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Long-term Outcomes After Moderate Hypofractionated Proton Therapy for Centrally Located Non-small Cell Lung Cancer

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Abstract. *Background/Aim: To investigate the outcomes of patients with centrally located non-small-cell lung cancer (NSCLC) treated with proton beam therapy (PBT) using moderate hypofractionation. Patients and Methods: Between 2006 and 2019, 34 patients with centrally located T1-T4N0M0 NSCLC who received moderate hypofractionated PBT were retrospectively reviewed. Results: The median follow-up was 50.8 months (range=5.8-100.4 months). The 3-year overall survival, progression-free survival (PFS), and local control rates were 70.4%, 55.5% and 80.5%, respectively. Grade 2 or 3 lung adverse events (AEs) after PBT were observed in five (14.7%) patients; however, grade 3 radiation pneumonitis was observed in one (2.9%) patient. Notably, no grade 4 or higher AEs were observed. Regarding the correlation between the lung dose and proximal bronchial tree maximum dose and grade 2 or higher lung AEs, a weak correlation was observed between the mean lung dose and AEs (p=0.035). Although the clinical target volume (CTV) was a risk factor for poor PFS, no significant correlation was found between the CTV and lung AEs after PBT. Conclusion: Moderate hypofractionated PBT may be a useful radiotherapy method for centrally located cT1-T4N0M0 NSCLC.*

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Key Words: Proton beam therapy, centrally located, non-small cell lung cancer, moderate hypofractionation, radiation pneumonitis, dose volume histogram.

Stereotactic body radiotherapy (SBRT) is the preferred treatment option for patients with early-stage non-small-cell lung cancer (NSCLC) who are medically inoperable or refuse surgery (1). Particularly, since peripheral early-stage NSCLC is not adjacent to normal tissues, which causes serious adverse events (AEs), SBRT has enabled physicians to prescribe high irradiation doses using hypofractionation to the target, thereby safely achieving favorable local control (2-5). However, hypofractionated SBRT for centrally located early-stage lung cancer causes higher rates of lethal AEs, such as pneumonitis and pulmonary hemorrhage, than that for the peripheral type (6-12). Therefore, the feasibility and efficacy of hypofractionated SBRT for the disease have not been confirmed, and the appropriate dose constraints for organs at risk (OARs), including the esophagus and main bronchus and dose fractionation schedules, should be determined (13, 14).

As proton beams provide better dose distribution than photon beams by limiting beam numbers and imparting a high dose to the target while sparing OARs, proton beam therapy (PBT) is theoretically safe for large lung tumors or centrally located tumors (15-19). Even for the peripheral type, large tumors are challenging to treat with SBRT or are less safe; however, PBT is less affected by size (15). Therefore, this study aimed to investigate the clinical outcomes of patients with centrally located cT1-4N0M0 NSCLC who received moderate hypofractionated high-dose PBT at our institution and to analyze the advantageous effects of PBT on clinical outcomes.

Patients and Methods

Patients. The institutional review board of our institution approved this study (approval no. R04-114). Consent from each patient was obtained, and data from 34 patients with centrally located NSCLC without lymph node metastasis (cT1-T4N0M0) and distant metastasis who underwent definitive PBT using moderate hypofractionation between January 2006 and December 2019 at our institution were retrospectively reviewed.

Table I. *Patient and tumor characteristics*.

Characteristics		N=34
Age (years)		55-88 (median=77)
Sex	Male/female	26/8
Performance status	0/1/2	17/13/4
Chronic obstructive pulmonary disease	Yes/No	12/22
Interstitial pneumonitis	Yes/No	3/31
Histology	Squamous cell carcinoma/adenocarcinoma/NSCLC NOS/not proven	9/14/2/9
PETCT received before PBT	Yes/No	25/9
T stage (7^{th} UICC clinical stage)	T1a/T1b/T2a/T2b/T3/T4	12/6/8/5/2/1
Tumor length diameter (cm)		0.8-6.2 (median=2.7)
Clinical target volume (cc)		3.3-117.0 (median=25.5)
Primary tumor site	Right upper/right middle/right lower/left upper/left lower	10/2/9/9/4
The main reason for centralized division	Right branch/trachea/left branch/esophagus	18/3/11/2
Operability	Operable/inoperable	11/23
Dose and fractionation	72.6 GyE/22 fr /75 GyE/25 fr	32/2
Follow-up time (months)		5.8-100.4 (median, 50.8)

NSCLC, Non-small cell lung cancer; NOS, not otherwise specified; UICC, Union for International Cancer Control; GyE, Gray equivalent; fr, fraction.

Definition of centrally located lung cancer. In this study, "central type" was defined in reference to the definitions of RTOG0813 and JROSG10-1, which were previously published (13, 14, 20). Principally, the tumor was located within 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchus, and bronchial tree to the second bifurcation) and immediately adjacent to the mediastinal or pericardial pleura. No cases where tumors invaded the left and/or right main bronchus (ultra-central type) were found in this study (21).

