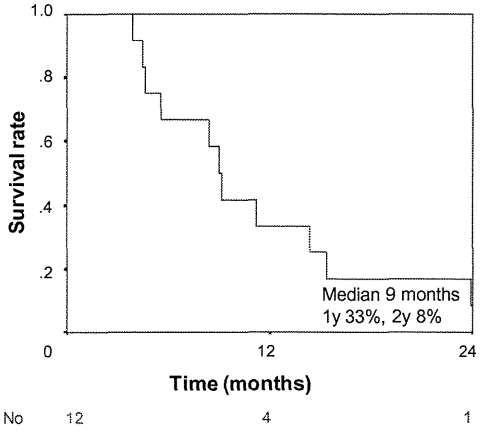


Fig. 5. Kaplan–Meier estimates of overall survival in patients who died due to liver failure without tumor recurrence.

hepatic insufficiency (PHI) [20]. In the current study, ICG R15 was also found to be a prognostic factor in all patients and in those with Child A liver function. Multivariate analysis also showed that a low ICG R15 was associated with good survival in all patients and in Child A cases. PBT may be conducted for Child C cases [27], but most patients who receive PBT have Child A liver function. [26]. In the current study, 78% of the cases were Child A. However, some patients had a high ICG R15 despite being in the Child A category, and ICG R15 significantly affected prognosis in these patients. These results indicate that ICG R15 is an important predictor of prognosis after PBT.

The risk of PHI was difficult to evaluate because PHI rarely occurs even with poor liver function of Child B or C [27,33]. In the current study, however, the risk of liver failure was low in cases with pretreatment ICG R15 $\leqslant$39%, whereas there was an increased risk of death due to liver failure without tumor recurrence after PBT (7 of 28 patients) for cases with pretreatment ICG R15 $\geqslant$40%. Five of 7 patients who died due to hepatic failure with a high ICG R15 had a poor Child-Pugh class (B/C), but 2 were Child-Pugh class A. All patients with Child-Pugh class B/C who died due to hepatic failure ($n = 6$) had a high ICG R15 (33–76, median 45). That is, patients with a high ICG R15 should be monitored especially carefully, even if they have Child-Pugh class A liver function.

Makuuchi et al. [40–42] developed criteria for hepatectomy using ICG R15, in which ICG R15 <10% is an indication for trisegmentectomy, 10–19% indicates left lobectomy or right monosegmentectomy, 20–29% indicates subsegmentectomy, 30–39% indicates limited resection, and $\geqslant$40 indicate that only enucleation can be performed. Using these criteria, hepatic resection can be performed safely with almost zero mortality. Hemming et al. showed that ICG R15 was useful for prediction of the risk of liver failure and mortality after surgery [43]. In an analysis of 101 patients who underwent major hepatic resection, Fan et al. [44] found a mortality rate of 13.8% and defined an ICG R15 of 14% as a cut-off in short-term analysis. Lau et al. suggested that ICG R15 was the only test that discriminated between survivors and non-survivors [45], with cut-offs of 14% and 23% for major hepatectomy and minor hepatectomy, respectively. In our hospital, PBT is used to irradiate the area of the tumor plus a 10-mm margin. Normal liver affected by PBT is basically limited to within the irradiated area and damage caused by PBT is probably similar to that caused by limited resection.

Using Makuuchi's criteria, only enucleation can be performed for such patients. With a minimum treatment margin, PBT may be similar to enucleation. However, the risk of liver failure is increased when ICG R15 is higher and the median survival time of patients with ICG R15 $\geqslant$40% was only 16 months. This is a poor prognosis compared to that of patients with normal liver function, but it should be noted that the prognosis of patients who cannot receive any treatment is only a few months [46,47]. Cabibbo et al. found that the median survival times of untreated HCC in Child-Pugh A, B and C cases were 9.8, 6.1, and 3.7 months, respectively. Therefore, the results in this study suggest that PBT for patients with high ICG R15 is acceptable. However, the median survival time of patients who died of liver failure without tumor recurrence was 9 months (median 8–10). This suggests that the treatment period is excessive in such cases and shorter-term treatment may be necessary in these cases. Thus, a further study is required to clarify the significance of ICG R15.

In conclusion, our results suggest that a high ICG R15 predicts a poor prognosis and a higher risk of PHI, even in Child A cases. Pretreatment ICG R15 is an important predictive factor for outcome after PBT for HCC, especially in cases with Child-Pugh A liver function.

Conflict of interest

None.

Acknowledgments

This work was supported in part by Grants-in-Aid for Scientific Research (B) (24390286); Young Scientists (B) (25861064); and Scientific Research (C) (24591832) from the Ministry of Education, Science, Sports and Culture of Japan.

