Results of Proton Beam Therapy without Concurrent Chemotherapy for Patients with Unresectable Stage III Non-small Cell Lung Cancer

Yoshiko Oshiro, MD,† Masashi Mizumoto, MD,* Toshiyuki Okumura, MD,* Takayuki Hashimoto, MD,* Nobuyoshi Fukumitsu, MD,* Ayako Ohkawa, MD,* Ayae Kanemoto, MD,* Haruko Hashii, MD,* Toshiki Ohno, MD,* Takeji Sakae, PhD,* Koji Tsuboi, MD,* and Hideyuki Sakurai, MD**

Introduction: This study was performed retrospectively to evaluate the outcome of patients with stage III non-small cell lung cancer (NSCLC) after proton beam therapy (PBT) alone.

Methods: The subjects were 57 patients with histologically confirmed NSCLC (stage IIIA/IIIB: 24/33) who received PBT without concurrent chemotherapy. The cohort included 32 cases of squamous cell carcinoma, 18 adenocarcinoma, and 7 non-small cell carcinoma. Lymph node metastases were N0 7, N1 5, N2 30, and N3 15. Planned total doses ranged from 50 to 84.5 GyE (median, 74 GyE).

Results: Planned treatment was completed in 51 patients (89%). At the time of analysis, 20 patients were alive, and the median follow-up periods were 16.2 months for all patients and 22.2 months for survivors. The median overall survival period was 21.3 months (95% confidence interval: 14.2–28.4 months), and the 1- and 2-year overall survival rates were 65.5% (52.9–78.0%) and 39.4% (25.3–53.5%), respectively. Disease progression occurred in 38 patients, and the 1- and 2-year progression-free survival rates were 36.2% (23.1–49.4%) and 24.9% (12.7–37.2%), respectively. Local recurrence was observed in 13 patients, and the 1- and 2-year local control rates were 79.1% (66.8–91.3%) and 64.1% (47.5–80.7%), respectively. Grade ≥3 lung toxicity was seen in six patients, esophageal toxicity occurred at grade ≤2, and there was no cardiac toxicity.

Conclusion: The prognosis of patients with unresectable stage III NSCLC is poor without chemotherapy. Our data suggest that high-dose PBT is beneficial and tolerable for these patients.

Key Words: Proton, Non-small cell lung cancer, Advanced lung cancer, Radiotherapy.

(*J Thorac Oncol.* 2012;7: 370–375)

*Department of Radiation Oncology, Tsukuba University and †Department of Radiation Oncology, Tsukuba Medical Center Hospital, Ibaraki, Japan.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Yoshiko Oshiro, MD, Department of Radiation Oncology, University of Tsukuba, Tennodai 1-1-1, Tsukuba, Ibaraki 305-8575, Japan. E-mail: ooyoshiko@pmrc.tsukuba.ac.jp

ISSN: 1556-0864/12/0702-0370

Non-small cell lung cancer (NSCLC) is a common cause of cancer death worldwide.[1] Surgery is recommended as the first choice for curative local treatment. However, in most cases, the disease is inoperable at the time of presentation because of metastasis or a locally advanced unresectable tumor. Many trials have shown a clinical benefit of concurrent chemoradiotherapy for the prognosis of patients with locally advanced inoperable disease. However, improvement of prognosis and reduction of side effects remains challenging, and previous clinical trials have often involved younger patients or patients with a good performance status.[2–6]

Treatment for NSCLC has not been established in elderly patients and patients with adverse prognostic factors or comorbidities. Radiotherapy or chemotherapy alone has been used for these patients, but the results of radiotherapy alone with standard doses (60–66 Gy) are extremely poor.[7–9] Proton beam therapy (PBT) gives superior dose localization compared with conventional radiation and is therefore expected to deliver a high dose to the tumor with less toxicity.[10] In our institution, PBT has been used for patients with advanced lung cancer with the goals of reduced toxicity and better local control.[11,12] Herein, we report an analysis of 57 patients with unresectable stage III NSCLC who were treated with PBT without concurrent chemotherapy.

PATIENTS AND METHODS

Patients

This study was conducted in accordance with the ethical standards defined in the Declaration of Helsinki and was approved by the ethics committee of the University of Tsukuba. All patients provided written informed consent after a comprehensive discussion covering the nature of their illness, the therapeutic goal, other therapeutic options, and potential adverse effects.

