

## Clinical Investigation

# Multi-Institutional Retrospective Analysis of the Outcomes of Proton Beam Therapy for Patients With 1 to 3 Pulmonary Oligometastases From Various Primary Cancers



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Received September 28, 2020; revised February 20, 2021; accepted February 24, 2021

## Abstract

**Purpose:** Our purpose was to evaluate the efficacy of proton beam therapy (PBT) in patients with 1 to 3 pulmonary oligometastases from various primary cancers in Japan.

**Methods and Materials:** This multi-institutional retrospective survey included 118 patients with 141 metastatic lung tumors from miscellaneous primary cancers, across 6 Japanese institutions, and involved the analyses of local progression-free rate (LPR), distant

Sources of support: This work had no specific funding.

Disclosures: No authors had any relevant conflict of interest for any aspect of the submitted work. However, there were relevant financial activities outside the submitted work. H.H. reports personal fees from Daiichi Sankyo Pharmaceutical Co during the conduct of the study, personal fees from Daiichi Sankyo Pharmaceutical Co, personal fees from Astrazeneca Pharmaceutical Co, personal fees from Brain Labo Co, personal fees from Chugai Pharmaceutical Co, grants from the Japan Agency for Medical Research and Development, and grants from The National Cancer Center Research and Development fund outside the

submitted work. S.T. reports grants from Nippon Boehringer Ingelheim, personal fees from Daiichi Sankyo, personal fees from Sanofi, personal fees from Takeda Pharmaceutical, personal fees from Bayer Yakuin, personal fees from Sysmex, personal fees from Chugai Pharmaceutical, and personal fees from Solasia Pharma outside the submitted work.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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<https://doi.org/10.1016/j.adro.2021.100690>

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progression-free rate, progression-free survival rate, cause-specific survival rate, and overall survival rate (OS). Treatment-induced adverse effects of grade  $\geq 2$  were evaluated according to the Common Terminology Criteria for Adverse Events (version 4.0). Cox proportional hazards regression models were used in univariable analysis and multivariable analysis (MVA) for the identification of the prognostic factors of LPF and OS.

**Results:** The median follow-up duration from the time of PBT was 25.5 months. The major primary disease sites included colorectal cancer (42.4%), lung cancer (11.9%), head and neck cancer (8.5%), and kidney cancer (8.5%). For years 1, 2, and 3, LPFs were 92.2%, 86.3%, and 78.4%; distant progression-free rates were 59.1%, 44.1%, and 34.0%; progression-free survival rates were 49.6%, 31.7%, and 24.2%; cause-specific survival rates were 83.4%, 72.5%, and 64.8%; and OS rates were 79.0%, 67.8%, and 59.6%, respectively. Eight patients developed acute adverse effects (grade  $\geq 2$ ). Ten patients developed radiation pneumonitis (grade 2) as a late adverse effect. None of the patients developed severe late toxicity (grade  $\geq 3$ ). Colorectal cancer as the primary disease was the only prognostic factor associated with LPF that remained independently significant in the MVAs performed using 3 sets of parameters (hazard ratio [HR], 3.31-4.76 in 3 MVA sets). In the MVA, the significant prognostic factors for OS were performance status (HR, 2.78; 95% confidence interval, 1.01-7.67) and total tumor volume (HR, 1.01; 95% confidence interval, 1.00-1.02).

**Conclusions:** PBT provides promising outcomes for pulmonary oligometastasis with acceptable toxicities.

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A multi-institutional retrospective study on the efficacy of proton beam therapy (PBT) in 118 patients with 1–3 pulmonary oligometastases demonstrated passive scattering PBT yielded promising outcomes, which were comparable to X-ray stereotactic body radiotherapy, with acceptable toxicities. For years 1, 2, and 3; local progression-free rates were 92.2%, 86.3%, and 78.4%, respectively; overall survival rates were 79.0%, 67.8%, and 59.6%, respectively. No severe late toxicity (grade  $\geq 3$ ) was observed.

## Introduction

Local aggressive treatment potentially extends survival in patients with pulmonary oligometastases of various primary cancers.<sup>1,2</sup> Although pulmonary metastasectomy is the standard treatment for patients with a limited metastatic pattern, several retrospective studies have shown that x-ray stereotactic body radiation therapy (SBRT) yields short-term promising outcomes that are comparable to those of surgery.<sup>3,4</sup>

Proton beam therapy (PBT) can reduce the volume of and radiation dose to the surrounding normal tissues using the sharp Bragg peak fall-off, as demonstrated in previous dosimetry studies.<sup>5,6</sup> Based on increasing evidence for the use of PBT for early-stage lung tumors, which shows acceptable outcomes with the potential benefit of reducing toxicities, PBT seems to yield outcomes similar to those of x-ray SBRT for pulmonary oligometastases.<sup>7,8</sup> However, to the best of our knowledge, only 1 study has focused on the outcomes of PBT in patients with limited metastatic pulmonary diseases.<sup>9</sup> Therefore, in this study, we aimed to evaluate the efficacy and safety of PBT retrospectively for patients with 1 to 3 pulmonary oligometastases from miscellaneous primary cancers across multiple facilities in Japan.