References

[1] Nagao Y, Fukuizumi K, Kumashiro R, et al. The prognosis for life in an HCV hyperendemic area. Gastroenterology 2003;125:628–9.
[2] Nagao Y, Tanaka K, Kobayashi K, et al. A cohort study of chronic liver disease in an HCV hyperendemic area of Japan: a prospective analysis for 12 years. Int J Mol Med 2004;13:257–65.
[3] Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243:321–8.
[4] Cucchetti A, Piscaglia F, Cescon M, et al. Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. World J Gastroenterol 2013;19:4106–18.
[5] Oeda S, Mizuta T, Isoda H, et al. Survival advantage of radiofrequency ablation for hepatocellular carcinoma: comparison with ethanol injection. Hepatogastroenterology 2013;60:1399–404.
[6] Kudo M. Radiofrequency ablation for hepatocellular carcinoma: updated review in 2010. Oncology 2010;78:113–24.
[7] Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–403.
[8] Cillo U, Vitale A, Bassanello M, et al. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. Ann Surg 2004;239:150–9.
[9] Yoo HY, Patt CH, Geschwind JF, et al. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. J Clin Oncol 2003;21:4329–35.
[10] Shibata T, Isoda H, Hirokawa Y, et al. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? Radiology 2009;252:905–13.
[11] Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006;131:461–9.
[12] Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
[13] Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–90.
[14] Phillips R, Murikami K. Preliminary neoplasms of the liver. Results of radiation therapy. Cancer 1960;13:714–20.

[15] Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e447–53.
[16] Yoon SM, Lim YS, Won HJ, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. Int J Radiat Oncol Biol Phys 2012;82:2004–11.
[17] Shirai S, Sato M, Suwa K, et al. Feasibility and efficacy of single photon emission computed tomography-based three-dimensional conformal radiotherapy for hepatocellular carcinoma 8 cm or more with portal vein tumor thrombus in combination with transcatheter arterial chemoembolization. Int J Radiat Oncol Biol Phys 2010;76:1037–44.
[18] Culleton S, Jiang H, Haddad CR, et al. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. Radiother Oncol 2014;111:412–7.
[19] Takeda A, Oku Y, Sanuki N, et al. Dose volume histogram analysis of focal liver reaction in follow-up multiphasic CT following stereotactic body radiotherapy for small hepatocellular carcinoma. Radiother Oncol 2012;104:374–8.
[20] Kawashima M, Furuse J, Nishio T, et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol 2005;23:1839–46.
[21] Chiba T, Tokuuye K, Matsuzaki Y, et al. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. Clin Cancer Res 2005;11:3799–805.
[22] Dionisi F, Widesott L, Lorentini S, et al. Is there a role for proton therapy in the treatment of hepatocellular carcinoma? A systematic review. Radiother Oncol 2014;111:1–10.
[23] 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.
[24] Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for hepatocellular carcinoma: the University of Tsukuba experience. Cancer 2009;115:5499–506.
[25] 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;74:831–6.
[26] Mizumoto M, Okumura T, Hashimoto T, et al. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. Int J Radiat Oncol Biol Phys 2011;81:1039–45.
[27] Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. Cancer 2006;107:591–8.
[28] 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;37:459–62.
[29] 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;71:462–7.
[30] Sugahara S, Nakayama H, Fukuda K, et al. Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis. Strahlenther Onkol 2009;185:782–8.
[31] Sugahara S, Oshiro Y, Nakayama H, et al. Proton beam therapy for large hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2010;76:460–6.
[32] Stenmark MH, Cao Y, Wang H, et al. Estimating functional liver reserve following hepatic irradiation: adaptive normal tissue response models. Radiother Oncol 2014;111:418–23.
[33] Mizumoto M, Okumura T, Hashimoto T, et al. Evaluation of liver function after proton beam therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2012;82:e529–35.
[34] Tsujii H, Tsuji H, Inada T, et al. Clinical results of fractionated proton therapy. Int J Radiat Oncol Biol Phys 1993;25:49–60.
[35] Ohara K, Okumura T, Akisada M, et al. Irradiation synchronized with respiration gate. Int J Radiat Oncol Biol Phys 1989;17:853–7.
[36] Tsunashima Y, Sakae T, Shioyama Y, et al. Correlation between the respiratory waveform measured using a respiratory sensor and 3D tumor motion in gated radiotherapy. Int J Radiat Oncol Biol Phys 2004;60:951–8.
[37] Paganetti H, Niemierko A, Ancukiewicz M, et al. Relative biological effectiveness (RBE) values for proton beam therapy. Int J Radiat Oncol Biol Phys 2002;53:407–21.
[38] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
[39] National Cancer Institute. National Cancer Institute Common Toxicity Criteria. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications /docs/ctcaev3.pdf; 2014 [accessed March 2014].
[40] Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298–304.
[41] Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. Hepatol Res 2009;39:107–16.
[42] Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198–206.
[43] Hemming AW, Scudamore CH, Shackleton CR, et al. Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. Am J Surg 1992;163:515–8.
[44] Fan ST, Lai EC, Lo CM, et al. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. Arch Surg 1995;130:198–203.
[45] Lau H, Man K, Fan ST, et al. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg 1997;84:1255–9.
[46] Yeung YP, Lo CM, Liu CL, et al. Natural history of untreated nonsurgical hepatocellular carcinoma. Am J Gastroenterol 2005;100:1995–2004.
[47] Cabibbo G, Maida M, Genco C, et al. Natural history of untreatable hepatocellular carcinoma: a retrospective cohort study. World J Hepatol 2012;4:256–61.

