Dose escalation study of proton beam therapy with concurrent chemotherapy for stage III non-small cell lung cancer

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In stage III non-small cell lung cancer (NSCLC), photon-radiation is used in combination with concurrent chemotherapy with curative intent. (1,2) Ranges of 60–66 Gy have been considered standard doses for thoracic radiotherapy in several stage III non-small cell lung cancer clinical trials. Treatment-related toxicities of concurrent chemoradiation include pneumonitis and esophagitis. Proton beam therapy (PBT) has the advantage of sparing lung tissue from low-dose irradiation. (3) Therefore, there is room for dose escalation using PBT without resulting in severe toxicities, in particular radiation pneumonitis.

At the time of planning of this trial, the results of several prospective phase I and II trials to establish the safety and efficacy of increasing the total radiation dose, in the setting of concurrent chemotherapy and photon radiotherapy, had been reported. (4,5) Each of these trials showed that a maximum radiation dose of 74 Gy, given with concurrent weekly paclitaxel and carboplatin, was safe and resulted in a median overall survival of approximately 24 months. Furthermore, our previous phase I study also demonstrated that proton radiotherapy at a dose of 74 Gy in 37 fractions, combined with cisplatin (CDDP) and S-1, was both safe and therapeutically promising. (6) Therefore, we aimed to establish the recommended dose (RD) of PBT, when combined with concurrent chemotherapy using CDDP and S-1, for stage III NSCLC patients.

The purpose of this study is to determine the recommended dose (RD) of proton beam therapy (PBT) for inoperable stage III non-small cell lung cancer (NSCLC). We tested two prescribed doses of PBT: 66 Gy (relative biological effectiveness [RBE]) in 33 fractions and 74 Gy (RBE) in 37 fractions in arms 1 and 2, respectively. The planning target volume (PTV) included the primary tumor and metastatic lymph nodes with adequate margins. Concurrent chemotherapy included intravenous cisplatin (60 mg/m², day 1) and oral S-1 (80, 100 or 120 mg based on body surface area, days 1–14), repeated as four cycles every 4 weeks. Dose-limiting toxicity (DLT) was defined as grade 3 or severe toxicities related to PBT during days 1–90. Each dose level was performed in three patients, and then escalated to the next level if no DLT occurred. When one patient developed a DLT, three additional patients were enrolled. Overall, nine patients (five men, four women; median age, 72 years) were enrolled, including six in arm 1 and three in arm 2. The median follow-up time was 43 months, and the median progression-free survival was 15 months. In arm 1, grade 3 infection occurred in one of six patients, but no other DLT was reported. Similarly, no DLT occurred in arm 2. However, one patient in arm 2 developed grade 3 esophageal fistula at 9 months after the initiation of PBT. Therefore, we determined that 66 Gy (RBE) is the RD from a clinical viewpoints. (Clinical trial registration no. UMIN000005585)

Patients and Methods

This is a single-institutional, open label, dose escalation phase I trial. All the patients gave written informed consent. Eligible patients were required to have histologically or cytologically proven inoperable stage IIIA or IIIB NSCLC as defined in the TNM Classification of Malignant Tumors (6th edition), no previous chemotherapy or radiation therapy, a performance status of 0–1 on the Eastern Cooperative Oncology Group scale, adequate bone marrow reserves, as well as normal liver and renal function. Patients were excluded if they had malignant pleural or pericardial effusion, supraclavicular lymphnode metastasis, active secondary cancer, or a concomitant serious illness that contraindicated chemoradiation or PBT. For staging, all the patients underwent computed tomography (CT) of the thorax and either CT or magnetic resonance imaging (MRI) of the brain. Fludeoxyglucose (18F)-positron emission tomography was also performed in all patients.

