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Proton Beam Therapy in Elderly Patients With cT1-3N0M0 Non-small Cell Lung Cancer

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Abstract. *Background/Aim: To investigate the outcomes of elderly patients with cT1-3N0M0 non-small cell lung cancer (NSCLC) undergoing proton beam therapy (PBT). Patients and Methods: Between 2009 and 2019, 110 patients receiving hypofractionated PBT for cT1-3N0M0 NSCLC were retrospectively reviewed. Results: The median follow-up was 36.5 months (range=4.9-131.0 months). In the elderly group (80 years or older), the 3-year overall survival and progression-free survival rates were 79.8% and 73.9%, respectively, and the corresponding rates in the younger group were 80.5% and 61.2%, respectively. Grade 3 radiation pneumonitis (RP) was observed in 4.4% patients in the young group, whereas no grade 3 RP was observed in the elderly group. Age was not a risk factor for symptomatic RP. There were no significant differences in the survival and adverse events between the elderly and younger groups. Conclusion: PBT may be a reasonable approach for treating lung cancer in elderly patients with T1-3N0M0 NSCLC.*

Globally, approximately 70 particle beam therapy facilities have been newly established in the last decade and more than 100 facilities are currently in operation. In Japan, there are 25 particle beam therapy facilities in operation, and the number of patients undergoing particle beam therapy has been increasing yearly according to the increase in the number of facilities (1). While photons exhibit the characteristic of depth dose build up, charged particles can be stopped at a specific depth in the body to impart maximal radiation dose to the target. Thus, particle beam therapy provides better dose distribution than radiotherapy (RT) photon beams by limiting beam numbers and imparts a high dose to the target while sparing the surrounding normal tissues (2, 3). In clinical practice, two types of charged particles, protons and carbon-ions are used, which are biologically different. Since carbon ions have a higher relative biological effectiveness (RBE) than protons, they are especially useful for the treatment of pathologically radioresistant tumors such as osteosarcoma, chordoma, and melanoma as well as large-sized hypoxic tumors (4-6). In contrast, the RBE of protons is similar to that of photons, and they are useful for concurrent chemoradiotherapy administered for locally advanced cancers, including lung cancer, with reduced toxicity due to lower doses to organs at risk (OARs) along with escalating RT doses to tumors (7-9).

In Japan, lung cancer is the third most common cancer and accounts for the highest number of deaths among all cancers. Additionally, the number of elderly patients with non-small cell lung cancer (NSCLC) has been increasing yearly because of the aging society in Japan. With regard to cancer therapy in the elderly, it is especially very important to reduce toxicity because they are less tolerant to adverse effects in addition to having a higher risk of developing severe toxicity (10, 11). Since there is an apparent dose-volume effect involved in the development of radiation-induced lung injuries during chest RT, proton beam therapy (PBT) may be a safe and curative RT for elderly NSCLC patients due to the lower irradiated doses and volumes of OARs (12-14). Although there is accumulating evidence on the efficacy of PBT in various cancers, there are still limited data on PBT in elderly NSCLC patients.

Hence, this study aimed to investigate the clinical outcomes of elderly patients with cT1-3N0M0 NSCLC who received hypofractionated high-dose PBT at our institution, and analyze the beneficial effects of PBT on survival and toxicity in elderly patients in comparison to those in young patients.

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Key Words: Proton beam therapy, elderly patients, non-small cell lung cancer.

Patients and Methods

Patients. The present study was approved by the institutional review board of the University of Tsukuba Hospital (Approval No. R02-160). Data from 110 patients with clinical stage T1-3N0M0 NSCLC who received definitive PBT with hypofractionation between April 2009 and May 2019 at our institution were retrospectively reviewed.

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

The clinical target volume (CTV) encompassed the primary tumor. The planning target volume encompassed the CTV along with a 5- to 8-mm margin in all directions, and an additional 5-mm margin in the caudal direction to compensate for any respiratory motion. Two to three ports were used. Dose and fractionation were principally determined by the tumor location (peripheral or central). We did not modify the radiation dose or the margin of the target due to age.