## Methods and Materials

### Patient eligibility

The patient eligibility criteria included (1) a histopathologic or clinical diagnosis of pulmonary metastasis, (2) number of metastatic pulmonary lesions  $\leq 3$ , (3) absence of recurrence in primary disease site after primary curative treatment, (4) absence of clinically detectable recurrent or metastatic disease other than the metastatic lung disease, (5) measurability of all pulmonary lesions, (6) delivery of PBT to all metastatic pulmonary lesions with curative intent, and (7) use of PBT between January 2001 and December 2016. In this survey, 3 was chosen as the maximal number of treated lesions because it was rare in clinical practice that more than 3 lung tumors were treated using PBT with curative intent.

### Toxicity evaluation

Toxicity was graded according to the Common Terminology Criteria for Adverse Events (v 4.0),<sup>10</sup> and toxicities of grade  $\geq 2$  were reviewed.

### Statistical analysis

Continuous and categorical variables were presented as medians with ranges and as frequencies with percentages, respectively. Local progression-free rate (LPF) was defined as the time from the initiation of PBT to the progression in the pulmonary lesions treated with PBT. Distant progression-free (DPF) rate was defined as the time from the initiation of PBT to the disease progression outside of the treated pulmonary sites. Progression-free survival (PFS) rate was defined as the time from the initiation of PBT to disease progression, irrespective of sites

treated with PBT, or death from any cause. Cause-specific survival (CSS) rate and overall survival (OS) rate were defined as the time from the initiation of PBT to death from primary disease or from any cause, respectively. The study endpoints, including LPF, DPF, PFS, CCS, and OS were estimated using the Kaplan-Meier method, starting from the initiation of PBT to the event of interest or last available follow-up. The log-rank test was used to test differences between the subgroups. Cox proportional hazards regression model was used in the univariable analysis (UVA) and multivariable analysis (MVA) for the identification of prognostic factors and estimation of hazard ratio (HR) and 95% confidence interval (CI) of each factor for LPF and OS. In the analysis of the prognostic factors for LPF, 3 different MVA parameters were used to minimize the unintended influence of potentially correlated parameters on the analyses. All reported *P* values were 2-sided, and a value lower than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using JMP 15 (SAS Institute Inc, Cary, NC).

## Ethics approval

The retrospective study protocol was approved by the ethics committees of all participating institutions.

## Results

This retrospective study used data from 141 metastatic pulmonary tumors in 118 patients (74 men and 44 women), who received PBT across 6 Japanese institutions. The median disease-free interval (DFI) between the radically curative therapy for the primary disease and diagnosis of pulmonary oligometastasis was 15 months (range, 0-216 months). The proportions of DFIs of less than 3 months, 3 to 6 months, and more than 6 months were 6.8% (8/118), 12.7% (15/118), and 80.5% (95/118), respectively.

## Patient and tumor characteristics

The median patient age was 69 years (range, 39-88 years). The characteristics of 118 patients are shown in Table 1. Table E1 presents the various primary disease sites and histopathologic types. The major primary disease sites were colorectal cancer (CRC) (*n* = 50, 42.4%), lung cancer (*n* = 14, 11.9%), head and neck cancer (*n* = 10, 8.5%), and kidney cancer (*n* = 10, 8.5%). The median follow-up period was 25.5 months (range, 1-143 months). The median biological effective dose (BED), obtained using the linear-quadratic model with  $\alpha/\beta = 10$  Gy (BED<sub>10</sub>), was 109.6 Gy (relative biological

effectiveness, [RBE]; range, 72-131.3 Gy [RBE]). All treatments were conducted using the passive scattering method without any treatment interruption. Thirty-nine patients (33.1%) received systemic therapy between the diagnosis of pulmonary oligometastases and the start of PBT, 4 patients (3.4%) received concomitant systemic therapy with PBT, and 90 patients (76.3%) received no treatment between the end of PBT and the last follow-up. Five patients (4.2%) had a history of thoracic radiation therapy, and 5 patients (4.2%) had been diagnosed with interstitial pneumonitis. Of the 20 patients with 2 or 3 lung tumors treated by PBT, 6 (30.0%) underwent simultaneous irradiation to all the tumors, whereas 9 (45.0%) and 5 (25.0%) patients received sequential irradiation to the tumors with either a short interval (<30 days) or a long interval ( $\geq 30$  days), respectively.

## Treatment outcomes

In 141 metastatic lung tumors, 22 tumors (15.6%) had local progression in the irradiated pulmonary sites. Of the 118 patients, 77 patients (65.3%) developed disease progression; 8 patients (6.8%) had only the local progression of irradiated pulmonary sites; 9 patients (7.6%) had local progression of irradiated lung sites and distant disease progression outside of irradiated sites; 60 patients (50.8%) had only distant disease progression outside of the irradiated pulmonary sites without any local progression. Forty-three (36.4%) and 11 (9.3%) patients died of primary disease progression and other causes, respectively. Across all the irradiated lung tumors, the 1-, 2-, and 3-year LPFs were 92.2%, 86.3%, and 78.4%, respectively (Fig 1a). The corresponding DPF rates were 59.1%, 44.1%, and 34.0%; PFS rates were 49.6%, 31.7%, and 24.2%; CSS rates were 83.4%, 72.5%, and 64.8%; and OS rates were 79.0%, 67.8%, and 59.6%, respectively (Fig 2a-d).

