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Preliminary results of proton-beam therapy for stage III non-small-cell lung cancer

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ABSTRACT

Background We conducted a preliminary retrospective evaluation of the efficacy and toxicity of proton-beam therapy (PBT) for stage III non-small-cell lung cancer.

Methods Between January 2009 and August 2013, 27 patients (26 men, 1 woman) with stage III non-small-cell lung cancer underwent PBT. The relative biologic effectiveness value of the proton beam was defined as 1.1. The beam energy and spread-out Bragg peak were fine-tuned such that the 90% isodose volume of the prescribed dose encompassed the planning target volume. Of the 27 patients, 11 underwent neoadjuvant chemotherapy. Cumulative survival curves were calculated using the Kaplan–Meier method. Treatment toxicities were evaluated using version 4 of the *Common Terminology Criteria for Adverse Events*.

Results Median age of the patients was 72 years (range: 57–91 years), and median follow-up was 15.4 months (range: 7.8–36.9 months). Clinical stage was IIIA in 14 patients (52%) and IIIB in 13 (48%). The median dose of PBT was 77 GyE (range: 66–86.4 GyE). The overall survival rate in the cohort was 92.3% at 1 year and 51.1% at 2 years. Locoregional failure occurred in 7 patients, and distant metastasis, in 10. In 2 patients, initial failure was both locoregional and distant. The 1-year and 2-year rates of local control were 68.1% and 36.4% respectively. The 1-year and 2-year rates of progression-free survival were 39.9% and 21.4% respectively. Two patients experienced grade 3 pneumonitis.

Conclusions For patients with stage III non-small-cell lung cancer, PBT can be an effective and safe treatment option.

Key Words Proton-beam therapy, chemotherapy, stage III non-small-cell lung cancer

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INTRODUCTION

The incidence of lung cancer has continued to increase worldwide, and lung cancer remains one of the most common causes of cancer-related death[1]. In Japan specifically, the mortality rate from lung cancer is increasing in men and women alike. Lung cancer accounts for about 20% of all cancer-related deaths, and approximately 70,000 lung cancer-related deaths occurred in a single year[2]. Currently, chemoradiotherapy is recommended as standard treatment for patients with unresectable stage III non-small-cell lung cancer (NSCLC). Concurrent use of regimens including cisplatin and of irradiation to more than 60 Gy is also strongly recommended[3–13]. Clinical outcomes in lung cancer have improved with the introduction of chemoradiotherapy, but prognosis in unresectable stage III NSCLC remains poor, with a median survival duration of only 16–22 months and 5-year overall survival rates of only 15%–20%[3–5,14]. Safe methods for dose escalation in radiotherapy, the development of molecularly targeted drugs, and new anticancer agents are therefore needed to improve clinical outcomes in these patients.

Compared with X-rays, proton beams offer good dose concentration as described by the characteristics of the Bragg peak, and it is possible to increase the dose that reaches the tumour while lowering the dose delivered to the surrounding normal tissue. Advances in proton-beam therapy (PBT), compared with conventional radiotherapy, are therefore expected to decrease toxicity and improve clinical outcomes. At our institute, PBT was originally applied predominantly for the treatment of patients with stage I NSCLC. However, approximately 30% of patients with NSCLC have locally advanced disease with lymph node metastasis, and some of those patients are judged to be

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inoperable because of age or other complicating factors. Therefore, starting in 2009, we also applied PBT in the treatment of patients whose primary tumour and lymph node metastases are in close proximity. In addition, we administer PBT with chemotherapy to any patients in good general condition, because toleration for concurrent chemotherapy and PBT in those patients has recently been reported[15,16].

The purpose of the present study was to make a preliminary retrospective evaluation of the efficacy and toxicity of PBT in treating patients with stage III NSCLC.