Follow-up and statistical analysis. The patients were followed up with a physical examination, chest radiography, blood test, CT or positron emission tomography (PET)/CT, and magnetic resonance imaging every 2-3 months during the first year, and at 3- to 6-month intervals thereafter. Local progression at the primary site was defined as an increase in the tumor size, significant positive accumulation on PET/CT, or a histological diagnosis. Regional recurrence was defined as regrowth or new lymphadenopathy in the hilar, mediastinal, or supraclavicular region. Distant metastasis was defined as failure at any other site. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The follow-up interval was defined from the first day of PBT to the date of death or last follow-up. The overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS), and local progression-free (LPF) rates were calculated from the first day of PBT to the date of that event or last follow-up using the Kaplan–Meier method. Significant differences between the survival curves were assessed using the generalized Wilcoxon test and Cox proportional hazard model. A p-value of <0.05 was considered significant. SPSS version 25 (IBM, Co., Armonk, NY, USA) software was used for the statistical analyses.

Results

Patient background. Table I shows the patients characteristics. The median age was 77 years (range=53-89 years) for the entire cohort, and 82 years (range=80-89 years) for those aged ≥80 years. According to the 8th version of the Union for International Cancer Control TNM classification, the clinical stage was IA in 72 patients, IB in 19, IIA in 11, and IIB in seven patients, and the elderly group tended to have larger tumors. Histopathological examination revealed that 20 and 34 tumors were squamous cell carcinoma and adenocarcinoma, respectively. Additionally, four tumors were diagnosed as NSCLC, whereas the remaining 52 patients were clinically diagnosed as NSCLC.

Survival and control. At the last follow-up, 77 (70%) patients were still alive, while 10 (9.1%) had died of lung cancer. The remaining 23 patients without lung cancer recurrences died of cardiopulmonary disease (n=12), liver disease (n=3), other cancers (n=3), non-occlusive mesenteric ischemia (n=1), or unknown disease (n=4). In the elderly group of 80 years or older, four out of 15 deaths were caused by lung cancer, eight due to intercurrent diseases, and three were classified as unknown deaths. In the young group aged under 80 years, six out of 18 deaths were caused by lung cancer, 11 were by other diseases, and one was considered an unknown death. The median follow-up time from the first day of PBT was 36.5 months (range=4.9-131.0 months) for all patients and 37.5 months (range=4.9-131.0 months) for the surviving patients.

In the elderly patients 80 years or older, the 3-year OS and PFS were 79.8% [95% confidence interval (CI)=67.3-92.3] and 73.9% (95%CI=59.8-88.1), respectively, while the corresponding rates in patients under 80 years of age were 80.5% (95%CI=69.9-91.0) and 61.2% (95%CI=48.4-73.9), respectively (Figure 1). There were no significant differences in the survival rates between the elderly and younger groups. The 3-year DMFS and LPF in the elderly 80 years or older, were 77.5% (95%CI=64.4-90.5%) and 93.1% (95%CI=83.5-100%), respectively, and the corresponding rates in patients under 80 years of age were 65.0% (95%CI=52.2-77.8%) and 93.0% (95%CI=86.4-99.7%), respectively (Figure 2). There were no significant differences in the DMFS and LPF between the two groups.

Significant factors. The results of univariable analysis for detecting the potential prognostic factors associated with OS are shown in Table II. A poor performance status (PS) and existence of interstitial pneumonia (IP) were associated with a significantly worse OS in octogenarians (elderly group), whereas sex, chronic obstructive pulmonary disease (COPD), and operability in addition to PS and IP were significant factors in the young (<80 years old) group. PS and IP were also significant factors for PFS in the elderly group, whereas in the young group, PS was the only significant factor (Table III). Multivariable analysis did not demonstrate any significant factors for OS in the elderly, while PS was a significant factor in the young (Table IV).