Outcomes and Prognostic Factors for Recurrence After High-Dose Proton Beam Therapy for Centrally and Peripherally Located Stage I Non–Small-Cell Lung Cancer

Ayae Kanemoto,[1] Toshiyuki Okumura,[1] Hitoshi Ishikawa,[1] Masashi Mizumoto,[1] Yoshiko Oshiro,[1] Koichi Kurishima,[2] Shinsuke Homma,[2] Takayuki Hashimoto,[1] Ayako Ohkawa,[1] Haruko Numajiri,[1] Toshiki Ohno,[1] Takashi Moritake,[1] Koji Tsuboi,[1] Takeji Sakae,[1] Hideyuki Sakurai[1]

Abstract

This study was conducted to determine disease control rates and prognostic factors after high-dose proton beam therapy (PBT) for centrally and peripherally located stage I non–small-cell lung cancer (NSCLC). Eighty tumors were treated. The 3-year overall survival and local control rate were 76.7% and 81.8%. Radiation dose was shown to be the more significant prognostic factor for tumor control than tumor diameter and others.

Introduction: This study was conducted to determine disease control rates and prognostic factors associated with recurrence of centrally and peripherally located stage I NSCLC treated using high-dose PBT. **Patients and Methods:** Seventy-four patients with 80 centrally or peripherally located stage I NSCLCs were treated with PBT. A protocol using 72.6 Gy (RBE) in 22 fractions was used for centrally located tumors, and 66 Gy (RBE) in 10 or 12 fractions was used for peripherally located tumors. Data were collected and control rates and prognostic factors for recurrence were evaluated retrospectively. **Results:** The median follow-up period was 31.0 months. The overall survival, disease-specific survival, and progression-free survival rates were 76.7%, 83.0%, and 58.6% at 3 years, respectively. Disease recurrence was noted in 30 patients and local recurrence of 11 tumors occurred. The 3-year local control rate was 86.2% for stage IA tumors and 67.0% for stage IB tumors. Radiation dose was identified as a significant prognostic factor for disease recurrence and local recurrence. Tumor diameter and age were only significantly associated with disease recurrence. The 3-year local control rate was 63.9% for centrally located tumors irradiated with 72.6 Gy (RBE) and 88.4% for peripherally located tumors irradiated with 66 Gy (RBE). **Conclusion:** Radiation dose was shown to be the most significant prognostic factor for tumor control in stage I NSCLC treated using high-dose PBT. Tumor diameter was not significant for local control. Further evaluation of PBT for centrally located tumors is warranted.

Clinical Lung Cancer, Vol. 15, No. 2, e7-12
Keywords: Outcome, Prognostic factor for tumor control, Proton beam therapy, Stage I lung cancer, Radiation dose

[1]Proton Medical Research Center and Department of Radiation Oncology, University of Tsukuba, Tsukuba, Ibaraki, Japan
[2]Department of Respiratory Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan

Submitted: Sep 5, 2013; Revised: Oct 15, 2013; Accepted: Nov 8, 2013; Epub: Nov 13, 2013

Address for correspondence: Ayae Kanemoto, MD, Proton Medical Research Center and Department of Radiation Oncology, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan
Fax: +81-29-853-7102; e-mail contact: ayaek@pmrc.tsukuba.ac.jp

Introduction

For stage I non–small-cell lung cancer (NSCLC), surgical resection is typically performed, yielding a 60% to 80% survival rate.[1] Stereotactic body radiotherapy (SBRT) has previously been used for patients with medically inoperable stage I NSCLC and more recently for operable tumors. For stage I NSCLC patients treated with SBRT consisting of photons and protons, the 3-year overall survival (OS) rate was reported to be 57% to 86%[2-7] and the 3-year local control rate was reported to be 74% to 95%.[2,4-6,8,9]

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2013.11.002

Treatment outcomes for SBRT have been reported to not differ between tumors that are diagnosed pathologically and those diagnosed solely based on clinically data,[10,11] and this procedure has been shown to be a safe and radical treatment for operable stage I NSCLC.[12,13]

In addition to peripherally located tumors, use of SBRT has also recently been reported for centrally located tumors.[14,15] However, the protocol for performing SBRT for centrally located tumors remains controversial. High-dose proton beam therapy (PBT) has been used to treat peripherally and centrally located tumors in our hospital. The purpose of this study was to determine the disease control rate and prognostic factors associated with recurrence of centrally and peripherally located stage I NSCLC treated using high-dose PBT.

Patients and Methods

Patients and Tumor Characteristics

From February 1997 to September 2011, 74 patients with stage I NSCLC received PBT at our hospital and were followed for at least 6 months after PBT until August 2012. These patients were evaluated retrospectively. The median age at the time of treatment was 75 years (range, 51-86 years). Patients fell into the following Eastern Cooperative Oncology Group performance status (PS) groups: PS = 0 (n = 44), PS = 1 (n = 21), PS = 2 (n = 8), and PS = 3 (n =1). Sixteen patients (21.6%) had cardiovascular disease, 33 (44.6%) had respiratory disease, and 32 (43.2%) had other cancers.