Study design. The clinical protocol and consent form were approved by the institutional review board. The dose escalation of PBT was decided based on consultation with the Independent Efficacy and Safety Evaluation Committee. Two total dose levels were tested in this study. The total doses were 66 Gy in arm 1 as the standard dose and 74 Gy (12% higher) in arm 2 as the elevated dose. The protocol was to treat three
patients at a given dose of PBT and perform follow-up for at least 90 days, and then to escalate to the next level if no dose-limiting toxicities (DLT) occurred. If one patient developed a DLT, then up to three additional patients were treated at the same dose. Dose escalation was stopped if two or more DLT occurred at a given dose level among six patients, and a maximum tolerated dose and RD was determined at the previous dose level. If a dose of 74 Gy (relative biological effectiveness; RBE) did not cause DLT, then the actual maximum tolerated dose was not determined; rather, 74 Gy (RBE) was defined as the RD. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. DLT was defined as PBT-related toxicities occurring within 1–90 days from the start of radiotherapy and included grade 3 non-hematologic toxicity, excluding nausea, vomiting and esophagitis, as well as grade 4 toxicity, excluding neutropenia.

Proton beam therapy. Proton beam therapy was delivered with a variable energy synchrotron. Volumetric CT images at the end of the exhalation phase were obtained for treatment planning using a respiratory gating system. External respiratory signals were obtained by monitoring abdominal wall movement throughout simulation on CT, and carried out at every treatment session. Each patient was positioned in an immobilization device at the treatment position on a flat table.

The primary tumor and clinically positive lymph nodes, seen either on the planning CT (short-axis diameter >1 cm) or pre-treatment positron emission tomography images, constituted the gross tumor volume. The clinical target volume was equal to the gross tumor volume in this study. The total planning target volume (PTV) included the clinical target volume plus a total margin of at least 1.0 cm. Elective nodal irradiation was not conducted in this study. Normalization of the treatment plan covered 95% of the PTV with the prescription dose. PBT started on day 1 of the first cycle of chemotherapy and was delivered once daily for 5 days per week. The total dose of PBT was 66 Gy (RBE) in 33 fractions in arm 1 and 74 Gy (RBE) in 37 fractions in arm 2. The spinal cord dose was limited to below 48 Gy (RBE). The volume of both lungs that received 20 Gy (RBE) or more of PBT was kept below 30% of the total volume of the lungs, and brachial plexus doses were limited to below 66 Gy (RBE). The mean dose to the esophagus and heart were optimally kept below 34 Gy (RBE) and 40 Gy (RBE), respectively. If the treatment volume is larger than the field size limit, PTV is divided into several PTVs with the same prescription dose, together with four cycles of chemotherapy. However, one patient developed grade 3 esophageal fistula 9 months after the initiation of PBT (Fig. 1). Among three patients in arm 2, the maximum esophageal dose of PBT did not exceed 74 Gy (RBE), with the exception of the patient with esophageal fistula, who received a dose of 75.8 Gy (RBE). This patient also experienced recurrence in the primary tumor site, but not in the lymph nodes, and second-line chemotherapy (docetaxel) had started 1 month before the appearance of esophageal fistula. None of the patients experienced grade 2 or severe lung toxicities. The overall toxicities are summarized in Table 2.

To explain our results, we compared the PBT plans with those of 3-Dimensional conformal photon radiotherapy (3DCRT) using the same targets and prescribed doses. For all patients, planning images and targets used in PBT were registered to the Pinnacle treatment planning system (Phillips, Milpitas, CA, USA). 3DCRT plans were typically generated using a five-field technique. Dose–volume histograms were obtained for each plan. All plans were normalized such that 95% of the PTV received the same dose of PBT. The lung and heart doses