Proton beam therapy. For treatment planning, chest computed tomography (CT) images were acquired at 2.5 mm or 5.0 mm intervals with the patient placed in a body cast during the end-expiratory phase using a respiratory-gating system (Engineering System Co., Matsumoto, Japan). In addition, protons of 155-250 MeV were delivered using the passive-scattering PBT method, and dose calculations were performed using the pencil beam method (Proton Treatment Planning Software version 1.7 or 2, Hitachi Inc., Ibaraki, Japan). The treatment planning system automatically estimated the conditions required for beam delivery, including a ridge filter, range shifter, collimator, and bolus. The beam delivery system created a homogenous dose distribution using the spread-out Bragg peak at the prescribed dose.

The clinical target volume (CTV) encompassed the primary tumor. The planning target volume encompassed the CTV along with a 5-8 mm margin in all directions and an additional 5 mm margin in the caudal direction to compensate for respiratory motion. Two different dose fractionations [72.6 Gray equivalents (GyE) in 22 fractions or 75 GyE in 25 fractions] were used for centrally located NSCLC according to tumor location. The treatment plans were modified as necessary during PBT to adapt to tumor size and shape changes.

Follow-up and statistical analysis. Follow-up examinations were performed by physical examination, chest radiography, blood test, CT, and magnetic resonance imaging every 2-3 months during the first year; subsequently, they were performed at 3-6 month intervals. Positron emission tomography (PET)/CT or bronchoscopy was performed when the development of recurrence was suspected. Local progression at the primary site was defined as an increase in tumor size, significant positive accumulation on PET/CT, or histological diagnosis. Regional recurrence was defined as lymphadenopathy newly observed in the hilar, mediastinal, or supraclavicular regions. Furthermore, AEs were assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (22). Acute AEs were defined as those occurring within 3 months of the start of irradiation, and late AEs as those occurring later. The relative proportion of lungs irradiated with ≥ X Gy to the total lungs was defined as Vx. The biological effective dose (BED) 10 was assumed to be an α/β ratio of 10 and was calculated as $d \times n\{1+d/(\alpha/\beta)\}$ (d=dose and n=number of fractions). When we compared doses with those from other studies, the dose calculations for tumors were performed at BED10 and for late effects at BED3.

The follow-up interval was defined from the first day of PBT to the date of death or last follow-up. Overall survival (OS), progression-free survival (PFS), and local control (LC) rates were calculated from the first day of PBT to the date of the event or last follow-up using the Kaplan–Meier method. In addition, significant differences between the survival curves were assessed using the generalized Wilcoxon test. The Cox proportional hazards model was used for multivariable analysis. $p<0.05$ was considered statistically significant. SPSS version 25 (IBM, Armonk, NY, USA) was used for statistical analyses.

Results

Patient background. Patient and tumor characteristics are presented in Table I. The median age was 77 years (range=55-88 years), and the patients included 26 men. According to the seventh edition of the Union for International Cancer Control (UICC) TNM classification, the clinical stage was IA in 18, IB in 8, IIA in 5, IIB in 2, and IIIA in one patient. Histopathological examination revealed that 9, 14, and 2 tumors were squamous cell carcinoma,

adenocarcinoma (AC), and NSCLC, respectively. The remaining nine tumors were clinically diagnosed as NSCLC. Three patients had interstitial pneumonitis (IP); two had a pulmonary fibrosis score of 1 point, and one had a score of 3 points (23). The reasons for centrally located NSCLC were the proximal bronchial tree in 29, a trachea in 3, and an esophagus in 2 patients. Of the five patients whose tumors were close to the trachea (n=3) or esophagus (n=2), three had almost no dose to the proximal bronchial tree, and the other two had high doses to the tree, approximately 90% of the prescription dose. The prescribed dose was 72.6 GyE (BED10=96.6) for 32 and 75.0 GyE (BED10=97.5) for 2.

For all patients, the median maximum proximal bronchial dose, median mean lung dose (MLD), median lung V20, median lung V5, and the median maximum esophagus dose were 64.8 (range=0-77.7) GyE, 4.6 (range=1.8-16.0) GyE, 9.5 (range=2.8-28.1) %, 13.4 (range=3.8-35.8) %, and 22.9 (range=0-75.6) GyE, respectively. Regarding BED3, the median maximum proximal bronchial and median maximum esophagus doses were 128.4 (range=0-169.0) GyE and 30 (range=0-162.2) GyE, respectively.

Survival and control. At the last follow-up, 15 (44%) patients were still alive, while 12 (35%) had died of recurrences of NSCLC. The remaining seven patients died of other intercurrent diseases without any NSCLC recurrence and severe treatment-related toxicities: bacterial pneumonia (n=2), other cancers (n=2), myocardial infarction (n=1), or intercurrent diseases (n=2). Two of these deaths were over 5 years after treatment without any signs of disease recurrence, and no specific adverse events occurred. The median follow-up time was 50.8 (range=5.8-100.4) months for all patients and 59.4 (range=26.0-86.4) months for surviving patients, respectively.

