ORIGINAL ARTICLE

WILEY

# Long-term outcomes of high-dose (74 GyE) proton beam therapy with concurrent chemotherapy for stage III nonsmall-cell lung cancer

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## Abstract

**Background:** To evaluate the long-term outcomes of high-dose (74 GyE) proton beam therapy (PBT) with concurrent chemotherapy for stage III non-small cell lung cancer (NSCLC).

**Methods:** Between July 2007 and March 2018, 45 patients with stage III NSCLC were treated with passive-scattering PBT of 74 GyE and concurrent chemotherapy. Among the 45 patients, the median age was 62 years (range 39–79 years) and 32 patients were men. The clinical stages were stage IIIA in 14 patients and stage IIIB in 31 patients. Thirty-six patients received chemotherapy consisting of cisplatin and vinorelbine.

**Results:** The median follow-up time was 42.1 months (range 6.4–127.0 months) for all patients and 63.5 months (range 9.4–127.0 months) for the 12 survivors. The 3- and 5-year overall survival rates were 63.7% and 38.8%, respectively, and the median overall survival was 49.1 months. Over the follow-up period, disease recurrence was observed in 32 (71%) patients. The 3- and 5-year progression-free survival rates were 22.2% and 17.7%, respectively, with a median progression-free survival of 13.1 months. In-field control improved survival and the in-field control rate was better in patients with T0–3 tumors (p = 0.023) and stage IIIA/IIIB-N3 disease (p = 0.030). Dosimetric parameters of the heart and lung were not associated with survival. No grade 4 or 5 acute or late non-hematologic toxicities were observed.

**Conclusions:** Passive-scattering PBT of 74 GyE with chemotherapy showed favorable survival and a low incidence of severe adverse events in patients with stage III NSCLC.

**KEYWORDS**
concurrent chemotherapy, proton beam therapy, stage III non-small cell lung cancer

## INTRODUCTION

The standard therapy for locally advanced inoperable non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CCRT).[1,2] The standard dose fractionation in CCRT for locally advanced NSCLC is a total dose of 60 Gy in 30 fractions over 6 weeks based on the results of the Radiation Therapy Oncology Group (RTOG) 7301 trial,[3] and this schedule has not changed over the past 30 years. Dose escalation beyond the standard dose of 60 Gy in CCRT has been evaluated by several phase I/II studies to improve local control (LC) and survival; a dose of 74 Gy with concurrent chemotherapy seemed to be tolerable and contributed to encouraging results, with a median survival of approximately 24 months.[4–6] On the other hand, a randomized trial (RTOG 0617) showed a worse overall survival (OS) in the

high dose (74 Gy) arm than that in the standard dose (60 Gy) arm.[7] In that trial, esophagitis/dysphagia and heart V5, which is the percentage of the heart volume receiving a dose of ≥5 Gy, as well as the radiation dose were associated with OS in multivariate analyses, and these factors possibly affected the poor outcomes in the high dose arm.

Proton beams can reduce the radiation dose and irradiated volume in healthy tissues such as the lung and heart in radiotherapy for stage III NSCLC compared with three-dimensional conformal radiotherapy or intensity-modulated radiotherapy.[8–10] 10 Therefore, high-dose proton beam therapy (PBT) with concurrent chemotherapy is a potential strategy for stage III NSCLC if dose escalation can be achieved safely using proton beams while limiting the dose to the normal lung, heart, and esophagus. A phase II study from the MD Anderson Cancer Center showed that PBT at a total dose of 74 Gy equivalent (GyE) administered concurrently with weekly carboplatin–paclitaxel chemotherapy for unresectable stage III NSCLC was well tolerated, with a median survival of 26 months.[11] We also conducted a phase II study of high-dose PBT (74 GyE) in the CCRT setting for stage III NSCLC, in which 15 patients (4 stage IIIA, 11 stage IIIB) were enrolled. In that study, late radiation-related grade 2 and grade 3 pneumonitis was observed in only one patient each, and the 2-year OS rate and median OS were 51% and 26.7 months, respectively.[12] However, that study was limited by the small number of patients and short follow-up. We herein report long-term follow-up outcomes of high-dose PBT with concurrent chemotherapy for stage III NSCLC in 45 patients, including 15 patients enrolled in the above-mentioned phase II study.