### Table 1. Patient characteristics and outcomes

| Number | Age (years) | Sex | PS | T, N | Histology | Dose (Gy, RBE) | Status | OS (months) | PFS (months) | First relapse site |
|--------|-------------|-----|----|-----|-----------|---------------|--------|-------------|--------------|------------------|
| 1      | 72          | M   | 0  | T1N2 | Ad        | 66            | NED    | 49          | 49           | Pleural effusion, brain |
| 2      | 73          | F   | 1  | T2N3 | Ad        | 60            | DOD    | 38          | 9            |                  |
| 3      | 73          | F   | 1  | T4N0 | NOS       | 66            | NED    | 49          | 49           |                  |
| 4      | 74          | M   | 0  | T2N2 | Sq        | 66            | Follow off | 24          | 15           | Primary site     |
| 5      | 65          | M   | 1  | T3N2 | Ad        | 66            | AWD    | 43          | 11           | Adrenal gland   |
| 6      | 72          | F   | 0  | T1N2 | Ad        | 74            | NED    | 35          | 35           | Bone, supraclavicular lymph node |
| 7      | 74          | M   | 1  | T1N2 | Sq        | 74            | AWD    | 37          | 10           | Adrenal gland   |
| 8      | 67          | M   | 1  | T3N2 | Sq        | 74            | AWD    | 12          | 8            | Primary site, kidneys, adrenal gland |

Ad, adenocarcinoma; AWD, alive with disease; DOD, dead on disease; NED, no evidence of disease (recurrence); NOS, no specific; OS, overall survival; PFS, progression-free survival; Sq, squamous cell carcinoma; M, male; F, female; PS, performance status.

Chemotherapy. Treatment in eligible patients began with the administration of two cycles of concurrent chemoradiotherapy and two cycles of consolidation chemotherapy. This consisted of oral administration of S-1 twice daily from day 1 to 14, along with a 60-min intravenous infusion of CDDP (60 mg/m²) on day 1 and, thereafter, at 4-week intervals. The patients received one of three fixed oral doses of S-1 based on their body surface area. The three doses administered were 40 mg (body surface area <1.25 m²), 50 mg (body surface area, 1.25–1.50 m²) and 60 mg (body surface area ≥1.50 m²).
are summarized in Table 3, and the esophageal doses for each patient are listed in Table 4.

**Discussion**

Proton beam therapy has an advantage over other radiation therapies in that the dose drops off and it is, therefore, utilized to reduce the risk to surrounding structures, particularly the low-dose regions in critical structures such as the heart, lungs and esophagus. Indeed, only radiation pneumonitis below grade 2 occurred in this PBT trial. Explanatory analyses revealed that lung V20 is significantly reduced in PBT compared to 3DCRT.

![Fig. 1. Grade 3 esophageal fistula occurring in a patient 9 months after the initiation of PBT. Upper left: (a) CT image at pre-treatment. Upper middle: (b) CT image at 2 months after the initiation of PBT. Upper right: (c) CT image at 9 months after the initiation of PBT. Lower left: (d) PBT dose distribution. Lower middle: (e) Upper GI endoscopy at 9 months after the initiation of PBT. Lower right: (f) Bronchial endoscopy at 9 months after the initiation of PBT. CT, computed tomography; GI, gastrointestinal; PBT, proton beam therapy.](image)

| Table 2. Overall toxicities experienced by patients following therapy |
| --- |
| **Toxicity** | Arm 1 (n = 6) | Arm 2 (n = 3) |
| | G2 | G3 | G2 | G3 |
| Anorexia | 3 | 1 | 1 | 0 |
| Esophagus | 2 | 0 | 1 | 1 |
| Mucositis | 0 | 0 | 1 | 0 |
| Diarrhea | 0 | 1 | 0 | 0 |
| Constipation | 2 | 0 | 1 | 0 |
| Dermatitis | 2 | 0 | 1 | 0 |
| Fatigue | 3 | 0 | 0 | 0 |
| Thromboembolic event | 1 | 0 | 0 | 0 |
| Infection | 1 | 1 | 0 | 0 |

| Table 3. Lung and heart doses for proton and photon radiotherapy |
| --- |
| **Proton (clinical use)** | **Photon** | **P-value** |
| Lung V5 (mean) | 31.1% | 44.3% | <0.01 |
| Lung V20 (mean) | 20.9% | 26.6% | 0.11 |
| MLD | 11.1 Gy(RBE) | 13.9 Gy | 0.06 |
| MHD | 12.0 Gy(RBE) | 16.9 Gy | 0.10 |