METHODS

Patients

Our study enrolled 27 patients with stage III NSCLC. Written informed consent was obtained from all patients after they had received detailed explanations of clinical stage and prognosis, treatment goals, treatment schedule, other treatment options, and adverse events. Between January 2009 and August 2013, all patients underwent PBT with or without chemotherapy at Southern Tohoku Proton Therapy Center. The complete patient evaluation included physical examination, biopsy or cytology (or both) by bronchoscopy, blood count, screening blood chemistry tests, electrocardiography, and respiratory function tests. Clinical TNM staging (International Union Against Cancer, 6th edition) was performed using chest radiographs, computed tomography (CT) imaging of chest and abdomen, and combined positron-emission tomography and CT (PET-CT) imaging. Follow-up was initiated at PBT initiation. Data were collected to the end of July 2014.

Proton-Beam Therapy

In a 3-dimensional planning procedure for treatment, chest CT imaging at 2-mm intervals with respiratory gating was performed in the supine position. The gross tumour volume was defined as the volume of the primary tumour and metastatic lymph nodes determined by CT and PET-CT imaging before treatment. Metastatic lymph nodes were defined as those that were 1 cm or more in size on CT imaging or positive on PET-CT imaging. The clinical target volume was defined as the gross tumour volume plus a 5-mm margin in all directions. The area that had to be treated for lymph node prophylaxis was avoided in all cases. The planning target volume was defined as the clinical target volume plus a 5-mm margin in all directions and an additional 2-mm margin in the craniocaudal direction depending on respiratory movements. The relative biologic effectiveness of the proton beam was set at 1.1[17]. The beam energy and spread-out Bragg peak were fine-tuned so that the 90% isodose volume of the prescribed dose encompassed the planning target volume.

Figure 1 shows the dose distribution with opposing portal irradiation for the primary tumour and regional lymph nodes. Dose constraints were set for the esophagus (≤55 GyE), thoracic spinal cord (≤40 GyE), trachea and bronchus (≤55 GyE) and heart (≤40 GyE). Treatment was administered during end-expiration using respiratory gating. The respiratory gating was controlled by using a laser range finder to monitor the motion of the patient's body surface.

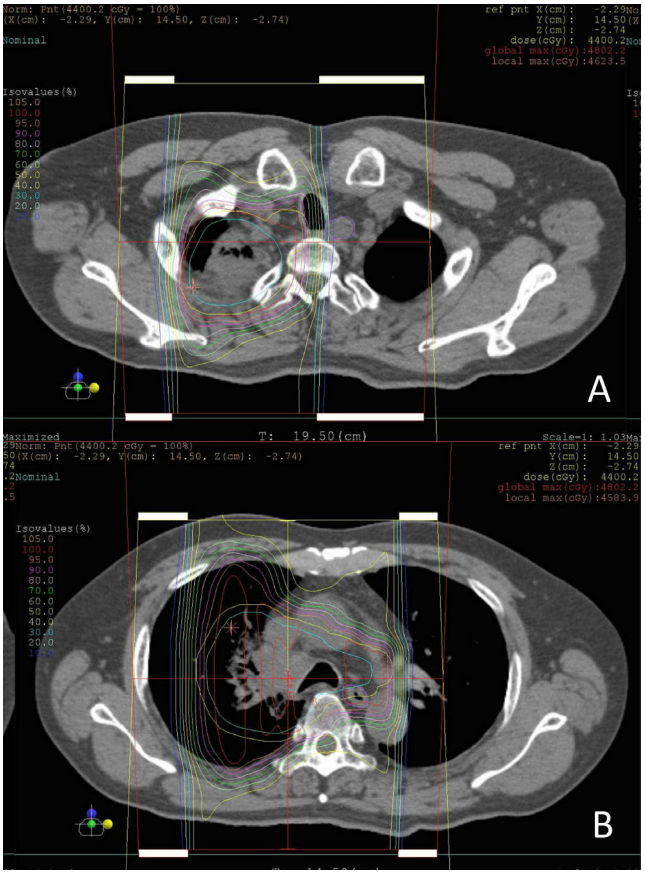

FIGURE 1 Dose distribution for (A) primary tumour and (B) regional lymph nodes, with opposing portal irradiation.