Adverse events. Regarding late toxicity, there were no grade 4-5 AEs in this study group, but grade 3 radiation pneumonitis (RP) was observed in three (4.4%) patients in

Table I. *Patient and tumor characteristics*.

Characteristics	<80 years (n=68)	≥80 years (n=42)	p-Value	All (n=110)
Median age (years) (range)	72 (53-79)	82 (80-89)		77 (53-89)
Sex				
Male	51	35		86
Female	17	7	0.429	24
PS				
0	46	15		61
1	18	23		41
≥2	4	4	0.005	8
COPD				
Yes	25	17		42
No	43	25	0.851	68
IP				
Yes	7	5		12
No	61	37	1.000	98
Operability				
Operable	27	13		40
Inoperable	41	29	0.470	70
Tumor histology				
SCC	12	8		20
Adenocarcinoma	20	14		34
No prove histology	33	19		52
NSCLC NOS	3	1	0.916	4
8th UICC stage at clinical				
Tis	1	0		1
T1a	6	1		7
T1b	27	12		39
T1c	18	8		26
T2a	7	12		19
T2b	7	4		11
T3	2	5	0.059	7
Dose and fraction				
66 GyE/10 fr	47	27		74
72.6 GyE/22 fr	17	14		31
70 GyE/25 fr	2	0		2
80 GyE/20 fr	2	1	0.573	3
CTV volume (cm^3) (range)	14.0 (3.7-95.6)	16.7 (3.8-147.3)	0.276	14.5 (3.7-147.3)

PS: Performance status; COPD: chronic obstructive pulmonary disease; IP: interstitial pneumonia; SCC: squamous cell carcinoma; NSCLC: non-small cell lung cancer; NOS: not otherwise specified; UICC: Union for International Cancer Control; GyE: Gray equivalent; CTV: clinical target volume.

the young group (Table V). However, no grade 3 RP was observed in the elderly group. With regard to grade 2 AEs, there were seven (10.3%) cases of radiation pneumonitis (RP), two (2.9%) of rim fractures, and one (1.5%) skin ulcer in the young group, with one (2.4%) RP and two (4.8%) rim fractures in the elderly group. There was no significant difference in the toxicity profile between the two groups.

Discussion

Although the gap between the OS curves of the young and elderly groups after the third year appeared to be widened, no significant difference between the two groups was detected statistically in the present study (p=0.198). Surprisingly, the elderly group included 21 (50%) patients with non-T1 tumors, whereas there were 16 (24%) non-T1 tumors in the young group. Furthermore, life expectancy in the elderly group may be shorter than that in the young. Since the proportions of operable patients with coexistent lung diseases such as COPD and IP in the two groups were similar, it is unclear why there was no difference in the OS between the two groups. In fact, there were no differences in the incidence rates of all, cancer-related, or intercurrent deaths between the two groups. In a meta-analysis that compared stereotactic body radiation therapy (SBRT) and PBT, Chi *et al*. reported that the 3-year OS and PFS after PBT were better than those after SBRT (59% *vs*. 70% p=0.005, and 51% *vs*. 64% p=0.01, respectively), and PBT was less toxic than SBRT, although the number of patients with non-T1 tumors was higher in the PBT than in the SBRT group (PBT: 43% *vs*.