## METHODS

### Patients

The present study was approved by the institutional review board at the University of Tsukuba Hospital (approval no. R01-158). Between July 2007 and March 2018, 83 consecutive patients with unresectable or medically inoperable stage II–III NSCLC, according to the 7th TNM classification of the International Union Against Cancer,[13] were treated with high-dose (74 GyE) PBT at our institution. Among them, 45 stage III patients (14 stage IIIA, 31 stage IIIB) who received PBT with concurrent chemotherapy were evaluated retrospectively in the present study. The patients who received PBT alone or sequential chemotherapy were excluded from this study. The indication for CCRT in each patient was determined by discussion at the multidisciplinary conference. In general, patients with age >75 years, performance status (PS) ≥2, contralateral hilar lymph node metastasis, intrapulmonary metastasis in a different ipsilateral lobe than that of the primary tumor, obvious interstitial pneumonitis on imaging, or uncontrollable diabetes and hypertension were not treated with CCRT. The patient and treatment characteristics are summarized in Table 1. Among the 45 patients, the median age was 62 years (range 39–79 years) and 32 were men. The T stage

**TABLE 1** Patient and treatment characteristics

| Characteristic | No. of patients (%) |
|---|---|
| Age (years) | 39–79 (median, 62) |
| Sex | |
| Male | 33 (73.3) |
| Female | 12 (26.7) |
| PS | |
| 0 | 29 (64.4) |
| 1 | 16 (33.6) |
| Histology | |
| Squamous cell carcinoma | 12 (26.6) |
| Adenocarcinoma | 25 (55.6) |
| Nonsmall-cell carcinoma, NOS, and others | 8 (17.8) |
| 7th UICC T stage | |
| 0 | 1 (2.2) |
| 1 | 8 (17.8) |
| 2 | 15 (33.3) |
| 3 | 7 (15.6) |
| 4 | 14 (31.1) |
| 7th UICC N stage | |
| 0 | 2 (4.4) |
| 1 | 2 (4.4) |
| 2 | 18 (40.0) |
| 3 | 23 (51.2) |
| Clinical stage | |
| IIIA | 15 (33.3) |
| IIIB | 30 (66.7) |
| CTV1 (cc) | 21.5–820.4 (median, 224.4) |
| Chemotherapy regimen | |
| Cisplatin and vinorelbine | 36 (80.0) |
| Carboplatin and vinorelbine | 1 (2.2) |
| Cisplatin and S-1 | 2 (4.4) |
| Carboplatin and S-1 | 4 (9.0) |
| Carboplatin and paclitaxel | 1 (2.2) |
| Carboplatin and pemetrexed | 1 (2.2) |
| Follow-up time (months) | 6.4–104.0 (median, 42.1) |

*Abbreviations*: CTV, clinical target volume; NOS, not otherwise specified; S-1, tegafur/gimeracil/oteracil; UICC, Union for International Cancer Control.

was T0 in one patient, T1 in eight, T2 in 15, T3 in seven, and T4 in 14 patients.

### Proton beam therapy

Passive-scattering PBT was delivered during the end-expiratory phase via a respiratory-gated system using 155–250 MeV protons. The patient's body was immobilized using a custom-shaped body cast (ESFORM, Engineering

System Co.). Prior to each treatment, the patient's position was confirmed by fluoroscopy.

For treatment planning, chest computed tomography (CT) images were obtained in 2.5- or 5-mm-thick slices in the treatment position using a respiratory-gated system during the end-expiratory phase. The clinical target volume (CTV) 1 encompassed the primary tumor and lymph node stations of clinically positive regional lymph nodes, defined as nodes ≥1 cm on CT scans or as positive lymph nodes on positron emission tomography (PET) scans, for example a primary tumor and whole nodal stations right 4 (4R), left 4 (4L), and right 2 (2R) were contoured as CTV1 in a patient with positive lymph nodes at stations 4R, 4L, and 2R (Figure S1). The CTV2 encompassed the primary tumor and clinically positive lymph nodes, and the CTV3 included only the primary tumor. The planning target volume (PTV) encompassed the CTV plus 7- to 10-mm margins in all directions and an additional 5-mm margin in the caudal direction to compensate for respiratory motion. After delivering a dose of 40 GyE in 20 fractions to the PTV1, 66 GyE in 33 fractions was delivered to the PTV2, followed by a total boost of 74 GyE in 37 fractions to the PTV3. In general, two to three ports in the optimal direction were used to meet the following dose constraints: the percentage of the lung volume receiving a dose of ≥20 GyE (V20) ≤35%, maximum dose to the spinal cord <46 GyE biologically equivalent dose in 2 GyE per fraction (EQD2), maximum dose to the esophagus <70 GyE (EQD2), and maximum dose to the bronchus <70 GyE (EQD2). When a lung V20 was higher than 35%, PBT was permitted if a patient made a fully informed decision to receive PBT. Adaptive planning was used depending on changes in the tumor volume during the treatment course. VQA Plan ver. 1.7 or 2.0 (Hitachi Inc.) was used to decide the treatment plans.