## Toxicity

Toxicity analysis revealed 7 patients with grade 2 acute adverse effects (pneumonitis in 3 patients and dermatitis in 4 patients) and 1 patient with grade 3 dermatitis. Eight (6.8%) patients developed acute adverse effects (grade  $\geq 2$ ). In terms of late adverse effects, 10 (8.5%) patients developed grade 2 radiation pneumonitis. No late toxicities of grade  $\geq 3$  were observed.

## Statistical analysis of prognostic factors

To identify the prognostic factors associated with LPF, UVA and MVA were conducted using several parameters (age, sex, performance status [PS], dose per fraction,

**Table 1** Characteristics of patients and metastatic lung tumors

Characteristics	
Age, years	
Median (range)	69 (39-88)
Sex, n (%)	
Male	74 (62.7)
Female	44 (37.3)
Performance status*, n (%)	
0-1	112 (94.9)
2-3	6 (5.1)
Follow-up time, months	
Median (range)	25.5 (1-143)
Disease-free interval, months <sup>†</sup>	
Median (range)	15 (0-216)
<3 months, n (%)	8 (6.8)
3-6 months, n (%)	15 (12.7)
>6 months, n (%)	95 (80.5)
Number of pulmonary metastases, n (%)	
1	98 (83.1)
2	17 (14.4)
3	3 (2.5)
Gross tumor volume, mL	
Median (range)	3.1 (6.0-137.2)
Maximal diameter, mm	
Median (range)	15 (6.0-63.6)
Total delivery dose, Gy (RBE)	
Median (range)	64 (52.8-89.6)
Dose per fraction, Gy (RBE)	
Median (range)	6.6 (2-13.2)
Number of treatment fractions, n	
Median (range)	10 (4-40)
BED <sub>10</sub> , Gy (RBE)	
Median (range)	109.6 (72-131.3)
Systemic therapy between the diagnosis of lung oligometastases and the start of PBT, n (%)	
No	79 (66.9)
Yes	39 (33.1)
Treatment after PBT, n (%)	
No	90 (76.3)
Yes	28 (23.7)
Surgery	1 (0.8)
Systemic therapy	18 (15.3)
Systemic therapy and radiation therapy	3 (2.5)
Radiation therapy	1 (0.8)
Unknown	5 (4.2)

Abbreviations: BED = biological effective dose; PBT = proton beam therapy; RBE = relative biological effectiveness.

\* According to the Eastern Cooperative Oncology Group.

<sup>†</sup> Disease-free interval is the period between initially radical therapy for the primary cancer and the diagnosis of lung oligometastasis.

BED<sub>10</sub>, tumor volume, number of metastatic tumors, CRC or non-CRC [NCRC] as the primary disease, DFI, and treatment after PBT). The UVA showed that dose per fraction (HR, 0.77; 95% CI, 0.64-0.92) and CRC as the

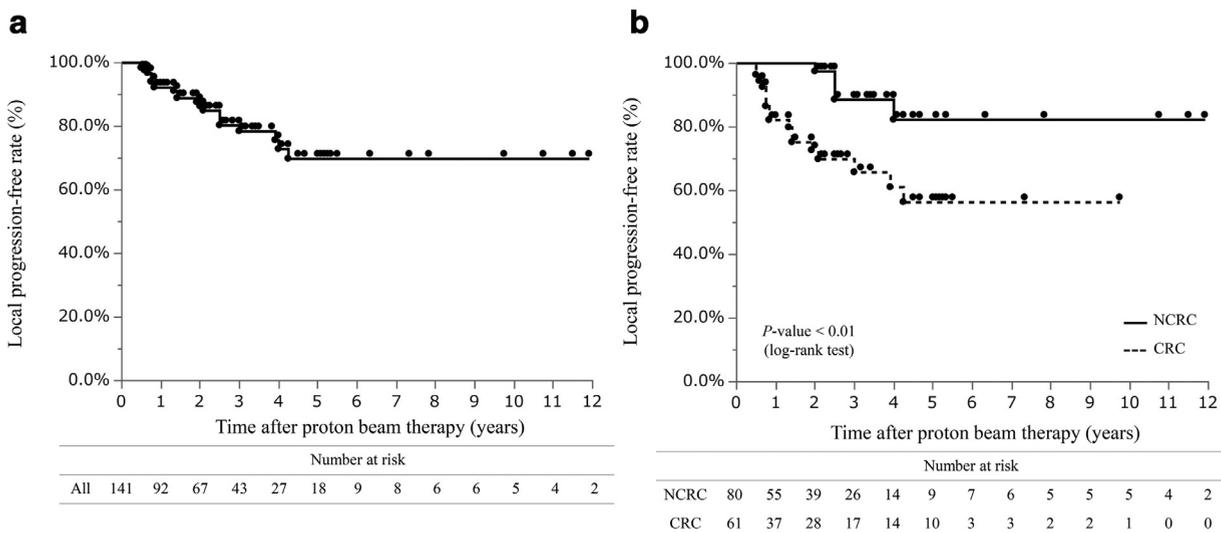
primary disease (HR, 4.56; 95% CI, 1.68-12.39) were both statistically significant (Table 2). The MVA including all parameters, however, revealed only 1 significant prognostic factor: CRC as the primary disease (HR, 3.58; 95% CI, 1.16-10.99). The MVA of all parameters except BED<sub>10</sub> revealed dose per fraction (HR, 0.70; 95% CI, 0.55-0.89) and CRC as the primary disease (HR, 3.31; 95% CI, 1.15-9.58) as statistically significant factors, whereas the MVA of all parameters except dose per fraction revealed that BED<sub>10</sub> (HR, 0.94; 95% CI, 0.89-0.98) and CRC as the primary disease (HR, 4.76; 95% CI, 1.59-14.27) were independently significant. The only prognostic factor that remained independently significant in the 3 MVA sets was CRC as the primary disease (HR, 3.31-4.76 in 3 MVA sets). In terms of LPF, CRC as the primary cancer was associated with significantly worse prognoses, while a higher dose per fraction and BED<sub>10</sub> were related to better prognoses. As shown in Figure 1b, for years 1, 2, and 3, the LPF rates of NCRC were 100%, 97.4%, and 88.6%; LPF rates of CRC were 82.2%, 72.7%, and 65.8%, respectively.

