apparent dose–volume effect of SBRT in the lung on radiation-induced pneumonitis in patients with lung tumors (7, 8, 20), particle therapy including PBT, which can provide a better dose distribution compared with SBRT, is theoretically safer than photon-based SBRT for providing curative radiation doses in patients with ILD. In our study, the incidence of grade ≥2 pneumonitis in patients with ILD was 17.6% and was comparable with the rates reported in previous particle therapy studies (14, 21, 22). Although the particle therapy series included more patients with larger (T2-3) tumors compared with the SBRT series, the incidence of pneumonitis induced by particle therapy appears to be lower than that induced by SBRT (5-8, 18-20) (Table IV).

We also aimed to identify predictive factors associated with pneumonitis development after PBT in patients with ILD to establish optimal thoracic RT conditions for patients with ILD. Although several factors associated with ILD have been reported to predict severe pneumonitis development after SBRT for NSCLC, including pretreatment serum levels of Krebs von den Lungen-6 and surfactant protein-D, diffusing capacity of the lungs for carbon monoxide, oxygen dependence, non-target lung FDG uptake, and severity of ILD (23-25), there are no established criteria for offering RT as an acceptable treatment option to patients with ILD. The PFS proposed by Kazerooni is used to evaluate the severity of idiopathic pulmonary fibrosis and is correlated with the pathological changes of fibrosis (17). In the present study, the incidence of grade ≥2 pneumonitis in patients with a PFS of 3 was 66.6%, whereas the corresponding rate was 7.1% in patients with a PFS of 1 or 2. Tsujino *et al*. reported that the PFS combined with the lung V20, absolute lung volume spared from a 5 Gy dose, and age can improve the predictability of developing severe radiation pneumonitis in NSCLC patients treated with chemoradiotherapy, supporting our results (26). The PFS on pretreatment CT images may help select patients with ILD appropriate for PBT for early-stage NSCLC.

Thus, PBT seems to be safe for cT1-2N0M0 NSCLC patients with a PFS of 1/2 even if they have ILD, but it was unclear whether PBT is truly safe for patients with ILD because their PTV margins were carefully reduced. There was no difference in the CTV between patients with and those without ILD, but the lung V5-20 and MLD were significantly lower in the patients with than in those without ILD (Table III). On the other hand, our treatment policy seems to be acceptable because there was no difference in RFS or LRF between the groups. Hence, the dose constraints of the lung as well as the setting of the PTV are very important in terms of the efficacy and toxicity of RT for cT1-2N0M0 NSCLC patients with ILD.

Only a few studies have reported the DVH parameters associated with the development of pneumonitis after SBRT in patients with ILD. Yoshitake *et al*. reviewed 260 patients who

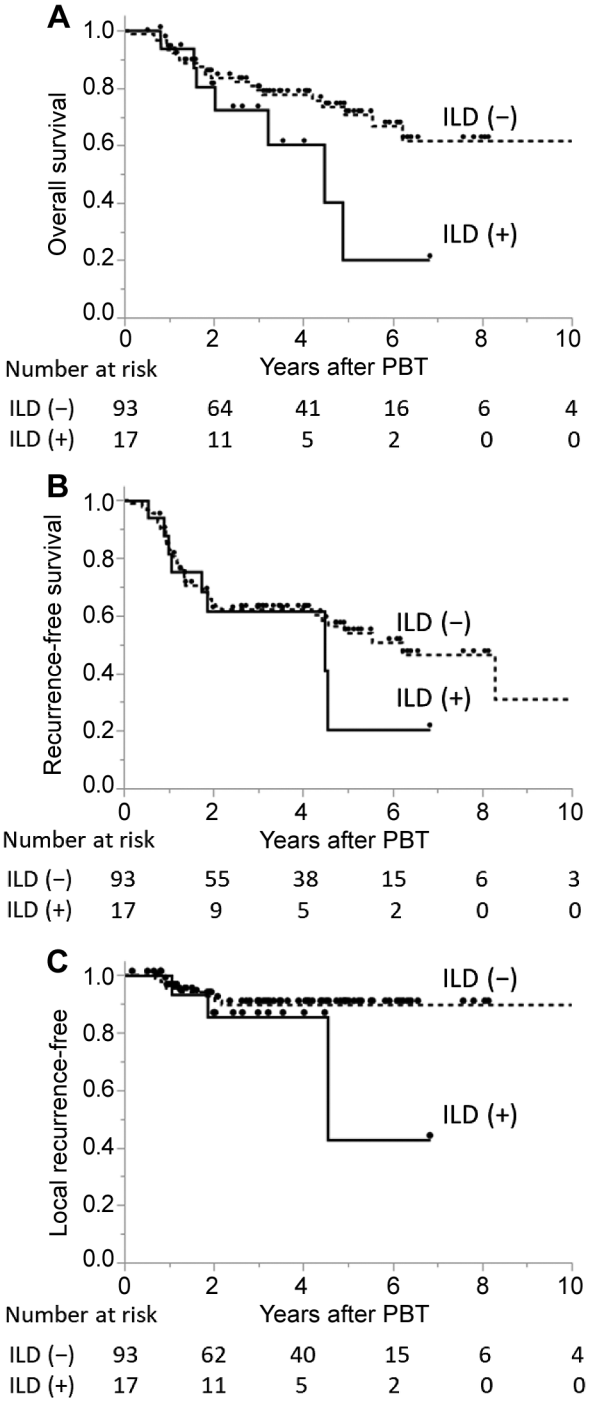

Figure 3. *Kaplan–Meier curves of survival and local recurrence-free rates according to the presence (straight lines) or absence (dashed lines) of interstitial lung disease (ILD). (A) Overall survival, (B) recurrence-free survival, and (C) local recurrence-free rates.*