### Chemotherapy

All patients received concurrent platinum-based doublet chemotherapy with PBT. Chemotherapy regimens are shown in Table 1. Thirty-six (80%) patients received chemotherapy consisting of cisplatin 80 mg/m$^2$ on day 1 and vinorelbine 20 mg/m$^2$ on days 1 and 8. The two courses of chemotherapy were administered during PBT. Adjuvant chemotherapy after completion of PBT was allowed and administered at the discretion of each institution because some of the patients referred back to the hospitals at their local area. Overall, 21 (46%) patients received adjuvant chemotherapy the same as concurrent chemotherapy. No patient received immune checkpoint inhibitors as consolidation therapy after PBT.

### Follow-up and statistical analysis

Post-treatment evaluation was performed every 2–3 months during the first year and 3–6 months thereafter.

The follow-up examinations included physical examinations, blood tests, chest X-rays, and CT or PET/CT scans. Local recurrence at the primary tumor site was defined as an increase in tumor size on serial CT scans, significant positive accumulation on PET/CT, or histological confirmation. Regional recurrence was defined as a regrowing or newly developed lymph node in the mediastinum or supraclavicular lesion. Distant metastasis was defined as failure at any other site. Treatment-related toxicities were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0. The rates of OS, progression-free survival (PFS), distant metastasis-free survival, LC, and regional control 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 log-rank test was used to compare the survival curves. A p value <0.05 was considered statistically significant. All statistical analyses were performed using JMP 11 (SAS Institute).

## RESULTS

### Dose–volume analysis of the lung and heart

The V5 and V20 of the lung, which are the percentages of the lung volume receiving doses of ≥5 and ≥20 GyE, respectively, ranged from 9.7% to 49.4% (median 24.8%) and 6.1% to 39.6% (median 19.7%), respectively, and the mean lung dose ranged from 1.1 to 21.5 GyE (median 10.7 GyE). The V20 of the lung was less than 25% in 41 (91%) of the 45 patients. The V5, V30, and mean dose to the heart ranged from 0 to 63.0% (median 5.6%), 0 to 38.0% (median 0.9%), and 0 to 20.7 GyE (median 1.07 GyE), respectively. The dosimetric parameters of the lung and heart are shown in Figure 1.

### Radiation-related toxicities

Acute and late radiation-related toxicities are summarized in Table 2. The incidences of grades 2, 3, 4, and 5 pneumonitis were 5 (11.1%), 4 (8.9%), 0 (0%), and 0 (0%), respectively. The incidences of grades 2, 3, 4, and 5 esophagitis were 22 (48.9%), 3 (6.7%), 0 (0%), and 0 (0%), respectively. Grade 2 or 3 adverse events including cardiac disorders other than esophagitis and pneumonitis were observed in three (6.7%) patients (grade 2 lung infection [n = 1], grade 3 lung infection [n = 1], and grade 2 rib fracture [n = 1]). No grade 4 or more severe adverse events were observed.

### Survival and local control

The median follow-up time was 42.1 months (range 6.4–127.0 months) for all patients and 63.5 months (range 9.4–127.0 months) for the 12 living patients. All but one living patients were followed up for more than 3 years (range 45.4–127.0 months, median 64.8 months). The 3- and

5-year OS rates were 63.7% (95% confidence interval [CI] 48.6–76.4) and 38.8% (95% CI 25.3–54.3), respectively, and the median OS was 49.1 months.

