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Clinical Investigation

Proton Beam Therapy for Histologically or Clinically Diagnosed Stage I Non-Small Cell Lung Cancer (NSCLC): The First Nationwide Retrospective Study in Japan

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Purpose: To investigate the efficacy and safety of proton beam therapy (PBT) for the treatment of stage I non-small cell lung cancer (NSCLC).

Methods and Materials: Six hundred sixty-nine patients with 682 tumors histologically or clinically diagnosed stage I NSCLC according to the seventh edition of Union for International Cancer Control who received passive-scattering PBT from April 2004 and December 2013 in Japan were retrospectively reviewed to analyze survival, local control, and toxicities.

Results: Of 669 patients, 486 (72.6%) were men, with a median age of 76 years (range, 42-94 years). NSCLC was histologically confirmed in 440 patients (65.7%). Clinical T stages included T1a (n = 265; 38.9%), T1b (n = 216; 31.7%), and T2a (n = 201; 29.4%). The total irradiation doses of PBT ranged from 74.4 to 131.3 biological effective dose GyE (median, 109.6

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biological effective dose GyE). The median follow-up period was 38.2 months (range, 0.6-154.5 months) for all patients. The 3-year overall survival and progression-free survival rates for all patients were 79.5% and 64.1%, respectively. For patients with stage IA tumors, the 3-year overall survival and progression-free survival rates were 82.8% and 70.6%, respectively, and the corresponding rates for patients with stage IB tumors were 70.8% and 47.3%, respectively. The 3-year local progression-free rates for all, stage IA, and stage IB patients were 89.8%, 93.5%, and 79.4%, respectively. The incidence of grade 2, 3, 4, and 5 pneumonitis was 9.8%, 1.0%, 0%, and 0.7%, respectively. The incidence of grade ≥3 dermatitis was 0.4%. No grade 4 or severe adverse events, other than pneumonitis, were observed.

Conclusions: PBT appears to yield acceptable survival rates, with a low rate of toxicities.

Introduction

Stereotactic body radiation therapy (SBRT) is a standard of care for medically inoperable patients with stage I non-small cell lung cancer (NSCLC) and is indicated for patients who refuse to undergo surgery.[1-3] In prospective trials of SBRT for medically inoperable patients, 3-year local control (LC) and overall survival (OS) rates were >85% and about 60%, respectively.[4-6] The incidence of grade 2 or severe radiation pneumonitis (RP), a key toxicity associated with thoracic radiation therapy (RT), was reported to range from 5% to 10% after SBRT among patients with stage I NSCLC.[3,7] However, fatal adverse events, such as RP and esophageal ulcers, were reported in several patients with centrally located tumors or interstitial pneumonia.[8-10] Therefore, it is necessary to deliver precisely high radiation doses to lung tumors while decreasing irradiated volumes and doses to the lung, other critical organs such as the trachea and heart, and the great vessels to improve outcomes.

Proton beams can reduce volumes and radiation doses to surrounding normal tissues using their sharp Bragg peak fall-off. Previous dosimetry studies showed that proton beam therapy (PBT) plans for early-stage lung cancer yielded better dose-volume histogram parameters of normal tissues, including the lungs, than did SBRT plans.[11-15] In Japan, PBT was used in patients with early-stage lung cancer before SBRT became common. Hata et al[16] reported that the 2-year progression-free survival (PFS) and LC rates were 79% and 95%, respectively, without severe toxicities in their phase 1/2 study of hypofractionated, high-dose PBT for stage I NSCLC. In the United States, Bush et al[17] reported 3-year PFS and LC rates of 72% and 74%, respectively, in a phase 2 study of hypofractionated PBT for stage I NSCLC. In recent institutional retrospective studies of patients with stage I NSCLC treated with PBT, the 3-year OS and LC rates ranged from 75% to 81% and from 81% to 96%, respectively; grade 3 RP was observed in 1.3% to 1.7% of patients.[18-20]