Lung V5, relative lung volume irradiated more than 5 Gy; Lung V20, relative lung volume irradiated more than 20 Gy; MLD, mean lung dose; MHD, mean heart dose; RBE, relative biological effectiveness.

| Table 4. Esophageal proton dose (RBE) and volume (cc) |
| --- |
| **Arm** | **Patient#** | **V66** | **V70** | **V74** |
| 1 | 1 | 0.00 | 0.00 | 0.00 |
| 2 | 2 | 8.27 | 3.26 | 0.00 |
| 3 | 3 | 3.95 | 2.41 | 0.00 |
| 4 | 4 | 5.52 | 0.00 | 0.00 |
| 5 | 5 | 0.00 | 0.00 | 0.00 |
| 6 | 6 | 3.11 | 0.00 | 0.00 |
| 7 | 7 | 0.00 | 0.00 | 0.00 |
| 8 | 8 | 0.00 | 0.00 | 0.00 |
| 9 | 9† | 11.38 | 10.02 | 7.81 |

†Patient #9 experienced esophageal fistula. RBE, relative biological effectiveness; V66, V70 and V74, the esophageal volume irradiated more than 66 Gy (RBE), 70 Gy (RBE) and V74 (RBE), respectively.
In general, sparing of normal tissues in the low-to-moderate dose range is superior with proton therapy compared to photon therapy. However, we noted a case with severe esophageal toxicity resulting in a thoraco-esophageal fistula without local recurrence in this lesion. There are several possible explanations for this toxicity. First, the esophageal dose may have been too high to avoid a late toxicity probably because the esophagus was within the PTV of this patient, and was, hence, irradiated more than the prescribed dose. Moreover, an adaptive planning strategy generally improves sparing of the esophagus; however, this was not performed in our study. Thus, the esophagus may be irradiated more than the planning dose.

A second potential reason for the observed toxicity is that combination with concurrent CDDP and S-1 chemotherapy was not feasible with high-dose radiotherapy. A previous phase I study demonstrated that 74 Gy photon radiotherapy, together with CDDP and S-1, was feasible and promising. However, other reports regarding high-dose thoracic radiotherapy adopted carboplatin and paclitaxel chemotherapy. In conclusion, considering these issues, we maintain that PBT at a dose of 66 Gy (RBE) is more appropriate to reduce overall toxicity and improve therapeutic ratios, and identified this as the RD for future clinical trials.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Le Chevalier T, Arrigada R, Quoix E et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in inoperable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst 1991; 83: 417–23.
2 Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995; 311: 899–909.
3 Allen AM, Pawlicki T, Dong L et al. An evidence based review of proton beam therapy: the report of ASTRO’s emerging technology committee. Radiother Oncol 2012; 103: 8–11.
4 Bradley JD, Bae K, Graham MV et al. Primary analysis of the phase II component of a phase II/I dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. J Clin Oncol 2010; 28: 2475–80.
5 Socolski MA, Blackstock AW, Bogatt JA et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol 2008; 26: 2457–63.
6 Harada H, Nishio M, Murakami H et al. Dose-escalation study of three-dimensional conformal thoracic radiotherapy with concurrent S-1 and cisplatin for inoperable stage III non-small-cell lung cancer. Clin Lung Cancer 2013; 14: 440–5.
7 Chang J, Zhang X, Wang X et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in stage I or stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006; 65: 1087–96.
8 Koay EJ, Lege D, Mohan R et al. Adaptive/non-adaptive proton radiation planning and outcome in a phase II trial for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012; 84: 1093–100.
9 Chang J, Komaki R, Lu C et al. Phase II study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III non-small cell lung cancer. Cancer 2011; 117: 4707–13.
10 Bradley JD, Paulus R, Komaki R et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015; 16: 187–99.
11 Culp LR, Pou AM, Jones DV et al. A case of radiation recall mucositis associated with docetaxel. Head Neck 2004; 26: 197–200.