Chemotherapy

Before PBT, 11 patients received neoadjuvant chemotherapy; the anticancer agent used varied. The regimen most commonly administered (7 patients) was a combination of carboplatin and paclitaxel (64%) as an intravenous infusion. Carboplatin was administered at 3–6 AUC (area under the curve), and paclitaxel was administered at 100–200 mg/m^2. Before PBT, all 11 patients underwent 2 cycles of their respective regimens.

Evaluation and Analysis

For our cohort of NSCLC patients, we evaluated overall survival, local control, progression-free survival, and toxicity of PBT. Patients were seen for follow-up every 2–4 months for the first year and every 4–6 months thereafter. At the follow-up examinations, the patients underwent CT or PET-CT imaging, and tumour response was evaluated using the Response Evaluation Criteria in Solid Tumors[18]. The cumulative survival curves were calculated from the first day of PBT by the Kaplan–Meier method, and significant differences in survival were evaluated using the log-rank test. Chi-square tests were used to analyze risk factors for pneumonitis, and averages were compared using t-tests. All analyses were performed using Prism (version 5.0f: GraphPad Software, San Diego, CA, U.S.A.). Grades of treatment toxicity were evaluated using version 4 of the *Common*

Terminology Criteria for Adverse Events. Acute and subacute toxicities were defined as those occurring within 6 months from PBT initiation, and late toxicities were defined as those occurring 6 months after treatment start.

RESULTS

Patient Characteristics

Table I summarizes the characteristics of the study patients. The 26 men and 1 woman who made up the cohort had a median age of 72 years (range: 57–91 years). At the time of analysis, 13 patients were living, and 14 patients had died. Median follow-up was 15.4 months (range: 7.8–36.9 months) for all patients and 14.5 months (range: 7.8–29.9 months) for the surviving patients. Clinical stage was IIIA in 14 patients (52%) and IIIB in 13 patients (48%). Histologically, 15 patients (55%) had squamous cell carcinoma, 10 (37%) had adenocarcinoma, and 1 (4%) had large-cell carcinoma. Histology by either biopsy or cytology could not be determined in 1 patient. Neoadjuvant chemotherapy was given to 11 patients before PBT.

The median dose of PBT in the entire cohort was 77 GyE (range: 66–86.4 GyE). The number of fractions ranged from 25 to 37 (2–3.2 GyE per fraction). The average PBT dose was 76.2 GyE for patients treated with PBT alone and 77.3 GyE for patients treated with chemotherapy and PBT—a difference that was not significant by t-test. The PBT used 2 portals in 16 patients (59%) and 1 portal in 11 (41%).

Survival and Local Control

The overall survival rate for the patients overall was 92.3% at 1 year and 51.1% at 2 years [Figure 2(A)]. The 1-year overall survival rate was 87.5% for patients treated with PBT alone ($n = 16$); it was 100% for the patients who also underwent chemotherapy ($n = 11$). Thus, survival at 1 year was significantly improved with chemotherapy (log-rank $p = 0.025$), but differences in clinical stage (IIIA vs. IIIB) and histology (squamous cell carcinoma vs. adenocarcinoma) had no significant effect on overall survival.

In 12 patients, death was a result of primary disease progression. An additional 2 patients died from infectious pneumonia. The 1-year and 2-year rates of local progression-free survival for the patients overall were 68.1% and 36.4% respectively [Figure 2(B)]. The 1-year local control rate was 62.4% for the patients treated with PBT alone; for patients who also underwent chemotherapy, the rate was 72.7% (nonsignificant difference). Overall survival differed significantly by clinical stage (92.3% for IIIA vs. 38.9% for IIIB, log-rank $p = 0.017$) and histology (90% for adenocarcinoma vs. 56.6% for squamous cell carcinoma, log-rank $p = 0.047$).

