

## Original Article

# Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced non-small cell lung cancer

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## Abstract

**Objective:** To assess the feasibility of proton beam therapy for the patients with locally advanced non-small lung cancer.

**Methods:** The dosimetry was analyzed retrospectively to calculate the doses to organs at risk, such as the lung, heart, esophagus and spinal cord. A dosimetric comparison between proton beam therapy and dummy photon radiotherapy (three-dimensional conformal radiotherapy) plans was performed. Dummy intensity-modulated radiotherapy plans were also generated for the patients for whom curative three-dimensional conformal radiotherapy plans could not be generated.

**Results:** Overall, 33 patients with stage III non-small cell lung cancer were treated with proton beam therapy between December 2011 and August 2014. The median age of the eligible patients was 67 years (range: 44–87 years). All the patients were treated with chemotherapy consisting of cisplatin/vinorelbine or carboplatin. The median prescribed dose was 60 GyE (range: 60–66 GyE). The mean normal lung V20 GyE was 23.6% (range: 14.9–32%), and the mean normal lung dose was 11.9 GyE (range: 6.0–19 GyE). The mean esophageal V50 GyE was 25.5% (range: 0.01–63.6%), the mean heart V40 GyE was 13.4% (range: 1.4–29.3%) and the mean maximum spinal cord dose was 40.7 GyE (range: 22.9–48 GyE). Based on dummy three-dimensional conformal radiotherapy planning, 12 patients were regarded as not being suitable for radical thoracic three-dimensional conformal radiotherapy. All the dose parameters of proton beam therapy, except for the esophageal dose, were lower than those for the dummy three-dimensional conformal radiotherapy plans. In comparison to the intensity-modulated radiotherapy plan, proton beam therapy also achieved dose reduction in the normal lung. None of the patients experienced grade 4 or worse non-hematological toxicities.

**Conclusions:** Proton beam therapy for patients with stage III non-small cell lung cancer was feasible and was superior to three-dimensional conformal radiotherapy for several dosimetric parameters.

**Key words:** proton beam therapy, locally advanced non-small cell lung cancer, dosimetric analysis, 3DCRT, IMRT

## Introduction

The treatment outcomes after thoracic radiotherapy remain challenging in patients with Stage III non-small cell lung cancer (NSCLC), with a 3-year survival of approximately 15–20% and a median survival duration of 15–20 months (1,2). The main reasons for the poor clinical outcomes of patients with locally advanced NSCLC are thought to be as follows: (i) the relatively high incidence of distant metastases (3), (ii) the existence of patients whose tumors have radio-resistant biological characteristics (4) and (iii) insufficient coverage of the prescribed or intended dose to the primary and metastatic lymph nodes because of extensive disease (5). Considering the high incidence of distant metastases and the radioresistant nature of some tumors, the development of effective multidisciplinary treatments that include an intensification of treatment could be an effective solution. However, dose escalation studies have not yet yielded satisfactory clinical outcomes or improved local control, partly because several important organs at risk (OARs) exist in the thorax, such as normal lung tissue and the spinal cord, esophagus and heart (6–9). Occasionally, patients with extensive regional lymph node involvement or those with large or centrally located tumors are considered to be not suitable for definitive conventional, three-dimensional conformal radiotherapy (3DCRT) because of excessive doses to OARs. The treatment options presently available for these patients are palliative radiotherapy, chemotherapy alone, or best-supportive care and the clinical outcomes have been disappointing even though thoracic radiotherapy has been established as a curative treatment for patients with stage III NSCLC (3,10).

The purpose of the current study was to evaluate the dosimetric parameters, focusing on the superiority of proton beam therapy (PBT) and to examine the treatment-related toxicities associated with PBT in patients with locally advanced NSCLC.

## Materials and methods

### Patients

After being approved by the National Cancer Center Institutional Review Board (2015-270), retrospective data for 33 consecutive patients with locally advanced NSCLC who were treated using definitive PBT at our institution between December 2011 and August 2014 were reviewed. Locally advanced NSCLC was defined as unresectable or medically inoperable and histologically or cytologically confirmed stage IIIA/B NSCLC disease. Clinical staging was based on the American Joint Committee on Cancer staging, 7th edition. Disease extent was assessed by a pretreatment work-up that included computed tomography (CT) of the chest and abdomen, a chest X-ray and magnetic resonance imaging of the brain. When necessary, 2-[18F]-fluoro-2-deoxy-D-glucose-positron emission tomography was performed.