The prognostic factors associated with OS after PBT were estimated using several parameters (age, sex, PS, total tumor volume, number of pulmonary tumors, DFI, and posttreatment after PBT). The total tumor volume was defined as the total volume of the irradiated targets in patients with 1 to 3 tumors. The results of the UVA and MVA are shown in Table 3. The UVA revealed age (HR, 1.03; 95% CI, 1.00-1.06), PS (HR, 4.79; 95% CI, 1.85-12.37), and total tumor volume (HR, 1.01; 95% CI, 1.00-1.02) as significant prognostic factors, whereas the MVA disclosed that PS (HR, 2.78; 95% CI, 1.01-7.67) and total tumor volume (HR, 1.01; 95% CI, 1.00-1.02) were significantly associated with OS. There were no statistically significant differences between the NCRC and CRC groups in DPF ( $P = .312$ ), PFS ( $P = .856$ ), and OS ( $P = .067$ ), although CRC as the primary cancer was associated with significantly worse prognoses in terms of the LPF.

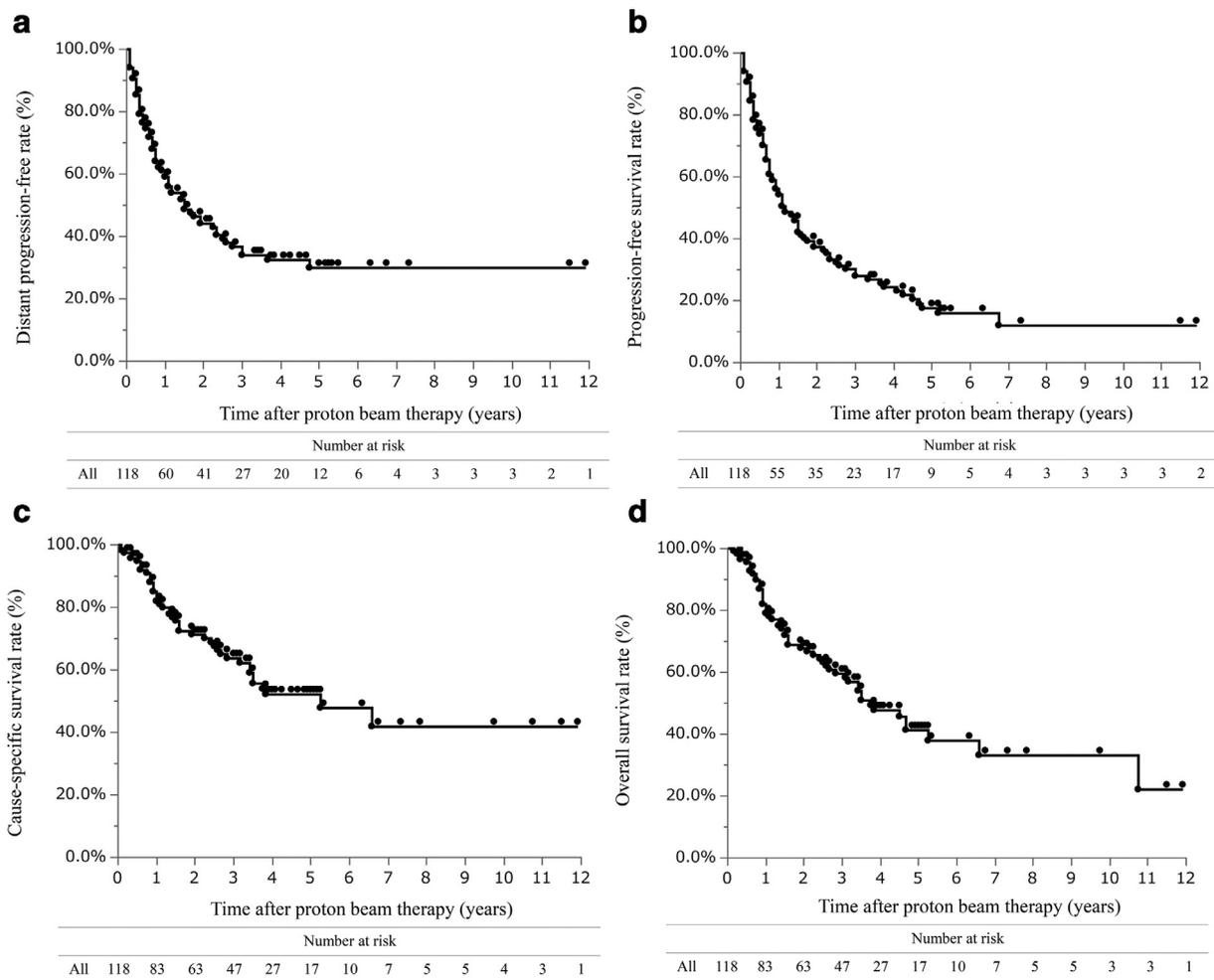
## Discussion

The present study demonstrated the promising outcomes of PBT in patients with pulmonary oligometastases with acceptable toxicity. There is currently insufficient evidence on the efficacy of PBT in treating pulmonary oligometastasis. To the best of our knowledge, this is the first study to report a multi-institutional survey focusing on the efficacy and toxicity of PBT in patients with pulmonary oligometastasis.

A previous Japanese single-center study reported the outcome of particle beam therapy using carbon ions and protons and showed the 2-year local control rate (LC), PFS, and OS values of 79%, 27%, and 54%, respectively,



**Figure 1** Local progression-free rates (a) for all tumors and (b) by primary disease (colorectal cancer [CRC] or noncolorectal cancer [NCRC]).



**Figure 2** Distant progression-free rate (a), progression-free survival rate (b), cause-specific survival rate (c), and overall survival rate (d) for all patients.

**Table 2** Results of the UVA and MVA of local progression-free rate

Factors	UVA			MVA(all parameters)			MVA(all parameters except BED <sub>10</sub> )			MVA(all parameters except D/F)		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age, years	1.01	0.96-1.05	.745	0.99	0.94-1.03	.568	0.98	0.94-1.03	.492	0.99	0.95-1.04	.781