Over the follow-up period, disease recurrence was observed in 32 (71.1%) patients. The 3- and 5-year PFS rates were 22.2% (95% CI 12.3–36.5) and 17.7% (95% CI 9.1–31.7), respectively, and the median PFS was 13.1 months (Figure 2). The first failure site was primary only (*n* = 9), regional lymph nodes only (*n* = 3), distant

organs only (*n* = 14), primary and regional lymph nodes (*n* = 2), regional lymph nodes and distant organs (*n* = 3), or all sites (*n* = 1). The 3- and 5-year distant metastasis-free survival rates were 31.5% (95% CI 19.5–46.7) and 23.3% (95% CI 12.8–38.7), respectively (Figure 2). The 3- and 5-year LC rates were 65.3% (95% CI 48.7–78.8) and 61.9% (95% CI 45.1–76.2), respectively, and the corresponding rates of in-field lymph node control were 85.9% (95% CI 70.1–94.0) and 85.9% (95% CI 70.1–94.0), respectively (Figure 3). The 3- and 5-year regional and out-of-field lymph node control rates were 84.3% (95% CI 67.0–93.4) and 84.3% (95% CI 67.0–93.4), respectively.

Table 3 summarizes the results of univariate analyses of predictive factors for OS, PFS, and in-field disease control. The OS was not significantly affected by sex (male vs. female), age (<63 vs. ≥63 years), performance status (0 vs. 1), histology (adenocarcinoma vs. squamous cell carcinoma), T stage (T0–3 vs. T4), N stage (N0–1 vs. N3), CTV1 (<225 vs. ≥225 cc), and stage (IIIA vs. IIIB and IIIA/IIIB-N3 vs. IIIB-T4). On the other hand, T0–3 stage and stage IIIA/IIIB-N3 were associated with better in-field disease control (*p* = 0.023 and *p* = 0.030, respectively) and PFS (*p* = 0.050 and *p* = 0.008, respectively). The 5-year in-field control, LC, regional control, and PFS rates were 63.8% (95% CI 44.6–79.5), 70.2% (95% CI 50.4–84.5), 75.2% (95% CI 56.2–87.7), and 24.2% (95% CI 12.6–41.5) in patients with IIIA/IIIB-N3 disease, respectively. Dose volume histogram (DVH) parameters of the heart (V5 <6% vs. ≥6%, V30 <1% vs. ≥1%, and mean dose <1 vs. ≥1 GyE) and lung (V5 <25% vs. ≥25%, V20 <20% vs. ≥20%, and mean dose <11 vs. ≥11 GyE) were not associated with OS. In addition, the 5-year OS (52.1% vs. 15.6%, *p* = 0.065) and PFS (27.5% vs. 0%, *p* = 0.007) rates were better in patients with in-field control than in-field progression, although the difference in OS was not statistically significant.
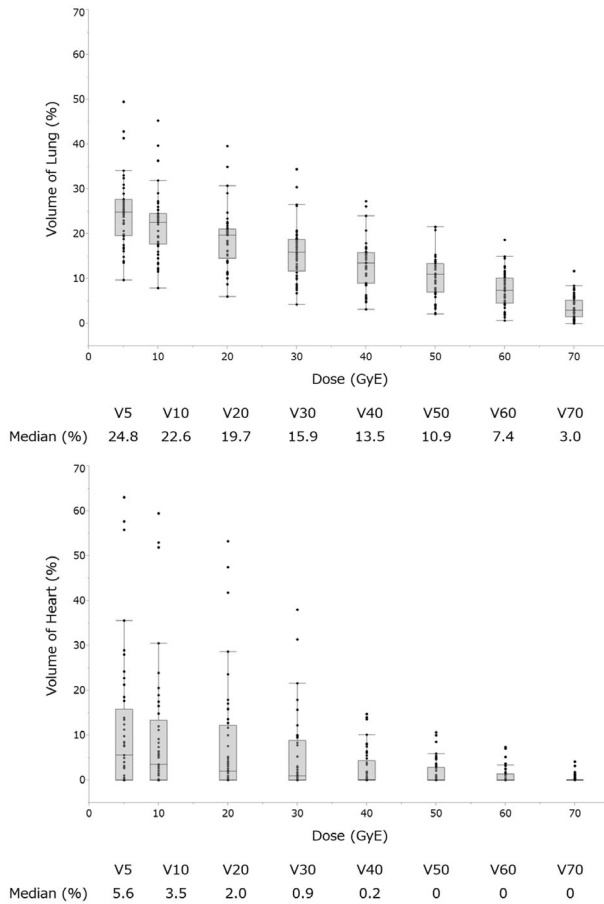
## DISCUSSION