### Treatment procedures for PBT

For the treatment simulation, all the patients were placed in a supine position, and were immobilized using a body cast. Simulation CT images were then obtained in 3-mm thick slices. We used an in-house treatment planning system with a calculation grid size of 1.876 mm. The dose calculations were performed using the pencil-beam dose calculation algorithm. The gross target volume (GTV) was defined as the primary tumor and clinically positive lymph nodes, and clinically positive lymph nodes were defined as nodes  $\geq 1$  cm on a CT scan. The clinical target volume (CTV)

encompassed the GTV and the subclinical tumor extension. The planned target volume (PTV) covered the CTV with a 5-mm margin in all directions. A total dose of 60–66 GyE in 30–33 fractions was prescribed for the PTV, and elective nodal irradiation of up to 40 GyE was routinely performed. The dose constraints for the OARs were set as follows: normal lung V20 GyE (percentage of the normal lung volume irradiated with more than 20 GyE),  $<35\%$  and the spinal cord Dmax (maximum point dose),  $<48$  GyE. Patients whose OAR doses exceeded the dose constraints were defined as not being suitable for PBT. The proton dose fields were generated using a wobbling or double-scattering system. Two to four portals were arranged. The beam output was modulated based on the relative biologic effectiveness (RBE) of the proton beam, which was 1.1, according to a previous animal examination (11). Image-guided position approval and respiratory gating were used.

### Dosimetric analysis

The dosimetric data for the OARs were collected from the treatment planning system. For normal lung tissue, the percentage of the volume receiving more than 20, 10 and 5 GyE (V20, V10 and V5 GyE, respectively) and the mean dose were calculated. The CTV was excluded from the volume of the normal lung tissue. For the esophagus, which was defined as the region from the caudal edge of the cricoid bone to the esophagocardiac junction on a simulation CT image, the percentage of the volume receiving more than 50 GyE (V50 GyE) and the mean dose were calculated. For the heart, which was delineated according to the contouring guideline by RTOG, the percentage of the volume receiving more than 40 GyE (V40 GyE) and the mean dose were calculated. For the spinal cord, the maximum point dose was calculated. These dosimetric constraints for OARs were determined based on the results of previous reports (12–14). To compare the dosimetric parameters between PBT and 3DCRT, dummy 3DCRT plans were created using the same simulation CT images, structures and dose prescription settings for PBT. The patients whose off-cord beam arrangement was not spatially possible in the 3DCRT dummy plan were regarded as being not suitable for 3DCRT ('off-cord impossible'). The dummy plans using IMRT, which is also regarded as a novel treatment modality capable of reducing doses to the OARs, were also generated for these patients. For the patients who had been regarded suitable to curative IMRT, dosimetric comparison between PBT and IMRT was also performed. The details of the dummy IMRT planning are described in the Supplemental material. The dummy plans of 3DCRT and IMRT were generated using Xio version 5.0 (Elekta, Sweden) and Eclipse treatment planning system (Varian Medical System, USA), respectively. In the dummy plans of 3DCRT, conventional anteroposterior/posteroanterior initial fields of up to 40 Gy and subsequent opposed boost oblique off-cord fields with a 6-MV X-ray were used. For dose calculation of the 3DCRT dummy plan, the superposition method without inhomogeneous correction was used, with a grid size of 4 mm. The plans were approved when the CTV could receive at least 95% of the prescribed dose without exceeding the dose constraints for OARs, which were described previously.

### Chemotherapy

Chemotherapy consisting of cisplatin (CDDP)/vinorelbine (VNR) or carboplatin (CBDCA) was administered when applicable. CDDP (80 mg/m<sup>2</sup> on day 1) and VNR (20 mg/m<sup>2</sup> on days 1 and 8) were administered every 4 weeks with a maximum of three cycles, and CBDCA (30 mg/m<sup>2</sup> daily) was administered concurrently with PBT.