received SBRT for lung cancer, including 18 with interstitial changes on pretreatment CT, and reported a significantly higher 6-month cumulative rate of grade ≥2 pneumonitis in the patients with than in those without interstitial changes (44.4% *vs.* 4.1%, $p<0.0001$), whereas there was no significant difference in the lung V5, V10, or V20 or the MLD (7). Liu *et al.* evaluated 109 early-stage NSCLC patients receiving SBRT, including 38 with subclinical ILD, and reported that the MLD was significantly higher in patients with grade ≥2 pneumonitis than in those with grade ≤1 pneumonitis among patients with subclinical ILD (5.5 Gy *vs.* 3.4 Gy, $p=0.042$) (20). Their findings suggest that stricter dose constraints of the lung are required when treating patients with ILD. In the present study, however, there were no significant differences in DVH parameters between ILD patients with grade ≥2 and those with grade ≤1 pneumonitis, although dose–volume effects on the development of pneumonitis were seen in patients without ILD. Similarly, Ono *et al.* could not determine any cut-off levels for DVH parameters in NSCLC patients with ILD treated with PBT (14). In our study, the cut-off values of the lung V5 and V10 and the MLD of all three patients who developed grade ≥2 pneumonitis among those with ILD were lower than the respective values among the patients without ILD. One explanation for these results is that our values were very low compared with those obtained after SBRT. Dosimetric risk factors for pneumonitis after SBRT in patients with ILD were reported to be a lung V5 ≥18%, V10 ≥12%, and MLD ≥4 Gy (7). The median lung V5 and V10 and MLD of the patients with ILD in the present study were only 8.0%, 7.1%, and 3.1 Gy, respectively. Thus, physiological superiority of PBT over SBRT contributed to a lower incidence of grade ≥2 pneumonitis (17.6%), with no grade 5 pneumonitis, after PBT in the present study. Conversely, the DVH parameters of the lung with asymptomatic (grade ≤1) pneumonitis were significantly lower in patients with than in those without ILD. Therefore, the abovementioned approaches in addition to reducing the lung dose using protons and carbon-ions are necessary to determine patient eligibility for curative RT after further data accumulation.

The major limitations of this study were its retrospective nature and small number of patients from a single institution. However, the number of patients with ILD referred to radiation oncologists is low because it is unclear whether RT, including PBT, is beneficial for NSCLC patients with ILD. Although the limitations of this study were unavoidable, a future large-scale multi-institutional study should be conducted. At present, NSCLC patients treated with RT using protons and carbon-ions in Japan are being prospectively registered, and the resulting data will not only confirm the effectiveness but also determine patient eligibility and the optimal treatment conditions in terms of safety.

In conclusion, passive-scattering PBT seems to be a feasible and effective treatment option for cT1-2N0M0 NSCLC patients with ILD. Patients with a maximum PFS of 1/2 who receive PBT have a low incidence of symptomatic pneumonitis if protons are used. However, predictive markers of pneumonitis after PBT for patients with a PFS of

Table IV. *Summary of the outcomes of SBRT and hypofractionated particle therapy for lung tumors in patients with ILD.*

Author	Modality	No. of ILD patients	Median age	Primary/ Metastatic tumor cases	T1/T2/T3	OS (year)	Pneumonitis			
							Grade ≥2	Grade ≥3	Grade 5	Criteria
Yamaguchi *et al*. (5)	SBRT	16	N/A	N/A	N/A	48% (3)	18.7%	18.7%	6.2%	CTCAE v.3.0
Ueki *et al*. (6)	SBRT	20	78	20/0	14/6/0	54% (3)	55.0%	10.0%	0%	CTCAE v.3.0
Yoshitake *et al*. (7)	SBRT	18	75	18/0	N/A	49% (2)	50.0%	38.8%	16.7%	CTCAE v.4.0
Onishi *et al*. (8)	SBRT	242	77	242/0	160/82/0	42% (3)	N/A	12.4%	6.9%	N/A
Bahig *et al*. (18)	SBRT	28	76	28/0	N/A	N/A	N/A	32%	21%	CTCAE v.3.0
Glick *et al*. (19)	SBRT	39	78	35/4	N/A	36% (3)	20.5%	10.3%	5.1%	CTCAE v.3.0
Liu *et al*. (20)	SBRT	38	N/A	38/0	N/A	N/A	47.3%	10.5%	2.6%	CTCAE v.5.0
Nakajima *et al*. (21)	CIRT	29	73	29/0	10/19/0	46% (3)	41.0%	27.5%	0%	CTCAE v.3.0
Okano *et al*. (22)	CIRT	26	76	26/0	18/8	59% (3)	7.6%	3.8%	0%	CTCAE v.4.0
Ono *et al*. (14)	PBT	16	76	15/1	7/6/2	44% (2)	18.7%	12.5%	6.2%	CTCAE v.3.0
Current study	PBT	17	79	17/0	11/6/0	72% (3)	17.6%	5.8%	0%	CTCAE v.4.0

SBRT: Stereotactic body radiation therapy; ILD: interstitial lung disease; OS: overall survival; N/A: not available; CTCAE: Common Terminology Criteria for Adverse Events; CIRT: carbon ion radiotherapy; PBT: proton beam therapy.

3 should be confirmed to determine the PBT indications and optimal treatment method in future studies.

Conflicts of Interest

The Authors have no conflicts of interest to disclose regarding this manuscript.

Authors' Contributions

Conceptualization, TS and KO; methodology, HI, TS, and KO; investigation, TS, KO, SH, and MN; resources, KO, HN, KNM, MM, and TO; data collection, TS and KO; writing (original draft preparation), TS and KO; writing (review and editing), HI; supervision, HS.

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