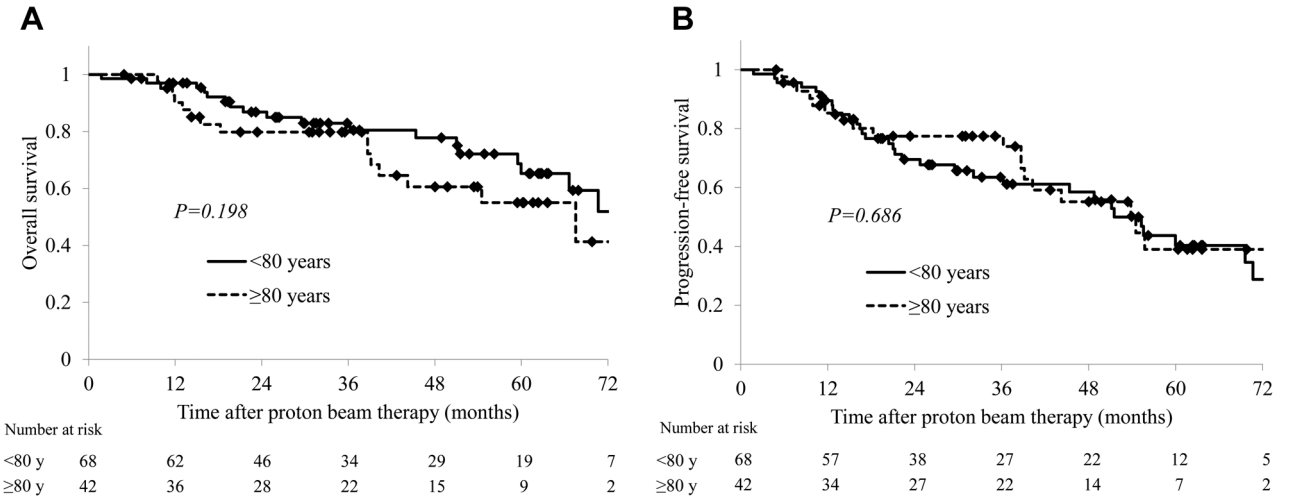

Figure 1. *Overall survival (A) and progression-free (B) survival curves of patients under 80 years of age and those 80 years or older.*

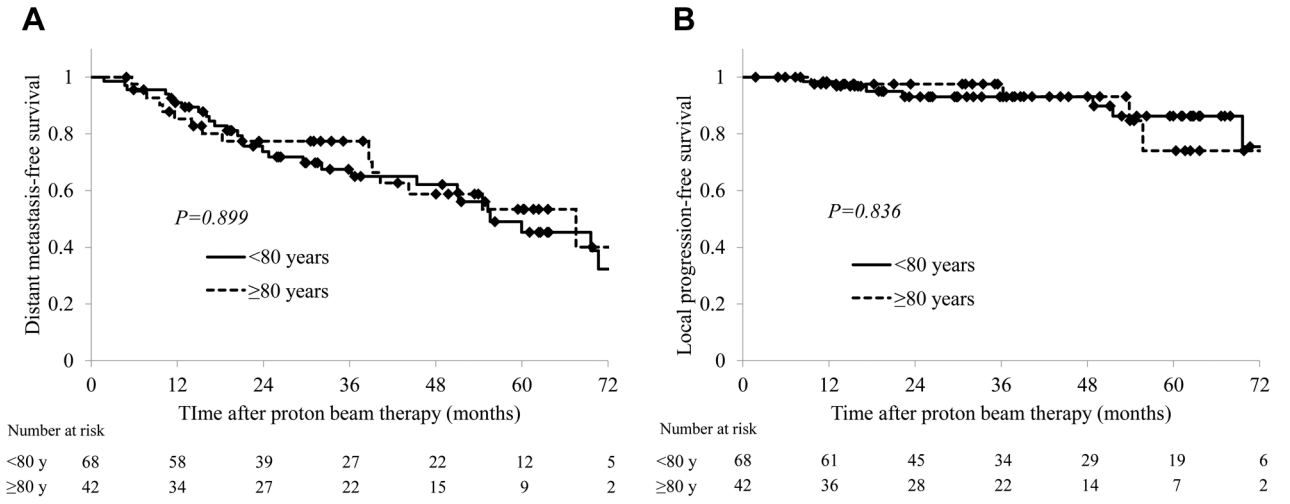

Figure 2. *Distant metastasis-free survival (A) and local progression-free (B) survival curves of patients under 80 years of age and those 80 years or older.*