Sex												
Male	1.00	0.18-1.32	.154	1.00	0.21-1.69	.332	1.00	0.22-1.71	.345	1.00	0.20-1.64	.298
Female	0.48			0.60			0.61			0.57		
Performance status*												
0-1	1.00	0.31-17.58	.415	1.00	0.26-29.58	.393	1.00	0.35-30.52	.300	1.00	0.14-11.48	.839
2-3	2.32			2.79			3.26			1.26		
D/F, doses	0.77	0.64-0.92	.005	0.74	0.51-1.08	.117	0.70	0.55-0.89	.004	-	-	-
BED <sub>10</sub> <sup>†</sup>	0.97	0.94-1.00	.086	0.98	0.91-1.06	.664	-	-	-	0.94	0.89-0.98	.010
Tumor volume, mL	1.01	0.99-1.02	.286	1.00	0.99-1.02	.775	1.00	0.99-1.02	.930	1.01	1.00-1.02	.175
Number of pulmonary tumors												
1	1.00		.313	1.00		.098	1.00		.089	1.00		
2-3	1.57	0.66-3.74		2.53	0.84-7.57		2.59	0.87-7.76		2.21	0.75-6.51	.153
CRC or not												
NCRC	1.00	1.68-12.39	.003	1.00	1.16-10.99	.026	1.00	1.15-9.58	.027	1.00	1.59-14.27	.005
CRC	4.56			3.58			3.31			4.76		
Disease-free interval <sup>‡</sup>	0.99	0.98-1.01	.512	0.99	0.97-1.01	.356	0.99	0.97-1.01	.397	0.99	0.97-1.01	.352
Treatment after PBT												
No	1.00	0.59-3.85	.394	1.00	0.45-4.61	.537	1.00	0.47-4.78	.493	1.00	0.45-4.28	.576
Yes	1.50			1.44			1.50			1.38		

*Abbreviations:* BED = biological effective dose; CI = confidence interval; CRC = colorectal cancer; D/F = dose per fraction; HR = hazard ratio; MVA = multivariate analysis; NCRC = noncolorectal cancer; PBT = proton beam therapy; UVA = univariate analysis.

\* According to the Eastern Cooperative Oncology Group.

<sup>†</sup> Biological effective dose, using the linear-quadratic model with  $\alpha/\beta = 10$  Gy.

<sup>‡</sup> Disease-free interval is the period between initial therapy for primary cancer and the diagnosis of oligometastatic pulmonary recurrence.