The 3-year OS, PFS, and LC were 70.4% [95% confidence interval (CI)=54.9-85.8], 55.5% (95% CI=38.6-72.3), and 80.5% (95% CI=66.5-94.6), respectively. The 5-year OS, PFS, and LC were 51.7% (95% CI=33.5-70.0), 39.2% (95% CI=21.0-57.4), and 70.0% (95% CI=51.5-88.4), respectively (Figure 1). In 26 patients with Stage I, the 3-year OS and PFS were 76.6% (95% CI=60.1-93.0) and 61.1% (95% CI=42.2-80.0), respectively, while the corresponding rates in the Stage II-III group (n=8) were 37.5% (95% CI=4.0-71.1) and 37.5% (95% CI=4.0-71.1), respectively.

The initial failure patterns after PBT were local failure in six patients, distant metastases in seven, and both local and distant recurrences in three. There were no cases of regional recurrence as initial relapse. Recurrences due to the clinical T stage are presented in Table II. Local recurrence was observed in 4 of the 26 patients in Stage I and 5 of the 8 patients in Stage II-III.

Prognostic factors. The potential prognostic factors associated with OS and PFS are presented in Table III. In univariate analysis, poor performance status and larger CTV were associated with significantly worse OS (p=0.010 and 0.020, respectively) and PFS (p=0.038 and p<0.001, respectively). A significant difference was observed in OS between patients with clinically and histopathologically diagnosed NSCLC (p=0.024). In addition, multivariable analysis of survival using the purposeful selection method (inclusion and exclusion criteria were p=0.1) showed no significant factor in OS but significantly poor PFS in patients with a larger CTV (p=0.017).

Adverse events. In this study, no grade 4-5 AEs were observed (Table IV). Regarding acute AEs, grade 2 dermatitis was observed in one (2.9%) patient and grade 2 esophagitis in one (2.9%). Regarding late AEs, grade 2 pneumonitis, grade 2 lung infection, and grade 3 pneumonitis were observed in three (8.8%), one (2.9%), and one (2.9%) patient, respectively.

The cases of late AEs in grades 2 and 3 are presented in Table V. Among the three patients with grade 2 symptomatic pneumonitis, the symptoms in all cases improved within approximately 2 months. However, the patient with grade 3 pneumonitis had a pulmonary fibrosis score of 3 points before PBT and a history of an acute flare-up of the IP. Therefore, he continued to take oral prednisone 20 mg; however, he was hospitalized to escalate doses of steroids for pneumonitis 10 months after the start of PBT. His lung doses were calculated during treatment planning as 11.2%, 7.2%, and 4.3 GyE for V5, V20, and MLD, respectively.

Pulmonary adverse events and dose-volume histogram. We evaluated the correlation between the proximal bronchial tree maximum dose, lung dose, and CTV and the incidence of grade 2 or higher lung-related AEs (Figure 2). The correlation ratio ($\eta 2$) between each factor and AEs was 0.018, 0.131, 0.082, 0.053, and 0.036 for bronchial maximum dose, MLD, lung V20, lung V5, and CTV, respectively; therefore, only MLD was weakly correlated with the incidence of grade 2 or higher lung-related AEs.

Case of treatment. An 85-year-old male patient with right upper lobe lung AC, clinical T1bN0M0 according to the 7th edition of the UICC, was treated with PBT instead of surgery because of his lower forced expiratory volume in one second (1.04 l) and advanced age. The pretreatment CT showed a 28 mm-sized nodule in S2 of the right lung, and the biopsy was diagnosed as AC (Figure 3). Furthermore, treatment planning was performed in the prone position with three ports: two from the dorsal and one from the lateral. The lateral port was designed to reduce the dose to the branches of the right main bronchus and upper lobe. A follow-up CT, 24 months after completion of PBT, showed that the radiation pneumonitis had resolved, and the upper lobe branch remained open, with no relapse.