Response of the Primary Tumour and Failure Pattern

Of the 27 patients, 8 (29.6%) were maintaining a complete response at last follow-up. The rates of progression-free survival for the patients overall were 39.9% at 1 year and 21.4% at 2 years [Figure 2(C)]. The 1-year rate of progression-free survival was 28.5% for patients treated with PBT alone and 54.5% for patients who also received chemotherapy (nonsignificant difference). The progression-free survival at 1 year differed significantly depending on clinical stage (57.1% for IIIA vs. 20.5% for IIIB, log-rank $p = 0.032$).

Table II lists sites of initial failure. Initial failure was locoregional in 7 patients (26%), and distant in 10 patients (37%). It was both locoregional and distant in 2 patients. The sites of initial distant metastasis were bone in 4 patients, lymph nodes in 2 patients, adrenal gland in 1 patient, lung in 1 patient, and multiple sites in 4 patients. Figure 3 shows images for 1 patient who experienced a remarkable response.

TABLE I Characteristics of the study patients

Characteristic	Value
Patients (*n*)	27
Sex [*n* (%)]	
Men	26 (96)
Women	1 (4)
Age (years)	
Median	72
Range	57–91
Performance status [*n* (%)]	
0	14 (52)
1	13 (48)
Stage [*n* (%)]	
IIIA	14 (52)
IIIB	13 (48)
Pathology [*n* (%)]	
Squamous cell carcinoma	15 (55)
Adenocarcinoma	10 (37)
Large cell carcinoma	1 (4)
Not diagnosed	1 (4)
Radiation dose (GyE)	
Median	77
Range	66–86.4
Combination chemotherapy [*n* (%)]	
Yes	11 (41)
No	16 (59)
Follow-up duration (months)	
Median	15.4
Range	7.8–36.9
Status [*n* (%)]	
Alive	13 (48)
Dead	14 (52)
Failure	
Yes	19 (70)
No	8 (30)

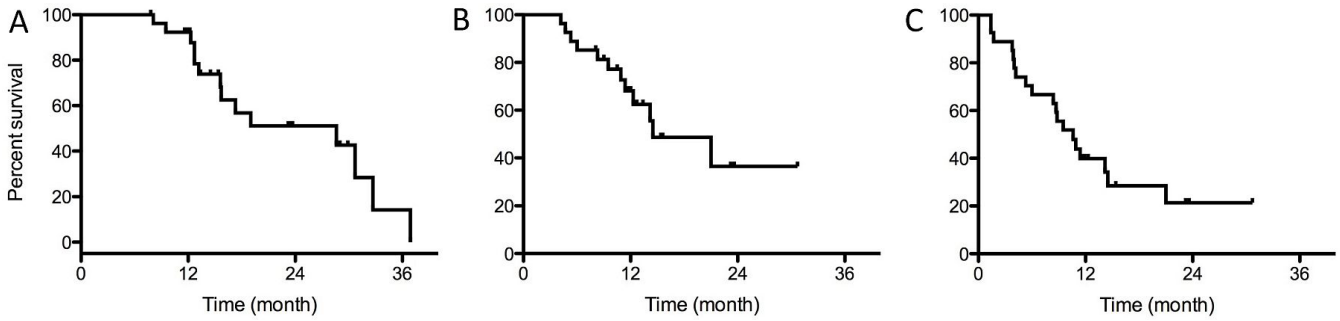

FIGURE 2 (A) Overall survival for all patients with stage III non-small-cell lung cancer ($n = 27$). (B) Local control rate for all patients. (C) Progression-free survival for all patients.

TABLE II Pattern of failure after proton-beam therapy

Sites of initial failure	Patients [*n* (%)]
Locoregional	7 (26)
Locoregional and distant	2 (7)
Distant	10 (37)
Bone	4
Lymph node	2
Adrenal grand	1
Intrapulmonary	1
Multiple lesions	4