SBRT: 29%) (15). Moreover, a Japanese multicenter study on PBT for stage I NSCLC analyzed 669 patients treated at eight institutes and reported the efficacy and feasibility. In the study, the 3-year OS rate in elderly patients (≥76 years old) was 74.1%, while the corresponding rate in young patients (<76 years old) was 85.1% (p<0.001) (3). In the present study, the 3-year OS rate in octogenarians with T1-3N0M0 NSCLC was 80.3%, which was slightly better than that in the abovementioned multicenter study. As for local control, in a previous study of RT for regional lymph node recurrence, we found that PBT tended to have better the 3-year LPF rates than photon RT (90.9% *vs*. 68.8%, p=0.054) and LPF contributed to improvement of OS. These results seemed to be provided by a difference in the target coverage between protons and photons, because the build-up and build-down of photons affect the dose reduction at the edge of target volumes located mostly in the lung adjacent to air (16). Actually, the 3-year LPF rate in the elderly group (≥80 years old) after PBT was 93.1% and the corresponding rate in the young group was 93.0% in the present study. Since no differences in the PFS, LPF, and AEs between the elderly and young groups were observed in the present study, it seems that PBT does not cause more severe damage in elderly T1-3N0M0 NSCLC patients compared to younger patients, and may be considered as a safe and effective treatment, especially in elderly patients.

Table II. *Univariable analysis of prognosis factors for overall survival (OS).*

	≥80 years			<80 years		
Factor	N=42	3-year (%)	*p*-Value	N=68	3-year (%)	*p*-Value
Sex						
Male *vs*. female	35 *vs*. 7	81.4 *vs*. 53.6	0.660	51 *vs*. 17	72.9 *vs*. 92.3	0.029
PS						
0 *vs*. ≥1	15 *vs*. 27	85.7 *vs*. 76.5	0.033	46 *vs*. 22	92.3 *vs*. 50.0	<0.001
COPD						
Yes *vs*. no	17 *vs*. 25	79.8 *vs*. 69.2	0.737	25 *vs*. 43	63.7 *vs*. 89.2	0.003
IP						
Yes *vs*. no	5 *vs*. 37	40.0 *vs*. 82.8	0.018	7 *vs*. 61	40.0 *vs*. 84.4	0.018
Operability						
Operable *vs*. inoperable	13 *vs*. 29	73.9 *vs*. 73.5	0.687	27 *vs*. 41	96.0 *vs*. 68.3	<0.001
Tumor histology						
Adenocarcinoma *vs*. others	14 *vs*. 28	78.6 *vs*. 80.0	0.303	20 *vs*. 48	95.0 *vs*. 73.0	0.190
8th UICC stage at clinical						
T1 *vs*. T2-4	21 *vs*. 21	79.8 *vs*. 72.4	0.770	52 *vs*. 16	79.1 *vs*. 74.6	0.870
Dose and fraction						
66 GyE/10 fr *vs*. others	27 *vs*. 15	81.2 *vs*. 77.4	0.618	47 *vs*. 21	79.7 *vs*. 82.2	0.901
CTV volume (cm^3)						
≤16.2 *vs*. >16.2	21 *vs*. 21	79.0 *vs*. 72.7	0.564	34 *vs*. 34	78.7 *vs*. 82.9	0.935

PS: Performance status; COPD: chronic obstructive pulmonary disease; IP: interstitial pneumonia; UICC: Union for International Cancer Control; GyE: Gray equivalent; CTV: clinical target volume.