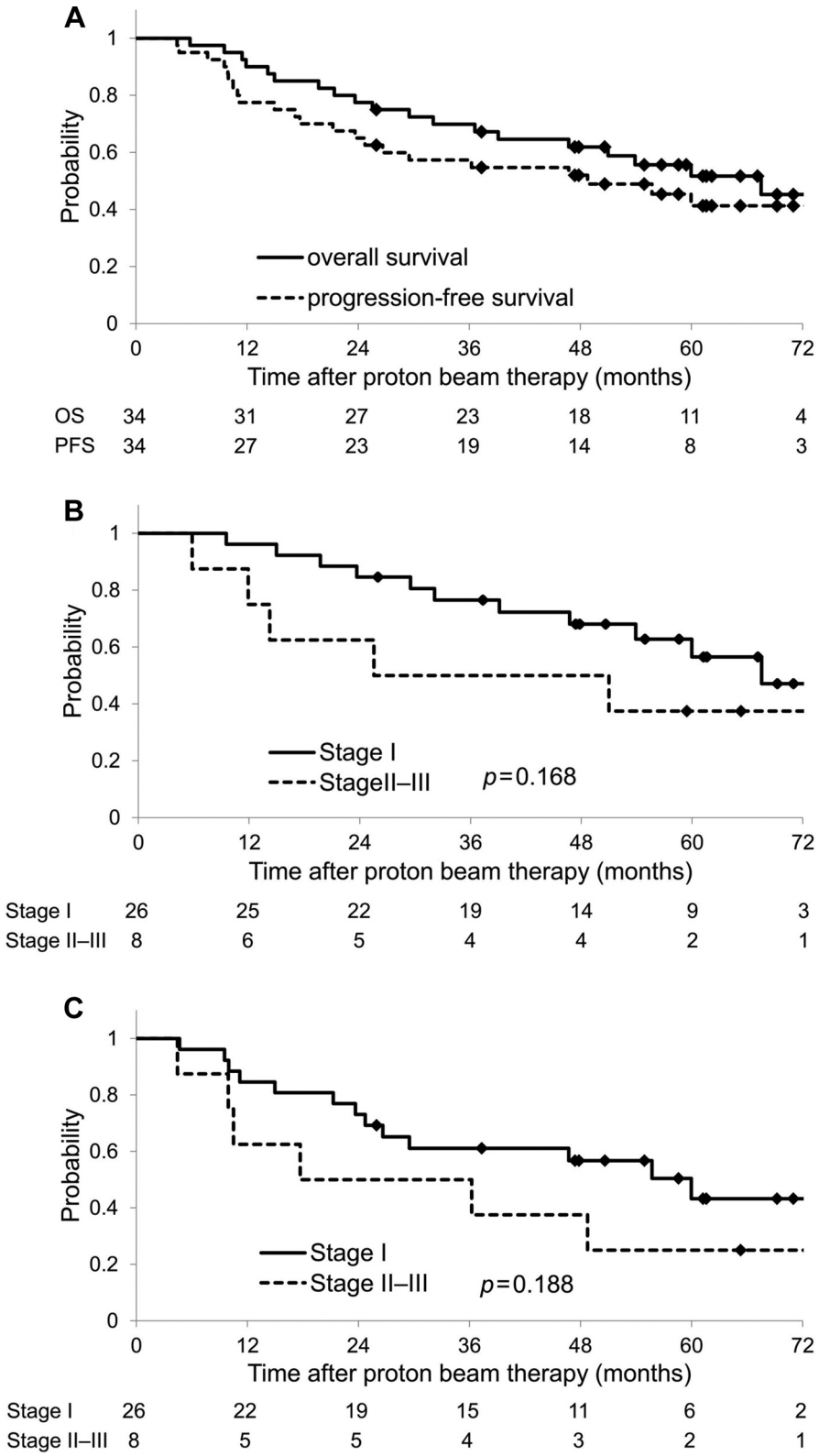

Figure 1. *Survival curves of the patients in this study. Straight and dashed lines indicate (A) overall survival and progression-free survival, respectively, (B) the overall survival curves of patients in stage I and those in stage II-III, respectively, and (C) progression-free survival curves of patients in stage I and those in stage II-III, respectively. Significant differences between the survival curves were assessed using the generalized Wilcoxon test.*

Table II. *Initial recurrence site after proton beam therapy.*

T stage	Local recurrence	Distant metastasis	Local recurrence and distant metastasis
T1a	2/12 (16.7%)	2/12 (16.7%)	1/12 (8.3%)
T1b	0/6 (0%)	0/6 (0%)	0/6 (0%)
T2a	1/8 (12.5%)	3/8 (37.5%)	0/8 (0%)
T2b	1/5 (20.0%)	2/5 (40.0%)	1/5 (20.0%)
T3	1/2 (50%)	0/2 (0%)	1/2 (50%)
T4	1/1 (100%)	0/1 (0%)	0/1 (0%)

Table III. *Univariable and multivariable analysis of prognosis factors for overall survival and progression-free survival.*