Of these patients, 80 centrally or peripherally located stage I NSCLCs, based on the tumor, node, metastases (TNM) classification defined by the 7th International Union Against Cancer, were identified and treated. Overall, 68 patients (92%) had a single tumor, and 6 (8%) had 2 tumor masses. Sixty-four tumors (80%) were histologically confirmed, and the remaining 16 (20%) were diagnosed using tumor markers, computed tomography (CT), and positron emission tomography (PET). Centrally located tumors were defined as tumors irradiated in parts of the mediastinum or located more central than the lobar bronchus, which definition did not absolutely equal T2a criteria. Overall, 21 tumors (26%) were centrally located and 59 (74%) were peripherally located. The median tumor diameter was 22 mm (range, 10-48 mm). Characteristics of these 80 tumors are summarized in Table 1.

Table 1 Tumor Characteristics

Characteristic	Value
Total Number of Tumors	80
Clinical Stage	
Stage IA	59 (74%)
Stage IB	21 (26%)
Histology	
Adenocarcinoma	32 (40%)
Squamous cell carcinoma	26 (33%)
Non–small-cell carcinoma	6 (8%)
Unproven	16 (20%)
Tumor Location	
Centrally located tumor	21 (26%)
Peripherally located tumor	59 (74%)
Tumor Site	
S1-3 and S6	51 (64%)
S4-5 and S7-10	29 (36%)

Abbreviation: S = lung segment.

Proton Beam Therapy

At our hospital, the following 2 treatment protocols are commonly used, depending on tumor location: 72.6 Gy (RBE) in 22 fractions and 66 Gy (RBE) in 10 or 12 fractions.[2,16] The 72.6 Gy (RBE) protocol was used for centrally located tumors, and the 66 Gy (RBE) protocol was used for peripherally located tumors. The photon equivalent dose was defined as the physical dose (Gy) × the relative biological effectiveness (RBE) of the proton beam, which was assigned a value of 1.1 in this study.[17] The biologically effective dose (BED) of 72.6 Gy (RBE) in 22 fractions calculated with an α/β ratio of 10 Gy was 97 Gy_{10} (RBE), and the dose of 66 Gy (RBE) in 10 or 12 fractions was 110 Gy_{10} (RBE) or 102 Gy_{10} (RBE).

The clinical target volume (CTV) encompassed the gross tumor volume with a 5- to 8-mm margin in all directions.[2,16] An additional 5-mm margin was included in the caudal axes to compensate for uncertainty due to respiration-induced organ motion. Two or 3 beams were used, and an additional margin of 5 to 10 mm was added to cover the entire CTV by enlarging the multileaf collimator and adjusting the range shifter. Proton beams of 155 to 250 MeV were generated using a synchrotron accelerator, and were delivered during the expiratory phase under a respiration-gated system.[18]

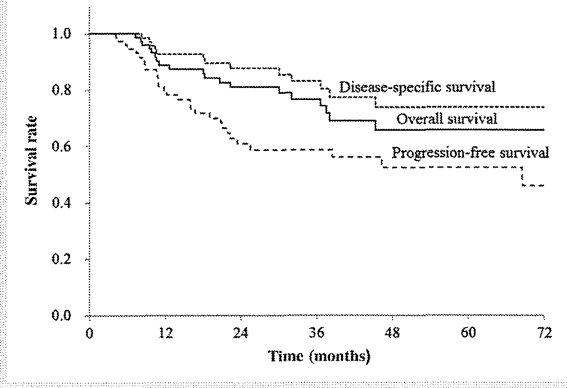
Follow-up and Evaluations

Follow-up examinations, including measurement of tumor marker levels and imaging, were performed periodically at intervals of 3 to 6 months. Acute and late treatment-related complications were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (v.4.0) and the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme. Recurrence, survival, and general condition of patients after PBT were also evaluated. Recurrences were holistically identified according to detection of clinical changes in levels of tumor markers and imaging results such as CT and PET.[19]

Statistical Analysis

Data were collected and analyzed retrospectively. Survival and local control rates were estimated using the Kaplan-Meier method. To analyze prognostic factors for recurrence, Cox regression analysis was used to evaluate difference in age at time of treatment, sex (men vs. women), PS (0-1 vs. 2-4), cardiovascular disease, respiratory disease, T factor (T1 vs. T2a), histology, tumor diameter, lung segment of tumor site (lung segment 1-3 and segment 6 vs. segment 4-5 and segment 7-10), and tumor location (centrally vs. peripherally located tumors) which is same meaning of radiation dose difference (72.6 Gy [RBE] vs. 66 Gy [RBE]). Data analysis was performed using the Ekuseru-Toukei software package (version 2010; Social Survey Research Information Co, Ltd); values of $P < .05$ were considered significant.

Figure 1 Overall Survival Rate, Disease-Specific Survival Rate, and Progression-Free Survival Rate After Proton Beam Therapy. Fifty-Five Patients Were Alive and 19 had Died. Recurrence Developed in 30 Patients. The Overall Survival Rate was 76.7% at 3 Years and 65.8% at 5 Years. The Disease-Specific Survival Rate was 83.0% at 3 Years and 73.8% at 5 Years. Median Follow-up for Overall Survival and Disease-Specific Survival was 31.0 Months (Range, 7.3-104.3 Months). The Progression-Free Survival Rate was 58.6% at 3 Years and 52.5% at 5 Years; Median Follow-up was 21.7 Months (Range, 4.2-99.0 Months)



Results

Survival and Recurrence

At the last follow-up, 55 patients (74%) were alive and 19 (24%) had died. The median follow-up period was 31.0 months (range, 7.3-104.3 months). The OS rate was 76.7% at 3 years and 65.8% at 5 years (Fig. 1). The disease-specific survival rate was 83.0% at 3 years and 73.8% at 5 years. The progression-free survival (PFS) rate was 58.6% at 3 years and 52.5% at 5 years. During the follow-up period, 30 of 74 patients (40.5%) experienced disease recurrence. Sites of recurrence included local (n = 11), regional lymph nodes (n = 16), lungs (n = 6), and other (n = 15).