Table III. *Univariable analysis of prognosis factors for progression-free survival (PFS).*

	≥80 years			<80 years		
Factor	N=42	3-year (%)	*p*-Value	N=68	3-year (%)	*p*-Value
Sex						
Male *vs*. female	35 *vs*. 7	77.1 *vs*. 42.9	0.440	51 *vs*. 17	55.8 *vs*. 68.0	0.259
PS						
0 *vs*. ≥1	15 *vs*. 27	79.0 *vs*. 70.6	0.041	46 *vs*. 22	69.5 *vs*. 40.1	0.033
COPD						
Yes *vs*. no	17 *vs*. 25	66.8 *vs*. 60.6	0.865	25 *vs*. 43	56.2 *vs*. 63.8	0.505
IP						
Yes *vs*. no	5 *vs*. 37	40.0 *vs*. 75.9	0.032	7 *vs*. 61	22.9 *vs*. 62.6	0.205
Operability						
Operable *vs*. inoperable	13 *vs*. 29	67.7 *vs*. 67.7	0.649	27 *vs*. 41	68.7 *vs*. 54.6	0.148
Tumor histology						
Adenocarcinoma *vs*. others	14 *vs*. 28	62.5 *vs*. 67.8	0.873	20 *vs*. 48	70.0 *vs*. 56.7	0.638
8th UICC stage at clinical						
T1 *vs*. T2-4	21 *vs*. 21	79.8 *vs*. 68.2	0.573	52 *vs*. 16	61.8 *vs*. 47.7	0.459
Dose and fraction						
66GyE/10fr *vs*. others	27 *vs*. 15	81.2 *vs*. 61.2	0.667	47 *vs*. 21	59.1 *vs*. 66.4	0.441
CTV volume (cm^3)						
≤16.2 *vs*. >16.2	21 *vs*. 21	79.0 *vs*. 68.2	0.869	34 *vs*. 34	62.5 *vs*. 60.6	0.376

PS: Performance status; COPD: chronic obstructive pulmonary disease; IP: interstitial pneumonia; UICC: Union for International Cancer Control; GyE: Gray equivalent; CTV: clinical target volume.

To successfully perform chest RT for thoracic malignancies including NSCLC, it is very important to avoid radiation-induced lung injuries such as RP, and many researchers have suggested that the irradiation doses and volumes of the normal lung are closely related to the development of RP (12, 13, 17, 18). Theoretically, PBT may be more advantageous for large-sized tumors than for small-sized tumors. Kadoya *et al*. showed that the difference in the irradiated volume in PBT compared

Table IV. *Multivariable analysis of prognosis factors.*

	≥80 years				<80 years			
Factor	N=42	HR	95%CI	*p*-Value	N=68	HR	95%CI	*p*-Value
(OS)								
PS								
0 *vs.* ≥1	15 *vs.* 27	3.801	0.80-17.9	0.092	46 *vs.* 22	6.099	1.89-19.7	0.003
COPD								
Yes *vs.* no	-	-	-	-	25 *vs.* 43	2.132	0.58-7.88	0.256
IP								
Yes *vs.* no	5 *vs.* 37	2.848	0.89-9.12	0.078	7 *vs.* 61	1.861	0.44-7.89	0.399
Operability								
Operable *vs.* inoperable	-	-	-	-	27 *vs.* 41	5.868	0.81-42.5	0.081
(PFS)								
PS								
0 *vs.* ≥1	15 *vs.* 27	3.739	1.00-13.9	0.049	-	-	-	-
IP								
Yes *vs.* no	5 *vs.* 37	2.377	0.78-7.23	0.127	-	-	-	-

OS: Overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; PS: performance status; COPD: chronic obstructive pulmonary disease; IP: interstitial pneumonia.

to SBRT was larger for lung V5 than for lung V20, meaning that the larger the tumor size, the more PBT could reduce the irradiated volume with a lower dose (19). It is possible that low dose irradiation to the lung in elderly or physically impaired patients with low respiratory function may be seriously affected, and PBT could reduce the volume of low dose irradiation and have advantages. It is known that age is one of the major risk factors for developing RP (11). However, in the present study, no grade 3 RP was observed in the elderly patients, although there were no differences in tumor size between the elderly and young groups. Compared to a report on SBRT for cT1-3N0M0 NSCLC in elderly patients 80 years and older, our study showed better survival and local control with a lower incidence of severe RP (20). These results suggest that the effects of tumor size and age are different on PBT compared to SBRT, and no severe lung injury induced by PBT may have led to the favorable survival outcomes among the elderly patients in the present study.