Factor		OS		PFS	
Univariable analysis	N=34	3-year rate (%)	*p*-Value	3-year rate (%)	*p*-Value
Age (<80 years *vs*. ≥80 years)	20 *vs*. 14	65.0 *vs*. 71.4	0.766	50.0 *vs*. 55.6	0.561
Sex (Male *vs*. Female)	26 *vs*. 8	65.0 *vs*. 87.5	0.180	53.3 *vs*. 62.5	0.531
PS (0 *vs*. ≥1)	17 *vs*. 17	82.4 *vs*. 52.3	0.010	70.6 *vs*. 39.7	0.038
COPD (yes *vs*. no)	12 *vs*. 22	66.7 *vs*. 67.4	0.263	66.7 *vs*. 67.4	0.263
IP (yes *vs*. no)	3 *vs*. 31	33.3 *vs*. 70.7	0.320	33.3 *vs*. 57.6	0.284
Diagnosis (Histological *vs*. Clinical)	9 *vs*. 25	59.5 *vs*. 100	0.024	47.4 *vs*. 77.8	0.053
Stage (I *vs*. II-III)	26 *vs*. 8	76.6 *vs*. 37.5	0.168	61.1 *vs*. 37.5	0.188
CTV (<50 cc *vs*. ≥50 cc)	24 *vs*. 10	78.8 *vs*. 40.0	0.020	70.6 *vs*. 20.0	<0.001
Cause of central type (branch *vs*. others)	29 *vs*. 5	61.6 *vs*. 100	0.403	47.6 *vs*. 100	0.245
Operability (operable *vs*. inoperable)	11 *vs*. 23	72.7 *vs*. 69.1	0.306	54.6 *vs*. 51.2	0.483
Multivariable analysis	N=34	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
PS (0 *vs*. ≥1)	17 *vs*. 17	2.83	0.56-7.20	0.068	1.67	0.59-4.76	0.334
Diagnosis (Histologic *vs*. Clinical)	9 *vs*. 25	0.32	0.07-1.53	0.136	0.48	0.13-1.72	0.259
CTV (<50 cc *vs*. ≥50 cc)	24 *vs*. 10	1.99	0.77-7.45	0.177	3.47	1.25-9.60	0.017

OS, Overall survival; PFS, progression-free survival; PS, performance status; COPD, chronic obstructive pulmonary disease; IP, interstitial pneumonitis; AC, adenocarcinoma; CTV, clinical target volume; HR, hazard ratio; CI, confidence interval.

Discussion

In this study, moderately hypofractionated PBT in 22-25 fractions provided favorable outcomes for central T1-4N0M0 NSCLC regarding both feasibility and efficacy. In actuality, the 3-year OS and PFS rates in stage I were 76.0% and 61.1%, respectively, and the corresponding rates in stages II-III were 37.5% and 37.5%, respectively. Moreover, the grade 3 lung AEs were only observed in one (2.9%) patient, and no grade 4-5 AEs were found in the study. The case of grade 3 AEs in this study required medication with steroids for IP before PBT and had pulmonary fibrosis score of 3 points; therefore, he was a very high-risk patient who had lung AEs after chest irradiation (24, 25). The reason why there were no cases of symptomatic pneumonitis even in elderly patients might be produced by reducing irradiated doses to the normal lung using PBT (26).

Unlike the peripheral type, developing serious AEs is an important problem after SBRT for centrally located NSCLC.

Table IV. *Adverse events in patients with centrally located non-small cell lung cancer.*

		Grade 0-1	Grade 2	Grade 3
Acute	Dermatitis	33 (97.1%)	1 (2.9%)	0
	Esophagitis	33 (97.1%)	1 (2.9%)	0
Late	Pneumonitis	30 (88.3%)	3 (8.8%)	1 (2.9%)
	Lung infection	33 (97.1%)	1 (2.9%)	0

Several reports have shown that SBRT for centrally located NSCLC is associated with a high risk of AEs, including fatal pneumonitis and bronchopulmonary hemorrhage, and the incidence of late AEs grade 3-5 and grade 5 have ranged from 2.0% to 41.5% and from 0 to 18.2%, respectively (Table VI). Timmerman *et al*. also reported the outcomes of a phase II study where patients with tumors in the

Table V. *Patient characteristics with grade 2 or higher late adverse events.*

Case	Adverse events	Age (year)	COPD	IP	FEV1% (%)	FEV1 (l)	Steroid therapy	Inhalation of oxygen	Time to symptom improvement (month)	CTV volume (cc)
1	Pneumonitis Grade 3	66	No	Yes (PSL 20 mg)	90.0	2.44	Increased quantity in hospital	Yes (Before PBT)	Unable to assess due to IP	11.7
2	Lung infection Grade 2	75	No	No	67.6	2.15	No	No	2.4	43.9
3	Pneumonitis Grade 2	86	No	No	67.7	1.11	No	No	2.3	63.6
4	Pneumonitis Grade 2	88	No	No	60.5	1.33	No	No	2.3	64.7
5	Pneumonitis Grade 2	76	No	No	62.2	1.61	Yes	No	1.5	68.0

COPD, Chronic obstructive pulmonary disease; IP, interstitial pneumonitis; FEV1, forced expiratory volume in one second; CTV, clinical target volume; PSL, prednisolone; PBT, proton beam therapy.

perihilar/central region, an area within 2 cm of proximal bronchial trees, had an 11-fold increased risk of experiencing severe (grade 3-5) toxicity compared with those with the peripheral type of tumors (27). They also reported that tumor volumes of >10 ml had an 8-fold risk of grade 3-5 AEs compared with smaller tumors (27). However, Chang *et al.* reported lower rates of severe AEs than these studies. Conversely, their favorable results appeared to be produced possibly by their definition of the central type, which included cases where the lesions were in proximity to the pulmonary hilum or mediastinum and the brachial plexus (9). Furthermore, their study included more than 80% of patients with Stage IA disease (Table VI). Despite including a larger population of elderly patients (41%) and T3-4 tumors (33%) in this study, the incidence of grade 3-5 AEs was 2.9%, which is lower than those in other studies. Compared with a multi-institutional retrospective study of PBT for stage I NSCLC, including 68% of patients with the peripheral type of tumors, our report on the occurrence of grade 3-5 AEs (2.9% *vs.* 1.7%) is consistent with that of their study. However, our study included 33% of patients with T3-4 tumors (19). Therefore, PBT is a reasonable approach for treating central cT1-4N0M0 NSCLC.