Dose reduction, the postponement of either drug or the discontinuation of PBT was implemented when excessive adverse events occurred.

### Follow-up schedules

After the completion of PBT with or without chemotherapy, patients were examined every 3 months for the first 2 years and every 6 months thereafter. In addition to routine examinations, adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 4.0, and the Radiation Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme. In this study, only non-hematological toxicities were evaluated.

### Statistical analysis

The statistical analysis was performed using JMP software version 9.0 (SAS, United States). A paired *t*-test was performed to compare the doses to the OARS. All the *P* values were two-sided, and the significance level was set at a *P* = 0.05.

## Results

### Patient characteristics

The patient characteristics are summarized in Table 1. All the patients had an Eastern Cooperative Oncology Group performance status (PS) of either 0 or 1. Overall, 20 patients (61%) had adenocarcinoma, 11 patients (33%) had squamous cell carcinoma and 2 patients (6%) had unspecified carcinoma. A total of 14 patients (40%) had stage IIIA, and 19 patients (60%) had stage IIIB. A total of 15 patients (45%) received a total dose of 66 GyE in 33 fractions, whereas 18 patients (55%) received a total dose of 60 GyE. Overall, 26 patients

**Table 1.** Patient characteristics GyE, Gray equivalent; CDDP, cisplatin; VNR, vinorelbine; CBDCA, carboplatin

Factors		
Age	Range	44–87 y/o
	Median	67 y/o
Gender	Male	23 (70%)
	Female	10 (30%)
Histology	Adeno	20 (61%)
	SCC	11 (33%)
	NOS	2 (6%)
T stage	1	7 (20%)
	2	16 (48%)
	3	3 (9%)
	4	6 (18%)
	x	1 (3%)
N stage	0	1 (3%)
	1	1 (3%)
	2	17 (52%)
	3	14 (40%)
Stage	IIIA	14 (40%)
	IIIB	19 (60%)
Chemotherapy sequence	Concurrent	26 (80%)
	Sequential	7 (20%)
Chemotherapy regimen	CDDP + VNR	31 (94%)
	CBDCA	2 (6%)
RT (dose/fraction)	66 GyE / 33 fx	15 (45%)
	60 GyE / 30 fx	18 (55%)
Follow up duration	Range (median)	4–36 months (14 months)

(80%) had received concurrent chemotherapy, and sequential chemotherapy was given to seven patients (20%). In all, 31 patients (94%) were treated with a chemotherapy regimen consisting of CDDP and VNR, and two patients (6%) received CBDCA alone.

### Compliance of PBT and toxicities evaluation

All 33 patients (100%) completed the planned course of PBT. However, four patients (12%) experienced interruptions of PBT for 5 days or more during their treatment courses. The reasons for the interruptions were esophagitis in two patients (6%), fever in one patient (3%) and atelectasis formation in the lung in one patient (3%), which necessitated a re-simulation. The median duration of the follow-up period for all the patients was 13.7 months (range: 4.3–35.5 months). Regarding the toxicity grades, the grades of radiation pneumonitis were as follows: 28 patients (85%) had grade 0, three patients (9%) had grade 1 and two patients (6%) had grade 2. None of the patients had grade 3 or higher pneumonitis. The grades of esophagitis were as follows: five patients (15%) had grade 0, 17 patients (52%) had grade 1, nine patients (27%) had grade 2 and two patients (6%) had grade 3, respectively. None of the patients developed grade 4 or higher esophagitis. The grades of dermatitis were as follows: one patient (3%) had grade 0, 24 patients (73%) had grade 1 and eight patients (24%) had grade 2. None of the patients had grade 3 or higher dermatitis. None of the patients experienced other severe toxicities (grade 3 or worse). The incidences and severities of the non-hematological toxicities are summarized in Table 2.