Tumor and patient characteristics were compared between tumors with and without disease recurrence. The univariate analysis showed that age, tumor diameter, and radiation dose were significant prognostic factors for disease recurrence (Table 2). The multivariate analysis was performed among these 3 factors. The most significant factor was radiation dose ($P = .014$) and the next was age ($P = .039$), although the tumor diameter did not show significant correlation ($P = .20$).

Local Control Rate and Risk Factors

Local recurrence developed in 11 of 80 tumors (13.8%). The local control rate was each 81.8% at 3 and 5 years (Fig. 2). The 3-year local control rate was 86.2% for stage IA tumors and 67.0% for stage IB tumors. Acute treatment-related Grade 2 complications included 2 cases (2.5%) of skin reaction and 1 case (1.3%) of esophagitis, and grade 3 complications included 1 case (1.3%) of pneumonitis. The RTOG/EORTC late radiation morbidity scoring Grade 3 complications included 1 case (1.3%) of pneumonitis and 1 case (1.3%) of skin ulcer; the skin ulcer occurred in an area that was irradiated twice because of a local recurrence and a regional lymph node recurrence. The only Grade 4 complication was rib fracture, which occurred in 11 (13.8%) patients. The patients had no severe pain.

Tumor and patient characteristics were compared between tumors with and without local recurrence (Table 2). The analysis showed that only radiation dose was a significant prognostic factor for local recurrence ($P = .026$). The local control rates for tumors irradiated at each radiation dose are shown in Figure 3. The 3-year local control rate was 63.9% for centrally located tumors irradiated with 72.6 Gy (RBE) and 88.4% for peripherally located tumors irradiated with 66 Gy (RBE); this difference was statistically significant (log-rank test; $P = .017$). Tumor diameter was not a significant prognostic factor for local control. The local control rates for tumors with a diameter ≤ 3 cm vs. those with a diameter > 3 cm are shown in Figure 4. Three centimeters was selected as a cutoff value because it demarcates stage IA tumors from stage IB tumors. No significant differences were observed between tumors ≤ 3 cm vs. > 3 cm in diameter for either tumors irradiated with 72.6 Gy (RBE) or 66 Gy (RBE) (log-rank test, $P = .57$ and $P = .54$, respectively).

Discussion

In the present study, in which the radiation dose was 72.6 Gy (RBE) in 22 fractions and 66 Gy (RBE) in 10 or 12 fractions, the 3-year OS and local control rates were 76.7% and 81.8%, respectively. Previously, patients with peripherally located stage I NSCLC tumors treated at our hospital experienced a 2-year OS rate of 74% and a 2-year local control of 95%.[2] In another study conducted at our hospital that included centrally and peripherally located tumors, patients experienced a 97.8% 2-year OS rate and a 97.0% 2-year local control rate, with a median follow-up period of only 17.7 months.[16] The present study had a longer follow-up period of 31.0 months. We reevaluated the outcomes of stage I NSCLC patients in light of this prolonged follow-up period, the inclusion of patients with centrally and peripherally located tumors, and changes in the TNM classification criteria. In stage I NSCLC treated with SBRT of photon and proton, the 3-year OS rate was reported as 57% to 86%[2,7] and the 3-year local control rate was reported as 74% to 95%.[2,4-6,8,9] The OS and local control rates of SBRT in the present study are greater than those associated with conventional radiotherapy, for which the local control rate is approximately 50%[20]; the present rates are consistent with those of previous SBRT studies.

The present study identified prognostic factors for recurrence after high-dose PBT. Radiation dose (72.6 Gy [RBE] vs. 66 Gy [RBE]) was decided depending on tumor location. Although tumor diameter was only significantly associated with disease recurrence, radiation dose was a significant factor in analyses for disease recurrence and local recurrence. Additionally, in multivariate analysis for disease recurrence, radiation dose was most significant. Therefore, radiation dose appears to be the most significant prognostic factor for tumor control in patients with stage I NSCLC treated using high-dose PBT.