The differences in BED, dose fractionation schedule, and irradiation type between the SBRT series and our study might influence the clinical outcomes of central NSCLC. Regarding the effect of irradiation dose and fractionation on adverse effects in RT for central NSCLC, in RTOG0813, they indicated that 60 Gy in 5 fractions is safe; however, this is based on the dose-limiting toxicity being set at 20% (14). Therefore, we should evaluate safety by considering the results of a future phase III trial. In addition, a meta-analysis of SBRT for centrally located NSCLC showed that similar to the peripheral type, BED10 ≥100 Gy is significant for local control; however, AEs also increase with BED10 ≥100 Gy (28, 29). Therefore, we used moderate hypofractionation with 22-25 factions rather than ultra-hypofractionation. Furthermore, other parameters, such as BED3, should be considered for less severe AEs compared with other reports.

Thus, it is recommended that the maximum dose to proximal bronchial trees should be less than 38 Gy in 4 fractions (BED3=158.3 Gy) and 60 Gy in 10 fractions (BED3=180.0 Gy) to prevent the development of severe pneumonitis, bronchopulmonary hemorrhage, and bronchial stenosis (9, 20, 30). Moreover, minimizing the volume of proximal bronchial trees irradiated with more than 75 Gy in the conventional fraction is also recommended (31). In this study, the median value of BED3 was 128.4 GyE, which was lower than that of SBRT, and the maximum proximal bronchial doses were not significantly high. In addition, we modified the treatment plans during 22 or 25 fractions to adjust the proximal bronchial tree dose to less than 75 Gy at 2 Gy equivalent per fraction to the extent that may have contributed to fewer severe AEs.

Lung V5, V20, and MLD have been reported as risk factors for symptomatic pneumonitis after SBRT (32-37). The difference in the irradiated volume in PBT compared with SBRT was larger for lung V5 than for lung V20, indicating that the larger the tumor size, the more PBT could reduce the irradiated volume with a lower dose (16). In this analysis, the MLD ranged from 1.8 to 16.0 GyE (median=4.6), lung V5 from 3.8%-35.8% (median=13.4), and lung V20 from 2.8%-28.1% (median=9.5), which were similar to those in PBT by Kadoya *et al.*, and no significant correlations were found between the development of serious AEs and lung V20 and V5 (16). In addition, although there were many cases with large tumors in our study, CTV also showed no significant correlation with the development of severe AEs, suggesting that PBT has the advantage of safe irradiation, even for patients with a large tumor.

Therefore, efficacy and safety should be considered in cancer radiotherapy to determine the appropriate dose fractionations. In RTOG0813, it was reported that the 2-year OS and LC rates were 72.4% and 87.9%, respectively, for 60 Gy in 5 fractions (14). In addition, a meta-analysis of SBRT for centrally located NSCLC showed pooled rates of 3-year