### Dosimetric analysis

The detailed results of the PBT dosimetry are summarized in Table 3. All the PBT plans for the eligible patients were approved within the dose constraints for the OARS, with the CTVs receiving at least 95% of the prescribed dose. The mean lung dose was 11.9 GyE (range: 6–19 GyE), and the mean lung V20, V10 and V5 GyE of all the patients were 23.6% (range: 14.9–32%), 30% (range: 19–47%) and 33% (range: 20–52%), respectively. The esophageal mean dose and the mean V50 GyE were 24.1 GyE

**Table 2.** Incidences and severities of non-hematological toxicities

Toxicities	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4 or 5
Pneumonitis	28 (85%)	3 (9%)	2 (6%)	0 (0%)	0 (0%)
Esophagitis	5 (15%)	17 (52%)	9 (27%)	2 (6%)	0 (0%)
Dermatitis	1 (3%)	24 (73%)	8 (24%)	0 (0%)	0 (0%)

**Table 3.** Summary of PBT dosimetry

OARs	DVH parameters	Mean	Range	SD
Lung	V20 GyE (%)	23.6	14.9–32	4.6
	V10 GyE (%)	30	19–47	5.8
	V5 GyE (%)	33	20–52	6.4
	Mean dose (GyE)	11.9	6–19	3.3
Esophagus	V50 GyE (%)	25.5	0.01–63.6	16.5
	Mean dose (GyE)	24.1	1.9–40.2	7.6
Heart	V40 GyE (%)	13.4	1.43–29.3	6.1
	Mean dose (GyE)	10.8	3.3–20.8	4.3
Spinal cord	Maximum dose (GyE)	40.7	22.9–47.9	6.2

PBT, proton beam therapy.

(range: 1.9–40.2 GyE) and 25.5% (range: 0.01–63.6 %), respectively. The mean heart dose and the mean V40 GyE were 10.8 GyE (range: 3.3–20.8 GyE) and 13.4% (range: 1.4–29.3%), respectively. The mean maximum dose to the spinal cord was 40.7 GyE, ranging from 22.9 to 47.9 GyE.

#### Dosimetric comparison among PBT, 3DCRT and IMRT

Dummy plans for 3DCRT at a radical dose could not be generated in 10 patients because of an undesirable spatial relationship between the extent of disease and the spinal cord. Among them, seven patients had contralateral supraclavicular lymph nodes metastases, and the remaining three had primary disease extending over the vertebrae (i.e., in the proximity of the spinal cord). A plan that would enable an acceptable dose to the spinal cord was impossible in these patients. Therefore, these patients were defined as ‘off-cord impossible’ cases with radical 3DCRT and were excluded from the dosimetry comparison between PBT and 3DCRT. A representative dose distribution of an ‘off-cord impossible’ case is shown in Fig. 1. The dosimetric results for PBT in these patients are summarized in Table 4, since these patients could be treated with PBT at a curative dose. Regarding the grades of non-hematological toxicities in these patients, all the patients except for one, who developed grade 3 esophagitis, developed grade 2 or lower toxicities (pneumonitis: nine patients with grade 0, one patient with grade 2; esophagitis: six patients with grade 1, three patients with grade 2, one patient with grade 3).

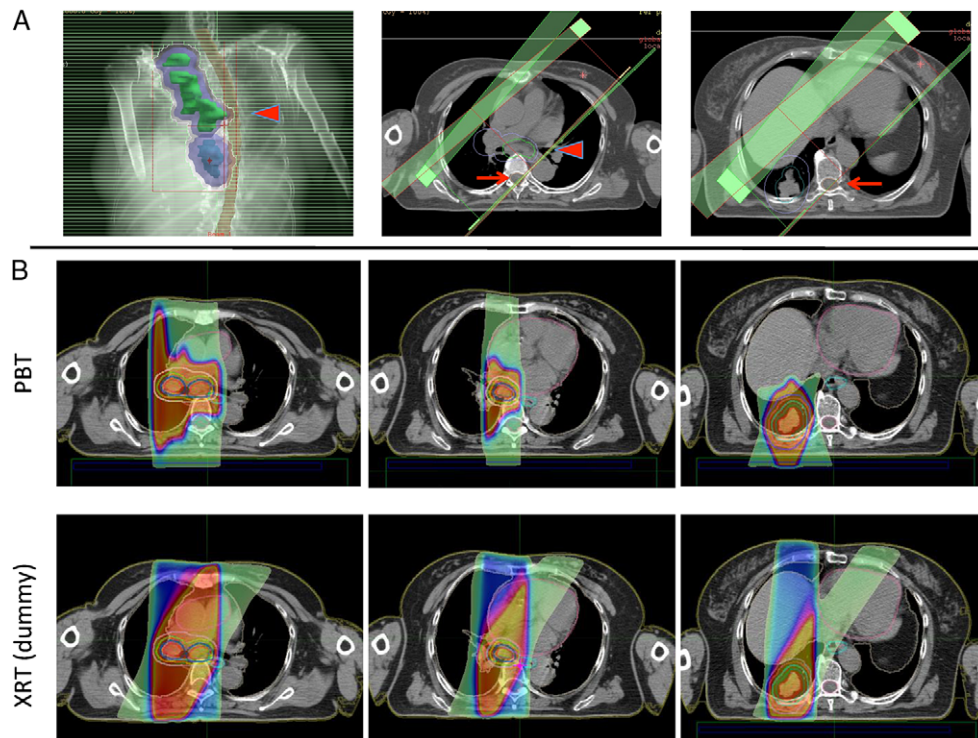
A paired *t*-test was performed to compare the dosimetric results between PBT and 3DCRT statistically (Table 5). All the CTVs of the