Whether PBT improves survival and LC while also decreasing the incidence of radiation-induced toxicities compared with SBRT in patients with stage I NSCLC remains unclear. Only one randomized phase 2 study has compared SBRT and PBT for early-stage NSCLC; this study ended prematurely because of poor accrual.[21] Additionally, 2 meta-analyses have been reported to date. Grutter et al[22] concluded in a meta-analysis that outcomes of particle therapy consisting of protons and heavy ions for stage I NSCLC might be comparable to outcomes of SBRT. However, their meta-analysis included only preliminary PBT results and had a small sample size.[23-25] In a more recent meta-analysis, Chi et al[26] reported that PBT did not improve OS and PFS in comparison with SBRT ($P = .11$) based on multivariate analysis, and PBT yielded a better 3-year LC ($P = .03$); the rate of grade ≥3 toxicity was lower (4.8% vs 6.9%, $P = .05$) based on pooled analysis. Thus, studies with a larger sample size with longer follow-up are required to accurately evaluate PBT in this patient population. We conducted a multi-institutional study to review and assess the efficacy and toxicities of PBT for patients with stage I NSCLC.

Methods and Materials

A retrospective observational study of patients who underwent passive-scattering PBT for stage I NSCLC at 8 institutions in Japan was conducted. The participating institutions, at which PBT was available in 2013, included National Cancer Center Hospital East, Shizuoka Cancer Center, Hyogo Ion Beam Medical Center, Southern TOHOKU Proton Therapy Center, University of Tsukuba Hospital, Medipolis Proton Therapy and Research Center, Nagoya City West Medical Center, and Fukui Prefecture Hospital. The present study was approved by the institutional review board of each institution (H28-158).

All patients aged ≥20 years who received passive-scattering PBT for histologically (including cytology) diagnosed or clinically diagnosed stage I NSCLC from January 2004 to December 2013 were enrolled, without any exclusion criteria. Clinical diagnosis as NSCLC was based on radiographic findings, tumor markers, and clinical course. The following data were collected: sex; age; performance status; smoking status; comorbidity; synchronous or metachronous cancer; history of thoracic RT; pulmonary function; operability (evaluated by a thoracic surgeon before referral to the PBT center); reason for PBT; clinical

T factor according to the seventh version of Union for International Cancer Control TNM classification; histology; tumor location (peripheral or central according to Radiation Oncology Treatment Group 0236[10]); start and end day of PBT; dose fractionation; last follow-up date or date of death; local progression at the primary site, according to imaging studies; regional lymph node recurrence and distant metastases; and radiation-related toxicities assessed based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. For PBT, the photon equivalent dose (gray equivalent [GyE] dose) was defined as the physical dose (Gy) × relative biological effectiveness of the proton beam, which was assigned a value of 1.1. The biological effective dose (BED) was calculated using a linear-quadratic model.[27] The BED was defined as $nd\ (1 + d/\alpha/\beta)$, where n is the fractionation number, d is the daily dose, and the α/β ratio of lung cancer is 10 Gy. The clinical information of each patient was anonymized and collected using an electronic data capture system.

The follow-up time was defined as the time from the first day of PBT to the date of death or last follow-up. The OS, PFS, and local progression-free (LPF) rates were calculated from the first day of PBT to the date of the event or the last follow-up using the Kaplan-Meier method. The statistical significance of differences between survival curves was assessed with the log-rank test. A P value less than .05 was considered to be statistically significant. JMP version 11 (SAS institution, Cary, NC) statistical software was used.

Results

Patient characteristics

A total of 680 patients with 694 tumors were registered in the present study. Eleven patients with 12 tumors were excluded because of no data input (n = 1) or insufficient recurrence data (n = 10), leaving 669 patients with 682 tumors for this analysis.

Patients and treatment characteristics are shown in Table 1. The median age was 76 years (range, 42-94 years), and 486 (72.6%) patients were men. The majority (92.9%) of patients had a good performance status (0 or 1). NSCLC was histologically confirmed in 440 patients (65.7%). Clinical T stages included T1a (n = 265; 38.9%), T1b (n = 216; 31.7%), and T2a (n = 201; 29.4%). Overall, 584 tumors (86.6%) were located peripherally and 98 (13.4%) were located centrally. The total irradiation doses of PBT ranged from 74.4 to 131.3 BED_{10} GyE (median, 109.6 BED_{10} GyE).