From 2001 to 2010, 57 patients with stage III NSCLC (stage IIIA/IIIB, 24/33, male/female, 47/10) were treated with PBT (Probeat; Hitachi, Tokyo, Japan) without concurrent chemotherapy. This report is based on data collected up to March 31, 2011. Patient and tumor characteristics are shown in Table 1. The median age of the patients was 72

TABLE 1. Patients and Tumor Characteristics ($n = 57$)

Patients	
Age (yr)	72 (42–85)
Sex	
Male	47
Female	10
Performance status	
0	33
1	20
2	4
Previous chemotherapy	
yes	14
No	43
Tumors	
Stage	
IIIA	24
T2N2M0	19
T3N0M0	1
T3N1M0	1
T3N2M0	3
IIIB	33
T1N3M0	3
T2N3M0	3
T3N3M0	2
T4N0M0	6
T4N1M0	4
T4N2M0	8
T4N3M0	7
Pathology	
Adenocarcinoma	18
Squamous carcinoma	32
Non-small cell carcinoma	7

years (range, 42–85 years), and 33, 20, and 4 patients had an Eastern Cooperative Oncology Group performance status of 0, 1, and 2, respectively. Concurrent chemotherapy was not performed due to old age, comorbidities (interstitial pneumonitis [IP], chronic obstructive pulmonary disease, obstructive pneumonitis, poor cardiac or lung function, cholangitis, diabetes, and dementia), and patient refusal for 23, 18, and 7 patients, respectively. Five of those 45 patients had induction chemotherapy followed by PBT. In addition, nine other patients had induction chemotherapy—in three the plan was to be reconsidered for surgery after a potential response to chemotherapy, and in six the initial tumor was deemed too bulky for radiotherapy. However, there was no response to chemotherapy in any of those patients. The fraction size was 2.0 to 6.6 GyE (median, 2.0 GyE) given once daily, 5 days per week. A fraction size of 6.6 GyE was used for one patient with a T4N0M0 tumor with vertebral body invasion. The planned total doses were 50 to 84.5 GyE (median, 74 GyE), and the median value for the equivalent dose in 2.0 Gy per fraction (assuming $\alpha/\beta = 10$) was 78.3 GyE. The cohort included 32 cases of squamous cell carcinoma, 18 adenocarcinoma, and 7 non-small cell carcinoma. The lymph node metastasis status was N0 7, N1 5, N2 30, and N3 15. Periodic follow-up examinations were performed for 6 months after the completion of PBT. Chest computed tomography (CT) after PBT was taken at least once every 3 months for 2 years, and once every 6 months thereafter. Adverse effects were scored using the Common Terminology Criteria for Adverse Effects, version 3.0.[13]

Proton Therapy

For treatment planning, chest CT images in 5-mm-thick slices were obtained in the treatment position in a body cast (Engineering System Co., Matsumoto, Japan) during the end-expiratory phase using a respiratory-gaited system (Hitachi). The clinical target volume (CTV) encompassed the tumor volume (defined as the primary tumor), clinically positive lymph nodes, and locoregional lymph nodes, plus a margin of 5 to 10 mm in all directions. Prophylactic lymph nodes were not included in the CTV. Clinically positive lymph nodes were defined as nodes $\geq$1 cm visualized on a CT scan or as positron emission tomography (PET)-positive lymph nodes. PET scans were available in 35 patients. The planned target volume covered the CTV with a 5-mm margin in all directions and an additional 5-mm margin in the caudal direction to compensate for respiratory motion.

Treatment was delivered through 200 MeV proton beams during the end-expiratory phase using a respiratory gating system, as described previously.[13–21] The patient's body was immobilized using an individually shaped body cast (ESFORM; Engineering System Co., Matsumoto, Japan). Respiratory gating was controlled using a laser range finder that monitors the movement of the patient's body surface. The photon equivalent dose (Gray equivalent dose; GyE) was defined as the physical dose (Gy) $\times$ the relative biological effectiveness of the proton beam. Based on the biological response of salivary gland tumor cells, the relative biological effectiveness of the proton beam was assigned a value of 1.1. Before each treatment, correct placement of the patient relative to the radiation field was confirmed fluoroscopically. The treatment time was approximately 15 to 20 minutes for each fraction. Patients were routinely examined once a week and the target volume was shrank due to tumor shrinkage once ($n = 32$), twice ($n = 11$), and thrice ($n = 1$) in 44 patients.