IP is known to be a representative prognostic factor for RT in NSCLC, and there is a high risk of fatality with the development of RP after radiotherapy in patients with IP (21-23). Indeed, a high rate of grade 5 RP of 5.1-21% has been reported after SBRT in patients with IP (21, 24-28). In the present study, univariable analysis showed that it was also an unfavorable predictive factor for OS and PFS in the elderly, although no grade 4-5 RP was observed irrespective of the coexistence of IP. In addition, multivariable analysis did not demonstrate the significant effects of IP on survival outcomes both in the elderly and young groups. Previous reports on chest RT in patients with IP have also revealed that lung V5, lung V20, and mean lung dose were risk factors for the development of severe RP (25-28). In light of the above, PBT may have advantages over SBRT for chest RT in cancer patients with IP because of the reduced lung dose, with the potential to perform definitive RT even in elderly with IP. However, it is necessary to carefully take into consideration other risk factors such as the tumor size and respiratory function for determining eligibility for PBT in elderly patients in order to avoid fatal toxicities (29). In Japan, clinical data from all patients treated with PBT are prospectively collected, and analysis of the large-scale data will determine the indication criteria for thoracic PBT in patients with IP in the future.

Table V. *Adverse events.*

	Late AEs	<80 years n=68	≥80 years n=42	*p*-Value
Gr2	RP	7 (10.3%)	1 (2.4%)	0.121
	Rib fracture	2 (2.9%)	2 (4.8%)	0.620
	Skin ulceration	1 (1.5%)	0	0.429
Gr3	RP	3 (4.4%)	0	0.168

AEs: Adverse events; Gr: grade; RP: radiation pneumonitis.

In summary, PBT for T1-3N0M0 NSCLC showed no significant difference in the survival, local control, and AEs between elderly and young patients, and unlike SBRT, age was not a risk factor for symptomatic RP. IP was a poor prognostic factor in the elderly, although the incidence of AEs was low among them. This indicates that the dose-

concentration of PBT could be reflected in the clinical outcome, and used in the elderly with the same risk as young patients with T1-3N0M0 NSCLC. At present, many ongoing clinical trials are investigating adjuvant therapy with targeted therapies, such as molecular therapy and immune checkpoint inhibitors, to reduce recurrence in patients treated with SBRT, especially in medically inoperable cases and the elderly. The combination of PBT with these adjuvant treatments is expected to be a promising approach (30).

The major limitation of the present study is that it was a single-center retrospective analysis with a relatively limited sample size; therefore, there may be some bias when comparing the outcomes between the elderly and young patients. However, the differences in the OS and PFS curves after PBT between the two groups were not significant, although the proportions of patients with a poor PS and large tumor were higher in the elderly group than in the young group. In addition, there was little variability in the treatment planning as it was a single institution research. Although it may be difficult to conduct a prospective multi-center clinical trial in the elderly only, in Japan, a multi-institutional registry for all patients treated with PBT is expected to provide important information regarding the efficacy, eligibility, and limitations of PBT, especially in elderly NSCLC patients.

In conclusion, PBT has the advantages of reducing the irradiation dose and volumes of the OARs, and it can safely deliver a curative dose to the tumor while reducing the toxicity. Therefore, PBT may be a reasonable approach for treating patients with T1-3N0M0 NSCLC with high risk of RP or inoperable or marginal resection, including elderly patients.

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 KN; resources, KO, TS (Taisuke Sumiya), MM (Masashi Mizumoto), and TO; data collection, KO, KB, and TS (Takashi Saito); writing (original draft preparation), MN; writing (review and editing), HI; supervision, HS.

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