Table 1 Patients and treatment characteristics

Characteristics	All	Histologic diagnosis	Clinical diagnosis
n	669	440	229
Age (y), median (range)	76 (42-94)	76 (42-89)	75 (47-94)
Sex			
Male	486	324 (73.6)	162 (70.7)
Female	183	116 (26.4)	67 (29.3)
Performance status			
0	432	279 (63.4)	153 (66.8)
1	190	131 (29.8)	59 (25.8)
2	45	30 (6.8)	15 (6.6)
3	1	0	1 (0.4)
4	1	0	1 (0.4)
Operability			
Operable	351	229 (52.4)	122 (53.3)
Inoperable	294	190 (44.0)	104 (45.4)
Unknown	24	21 (3.6)	3 (1.3)
Histology			
Adenocarcinoma		277 (61.8)	
Squamous cell carcinoma		139 (31.0)	
NSCLC, NOS		16 (3.6)	
Others		16 (3.6)	
UICC seventh stage			
IA	470	277 (63.0)	193 (84.3)
IB	199	163 (37.0)	36 (15.7)
UICC seventh T-stage			
T1a	265	135 (30.1)	130 (55.6)
T1b	216	149 (33.3)	67 (28.6)
T2a	201	164 (36.6)	37 (15.8)
Tumor location			
Peripheral site	584	379 (84.6)	205 (87.6)
Central site	98	69 (15.4)	29 (12.4)
Total dose (BED_{10} GyE)			
Median	109.6	109.6	109.6
Range	74.4-131.3	74.4-131.3	78.0-131.3
Follow-up time (mo)			
Median	38.2	37.6	41.0
Range	0.6-154.5	0.6-154.5	1.0-145.6

Abbreviations: BED = biological effective dose; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; UICC = Union for International Cancer Control.

Outcomes

At the last follow-up, 97 patients had died of the disease, 65 had died of intercurrent disease, and 12 had died of unknown causes. The median follow-up period was 38.2 months (range, 0.6-154.5 months) for all patients and 42.5 months (range, 3.2-154.5 months) for surviving patients. Disease recurrences were observed in 209 (31.2%) patients: primary site only (n = 38), regional lymph nodes only (n = 46), distant organs only (n = 80), primary and regional lymph nodes (n = 8), primary and distant organs (n = 10), regional lymph nodes and distant organs (n = 26), and all of the above (n = 1).