dummy plan received at least 95% of the prescribed dose. All the PBT dosimetric variables regarding lung dose were significantly lower than those of the dummy plan for 3DCRT ( $P < 0.01$ ). In terms of the normal lung V20 Gy, the dosimetric parameters of two patients exceeded the constraints (V20 Gy  $< 35\%$ ) in the dummy plans for 3DCRT. Regarding the dose to the heart, the mean heart dose and the heart V40 GyE of PBT were both significantly lower than those of the dummy plans for 3DCRT ( $P < 0.01$  for both). Though the mean esophageal V50 GyE of the PBT was slightly higher than that of the photon dummy photon plan (20.2 GyE vs. 16.6 Gy), the difference was not significant. In contrast, the mean esophageal dose of the PBT was slightly lower than that of the photon dummy plans (21.8 GyE vs.

**Table 4.** Summary of PBT dosimetry in patients who were regarded as being ‘off-cord impossible’ using 3DCRT

OARs	DVH parameters	Mean	Range	SD
Lung	V20 GyE (%)	25.7	16–30	4
	V10 GyE (%)	31	19.6–37	4.8
	V5 GyE (%)	34	22.6–42	5.2
	Mean dose (GyE)	13.7	7.4–16.4	2.7
Esophagus	V50 GyE (%)	37.6	6.8–63.6	18.5
	Mean dose (GyE)	29.3	14.8–40.2	7.4
Heart	V40 GyE (%)	13.7	1.4–20.5	5.9
	Mean dose (GyE)	11	6.3–15.2	3.3
Spinal cord	Maximum dose (GyE)	45.2	39.3–48	2.8

3DCRT, conventional three-dimensional conformal radiotherapy.



**Figure 1.** ‘Beam’s eye view’ and dose distribution of 3DCRT and PBT in a patient who was regarded as ‘off-cord impossible’. (A) ‘Beam’s eye view’ in a patient with T2N2 disease who was regarded as ‘off-cord impossible’. A metastatic lymph node (arrowhead) protruding toward the contralateral side and the primary tumor, which was located posteriorly, hindered an adequate beam arrangement (i.e. the spinal cord blocked coverage of the target c [arrow]). Structures: green, GTV lymph nodes; blue, GTV primary; purple, PTV. (B) Dose distributions for PBT (upper) and for the dummy plan for 3DCRT (lower). The spinal cord in the PBT treatment plan could be spared, even if the anteroposterior portals were applied. In contrast, the spinal cord would have been irradiated with a high, curative dose of up to 60 Gy in the dummy plan for 3DCRT. 3DCRT, conventional three-dimensional conformal radiotherapy; PBT, proton beam therapy; GTV, gross tumor volume; PTV, planning target volume; GyE, Gray equivalent.

23.4 Gy), with no significant difference observed between them. The maximum spinal cord dose associated with PBT was significant lower than that of the photon dummy plan ( $P < 0.01$ ).