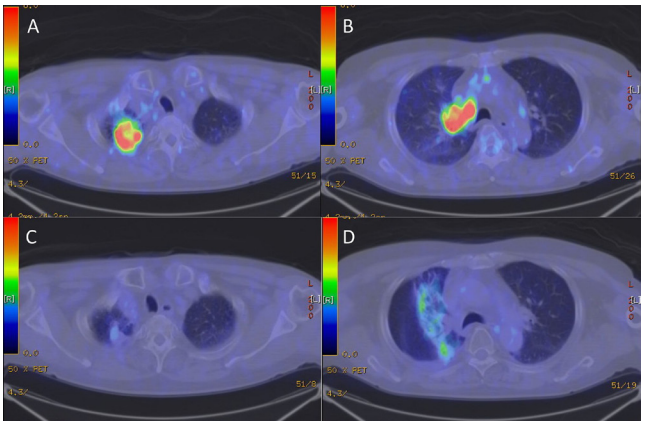

FIGURE 3 Positron-emission tomography–computed tomography images for a 56-year-old man with stage IIIB squamous cell carcinoma. (A,B) The primary tumour (right upper lobe and regional lymph node metastasis) after neoadjuvant chemotherapy and before proton-beam therapy. (C,D) At 6 months after treatment, the primary tumour and regional lymph node metastasis have almost disappeared.

Toxicities

Table III presents data for acute toxicities greater than grade 2 and hematologic toxicities from neoadjuvant chemotherapy. No patient died as a result of treatment toxicity.

Of the 27 patients, 8 (29.6%) developed symptomatic pneumonitis (≥grade 2), with a median time to onset of 2.95 months (range: 1.7–5.6 months). Two patients who underwent neoadjuvant chemotherapy developed grade 3 pneumonitis: one at 5.6 months and the other at 4.5 months after PBT. Those patients were started on steroids, but they eventually required oxygen therapy. Compared with patients treated with PBT alone, those treated with neoadjuvant chemotherapy had a higher incidence of symptomatic pneumonitis: 54.5% (6 of 11) versus 12.5% (2 of 16), $p = 0.018$ by chi-square test. In addition, the total dose of PBT was greater in patients with grade 2 or greater pneumonitis than in those with pneumonitis of less than grade 2 (mean dose: 78 GyE vs. 76 GyE), but the difference was nonsignificant. The most common grade 3 toxicity related to PBT was dermatitis, which was experienced by 3 patients (11%). Grade 2 dermatitis was occurred in 8 patients (29.6%). Grades 3 and 2 acute esophagitis occurred in 1 patient (3.7%) and in 6 patients (22.2%) respectively. Among the patients who underwent neoadjuvant chemotherapy ($n = 11$), 2 (18%) developed grade 4 neutropenia; however, all 11 patients were able to complete 2 cycles of neoadjuvant chemotherapy. No severe late toxicities such as radiation myelopathy, pericarditis, or rib fractures have occurred in any patients as of the last follow-up.

TABLE III Toxicity of therapy

Therapy type	Toxicity	Grade				
		0–1	2	3	4	5
Proton-beam therapy (*n* of 27)						
	Pneumonitis	19	6	2	0	0
	Esophagitis	20	6	1	0	0
	Dermatitis	16	8	3	0	0
Chemotherapy (*n* of 11)						
	Leukocytopenia	8	2	0	0	0
	Neutropenia	7	1	1	2	0
	Thrombocytopenia	10	0	1	0	0

DISCUSSION

At our institution, the 1- and 2-year overall survival rates for our study cohort were 92.3% and 51.1% respectively. In earlier published reports, the 1- and 2-year overall survival

rates in patients with stage III NSCLC undergoing PBT with or without chemotherapy were 65.5%–86% and 39.4%–58.9% respectively[15,16,19–21]. In the present study, the reliability of the 2-year overall survival rate is questionable because of the short median follow-up (15.4 months), but we believe that the results reported here are approximately equivalent to those from previous studies. The overall survival rate was significantly better in patients who underwent chemotherapy than in those who did not, but chemotherapy had no significant effect on the rates of local control and progression-free survival. Because of the retrospective nature of the study, bias in the selection of patients who did and did not undergo chemotherapy was greater than would be seen in a prospective study.