**Table 3** Results of the UVA and MVA of the overall survival rate

Factors	UVA			MVA		
	HR	95% CI	P value	HR	95% CI	P value
Age, years	1.03	1.00-1.06	.026	1.03	1.00-1.06	.099
Sex						
Male	1.00	0.46-1.48	.520	1.00	0.61-2.05	.726
Female	0.83			1.12		
Performance status*						
0-1	1.00	1.85-12.37	.001	1.00	1.01-7.67	.048
2-3	4.79			2.78		
Total tumor volume, mL <sup>†</sup>	1.01	1.00-1.02	.005	1.01	1.00-1.02	.035
Number of pulmonary tumors						
1	1.00	0.43-1.95	.818	1.00	0.30-1.59	.386
2-3	0.92			0.69		
Disease-free interval <sup>‡</sup>	0.99	0.98-1.01	.273	0.99	0.98-1.00	.194
Treatment after PBT						
No	1.00	0.27-1.23	.153	1.00	0.30-1.43	.289
Yes	0.58			0.66		

Abbreviations: CI = confidence interval; HR = hazard ratio; MVA = multivariable analysis; PBT = proton beam therapy; UVA = univariable analysis.

\* According to the Eastern Cooperative Oncology Group.

† Total tumor volume was defined as the total volume of the irradiated targets in patients with 1 to 3 tumors.

‡ Disease-free interval is the period between initial therapy for primary site and the diagnosis of oligometastatic pulmonary recurrence.

with the efficacy of PBT being equivalent to carbon ion therapy for treating pulmonary oligometastasis.<sup>9</sup> Although there is insufficient evidence on the effectiveness of PBT for pulmonary oligometastasis, several studies on x-ray SBRT for pulmonary oligometastasis were reported.<sup>3,11-19</sup> Baschangel et al,<sup>13</sup> in a retrospective analysis of 32 patients with 1 to 3 pulmonary oligometastases, showed that the 2-year LCs of CRC, NCRC, and all patients were 80%, 100%, and 92%, respectively. The 2-year OS of the total population was 76%, with grade 2 and 3 pneumonitis observed in 1 patient. Another study of 77 patients with 122 tumors demonstrated the 2-year LCs of CRC, NCRC, and all patients were 57.3%, 90.1%, and 83.8%, respectively, and the 2-year OS of all patients was 74.6%; 8 patients developed grade 2 pneumonitis.<sup>14</sup> These findings are consistent with our results. Table 4 shows the studies on radical radiation therapy for pulmonary metastases, which were selected based on the following criteria: (1) a study reporting at least the LC rate and pulmonary toxicity of x-ray SBRT and PBT for pulmonary metastases with radical intent; (2) a study comprising data for more than 30 patients and the proportion of the patients with CRC as primary cancer; and (3) the median follow-up duration of a study being more than 12 months.

As shown in Table 4, PBT seemed to guarantee acceptable outcomes that were similar to those achieved with x-ray SBRT without exacerbations in the patient toxicity profile. The median delivery dose and interquartile range in our series were 109.6 Gy (RBE) and 10.2 Gy

(RBE), respectively, and 90% of the tumors in our series received more than 95.2 Gy (RBE). The LPF of our series, which was comparable to those observed in the x-ray SBRT series, may be attributed to the use of relatively high-dose delivery with curative intent. Additionally, the physical features of PBT, which is characterized by dose delivery with a Bragg peak, had a potential effect on the absence of grade  $\geq 3$  pneumonitis,<sup>5,6</sup> although the passive scattering method was employed in all the PBTs of our series.

To investigate the prognostic factors for LPF, we performed UVA and 3 sets of MVAs: using all the parameters, all the parameters except BED<sub>10</sub>, and all the parameters except dose per fraction, because dose per fraction and BED<sub>10</sub> are potentially correlated (correlation coefficient 0.69,  $P < .001$ ). In the UVA and MVA, CRC as the primary cancer was associated with significantly worse LPF. Additionally, patients who could receive PBT with a higher dose per fraction or BED<sub>10</sub> experienced the potential benefits of better LPF. The results of the analyses of our series are consistent with those of other studies involving x-ray SBRT for lung metastases.<sup>11-19</sup> A systematic review and meta-analysis by Jingu et al<sup>20</sup> reported that the LC in patients with pulmonary oligometastases from CRC was significantly lower than in patients with pulmonary oligometastases from NCRC (odds ratio, 3.10;  $P < .00001$ ), indicating that the use of a higher prescription dose was valid for achieving a better LC from CRC. In our series, the median BED<sub>10</sub> of the prescribed doses to the metastatic tumors from CRC was