The standard treatment for unresectable stage III NSCLC is CCRT. A meta-analysis reported 3- and 5-year survival rates



| | V5 | V10 | V20 | V30 | V40 | V50 | V60 | V70 |
|---|---|---|---|---|---|---|---|---|
| Median (%) | 24.8 | 22.6 | 19.7 | 15.9 | 13.5 | 10.9 | 7.4 | 3.0 |

| | V5 | V10 | V20 | V30 | V40 | V50 | V60 | V70 |
|---|---|---|---|---|---|---|---|---|
| Median (%) | 5.6 | 3.5 | 2.0 | 0.9 | 0.2 | 0 | 0 | 0 |

**FIGURE 1** Dosimetric parameters of the lung and heart

**TABLE 2** Summary of toxicities

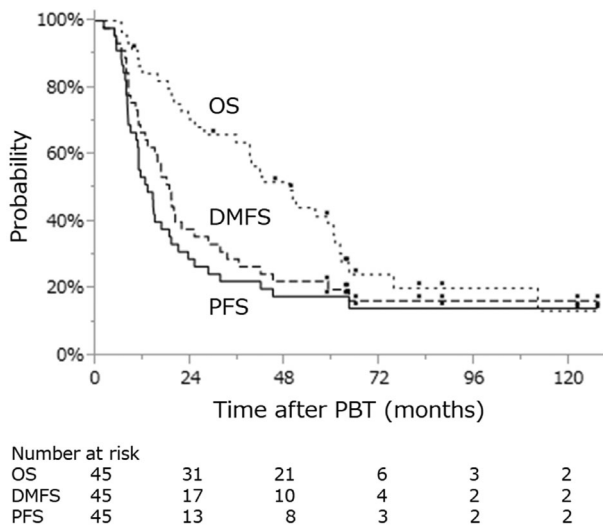| | No. of patients (%) | | | |
|---|---|---|---|---|
| Type of toxicity | Grade 0, 1 | Grade 2 | Grade 3 | Grade 4 |
| Bone marrow | | | | |
|   Decreased white blood cell count | 6 (14.0) | 12 (27.9) | 20 (46.5) | 5 (11.6) |
|   Decreased neutrophil count | 8 (18.5) | 11 (25.6) | 10 (23.3) | 14 (32.6) |
|   Anemia | 26 (60.5) | 12 (27.9) | 5 (11.6) | 0 |
|   Decreased platelet count | 39 (90.7) | 0 | 4 (9.3) | 0 |
| Febrile neutropenia | – | – | 2 (4.7) | – |
| Dermatitis | 25 (55.6) | 16 (35.5) | 4 (8.9) | 0 |
| Esophagitis | 20 (44.4) | 22 (48.9) | 3 (6.7) | 0 |
| Pneumonitis | 36 (80.0) | 5 (11.1) | 4 (8.9) | 0 |

**FIGURE 2** Overall, progression-free, and distant metastasis-free survival curves for all patients. Dotted, straight, and dashed lines indicate overall (OS), progression-free (PFS), and distant metastasis-free survival (DMFS) rates, respectively
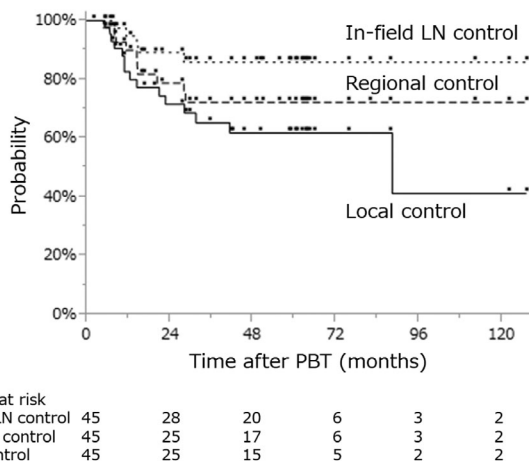