Statistical Analysis

Actuarial survival and disease control rates were calculated from the first day of treatment with PBT using the Kaplan-Meier method. Progression-free survival was determined as the period from the beginning of PBT to the date of relapse, as assessed by imaging according to the Response Evaluation Criteria in Solid Tumors, or death. The local control rate was calculated based on the time until the tumor size increased by more than 20%. Differences in survival were evaluated by log-rank test.[22] A p value <0.05 was considered to be statistically significant. All statistical analyses were performed using commercially available software (SPSS Inc., Chicago, IL).

RESULTS

Planned treatment was completed in 51 patients (89%). The prescribed regimen could not be completed due to

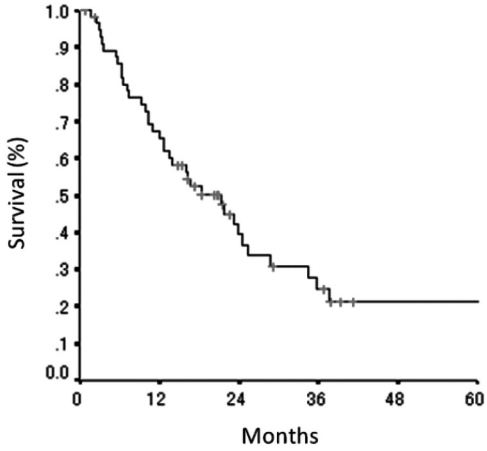

FIGURE 1. Overall survival of all patients treated with proton beam therapy.

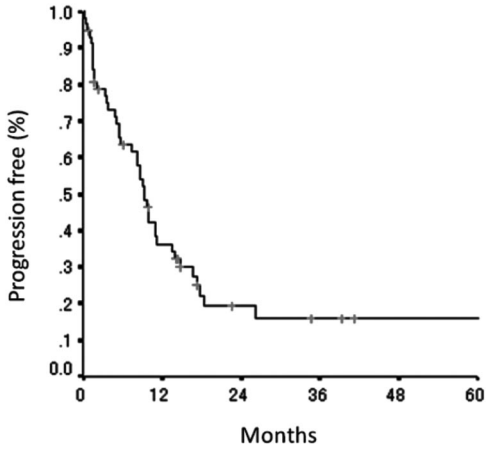

FIGURE 2. Progression-free survival of all patients treated with proton beam therapy.

pneumonitis (three patients), disease progression (two patients), and technical problems (one patient). At the time of analysis, 20 patients were alive, and the median follow-up periods were 16.2 months for all patients and 22.2 months for survivors. The median overall survival period was 21.3 months (95% confidence interval: 14.2–28.4 months), and the overall survival rates at 1 and 2 years were 65.5% (52.9–78.0%) and 39.4% (25.3–53.5%), respectively (Figure 1). Stage (IIIB and IIIA), pathology, and previous chemotherapy had no significant effect on overall survival ($p = 0.53$, 0.14, and 0.78, respectively). However, patients with N0,1 disease had a better outcome than those with N2,3 disease ($p = 0.04$).

Disease progression occurred in 38 patients. The progression-free survival rates at 1 and 2 years were 36.2% (23.1–49.4%) and 24.9% (12.7–37.2%), respectively (Figure 2). Initial relapse sites were as follows: primary tumor or lymph nodes within the field: 7, extrafield regional lymph nodes: 4, primary tumor plus distant metastases: 2, distant metastases only: 17, and intrapulmonary metastases: 8 (Table 2). Local recurrence was observed in 13 patients, and the 1- and 2-year complete local control rates were 79.1% (66.8–91.3%) and 64.1% (47.5–80.7%), respectively (Figure 3).