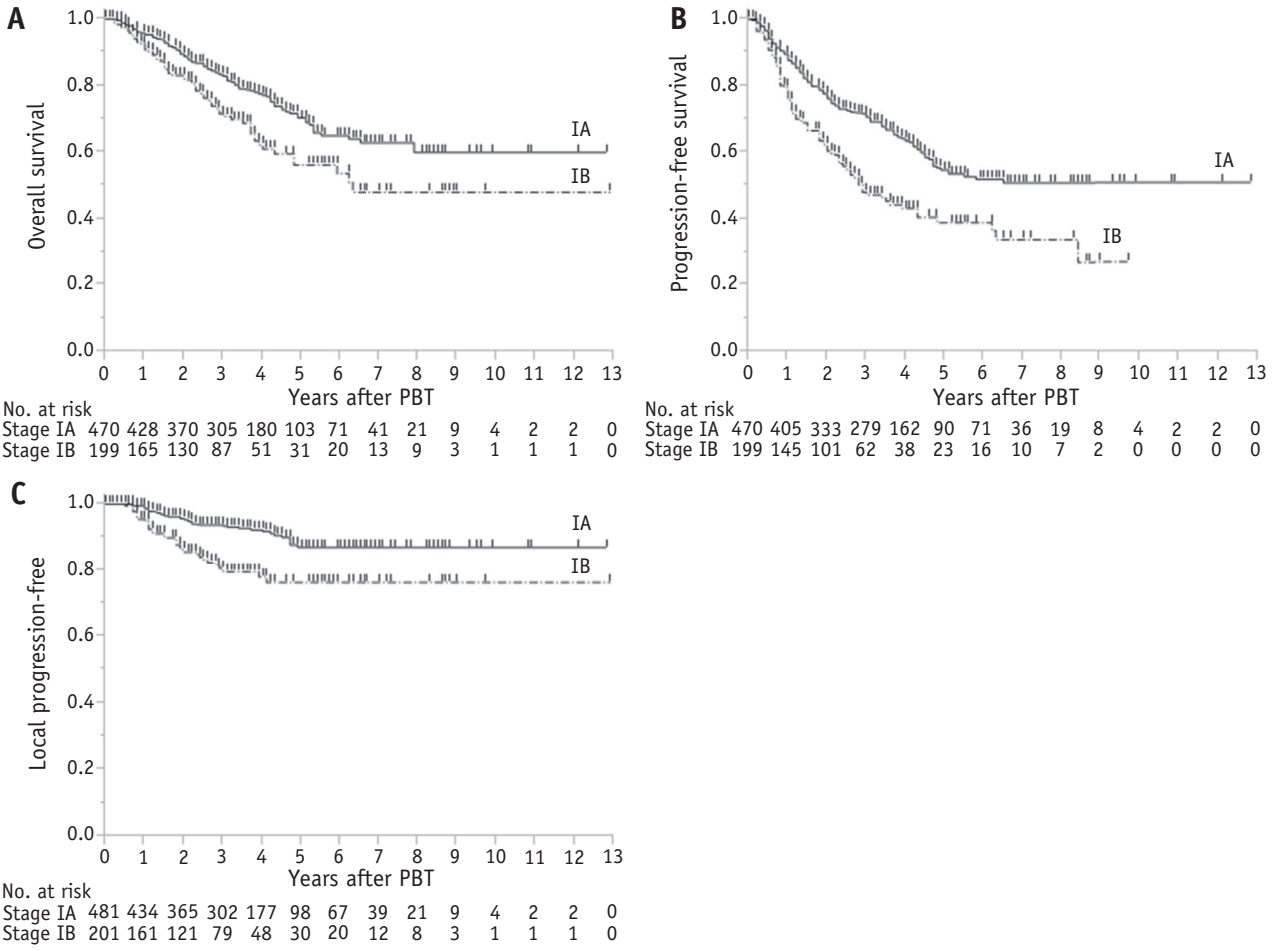

Fig. 1. Kaplan-Meier curves of survival and local control probabilities by stage in all 669 patients: (A) overall survival, (B) progression-free survival, and (C) local progression-free rate.

The 3-year OS and PFS rates for all patients were 79.5% (95% confidence interval [CI], 76.0%-82.6%) and 64.1% (95% CI, 60.2%-67.8%), respectively. For patients with stage IA tumors, the 3-year OS and PFS rates were 82.8% (95% CI, 78.9%-86.1%) and 70.6% (95% CI, 66.1%-74.6%), respectively, and the corresponding rates for patients with stage IB tumors were 70.8% (95% CI, 63.1%-77.4%) and 47.3% (95% CI, 39.8%-55.0%), respectively (Fig. 1). Patients with stage IA disease had significantly better OS ($P = .001$) and PFS ($P < .0001$) than patients with stage IB disease. The 3-year LPF rates for all, stage IA, and stage IB patients were 89.8% (95% CI, 86.9%-92.1%), 93.5% (95% CI, 90.6%-95.5%), and 79.4% (95% CI, 71.9%-85.4%), respectively, indicating better LPF rate among patients with stage IA disease compared with those with stage IB disease ($P < .0001$). Survival and LPF rates by stage are summarized in Table 2. Survival and LPF rates according to possible prognostic factors are shown in Table 3.