Dummy IMRT plans were generated and a dosimetric analysis was performed for the ten patients who were regarded as 'off-cord impossible' with 3DCRT. Several patients were not suited for clinical treatment even with application of IMRT as follows. One patient exceeded both the dose constraints for the normal lung dose V20 Gy ( $<35\%$ ) and the spinal cord maximum dose ( $<48$  Gy), one patient exceeded the normal lung V20 Gy dose constraint, and the remaining two patients exceeded the spinal cord dose constraint. Therefore, 6 of the 10 patients were regarded as suitable to be treated with IMRT in curative intent. A dosimetric comparison between PBT and IMRT were then performed in these six patients (Table 6). Again, all the normal lung doses of PBT were significantly lower than those of IMRT. However, the mean esophagus V50 Gy was significantly lower in the dummy IMRT plan than that of PBT (17.2 Gy vs. 32.0 GyE, respectively,  $P = 0.04$ ). There was no significant difference in other dosimetric parameters.

When the grades of non-hematological toxicities including pneumonitis and esophagitis and the DVH parameters were compared, the differences in the doses to the esophagus or lung between patients with grade 0–1 and those with grade 3 or higher were not significant (Table 7).

## Discussion

The results of this study demonstrated that PBT yielded a significant reduction in the dose to OARs, especially the lung and heart, while maintaining an optimal dose to the targets compared to 3DCRT. In addition, among the 33 patients who were actually treated with

definitive PBT with or without chemotherapy in the current study, 12 (36%) were not suited for definitive thoracic radiotherapy using photons because of the excessive dose to OARs, such as the spinal cord or normal lung tissue (10 were regarded as 'off-cord impossible' and two did not fulfill the dose constraint of the normal lung V20 Gy). Had it not been for PBT treatment, these patients would have been treated with chemotherapy alone, palliative radiotherapy, or best-supportive care, which would have inevitably led to a shorter survival period. These results indicate that PBT is a useful alternative for a curative treatment option for patients with inoperable stage III NSCLC, even if such patients are not suited for radical 3DCRT because of an excessive dose to OARs.

Dose reduction to the OARs may lead to a decrease in treatment-related acute/late toxicities. Compared with the dummy plans for conventional photon 3D-CRT, our data demonstrated that PBT could reduce the doses to several OARs such as the lung and heart; these results are similar to those of previous reports (15–17). Chang et al. compared the DVH parameters between PBT and 3DCRT/IMRT in 26 patients with stage III NSCLC. They demonstrated that the mean total lung dose values (V5 GyE, V10 GyE and V20 GyE) for PBT were significantly lower than those for photon 3D-CRT, even with an escalated PBT dose of up to 74 GyE (15). Nichols et al. (16) also showed in their analysis of eight patients with unresectable stage III NSCLC that PBT plans achieved a median 29% reduction in the normal lung V20GyE and a median 33% reduction in the mean lung dose. In the current study, a significant reduction of the normal lung dose value associated with PBT, compared with that for conventional 3D-CRT, was obtained for all the lung dose variables that were analyzed, demonstrating that PBT has the potential to reduce the probability of radiation-induced pneumonitis in patients with stage III NSCLC, since the normal mean lung dose and the V20 GyE have been shown to act as

**Table 5.** Dosimetric comparison between PBT and 3DCRT

OARs	DVH parameters mean (range, SD)	Proton plan	Photon dummy plan	P value (t-test)
Lung	V20 GyE or Gy (%)	22.6 (15–32, 4.5)	26.2 (16.7–39.1, 6.0)	$<0.01$
	V10 GyE or Gy (%)	28.9 (19–47, 6.2)	29.9 (12.4–48.8, 8.9)	$<0.01$
	V5 GyE or Gy (%)	32.3 (20–52, 6.9)	35.4 (18.8–48.8, 9.0)	$<0.01$
	mean dose (GyE or Gy)	11.1 (6–19, 3.2)	14.2 (6.5–20.1, 3.7)	$<0.01$
Esophagus	V50 GyE or Gy (%)	20.2 (0.01–49.6, 12.7)	16.6 (0–54.7, 15.5)	0.17
	mean dose (GyE or Gy)	21.8 (1.9–33.9, 6.6)	23.4 (7–36.8, 7.5)	0.11
Heart	V40 GyE or Gy (%)	13.3 (2.0–29.5, 6.3)	23.4 (6.5–36.4, 8.2)	0.01
	mean dose (GyE or Gy)	10.8 (3.3–20.8, 4.7)	16.4 (6.2–33.3, 7.4)	0.01
Spinal cord	max dose (GyE or Gy)	38.8 (22.8–48.0, 6.4)	46.0 (42.8–48.0, 1.7)	0.01

DVH, dose volume histogram.