**Table 4** Outcomes of radical radiation therapy for lung oligometastases

First author (reported year)	Number of patients/targets	Proportion of CRC (%)	Treatment modality	Median follow-up duration (months)	Evaluated term (years)	LPF (%)	PFS (%)	OS (%)	Pulmonary AE
Takeda (2011) <sup>11</sup>	34/44	44	X-SBRT	29 (CRC) 15 (NCRC)	2	82 (all) 73 (CRC) 94 (NCRC)	NA	NA	G3 RP, 1 patient G2 RP, 2 patients
Takahashi (2012) <sup>12</sup>	42/52	17	X-SBRT	20	2	87 (all) 67 (CRC) 89 (NCRC)	NA	65 (all) 85 (CRC) 63 (NCRC)	G2 RP, 3 patients
Baschnagel (2013) <sup>13</sup>	32/47	31	X-SBRT	27.6	2	92 (all) 80 (CRC) 100 (NCRC)	NA	76 (all)	G3 RP, 1 patient G2 RP, 1 patient
Binkley (2015) <sup>14</sup>	77/122	34	X-SBRT	22	2	83.8 (all) 57.3 (CRC) 90.1 (NCRC)	24.8	74.6	G2 RP, 8 patients
Rieber (2016) <sup>15</sup>	700/NA	20	X-SBRT	14.7	2	81.2 (all)	NA	54.4	G5 RP, 1 patient G2 RP, 42 patients
Jingu (2017) <sup>16</sup>	93/104	100	X-SBRT	28	3	65.2	NA	55.9	G5 RP, 1 patient G3 RP, 2 patients
Helou (2017) <sup>17</sup>	120/184	55	X-SBRT	22	2	84.8 (all) 76.4 (CRC) 91.7 (NCRC)	NA	45.7-74.9	G5 RP, 1 patient G3 RP, 1 patient G2 RP, 8 patients
Franceshini (2017) <sup>18</sup>	200/NA	50	X-SBRT	24.2	2	84.9 (all) 78.0 (CRC) 88.2 (NCRC)	57.7	65.4	G1-2 RP, 16 patients
Yamamoto (2020) <sup>19</sup>	1378/1547	25	X-SBRT	24.2	3	81.3 (all)	NA	60.3 (all)	G 5 AE, 0.7% G≥3 AEs, 2.5% G≥2 AEs, 11.7%
Sulaiman (2014) <sup>9</sup>	47/59	23	CIRT PBT	17	2	79.3 (all)	27.3 (all)	54.0 (all)	G2 RP, 2 patients
Present study	118/141	42	PBT	25.5	2	86.3 (all) 72.7 (CRC) 97.4 (NCRC)	31.7 (all)	67.8 (all) 80.7 (CRC) 58.7 (NCRC)	G2 RP, 10 patients
					3	78.4 (all) 65.8 (CRC) 88.6 (NCRC)	24.2 (all)	59.6 (all) 71.4 (CRC) 51.3 (NCRC)	

*Abbreviations:* AE = adverse event; CIRT = carbon ion beam therapy; CRC = colorectal cancer; GX = grade X; LPF = local-progression-free rate; NA = not available; NCRC = noncolorectal cancer; OS = overall survival rate; PBT = proton beam therapy; PFS = progression-free survival rate; RP = radiation pneumonitis; X-SBRT = x-ray stereotactic body radiation therapy.

112.0 Gy (RBE), which was similar to the dose (higher than 100 Gy) identified by the aforementioned systematic review as being required for the improved LC of lung metastases from CRC. This relatively high-dose delivery method employed in our series may have resulted in efficacy values that were similar to those observed in the x-ray SBRT series (Table 4). However, the LPF in our series remains insufficient, especially in patients with CRC. Dose escalations with a higher total dose or dose in fraction may lead to improved LC.<sup>16,21</sup> PBT has the potential to deliver higher dose-escalated radiation with an acceptable toxicity profile based on the physical features of particle therapy.<sup>22</sup> Furthermore, the advancement of FLASH-radiation therapy using ultra-high dose rates in PBT<sup>23</sup> might have the potential to trigger a paradigm shift in the treatment of lung metastases in the future. Further informative reports on the outcomes of PBT for pulmonary oligometastasis are necessary to validate its efficacy and safety, and collecting more evidence on the outcome of PBT with novel treatment techniques is essential to improve the treatment outcomes of pulmonary oligometastasis.

For prognostic factors associated with OS, the MVA in our series showed that the PS and total tumor volume were statistically significant factors. This result is in alignment with that of previous studies.<sup>15,19</sup> Rieber et al<sup>15</sup> showed that the PS and tumor size (maximum metastasis diameter) were significant prognostic factors for OS in the MVA with a multi-institutional database of 700 patients. Another multi-institutional investigation by Yamamoto et al<sup>19</sup> disclosed that OS was significantly influenced by PS and tumor size (maximum tumor diameter) in the MVA on the data of 1378 patients. Therefore, PS and total tumor volume (tumor size) seem to be the factors that need to be considered for the appropriate selection of radical local therapy for pulmonary oligometastases.

This study has several limitations. The multi-institutional retrospective nature of this study could bias all statistical analyses. The methods of PBT, the follow-up examinations, and the procedures to evaluate the events of interest were different between institutions. There were also unmeasured or uncontrolled factors involved. Owing to the relatively short follow-up period and heterogeneity of primary cancers, the effect of the statistical analyses was relatively low. However, most previously published studies focusing on the outcomes of pulmonary oligometastases also had a retrospective design and short duration with heterogeneity of primary disease sites; this may be attributed to the clinical features of the oligometastatic disease.