For the 440 patients with histologically confirmed NSCLC, the 3-year OS and PFS rates were 78.0% (95% CI, 73.5%-81.9%) and 61.2% (95% CI, 56.3%-65.9%). The 3-year OS and PFS rates among patients with stage IA disease were 80.7% (95% CI, 75.3%-85.1%) and 68.2% (95% CI, 62.2%-73.6%), respectively, but the corresponding rates for patients with stage IB disease were 73.0% (95% CI, 64.7%-80.0%) and 48.3% (95% CI, 40.0%-56.7%), respectively. Patients with stage IA

Table 2 Survival and local control rates by clinical stage

	All	Histologic diagnosis	Clinical diagnosis	Univariate *P* value
OS (3y)				
Stage IA	82.8%	80.7%	86.0%	.075
Stage IB	70.8%	73.0%	60.4%	.95
PFS (3y)				
Stage IA	70.6%	68.2%	74.0%	.17
Stage IB	47.3%	48.3%	42.6%	.96
LPF (3y)				
Stage IA	93.5%	92.2%	95.1%	.34
Stage IB	79.4%	79.0%	80.0%	.42

Abbreviations: LPF = local progression-free rate; OS = overall survival; PFS = progression-free survival.

Table 3 Outcomes by clinical and therapeutic factors

Factor	n	OS (3-y) %	OS (3-y) Univariate *P* value	PFS (3-y) %	PFS (3-y) Univariate *P* value	LPF (3-y) %	LPF (3-y) Univariate *P* value
Age, y							
<76	321	85.1	<.0001	67.4	.021	89.4	.64
≥76	348	74.1		60.9		89.8	
Sex							
Male	486	74.9	<.0001	59.5	<.0001	87.6	.020
Female	183	91.0		75.7		94.3	
PS							
0	432	84.2	<.0001	67.8	.0002	90.1	.85
1, 2, 3, 4	237	70.7		57.4		88.9	
Operability							
Operable	351	86.7	<.0001	70.6	<.0001	91.3	.20
Inoperable	294	70.5		56.6		87.5	
Histology							
Adenocarcinoma	270	82.7	.0047	65.4	.049	91.4	.022
Non-adenocarcinoma	170	70.3		54.7		81.6	
Stage							
IA	470	82.8	.0015	70.6	<.0001	93.5	<.0001
IB	199	70.8		47.3		79.4	
Tumor location							
Peripheral	575	80.3	.44	65.3	.11	90.4	.037
Central	94	74.6		56.6		84.7	
Prescribed dose							
<100 GyE	120	71.4	<.0001	49.8	<.0001	83.9	.018
≥100 GyE	549	81.3		67.2		90.8	

Abbreviations: LPF = local progression-free rate; OS = overall survival; PFS = progression-free survival; PS = performance status.

disease had significantly better OS ($P = .042$) and PFS ($P = .0004$) than did stage IB patients. The 3-year LPF rates for all, stage IA, and stage IB patients were 87.7% (95% CI, 83.9%-90.8%), 92.2% (95% CI, 88.0%-95.1%), and 79.0% (95% CI, 70.7%-85.4%), respectively, indicating better LPF rate among patients with stage IA disease compared with those with stage IB disease ($P = .0009$).

For the 229 patients with clinically diagnosed NSCLC, the 3-year OS and PFS rates were 82.4% (95% CI, 76.4%-87.1%) and 69.6% (95% CI, 63.1%-75.5%), respectively. The 3-year OS and PFS rates among patients with stage IA disease were 86.0% (95% CI, 79.9%-90.4%) and 74.0% (95% CI, 67.1%-79.9%), respectively, whereas the corresponding rates in patients with stage IB disease were 60.4% (95% CI, 40.9%-77.0%) and 42.6% (95% CI, 25.9%-61.1%), respectively. Patients with stage IA disease had significantly better OS ($P = .045$) and PFS ($P = .005$) than did stage IB patients. The 3-year LPF rates for all, stage IA, and stage IB patients were 93.3% (95% CI, 88.6%-96.1%), 95.1% (95% CI, 90.5%-97.5%), and 80.0% (95% CI, 57.0%-92.3%), respectively. No significant differences in LPF were observed between patients with stage IA and IB disease ($P = .14$).