**Table 6.** Dosimetric comparison of PBT and IMRT in patients who were regarded as being 'off-cord impossible' using 3D-CRT

OARs	DVH parameters, mean (range, SD)	PBT	IMRT (dummy)	P value by comparison (t-test)
Lung	V20 GyE or Gy (%)	24.5 (16.6–30, 4.6)	27.8 (19–37.7, 5.6)	$<0.01$
	V10 GyE or Gy (%)	31 (19.6–37, 5.9)	56.9 (41.2–70.8, 11)	$<0.01$
	V5 GyE or Gy (%)	34 (22.6–42, 6.4)	73 (50.2–90.7, 16.1)	$<0.01$
	Mean dose (GyE or Gy)	12.8 (7.4–15.3, 2.9)	15.4 (10.5–17.9, 2.7)	$<0.01$
Esophagus	V50 GyE or Gy (%)	32.0 (6.8–63.6, 22)	17.2 (1.9–35.2, 17.7)	0.04
	Mean dose (GyE or Gy)	27.9 (14.8–40.2, 9.01)	25.0 (19.8–31.5, 4.8)	0.75
Heart	V40 GyE or Gy (%)	11 (1.4–20, 6.3)	10.3 (8.0–14.5, 3.0)	0.11
	Mean dose (GyE or Gy)	9.4 (6.3–14.5, 2.9)	20.9 (9.2–50.6, 16.9)	0.21
Spinal cord	Maximum dose (GyE or Gy)	44.8 (39.3–48.0, 3.4)	45.5 (42.9–46.7, 1.6)	0.68

IMRT, intensity-modulated radiotherapy.

**Table 7.** Dosimetric comparison between patients who experienced grade 0–1 toxicities and those who experienced grade 2–3 toxicities

DVH parameter mean (range, SD)	Esophagitis G 0–1	Esophagitis G 2–3	P value (t-test)
Esophagus V50 GyE	30.0 (0.01–64.6, 16.8)	28.6 (5.4–55.0, 14.7)	0.45
Esophagus mean dose	24.0 (1.9–40.2, 7.7)	24.4 (13.9–36.0, 7.1)	0.87
	Pneumonitis G 0–1	Pneumonitis G 2	P value (t-test)
Lung V20 GyE	23.4 (14.9–32.0, 4.5)	24.0–29.0 (26.5, 2.5)	0.41
Lung mean dose	11.7 (6.0–19, 3.2)	14.2 (12.0–16.4, 2.2)	0.45

predictors of severe pneumonitis after thoracic radiotherapy (6). The heart V40GyE and the mean heart dose were also shown to be significantly lower than those for the dummy plans for 3DCRT. Achieving a reduction in heart doses may not have a large impact on treatment-related late morbidity in locally advanced NSCLC, such as heart failure and/or coronary heart disease, compared with the effect of a reduced lung dose. However, late toxicities, including heart congestion or pericardial effusion, developed in a minor but substantial percentage of patients who received chemoradiotherapy (CRT) for esophageal squamous cell carcinoma (18). The difference in the impact of the reduced heart dose between stage III NSCLC and esophageal cancer might arise from the lower survival rate of patients with stage III NSCLC, compared with that of patients with esophageal cancer. However, we consider that the reduced heart dose would have a positive impact on the development of late toxicities even in patients with locally advanced NSCLC. On the contrary, the esophageal doses could not be reduced in the treatment plans for PBT, compared with those for 3DCRT. The esophageal V50 GyE was even slightly higher than that for 3DCRT. This contradicting result might be explained by the following reasons: the current study included more patients with diseases that were difficult to treat, such as those with metastatic mediastinal lymph nodes located close to the esophagus. The inclusion of the esophagus in the PTV or high-dose area of treatment planning for locally advanced NSCLC was inevitable in these patients. In addition, the restriction of the proton beam arrangement because of the physical limitations of our machinery and the relatively broad lateral proton beam penumbra might have resulted in an unavoidably high dose to the esophagus in several patients. These weaknesses are intrinsic to our current proton beam irradiation system using wobbler or double scattering methods. However, with the recent use of a novel proton beam irradiation method, the scanning method, that has only recently begun to be used at our institution, a more conformal and desirable dose distribution may be achievable (19). The scanning method is expected to reduce not only the esophageal dose, but also the doses for other OARs.