TABLE 2. Initial Site of Relapse

Sight	No. of Patients
Primary tumor and lymph node within the field	7
Primary tumor + distant metastasis	2
Extra-field regional lymph node	4
Distant metastasis	17
Bone	6
Brain	2
Liver	1
Stomach	1
Multiple (bone, brain, liver, adrenal, muscle, abdominal lymph nodes)	7
Intrapulmonary metastasis	8

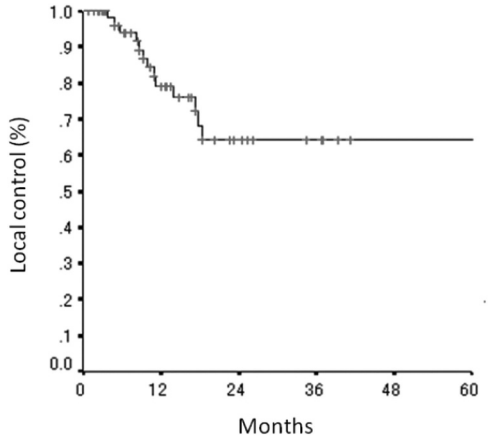

FIGURE 3. Local control for all patients treated with proton beam therapy.

TABLE 3. Early Toxicity ($n = 57$)

	Grade					
	0	1	2	3	4	5
Pneumonitis	49	1	4	1	1	1
Esophagitis	48	8	1	0	0	0
Cough	55	1	1	0	0	0
Dyspnea	57	0	0	0	0	0
Skin	36	16	5	0	0	0

Acute and late toxicities are summarized in Tables 3 and 4, respectively. Acute esophageal toxicity was grade ≤2. Grade ≥3 acute lung toxicity occurred in three patients. The patient with grade 3 pneumonitis was treated effectively with steroid therapy. One patient developed grade 4 pneumonitis during treatment and had to discontinue treatment, and another patient with severe died of pneumonitis during treatment. These two patients had preexisting severe IP before diagnosis of NSCLC and had taken oral steroid for the disease. They were unable to undergo surgery and photon

radiotherapy because of IP. The patients with grade 5 pneumonitis had received chemotherapy, but the disease had progressed. Proton therapy was also challenging for these two patients but was conducted in accordance with their strong wishes. The median percentage of lung volume receiving 20 Gy (V20) and the mean lung dose were 15% and 7.9 GyE, respectively, in all patients. V20s in the grade 4 and grade 5 patients were 10.5 and 20%, respectively, and mean lung dose were 5.8 and 9.1 GyE, respectively, which were not significantly higher than these values in other patients.

Late toxicity could be evaluated in 48 patients. Fibrotic reactions in the treated regions were observed in follow-up CT in every case. There was no cardiac toxicity. Two patients developed grade 3 dyspnea and one case showed grade 5 hemoptysis; however, this patient had undergone repeated biopsy of the irradiated bronchus.

DISCUSSION

Concurrent chemoradiotherapy has become the standard treatment for patients with locally advanced unresectable NSCLC.[2–6] However, some patients cannot tolerate this treatment because of its toxicity. These patients are treated with radiotherapy alone, but their survival is extremely poor.[7–9] van Meerbeeck et al.[23] reported a randomized study comparing surgery versus radiotherapy of 66 Gy in 33 fractions followed by induction chemotherapy in stage IIIA patients and demonstrated that the mean survival time from random assignment was 17.5 months for patients who received radiotherapy. Also, Atagi et al.[24] reported a randomized study comparing concurrent radiotherapy (60 Gy in 30 fractions) versus radiotherapy alone (60 Gy in 30 fractions) for elderly patients (≥71 years) with stage III patients and found that the mean survival time of patients treated by radiotherapy alone was 14.2 months.

Recently, it has been proposed that more aggressive local treatment can improve survival.[6,25,26] Conformal 3D radiotherapy enables delivery of higher doses to the tumor, and favorable survival outcomes have been reported in many dose escalation studies.[6,25,27–31] With 74 Gy conformal radiotherapy for stage III disease, Kong et al.[31] obtained overall survival rates at 2 and 3 years of 50 and 47%, respectively. Yuan et al.[29] also showed favorable results of dose escalation and omission of elective nodal irradiation for inoperable stage III disease, with delivery of 68 to 74 Gy with concurrent chemotherapy giving 1-, 2-, and 5-year survival rates of 69.9, 39.4, and 25.1%. However, dose escalation is limited by the high incidence of pulmonary and esophageal toxicity. The frequency of effects on the esophagitis is influenced by the length of the esophagus receiving 40 to 60 Gy,[30] and irradiation of large volumes and at high doses increases the risk of pulmonary complications. Maguire et al.[32] found grade ≥3 esophagitis and late pulmonary toxicity in 15 and 17% of cases irradiated at 73.6 Gy, and Rosenman et al.[30]