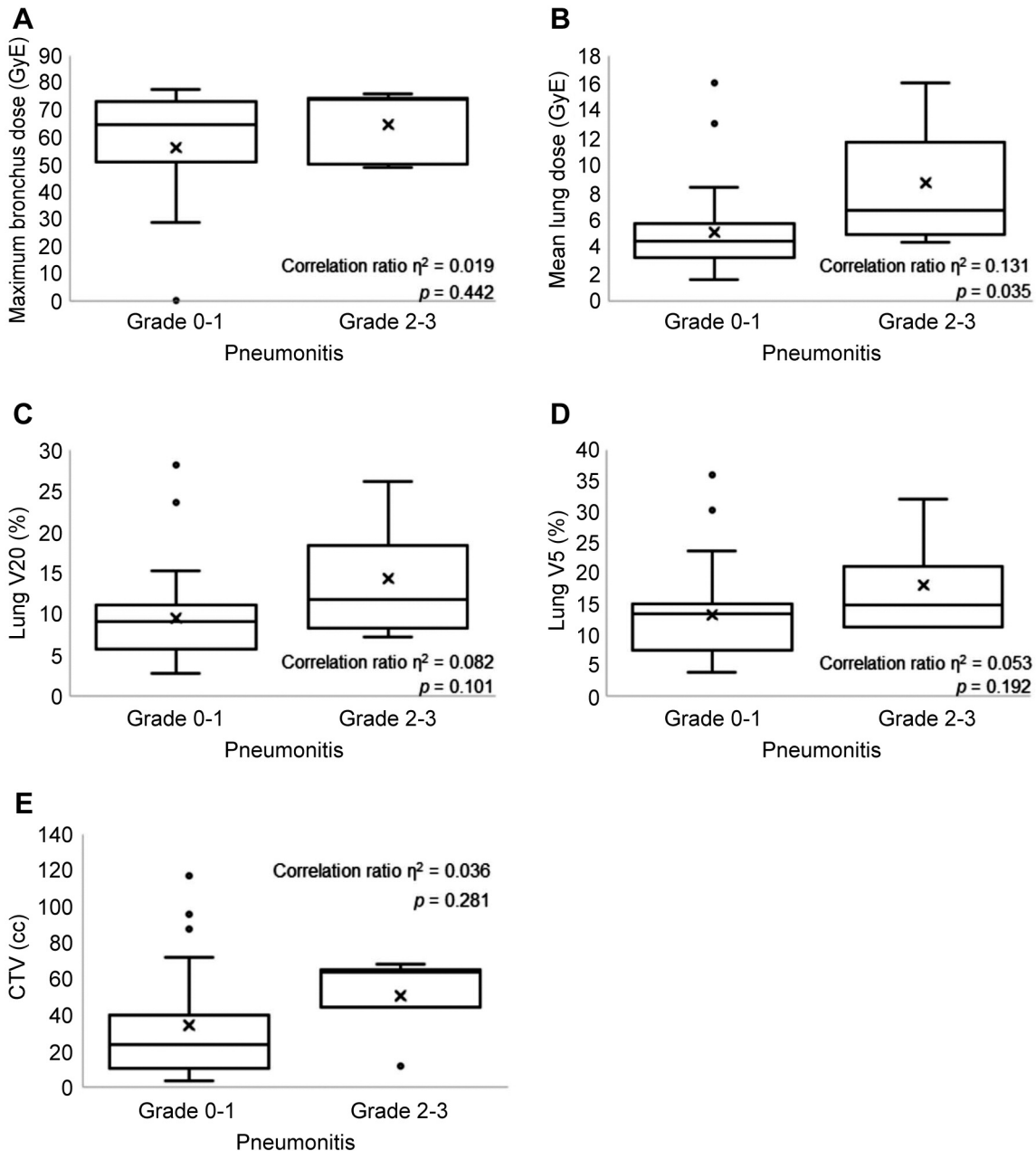

Figure 2. *Box plot of lung-related late adverse events vs. lung dose, the dose of the carina and main bronchus and bronchial tree to the second bifurcation, or clinical target volume (CTV). The relative proportion of lungs irradiated with ≥ X Gy to the total lungs was defined as Vx. (A) Maximum bronchus dose (B) Mean lung dose (C) Lung V20 (D) Lung V5 (E) CTV. Significant differences were assessed using the test static in the F-distribution.*

OS and LC rates of 50.5% (95% CI=39.4%-61.5%) and 72.2% (95% CI=55.0%-84.7%), respectively (29). In our study, despite BED10 <100 Gy, the 2- and 3-year OS and LC rates were 75.0% and 67.2%, and 83.9% and 80.7%, respectively, which are similar or somewhat higher compared with the above results. There are several reasons this dose fractionation was effective, despite the slightly lower BED10 of PBT in our study. Firstly, the linear quadratic (LQ) model may overestimate the effect of a single large dose. Various preconditions are necessary for LQ model reliability; however, the validity of SBRT is controversial because of factors, such as the effects on the stroma and blood vessels (38). Secondly, while there are advantages, including reoxygenation and redistribution due to fractionated irradiation, another

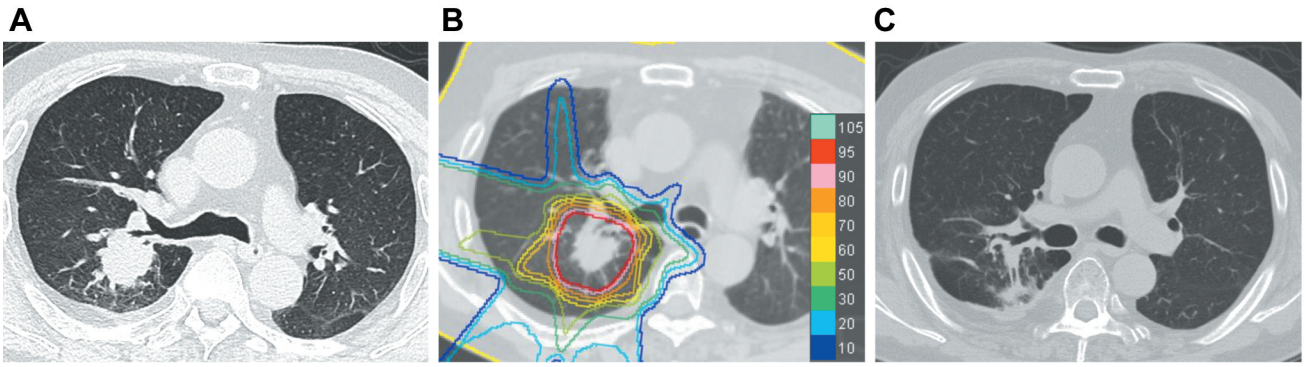

Figure 3. *Example of a treated case. (A) Computed tomography at pretreatment diagnosis. (B) Dose distribution of proton beam therapy. (C) Twenty-four months after proton beam therapy.*