Recently, IMRT is also being widely utilized to treat locally advanced NSCLC in clinical trials and practices (20,21). Integrated small patchy fields using computer based inverse-planning is able to generate dose inhomogeneity to achieve dose reduction to the OARs. Dosimetric feature of IMRT consists in converging beams to targets at the expense of scattering low dose to the surrounding

tissue widely. In the current study, only 6 of 10 patients who were regarded as ‘off-cord impossible’ with 3DCRT could meet the dose constraints of the OARs in the dummy IMRT plans. When comparing the dosimetric parameters, the normal lung doses by the dummy IMRT plans were significantly higher than those by the PBT plans. IMRT would also provide further opportunities of curative radiotherapy for patients with advanced NSCLC, however, PBT still seems superior to IMRT in terms of normal lung dose reduction. In the meantime, the esophageal V50 Gy was significantly lower with IMRT than PBT. This might have resulted from the difference of dosimetric feature between the two treatment modalities as mentioned above. For the patients in whom high dose irradiation to the esophagus are not desirable, use of IMRT might be a treatment option.

The incidences and severities of acute and late non-hematological toxicities of PBT in the current study were considered to be acceptable, compared with previously reported results (22–25). Chang et al. reported the results of a prospective dose escalation (74 GyE) study for concurrent CRT with PBT in 44 patients with locally advanced NSCLC. In their series, no grade 4 or higher adverse events occurred, and only one patient (2%) developed grade 3 radiation pneumonitis (22). Oshiro et al. also reported their experience with concurrent dose-escalated chemo-PBT (74 GyE for the primary disease and 66 GyE for the metastatic mediastinum lymph nodes) in 15 patients with stage III NSCLC. In their study, none of the patients experienced grade 4 or 5 non-hematological toxicity, and a favorable treatment outcome was obtained, with a median survival period of 26.7 months (23).

As mentioned above, the results of this study indicated that PBT with concurrent chemotherapy might be an effective treatment option for patients with locally advanced NSCLC, based on a comparison of the dose distributions for PBT and 3DCRT. In addition, the application of PBT may be feasible in patients who are not candidates for radical 3DCRT or even IMRT because of excessive doses to OARs. However, the present study has several limitations. First, the follow-up period for evaluating long-term toxicities was somewhat short. Actually, a longer follow-up period is needed to evaluate the treatment outcomes and to obtain a proper perspective of late toxicities in this cohort of patients. In addition, the number of patients was also insufficient to draw a definite conclusion. However, the results of this study demonstrated that PBT can be used to attain a superior dose distribution for patients with locally advanced NSCLC, especially those who are not candidate for 3DCRT with radical intent because of excessive doses to OARs.

## Abbreviations

NSCLC, non-small cell lung cancer; PBT, proton beam therapy; OARs, organs at risk; SCC, squamous cell carcinoma; NOS, not otherwise specified; 3DCRT, conventional three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CT, computed tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; GyE, Gray equivalent; DVH, dose volume histogram; RBE, relative biologic effectiveness; CDDP, cisplatin; VNR, vinorelbine; CBDCA, carboplatin.

## Presentation at conference

A portion of the data in this article was presented at the poster session in the 56<sup>th</sup> annual meeting of the American Society of Therapeutic Radiation Oncology.

## Supplementary data

Supplementary data are available at <http://www.jjco.oxfordjournals.org>.

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## Conflict of interest statement

None declared.

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