TABLE 4. Late Toxicity (n = 48)

	Grade					
	0	**1**	**2**	**3**	**4**	**5**
Dyspnea	41	2	3	2	0	0
Pneumonitis	44	1	3	0	0	0
Esophagitis	48	0	0	0	0	0
Skin	47	1	0	0	0	0
Hemoptysis	47	0	0	0	0	1

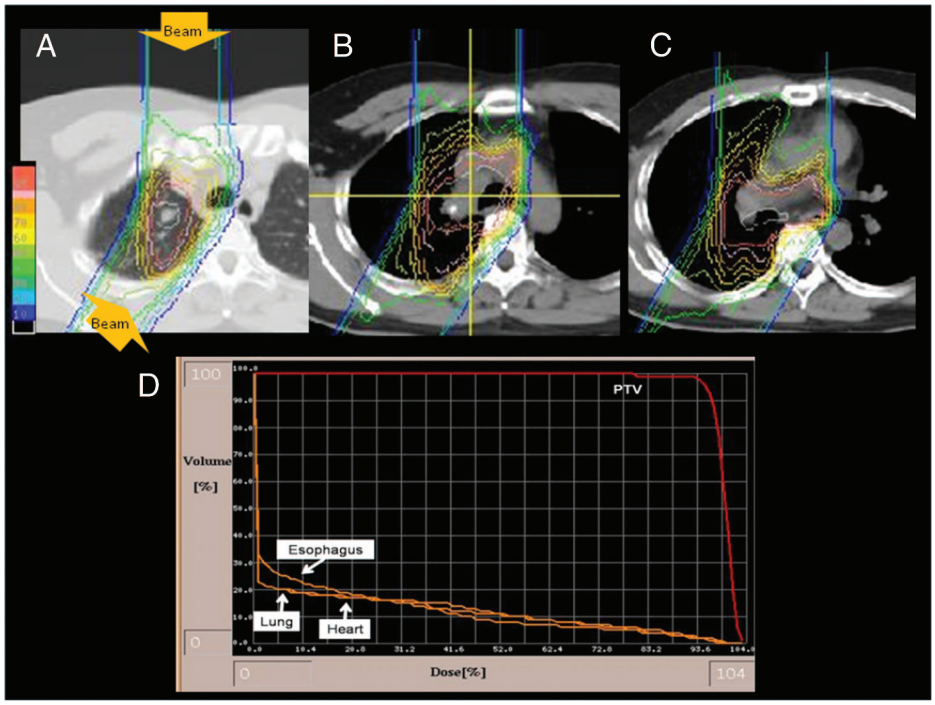

FIGURE 4. Dose distribution (*A*, *B*, *C*) and dose-volume histogram (*D*) of proton beam therapy. *A*, Primary tumor. *B* and *C*, The doses of esophagus, heart, and lung were reduced.

reported that 8% of patients had grade ≥3 esophagitis after irradiation at 66 to 74 Gy.

For most patients in the current study, chemotherapy was not suitable or prior standalone chemotherapy had not been effective. For 14 patients who did not respond to prior chemotherapy, the prognosis was expected to be extremely poor. However, our results for survival were better than those for patients treated with radiotherapy alone or those who responded to induction chemotherapy. Also, cases with severe toxicity were less frequent than in other dose escalation studies. These outcomes may have been due to dose escalation, recent improvement of salvage treatment, and the excellent dose localization of PBT. Figure 4 shows the dose distribution and dose-volume histogram for one patient. Using proton beams allowed the doses to the lung, esophagus, and heart to be reduced.