**FIGURE 3** Local control, regional control, and in-field lymph node control curves for all patients. Straight, dashed, and dotted lines indicate local control, regional control, and in-field lymph node control rates, respectively

of 23.8% and 15.1%, respectively, in patients with locally advanced NSCLC treated with CCRT.[14] Control of locoregional disease after CRT remains inadequate. Although the reported rate of locoregional control has varied widely, a study analyzing locoregional control in seven RTOG trials showed a 3-year locoregional control rate of 38%.[15] To improve OS, CRT dose escalation to increase the LC rate would be effective; however, the RTOG 0617 trial, comparing 74 Gy with 60 Gy photons in CRT for stage III NSCLC, revealed an inferior OS in the 74 Gy arm compared to the 60 Gy (standard dose) arm. In a recent report of the long-term results from the RTOG 0617 trial, the 5-year OS rate and median OS in the standard dose arm were 32.1% and 28.7 months, respectively, which were significantly higher than those reported in the abovementioned

meta-analysis.[7,14] Thus, a total dose of 60 Gy in 30 fractions in the CRT setting using photons remains the standard dose fractionation schedule in clinical practice.

PBT has an advantage of reducing the radiation dose and irradiated volume in surrounding normal organs. Because the use of PBT with CRT for stage III NSCLC is relatively recent, within the past decade, there are only a few reports that have analyzed the long-term outcomes of PBT and CCRT in patients with NSCLC (Table 4). Nguyen et al. conducted an observational study of PBT using a total dose ranging from 60 to 74 GyE for locally advanced NSCLC in the CRT setting and reported 5-year OS rates of 25.3% and 31.8% in patients with stage IIIA and IIIB disease, respectively; the median OS of all 113 stage III patients was 30.4 months.[16] Thereafter, the same group evaluated PBT (74 GyE) with CCRT for stage III NSCLC in a phase II study and reported a 5-year OS rate and median OS of 29% and 26.5 months, respectively.[11] In the present study, the 3- and 5-year OS rates were 63.7% and 38.8%, respectively, with a median OS of 49.1 months. Although the proportion of patients with stage IIIB disease was relatively higher in the present study than in that study (67% vs. 53%), our OS was slightly better (Table 4).[11] Our median OS (49.1 months) was also better than that reported in the RTOG 0617 trial and other Japanese studies of CCRT using photons to treat stage III NSCLC (19.8–30.0 months).[17–19]

Elimination of locoregional disease by CCRT leads to improved survival, according to a meta-analysis analyzing the outcomes of CCRT versus sequential CRT for locally advanced NSCLC.[14] This is consistent with our finding that patients achieving in-field disease control had better PFS and OS. Several factors including sex, histology, tumor volume, T stage, disease stage, and radiation dose have been identified as predictive factors for locoregional control and survival.[7,16,20–23] In the present study, T stage and disease stage were significant factors associated with in-field control and PFS, whereas the CTV was not associated with either. The 5-year LC, regional control, and PFS rates for patients with stage IIIA/IIIB-N3 diseases, including supraclavicular lymph nodes metastases, were 70%, 75%, and 24%, respectively. These rates are slightly better than those in RTOG 0617 (the corresponding rates in the standard dose arm were 62%, 65%, and 18%, respectively). Although the impact of dose escalation using PBT on survival is still unclear, patients with stage IIIA/IIIB-N3 disease, compared with other stage III diseases, may benefit from high-dose PBT.

In the RTOG 0617 trial, heart V5 and the highest grades of esophagitis/dysphagia were identified as prognostic factors for OS.[6] One possible reason for the promising OS in the present study may be the reduced dose delivered to, and the irradiated volume of, the surrounding normal tissues such as the heart and lung. Speirs et al. also reported similar findings, in that heart V50 and lung V5 were independently associated with OS in NSCLC patients treated with photon-based CRT.[24] In their study, the 2-year OS rate was significantly higher in patients with a heart V50 <25% compared with ≥25% (45.9% vs. 26.7%, $p < 0.0001$). No patient in the