With respect to radiation-associated toxicity, the incidence of grade 2, 3, 4, and 5 pneumonitis was 9.8%, 1.0%, 0%, and 0.7%, respectively. The incidence of grade 2, 3, 4, and 5 dermatitis was 6.8%, 0.4%, 0%, and 0%, respectively. Grade 3 adverse events other than dermatitis and pneumonitis were observed in 5 (0.7%) patients (lung infection [n = 1], rib fracture and skin ulceration [n = 1], skin ulceration [n = 1], dyspnea [n = 1], and hypoxia [n = 1]). No grade 4 or severe adverse events, other than pneumonitis, were observed. Details about dermatitis and pneumonitis are provided in Table 4.

Discussion

PBT is well known to have the advantage of reducing the irradiated volume and dose to surrounding normal tissue in patients with lung cancer compared with SBRT, because appropriate dose distributions can be made with limited irradiation fields.[11-15] Hypofractionated, high-dose PBT has been used to treat inoperable patients or patients who refuse to undergo surgery in Japan, and previous single-institute studies have demonstrated promising results of PBT for stage I NSCLC.[18-20] The present study is the first multi-institutional study to evaluate the feasibility and efficacy of PBT for stage I NSCLC in a large number of patients. These results may therefore represent the outcomes of PBT

Table 4 Incidence of dermatitis and pneumonitis

		Dermatitis, n (%)			Pneumonitis, n (%)		
	n	Grade 2	Grade 3	Grade ≥4	Grade 2	Grade 3	Grade ≥4
Stage IA							
All	470	34 (7.2)	1 (0.2)	0 (0.0)	47 (10.0)	4 (0.8)	1 (0.2)
Histologic diagnosis	277	18 (6.4)	1 (0.3)	0 (0.0)	23 (8.3)	2 (0.7)	1 (0.3)
Clinical diagnosis	193	16 (8.2)	0 (0.0)	0 (0.0)	24 (13.4)	2 (1.0)	0 (0.0)
Stage IB							
All	199	12 (6.0)	2 (1.0)	0 (0.0)	19 (9.5)	3 (1.5)	4 (2.0)
Histologic diagnosis	163	11 (6.7)	1 (0.6)	0 (0.0)	15 (9.2)	3 (1.8)	3 (1.8)
Clinical diagnosis	36	1 (2.7)	1 (2.7)	0 (0.0)	4 (11.1)	0 (0.0)	1 (2.7)

in clinical practice and provide important information for future clinical trials.

The 3-year OS and LPF rates for PBT in patients with histologically confirmed stage I, stage IA, and stage IB NSCLC were 78.0% and 87.9%, 80.7% and 92.4%, and 60.4% and 79.1%, respectively, in the present study. In contrast, in prospective trials of SBRT, the 3-year OS and LC rates ranged from 55% to 76% and from 85% to 97%, respectively.[4-6] In the multi-institutional retrospective study of SBRT in Japan, the 3-year OS rate ranged from 56% to 69% (Table 5).[2,3] The present survival and LPF rates of PBT are comparable to those of these previous SBRT studies, and the 3-year OS rate of operable patients in the present study was 85%.

With respect to pneumonitis, which is an important dose-limiting toxicity associated with thoracic RT, the rates of CTCAE v.4.0 grade ≥3 pneumonitis for histologically confirmed stage IA and stage IB NSCLC were 1.0% and 3.6%, respectively, and the rates of grade ≥2 pneumonitis were 9.3% and 12.8%, respectively, in the present study. In the Japan Clinical Oncology Group 0403 trial in patients with peripherally located stage IA NSCLC, the rates of CTCAE v.3.0 grade ≥3 pneumonitis in operable and inoperable patients were 3.0% and 8.6%, respectively.[6] Furthermore, the rates of CTCAE v.3.0 grade ≥2 pneumonitis in patients with peripherally located stage IA and IB tumors ranged from 4% to 10% and from 16% to 21%, respectively.[28-30] Therefore, PBT appears to be a safe treatment option and is associated with a low incidence of symptomatic pneumonitis, particularly in patients with stage IB disease.