## Conclusions

This multi-institutional investigation identified PBT as a promising treatment for pulmonary oligometastases with acceptable toxicity and demonstrated that passive

scattering PBT yielded outcomes that were comparable to those of x-ray SBRT.

## Acknowledgments

The authors wish to thank Editage ([www.editage.jp](http://www.editage.jp)) for the English language editing.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.adro.2021.100690>.

## References

1. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: Prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg.* 1997;113:37–49.
2. Cheung FP, Alam NZ, Wright GM. The past, present and future of pulmonary metastasectomy: A review article. *Ann Thorac Cardiovasc Surg.* 2019;25:129–141.
3. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: A systematic review. *J Thorac Oncol.* 2010;5:1091–1099.
4. Londero F, Grossi W, Morelli A, et al. Surgery versus stereotactic radiotherapy for treatment of pulmonary metastases. A systematic review of literature. *Future Sci OA.* 2020;6:FSO471.
5. Hoppe BS, Huh S, Flampouri S, et al. Double-scattered proton-based stereotactic body radiotherapy for stage I lung cancer: A dosimetric comparison with photon-based stereotactic body radiotherapy. *Radiother Oncol.* 2010;97:425–430.
6. Kadoya N, Obata Y, Kato T, et al. Dose-volume comparison of proton radiotherapy and stereotactic body radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011;79:1225–1231.
7. Chi A, Chen H, Wen S, et al. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis. *Radiother Oncol.* 2017;123:346–354.
8. Ohnishi K, Nakamura N, Harada H, et al. Proton beam therapy for histologically or clinically diagnosed stage I non-small cell lung cancer (NSCLC): The first nationwide retrospective study in Japan. *Int J Radiat Oncol Biol Phys.* 2020;106:82–89.
9. Sulaiman NS, Fujii O, Demizu Y, et al. Particle beam radiation therapy using carbon ions and protons for oligometastatic lung tumors. *Radiat Oncol.* 2014;9:183.
10. Common Terminology Criteria for Adverse Events (CTCAE). *Cancer therapy evaluation program.* 2010. Available at: [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_40](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). Accessed January 12, 2021.
11. Takeda A, Kunieda E, Ohashi T, et al. Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer. *Radiother Oncol.* 2011;101:255–259.
12. Takahashi W, Yamashita H, Niibe Y, et al. Stereotactic body radiotherapy for metastatic lung cancer as oligo-recurrence: An analysis of 42 cases. *Pulm Med.* 2012;2012: 454107.
13. Baschnagel AM, Mangona VS, Robertson JM, et al. Lung metastases treated with image-guided stereotactic body radiation therapy. *Clin Oncol R Coll Radiol.* 2013;25:236–241.

14. Binkley MS, Trakul N, Jacobs LR, et al. Colorectal histology is associated with an increased risk of local failure in lung metastases treated with stereotactic ablative radiation therapy. *Int J Radiat Oncol Biol Phys.* 2015;92:1044–1052.
15. Rieber J, Streblow J, Uhlmann L, et al. Stereotactic body radiotherapy (SBRT) for medically inoperable lung metastases-A pooled analysis of the German working group “stereotactic radiotherapy. *Lung Cancer.* 2016;97:51–58.
16. Jingu K, Matsuo Y, Onishi H, et al. Dose escalation improves outcome in stereotactic body radiotherapy for pulmonary oligometastases from colorectal cancer. *Anticancer Res.* 2017;37:2709–2713.
17. Helou J, Thibault I, Poon I, et al. Stereotactic ablative radiation therapy for pulmonary metastases: Histology, dose, and indication matter. *Int J Radiat Oncol Biol Phys.* 2017;98:419–427.
18. Franceschini D, Cozzi L, De Rose F, et al. Role of stereotactic body radiation therapy for lung metastases from radio-resistant primary tumours. *J Cancer Res Clin Oncol.* 2017;143:1293–1299.
19. Yamamoto T, Niibe Y, Aoki M, et al. Analyses of the local control of pulmonary oligometastases after stereotactic body radiotherapy and the impact of local control on survival. *BMC Cancer.* 2020;20:997.
20. Jingu K, Matsushita H, Yamamoto T, et al. Stereotactic radiotherapy for pulmonary oligometastases from colorectal cancer: A systematic review and meta-analysis. *Technol Cancer Res Treat.* 2018;17: 1533033818794936.
21. Takeda A, Sanuki N, Tsurugai Y, et al. Stereotactic body radiotherapy for patients with oligometastases from colorectal cancer: Risk-adapted dose prescription with a maximum dose of 83-100 Gy in five fractions. *J Radiat Res.* 2016;57:400–405.
22. Mohan R, Grosshans D. Proton therapy - Present and future. *Adv Drug Deliv Rev.* 2017;109:26–44.
23. van Marlen P, Dahele M, Folkerts M, et al. Bringing FLASH to the clinic: Treatment planning considerations for ultrahigh dose-rate proton beams. *Int J Radiat Oncol Biol Phys.* 2020;106:621–629.