Some previous studies have indicated that outcomes are not significantly different between patients with centrally and

Table 2 Univariate Analysis of Risk Factors for Local and Disease Recurrence

Factor	Local Recurrence			Disease Recurrence		
	Tumor With Local Recurrence (n = 11)	Tumor Without Local Recurrence (n = 69)	*P*	Tumor With Recurrence (n = 31)	Tumor Without Recurrence (n = 49)	*P*
Age at Time of Treatment						
Median years (range)	76 (66-82)	74 (51-86)	.22	75 (53-86)	73 (51-86)	.030
Men vs. Women	11:0	54:15	.071	24:7	41:8	.96
Performance Status						
0-1 vs. 2-4	10:1	61:8	.99	26:5	45:4	.059
Cardiovascular Disease						
Yes vs. no	2:9	15:54	.93	4:27	13:36	.41
Respiratory Disease						
Yes vs. no	7:4	29:40	.10	15:16	29:20	.24
Stage						
Stage IA vs. stage IB	6:5	53:16	.057	20:11	39:10	.11
Tumor Diameter						
Median, mm (range)	30 (16-42)	22 (10-48)	.11	30 (12-42)	21 (10-48)	.020
Radiation Dose (Tumor Location)						
72.6 Gy (RBE) vs. 66 Gy (RBE) (centrally vs. peripherally located)	6:5	15:54	.026	13:18	8:41	.010
Tumor Site						
S1-3 and S6 vs. S4-5 and S7-10	5:6	46:23	.15	17:14	34:15	.15
Histology						
Adeno vs. SqCC vs. cancer vs. unproven	4:4:1:2	22:28:5:14	.85	10:12:3:6	16:20:3:10	.69

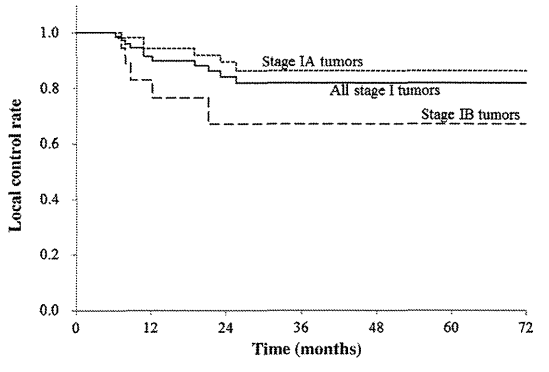
Abbreviations: adeno = adenocarcinoma; RBE = relative biological effectiveness; S = lung segment; SqCC = squamous cell carcinoma.

peripherally located tumors, with more than 90% achieving local control with minimal irradiation-associated complications.[14,15,21,22] However, other studies reported a high risk of long-term late complications of SBRT in patients with centrally located tumors,[23,24] with 1 study reporting a 2-year severe complication rate of 46%.[24] In addition to parallel organs, such as the normal lung, serial organs, including the trachea, bronchial tree, and esophagus close to the tumor are at risk.[1] Thus, decreasing the radiation dose of all of these internal organs must be considered at the time of irradiation of centrally located tumors. In the present study, to reduce the risk of late complications, different protocols were used for centrally vs. peripherally located tumors. As a result, the rate of Grade 3 to 4 complications in internal organs was low. Previously, a $BED_{10} \geq 100$ Gy was reported to be necessary for achieving optimal tumor control.[15,25] For centrally located tumors, Chang et al. reported that 40 Gy in 4 fractions (BED_{10}; 80 Gy) resulted in lower local control (57%), and 50 Gy (BED_{10}; 112.5 Gy) resulted in no recurrences during the median follow-up period of 17 months.[14] In addition, Haasbeek et al. reported that 60 Gy in 8 fractions (BED_{10}; 105 Gy) yielded a 3-year local control rate of 92.6%, and that peripherally located tumors treated with the same protocol had similar outcomes.[15] In the present study, the radiation dose was decided depending on tumor location; the BED_{10} of 72.6 Gy (RBE) for centrally located tumors was 97 Gy_{10} (RBE), and the dose of 66 Gy (RBE) for peripherally located tumors was 110 Gy_{10} (RBE) or 102 Gy_{10} (RBE). Although the use of SBRT for centrally located tumors remains controversial, 97 Gy_{10} (RBE) of BED_{10} has been shown to result in a lower tumor control rate. In addition, the analysis of prognostic factors for tumor control detected that radiation dose was most significant. Thus, further evaluation of this treatment method for centrally located tumors is warranted.

Tumor diameter has been previously reported to be a significant prognostic factor in this patient population.[26] Dunlap et al. showed that increasing tumor diameter was correlated with worse local control and shorter OS.[26] All of the tumors in their study were peripherally located, and the median irradiated dose was 60 Gy in 3 to 5 fractions (median BED_{10}; 150 Gy). These investigators observed a lower local control rate for T2 tumors than for T1 tumors: the 2-year local control rate was 90% for T1 tumors and 70% for T2 tumors. Bush et al. showed that high-dose PBT, in which radiation dose was 70 Gy in 10 fractions (BED; 127Gy), yielded a 4-year local control rate of 91% for T1 tumors and 75% for T2 tumors.[27] In contrast, in the present study, tumor diameter was not significantly associated with local recurrence, and local control rates did not differ between patients with tumors ≤ 3 cm vs. > 3 cm, even when centrally and peripherally located tumors were evaluated separately. Radiation dose was a more significant prognostic factor than tumor diameter.