Chang et al.[33] compared dose-volume histograms in patients with stage III NSCLC treated by photon therapy or PBT and demonstrated that the doses to the normal tissue were lower with PBT, compared with intensity modulated radiotherapy, and that PBT could reduce the doses to the lung, esophagus, and heart. In this study, elective nodal irradiation was omitted, and the 1- and 2-year local control rates were 79.1% (66.8–91.3%) and 64.1% (47.5–80.7%), respectively. The first recurrence at extrafield regional lymph nodes was observed in only four patients (7%). Recent advances in imaging using PET have resulted in more precise detection of lymph node metastases, and therefore we suggest that omission of elective nodal irradiation is reasonable. However, distant metastases is still a problem, and 31 (44.3%) of our patients had initial relapse with intrapulmonary or distant metastases. This emphasizes the difficulty of establishing an effective and less toxic systematic therapeutic approach. However, taking into consideration that the prognosis of patients with unresectable stage III NSCLC who could not be treated with concurrent chemotherapy or who did not respond to induction chemotherapy is expected to be poor, we conclude that our data suggest that high-dose standalone PBT is beneficial and tolerable for these patients.

ACKNOWLEDGMENTS

Supported in part by Grant-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: globocan 2000. *Int J Cancer* 2001;94:153–156.
2. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
3. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2005;23:5910–5917.
4. Jeremic B, Shibamoto Y, Acimovic L, et al. Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. *J Clin Oncol* 1995;13:452–458.
5. Jeremic B, Shibamoto Y, Acimovic L, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. *J Clin Oncol* 1996;14:1065–1070.
6. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524–530.
7. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210–1215.
8. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. *J Clin Oncol* 1999;17:3188–3194.
9. Sause W, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000;117:358–364.
10. Auberger T, Seydl K, Futschek T, et al. Photons or protons: precision radiotherapy of lung cancer. *Strahlenther Onkol* 2007;183 Spec No 2:3–6.
11. Nakayama H, Satoh H, Sugahara S, et al. Proton beam therapy of stage II and III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81:979–984.
12. Kagei K, Tokuuye K, Sugahara S, et al. [Initial experience of proton beam therapy at the new facility of the University of Tsukuba]. *Nippon Igaku Hoshasen Gakkai Zasshi* 2004;64:225–230.
13. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for aged patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2007;69:805–812.
14. Hata M, Tokuuye K, Kagei K, et al. Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. *Int J Radiat Oncol Biol Phys* 2007;68:786–793.
15. Fukumitsu N, Sugahara S, Nakayama H, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2009;74:831–836.
16. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. *Cancer* 2006;107:591–598.
17. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. *Cancer* 2005;104:794–801.
18. Mizumoto M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with inferior vena cava tumor thrombus: report of three cases. *Jpn J Clin Oncol* 2007;37:459–462.
19. Mizumoto M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma adjacent to the porta hepatis. *Int J Radiat Oncol Biol Phys* 2008;71:462–467.
20. Sugahara S, Nakayama H, Fukuda K, et al. Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis. *Strahlenther Onkol* 2009;185:782–788.
21. Sugahara S, Oshiro Y, Nakayama H, et al. Proton beam therapy for large hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2010;76:460–466.
22. Altman DG. Practical Statistics for Medical Research, 2nd Ed. London: Chapman and Hall, 2004.
23. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442–450.
24. Atagi S, Kawahara M, Tamura T, et al. Standard thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced non-small cell lung cancer: a phase III trial of the Japan Clinical Oncology Group (JCOG9812). *Jpn J Clin Oncol* 2005;35:195–201.
25. Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol* 1999;52:137–148.
26. Saunders MI, Bennett MH, Dische S, et al. Primary tumor control after radiotherapy for carcinoma of the bronchus. *Int J Radiat Oncol Biol Phys* 1984;10:499–501.
27. Martel MK, Ten Haken RK, Hazuka MB, et al. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. *Lung Cancer* 1999;24:31–37.

28. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991;83:417–423.
29. Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol* 2007;30:239–244.
30. Rosenman JG, Halle JS, Socinski MA, et al. High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002;54:348–356.
31. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005; 63:324–333.
32. Maguire PD, Marks LB, Sibley GS, et al. 73.6 Gy and beyond: hyperfractionated, accelerated radiotherapy for non-small-cell lung cancer. *J Clin Oncol* 2001;19:705–711.
33. Chang JY, 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;65:1087–1096.