In the last decade, SBRT has provided favorable outcomes in patients with stage I NSCLC, and is used throughout the world. Thus, it is important to establish for which patients PBT, but not SBRT, would be more suitable. A probable advantage of PBT is that it is considered

Table 5 Summary of outcomes of SBRT and PBT for histologically confirmed stage I NSCLC

									Pneumonitis	
Study	Modality	n	Operability	Median age, y	Sex (% female)	Stage (% IA)	OS (y)	LPF (y)	Rate	Criteria
Prospective study										
Nagata[6]	SBRT	65	Operable	79	31%	100%	76% (3)	85% (3)	3.0%	CTCAE v3 grade ≥3
Baumann[4]	SBRT	57	Inoperable	75	45%	70%	60% (3)	92% (3)	0%	
Timmerman[5]	SBRT	55	Inoperable	72	62%	80%	55% (3)	97% (3)	NA	
Nagata[6]	SBRT	104	Inoperable	78	26%	100%	59% (3)	87% (3)	8.6%	CTCAE v3 grade ≥3
Multi-institutional Japanese retrospective study										
Onishi[2]	SBRT	87	Operable	74	27%	73%	69% (5)	86% (5)	5.7%	NCI-CTC grade ≥2
Onishi[3]	SBRT	257	Operable (61%)	74	NA	63%	56% (3)	NA	5.4%	NCI-CTC grade ≥2
Present study	PBT	229	Operable	75	34%	67%	85% (3)	90% (3)	0.4%	CTCAE v4 grade ≥3
	PBT	190	Inoperable	77	16%	57%	69% (3)	84% (3)	4.2%	CTCAE v4 grade ≥3

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; LPF = local progression-free rate; NA = not available; NIC-CTC = National Cancer Institute - Common Toxicity Criteria; OS = overall survival; PBT = proton beam therapy; SBRT = stereotactic body radiation therapy.

to be safer for large tumors. Kadoya et al[14] reported that, compared with SBRT, PBT reduced the irradiated lung volumes involved with larger tumors. In the pooled analysis, the rate of grade ≥3 RP was significantly lower for PBT than for SBRT (0.9% [95% CI, 1.1%-3.3%] vs 3.4% [95% CI, 2.9%-4.0%], $P < .001$), even though tumors that were more advanced in size and T-stage were treated with PBT.[26] A second advantage is that PBT can be used to treat centrally located tumors. Timmerman et al[10] reported that patients with centrally located tumors had a higher rate of grade ≥3 toxicities and a lower 2-year rate of freedom from severe toxicity (54%), compared with 83% for patients with peripheral tumors. However, even though 15% of the tumors were located centrally, no grade ≥3 or severe toxicities other than pulmonary, skin, and bone toxicities were observed in the present study. In fact, Register et al[31] reported that PBT significantly reduced the mean maximal radiation dose to the aorta, bronchial plexus, heart, pulmonary vessels, and spinal cord when the planning target volume was within 2 cm of these critical structures. Finally, PBT might have an advantage in treating patients with comorbidities such as extremely poor pulmonary function and interstitial lung disease (ILD). In particular, ILD is considered to be a relative contraindication for SBRT. The rates of grade ≥3 pneumonitis after SBRT in patients with interstitial changes on CT images or ILD have been reported to range from 10% to 38%.[32-34] In a recent multi-institutional study in Japan, the incidence of fatal RP was 6.9% after SBRT in patients with pulmonary interstitial change.[35] Further evaluation is planned to define which patients are the best candidates for PBT.

The major limitations of this study were its retrospective nature, patient and tumor characteristic heterogeneity, lack of criteria for clinical diagnosis and for defining operability, and absence of standardized follow-up schedules. For PBT, various dose fractionation schedules were used. In addition, the details of PBT plans, such as the margins of the target volume and motion management, were not fully evaluated. Future randomized trials comparing PBT and SBRT are essential. Because the previous phase 2 trial terminated prematurely because of poor accrual, Nantavithya et al[21] suggested that health insurance coverage of PBT and an advanced PBT technique are needed to conduct randomized trials comparing PBT and SBRT.

Conclusions

This first multi-institutional retrospective study of PBT for stage I NSCLC in Japan revealed that PBT yielded acceptable survival rates, with a low rate of toxicities. Accumulation of clinical data and further evaluation through large multi-institutional prospective PBT studies are required to confirm the efficacy of PBT for early-stage NSCLC.

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