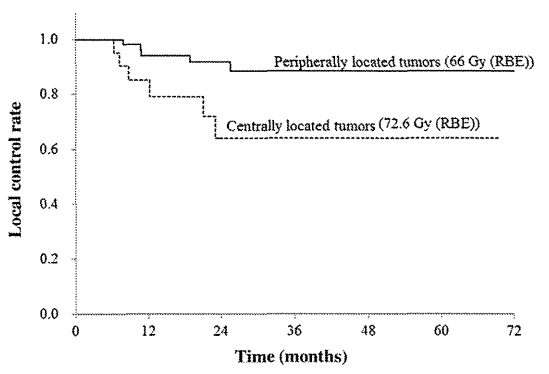
The outcome of SBRT consisting of protons and photons has been reported to not differ for medically inoperable stage I

Figure 2 Local Control Rate After Proton Beam Therapy. Local Recurrence Developed for 11 Tumors. The Local Control Rate was 81.8% at 3 and 5 Years; Median Follow-up was 23.2 Months (Range, 4.7-101.4 Months). The 3-Year Local Control Rate was 86.2% for Stage IA Tumors and 67.0% for Stage IB Tumors



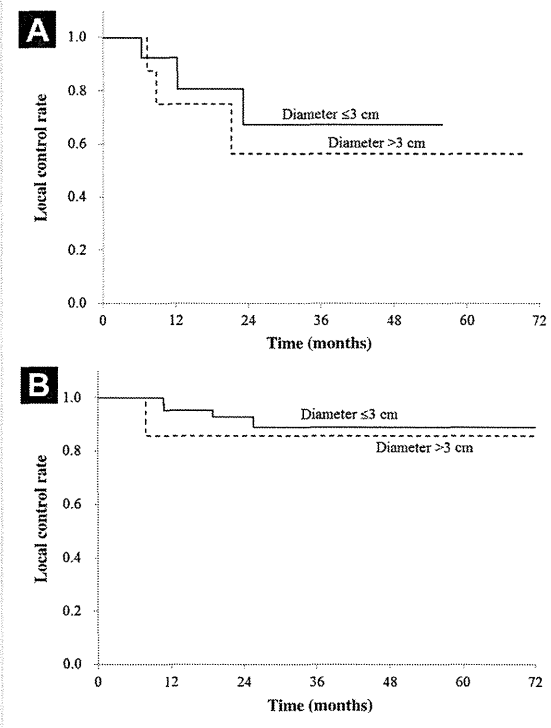
NSCLC.[28] Meanwhile, because of the presence of a Bragg peak, which is a characteristic of PBT, Kadoya et al. reported that PBT was more advantageous than SBRT consisting of photons when treating tumors with a relatively large planning target volume (PTV) or several tumors.[29] Register et al. also reported that the > 95% PTV coverage and maximum tolerated dose of protons were better than those of photons.[30] In contrast, Seco et al. reported that protons had proximal-range uncertainty for a spread-out Bragg peak, although there were fewer hot spots than with photons.[31] The proton range uncertainties result in larger planning margins for protons. In a clinical report, Bush et al. showed 75% local control

Figure 3 Local Control Rate for Centrally vs. Peripherally Located Tumors Irradiated With Each Radiation Dose Protocol. The 3-Year Local Control Rate was 63.9% for Centrally Located Tumors Irradiated With 72.6 Gy (RBE) and 88.4% for Peripherally Located Tumors Irradiated With 66 Gy (RBE); This Difference was Statistically Significant (log-Rank Test; $P = .017$)



Abbreviation: RBE = relative biological effectiveness.

Figure 4 Local Control Rate for Tumors With a Diameter of ≤ 3 cm vs. > 3 cm. The Local Control Rates for Tumors With Diameters of ≤ 3 cm and > 3 cm for Tumors Irradiated With 72.6 Gy (RBE) (A) and Tumors Irradiated With 66 Gy (RBE) (B) are Shown. No Significant Differences Were Observed Between Tumors With a Diameter ≤ 3 cm vs. > 3 cm for Either Centrally Located Tumors Irradiated With 72.6 Gy (RBE) or Peripherally Located Tumors Irradiated With 66 Gy (RBE) (log Rank Test, $P = .57$ and $P = .54$, Respectively)



Abbreviation: RBE = relative biological effectiveness.

rate for T2 tumors, although 52% of these T2 tumors were > 5 cm in diameter.[27] Considering that SBRT is generally limited to < 5 cm tumors, their results in larger tumors seemed to be improved. Therefore, when a sufficient radiation dose with a BED ≥ 100 Gy and a sufficient margin can be given to tumors considering the range uncertainties, PBT might provide better coverage of the PTV compared with SBRT consisting of photons, potentially limiting the possibility of different control rates associated with tumor diameter.

In addition, PBT plans significantly reduce the mean maximal dose to the aorta, bronchial plexus, heart, pulmonary vessels, and spinal cord for centrally located tumors, because of the spread-out Bragg peak.[30] In the present study, the local control rate for centrally located tumors was lower than that for peripherally located tumors, although the severe complication rate was low, likely because of the different radiation doses used to avoid late severe complications.

In conclusion, radiation dose was shown to be the most significant prognostic factor for tumor control in patients with stage I NSCLC treated using high-dose PBT. Tumor diameter was not

significant for local control, which was only significantly associated with disease recurrence. Further evaluation of high-dose PBT for centrally located tumors is warranted.