**T A B L E 3** Univariate analyses of potential factors predicting survival and disease control

| Factor | | *n* | 3-year OS | *p* | 3-year PFS | *p* | 3-year in-field control | *p* |
|---|---|---|---|---|---|---|---|---|
| Sex | Male | 33 | 60.4% | 0.195 | 18.1% | 0.369 | 58.3% | 0.397 |
| | Female | 12 | 73.3% | | 33.3% | | 64.8% | |
| Age | <63 years | 23 | 52.7% | 0.194 | 13.0% | 0.173 | 42.4% | 0.010 |
| | ≥63 years | 22 | 61.8% | | 31.8% | | 83.2% | |
| PS | 0 | 29 | 68.7% | 0.883 | 20.6% | 0.877 | 71.1% | 0.050 |
| | 1 | 16 | 53.5% | | 25.0% | | 39.3% | |
| Histology | SqCC | 12 | 41.6% | 0.227 | 8.3% | 0.432 | 32.9% | 0.090 |
| | Adeno | 25 | 71.0% | | 20.0% | | 65.7% | |
| Primary tumor site | Upper lobe | 29 | 62.0% | 0.433 | 20.7% | 0.676 | 55.7% | 0.325 |
| | Others | 16 | 66.9% | | 25.0% | | 68.8% | |
| T stage | T0–3 | 31 | 73.3% | 0.271 | 21.7% | 0.050 | 69.1% | 0.023 |
| | T4 | 14 | 42.8% | | 14.2% | | 38.3% | |
| N stage | N0–2 | 22 | 54.5% | 0.877 | 22.7% | 0.593 | 53.5% | 0.500 |
| | N3 | 23 | 72.7% | | 21.7% | | 67.2% | |
| Stage | IIIA | 14 | 57.1% | 0.806 | 21.4% | 0.277 | 58.0% | 0.875 |
| | IIIB | 31 | 68.1% | | 22.5% | | 60.9% | |
| Stage | IIIA/IIIB-N3 | 33 | 71.8% | 0.105 | 27.2% | 0.008 | 68.1% | 0.030 |
| | IIIB-T4 | 12 | 41.6% | | 8.3% | | 35.0% | |
| CTV1 | <225 cc | 22 | 63.6% | 0.236 | 27.2% | 0.482 | 60.5% | 0.573 |
| | ≥225 cc | 23 | 63.5% | | 17.3% | | 60.3% | |
| Heart V5 | <6% | 23 | 60.8% | 0.102 | 27.2% | 0.693 | 61.2% | 0.764 |
| | ≥6% | 22 | 66.8% | | 17.3% | | 59.3% | |
| Heart V30 | <1% | 24 | 62.5% | 0.317 | 25.0% | 0.486 | 61.3% | 0.629 |
| | ≥1% | 21 | 65.1% | | 19.0% | | 58.7% | |
| Mean heart dose | <1 GyE | 22 | 63.6% | 0.176 | 26.0% | 0.853 | 62.5% | 0.940 |
| | ≥1 GyE | 23 | 63.7% | | 18.1% | | 57.8% | |
| Lung V5 | <25% | 24 | 70.8% | 0.917 | 25.0% | 0.706 | 57.8% | 0.901 |
| | ≥25% | 21 | 54.6% | | 19.0% | | 63.4% | |
| Lung V20 | <20% | 24 | 58.3% | 0.338 | 20.8% | 0.803 | 54.0% | 0.594 |
| | ≥20% | 21 | 69.8% | | 23.8% | | 67.0% | |
| Mean lung dose | <11 GyE | 23 | 60.8% | 0.758 | 21.7% | 0.717 | 59.6% | 0.816 |
| | ≥11 GyE | 22 | 66.6% | | 22.7% | | 61.0% | |

*Abbreviations*: Adeno, adenocarcinoma; CTV, clinical target volume; OS, overall survival; PFS, progression-free survival; PS, performance status; SqCC, squamous cell carcinoma. V5, V20 and V30, the percentages of the volume receiving a dose of ≥5, ≥20, and ≥30 GyE, respectively.

present study had a heart V50 ≥25%. Furthermore, the DVH parameters of the lung might also affect OS in the present study because the 2-year OS rate in the present study (70.6%) was better than that in patients with a V50 <25% in their study (45.9%). Teoh et al. suggested that intensity-modulated proton therapy can reduce cardiac toxicity by delivering low doses to the heart (mean dose, V5, and V30) compared with volumetric modulated arc photon therapy.[25] No cardiac event or treatment-related death was observed in the present study. Thus, in CRT, protons can simultaneously improve DVH parameters of the heart and lung and might reduce late cardiopulmonary toxicities in patients with NSCLC.