Table VI. *Studies reporting outcomes and adverse events of stereotactic body radiotherapy for patients with centrally located non-small cell lung cancer.*

	Design	N	Modality	Dose and fractionation	BED10	Median follow-up time (months)	Age (years)	Stage IA (%)	3-year OS (%)	3-year LC (%)	Grade 3-5 late toxicities (%)	Grade 5 late toxicities (%)
Fakiris *et al*. (2009)	P	22	X	54 Gy/3 fr, 60 Gy/3 fr (80% isodose)	151.2, 180.0	50.2	72	N/A	24.4 months (MST)	N/A	27.3	18.2
Rowe *et al*. (2012)	R	47	X	50 Gy/4 fr (PTV-D95)	112.5	11.3	72	N/A	N/A	95.7 (2 years)	10.6	2.1
Chang *et al*. (2014)	R	100	X	50 Gy/4 fr, 70 Gy/10 fr (PTV-D95)	112.5, 119.0	30.6	73	80.2	70.5	96.5	2.0	0
Tekatli *et al*. (2015)	R	80	X	60 Gy/8 fr (PTV-D95)	105.0	45	73	35	53.0	N/A	14.1	7.7
Park *et al*. (2015)	R	111	X	50 Gy/5 fr, 50 Gy/4 fr (PTV-D95)	100, 112.5	31.2	76	72.1	71.6 (2 years)	87.1 (2 years)	8.1	0.9
Roach *et al*. (2018)	P	51	X	55 Gy/5 fr (PTV-D95)	115.5	17.0	73	45.1	43.0 (2 years)	85.0 (2 years)	41.5	2.4
Ohnishi *et al*. (2019)	P	94	P	N/A	N/A	N/A	N/A	N/A	74.6	84.7	N/A	0%
This study	R	34	P	72.6 GyE/22 fr, 75 GyE/25 fr	96.6, 97.5	50.8	77	52.9	70.4	80.5	2.9	0

P, Prospective; R, retrospective; X, X-ray; P, proton; Gy, gray; fr, fraction; PTV, planning target volume; D95, minimum dose delivered to 95%; BED10, biologically effective dose at an alpha/beta ratio of 10; OS, overall survival; MST, median survival time; LC, local control; N/A, not applicable.

advantage of our moderate hypofractionation is that it reduces the disadvantage of accelerated repopulation during the irradiation period (approximately 1 month) (39, 40). Finally, PBT is easier to fine-tune in the high-dose range than SBRT owing to the smaller number of beams. Register *et al*. reported that PBT delivered definitive doses to the target and significantly reduced doses to the surrounding normal tissues compared to SBRT (41). However, even with PBT, local recurrence was found as the site of initial recurrence in five of the eight patients with stage II-III disease. It is possible that this dose fractionation of BED10 <100 Gy is insufficient for large tumors. Therefore, appropriate treatment methods for large tumors with enhanced antitumor effects using dose escalation, combined chemotherapy, or combined immune checkpoint inhibitors are necessary.

This study had some limitations. Firstly, the major limitation of this study is that it was a single-center retrospective study

with a small sample size and long-term accrual. However, the PBT protocol, such as the CTV definitions, prescription dose and fractionation, beam arrangement, treatment machine, and methods of respiratory motion management, remained unchanged over the study period. In Japan, a multi-institutional registry of all patients treated with PBT has been conducted and is expected to provide useful information on PBT in patients with centrally located NSCLC in the future. Secondly, we experienced one case of grade 3 pneumonitis; however, no remarkable correlation was found between dosimetric parameters and late AEs in this study due to the small sample size. Therefore, we should determine the dose constraints of risk organs, such as proximal bronchial trees, to standardize the appropriate PBT planning.

Conclusion

In conclusion, moderately hypofractionated PBT is an effective and safe irradiation strategy that balances efficacy and safety by reducing the dose and volume of OARs while delivering a high dose to the target for centrally located and large-sized NSCLC. Although it may be a treatment option, dose escalation and combined drug is an issue to be considered in treating especially for large tumors. Prospective and multi-institutional studies are necessary to validate the efficacy of PBT and to determine optimal dose constraints for OARs.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this manuscript.

Authors' Contributions

Conceptualization, MN and HI; methodology, MN and HI; investigation, KO, MM (Motohiro Murakami), YH, and TS; resources, KO, KB, and MM (Masashi Mizumoto); TO, data collection; MN, KO, and KB; writing (original draft preparation); MN, writing (review and editing); HI, supervision; HS.

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