The 1- and 2-year rates of local control in the overall cohort were 68.1% and 36.4% respectively. No significant differences with the use of chemotherapy were observed, but the local control rate was significantly better in cases of adenocarcinoma than in cases of squamous cell carcinoma. We think that this result reflects the bias of histologic type within the clinical stages. Although the difference was nonsignificant, most stage IIIA patients (60%) had adenocarcinoma, and most stage IIIB patients (60%) had squamous cell carcinoma.

The 1- and 2-year rates of progression-free survival in the overall study cohort were 39.9% and 21.4% respectively. A potential explanation for the poor progression-free survival is the high rate of distant metastasis after treatment. However, even in earlier published reports, the 1- and 2-year rates of progression-free survival were only 24.2%–63% and 16.1%–29.2%[15,16,19–21] respectively, and the present results are comparable.

With regard to acute adverse events, 2 patients developed grade 3 radiation pneumonitis. Both had undergone chemotherapy as well as PBT. Thus, the incidence of grade 3 radiation pneumonitis was significantly higher in patients who had undergone chemotherapy than in those who had not. The combination of radiotherapy and chemotherapy is known to have the potential to increase the risk of radiation pneumonitis[22,23]. In addition, 1 study patient who developed grade 3 radiation pneumonitis had severe pre-existing pulmonary emphysema before the development of NSCLC, and the emphysema became a cause of deterioration because of the pneumonitis.

Although the most common grade 3 toxicity was dermatitis, it was treatable with external preparations alone. The 3 patients who developed grade 3 dermatitis were irradiated using 1 portal. Compared with patients irradiated using 2 portals, those irradiated using 1 portal had a higher incidence of grade 2 or greater dermatitis [63.6% (7 of 11) vs. 25% (4 of 16), $p = 0.015$ by chi-square test]. The skin dose in patients who developed grade 3 dermatitis was covered in the 80%–100% isodose volume. Because skin dose is increased in 1-portal irradiation, we suggest that, in future, all irradiation be performed using multiple portals.

Grade 3 acute esophagitis occurred in 1 patient who had subcarinal lymph node metastasis, and the esophageal dose was covered in the 100% isodose volume.

No grade 4 or greater toxicities were observed in this cohort. The results of the study therefore indicate that PBT with or without chemotherapy is a feasible and relatively safe treatment option in stage III NSCLC. As of the last follow-up, no severe late toxicities have occurred in our patients, but further monitoring is required.

The 2-year overall survival rates reported in recent clinical trials involving patients with stage III NSCLC who underwent chemoradiotherapy were 41%–60%[24,25]. Those rates resemble the rates after PBT in the present study, and thus any advantages of PBT are not obvious on a first look. However, many clinical trials exclude elderly patients, and the present study included many elderly patients. The superiority of PBT might therefore be understood to be the equivalent survival rates achieved in a disadvantaged population. Recently, Bradley *et al.*[26] reported that dose escalation lowered the survival rate and that mean heart dose was associated with increased mortality after chemoradiotherapy. Those results suggest that dose escalation in radiotherapy has limits. In comparison, the evidence shows that the dose administered to normal structures is lower in PBT than in radiotherapy[27]. Thus, compared with radiotherapy, PBT could be expected to lessen toxicities and improve clinical results with dose escalation.

Although the follow-up period is short, our preliminary efficacy and toxicity results for PBT in the treatment of stage III NSCLC are satisfactory. Many patients were able to be treated without the need for hospitalization, and life-threatening adverse events did not occur in the present study cohort. There is room for improvement in factors such as the treatment methods and total dose used at our institution. If safety for normal structures is further improved, indications for PBT in elderly patients and in those with complications will expand. Proton-beam therapy is useful for treating stage III NSCLC, and the indications for PBT are expected to increase in aging societies such as Japan's.

CONCLUSIONS

Proton-beam therapy is a reliable and relatively safe treatment option in stage III NSCLC. Treatment-related acute toxicities were manageable in the present study. Although the follow-up period is short, the preliminary results are satisfactory. However, late toxicities remain unclear, and patients should continue to be followed to clarify any such effects.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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