With respect to esophagitis, the RTOG 0617 trial reported a significantly higher rate of grade ≥3 esophagitis or dysphagia in the high dose arm than in the standard dose arm (20.8% vs. 7.3%, $p < 0.0001$).[7] In the present study, the incidence of grade 3 esophagitis was 6.7%, which was similar to the rate in the standard dose arm in the RTOG 0617 trial, and there was no grade ≥2 late toxicities related to the esophagus, such as dysphagia, ulcer, or stenosis. In the present study, the prescribed dose to the positive lymph nodes in the mediastinum and hilum was 66 GyE, rather than 74 GyE and this dose might not increase the incidence of severe esophageal toxicities. Because our 5-year in-field lymph node control rate was 86%, 66 GyE might be a reasonable dose to sterilize metastasized lymph nodes without increasing severe esophageal toxicities.

The standard treatment for unresectable stage III NSCLC has changed to incorporate the anti-PD-L1 antibody

**TABLE 4** The outcomes of concurrent chemoradiotherapy for stage III non-small cell lung cancer

| Author | n | Type of RT | Dose (Gy/GyE) | Chemotherapy regimen | Proportion with stage IIIB | Median OS (months) | OS rate (years) | PFS rate (years) |
|---|---|---|---|---|---|---|---|---|
| Prospective study | | | | | | | | |
| Segawa[15] | 99 | X-ray | 60 | CDDP + DTX | 67% | 26.8 | 60% (2) | NA |
| Yamamoto[16] | 147 | X-ray | 60 | CBDCA + CPT11 | 68% | 19.8 | 17% (5) | NA |
| | 147 | | 60 | CBDCA + PTX | 67% | 22.0 | 19% (5) | NA |
| Bradley[6] | 218 | X-ray | 60 | CBDCA + PTX | 34% | 28.7 | 32% (5) | 18% (5) |
| | 207 | | 74 | CBDCA + PTX | 37% | 20.3 | 23% (5) | 13% (5) |
| Chang[10] | 64 | Proton | 74 | CBDCA + PTX | 53% | 26.5 | 29% (5) | 22% (5) |
| Retrospective study | | | | | | | | |
| Horinouchi[17] | 111 | X-ray | 60 | CDDP + VNR | 54% | 30.0 | 25% (5) | 15% (5) |
| Nguyen[14] | 113 | Proton | 74 (median) | NA | 38% | 30.4 | IIIA 25% (5) | 17% (5) |
| | | | | | | | IIIB 31% (5) | 14% (5) |
| Current | 45 | Proton | 74 | CDDP + VNR (80%) | 68% | 49.1 | 38% (5) | 17% (5) |

*Abbreviations*: CBDCA, carboplatin; CDDP, cisplatin; CPT11, irinotecan; DTX, docetaxel; NA, not available; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel; RT, radiotherapy.

durvalumab as a consolidation therapy after completion of CRT.[26] In the PACIFIC trial, the updated 3-year OS rate and median OS of NSCLC patients treated with durvalumab was 57.0% and not reached, respectively.[27] Recent studies have suggested an important role of the immune system in patients with stage III NSCLC treated with CRT. Jin et al. showed a relationship between a higher radiation dose to the immune system and inferior LC and OS in patients with stage III NSCLC,[28] and their findings were supported by another study.[29] In addition, increases in the neutrophil-to-lymphocyte ratio and lymphopenia after CRT resulted in a worse OS in stage III NSCLC patients[30]; PBT prevented these increases and contributed to better survival in patients with locally advanced lung cancer as well as locally advanced esophageal cancer.[31–33] Thus, the dosimetric properties of PBT that reduce the volumes of the lung and other normal organs irradiated by low to intermediate doses may minimize changes in lymphocytes and immune system and may be a reasonable modality when combined with immune checkpoint inhibitors.

The major limitations of this study were its retrospective nature, small number of patients, and long period of patient accrual. Another limitation was that passive-scattering technique was used in the present study, although spot-scanning irradiation techniques, which can further reduce the irradiated doses at the organs at risk, have become widespread, recently. Therefore, it is anticipated that high-dose PBT combined with concurrent chemotherapy would be delivered more safely in the near future. On the other hand, we have not changed the protocol of PBT, such as the definition of the CTV, beam arrangement, and methods of respiratory-motion management. The findings from a multi-institutional prospective study such as RTOG 1308 are needed to resolve the question of whether PBT can truly improve survival in patients with stage III NSCLC by minimizing the dose to normal organs.

In conclusion, passive-scattering PBT (74 GyE) with chemotherapy showed favorable survival and a low incidence of severe adverse events in patients with stage III NSCLC. Further large multi-institutional prospective PBT studies are required to confirm the advantages of PBT over photon therapy.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.