Clinical Practice Points

- For stage I NSCLC, SBRT was given a better outcome compared with conventional radiotherapy. Recently, SBRT of photon and proton has been used for not only peripherally located tumors but also centrally located tumors. The prognostic factor for local control of tumors including centrally located tumors was recently discussed.
- The new finding of this study was reevaluation and determination of the treatment outcome and prognostic factors of stage I NSCLC irradiated using high-dose PBT. Although tumor diameter was only significantly associated with disease recurrence, radiation dose was a significant factor in analyses for disease recurrence and local recurrence. Additionally, in multivariate analysis for disease recurrence, radiation dose was most significant. Therefore, radiation dose appears to be the most significant prognostic factor for tumor control in patients with stage I NSCLC treated using high-dose PBT. Further evaluation of high-dose PBT for centrally located tumors is warranted.
- The results of the study indicated that the tumor diameter was not statistically significant for tumor local control in the patients with stage I NSCLC treated using high-dose PBT. This result suggested that when a sufficient radiation dose with a BED $\geq$ 100 Gy and a sufficient margin can be given to tumors considering the range uncertainties, PBT might provide better coverage of the PTV compared with SBRT consisting of photons, potentially limiting the possibility of different control rates associated with tumor diameter.

Acknowledgments

This research was partly supported by the "Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program)," initiated by the Council for Science and Technology Policy (CSTP), and by a Grand-in Aid for Scientific Research from the Japanese Society for the Promotion of Science, Tokyo, Japan (B) 24390286.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Stephans K. Stereotactic body radiotherapy for stage I non-small cell lung cancer. *Cleve Clin J Med* 2012; 79:eS26-31.
2. 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; 68:786-93.
3. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012; 83:348-53.
4. Nihei K, Ogino T, Ishikura S, et al. High-dose proton beam therapy for Stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 65:107-11.
5. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. *Lung Cancer* 2010; 68:72-7.
6. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012; 13:802-9.
7. Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys* 2001; 51:666-70.
8. Bush DA, Slater JD, Shin BB, et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest* 2004; 126:1198-203.
9. Widesott L, Amichetti M, Schwarz M. Proton therapy in lung cancer: clinical outcomes and technical issues. A systematic review. *Radiother Oncol* 2008; 86: 154-64.
10. Takeda A, Kunieda E, Sanuki N, et al. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. *Lung Cancer* 2012; 77: 77-82.
11. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. *Int J Radiat Oncol Biol Phys* 2012; 82:967-73.
12. Louie AV, Rodrigues G, Hannouf M, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: a Markov model-based decision analysis. *Int J Radiat Oncol Biol Phys* 2011; 81:964-73.
13. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011; 81:1352-8.
14. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; 72:967-71.
15. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. *J Thorac Oncol* 2011; 6: 2036-43.
16. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for patients with medically inoperable stage I non-small-cell lung cancer at the university of tsukuba. *Int J Radiat Oncol Biol Phys* 2010; 78:467-71.
17. Paganetti H, Niemierko A, Ancukiewicz M, et al. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys* 2002; 53: 407-21.
18. Tsunashima Y, Sakae T, Shioyama Y, et al. Correlation between the respiratory waveform measured using a respiratory sensor and 3D tumor motion in gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; 60:951-8.
19. Dunlap NE, Yang W, McIntosh A, et al. Computed tomography-based anatomic assessment overestimates local tumor recurrence in patients with mass-like consolidation after stereotactic body radiotherapy for early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012; 84:1071-7.
20. Shioyama Y, Tokuuye K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003; 56: 7-13.
21. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; 70:685-92.
22. Xia T, Li H, Sun Q, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 66:117-25.
23. Song SY, Choi W, Shin SS, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. *Lung Cancer* 2009; 66:89-93.
24. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; 24:4833-9.
25. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004; 101:1623-31.
26. Dunlap NE, Larner JM, Read PW, et al. Size matters: a comparison of T1 and T2 peripheral non-small-cell lung cancers treated with stereotactic body radiation therapy (SBRT). *J Thorac Cardiovasc Surg* 2010; 140:583-9.
27. Bush DA, Cheek G, Zaheer S, et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-year experience at loma linda university medical center. *Int J Radiat Oncol Biol Phys* 2013; 86:964-8.
28. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol* 2010; 95:32-40.
29. Kadoya N, Obata Y, Kato T, et al. Dose-volume comparison of proton radiotherapy and stereotactic body radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 79:1225-31.
30. Register SP, Zhang X, Mohan R, et al. Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 80:1015-22.
31. Seco J, Panahandeh HR, Westover K, et al. Treatment of non-small cell lung cancer patients with proton beam-based stereotactic body radiotherapy: dosimetric comparison with photon plans highlights importance of range uncertainty. *Int J Radiat Oncol Biol Phys* 2012; 83:354-61.

Journal of Radiation Research, 2015, 56, 128–133
doi: 10.1093/jrr/rru082 Advance Access Publication 3 November 2014

Comparison of dose–volume histograms between proton beam and X-ray conformal radiotherapy for locally advanced non-small-cell lung cancer

Toshiki OHNO*, Yoshiko OSHIRO, Masashi MIZUMOTO, Haruko NUMAJIRI, Hitoshi ISHIKAWA, Toshiyuki OKUMURA, Toshiyuki TERUNUMA, Takeji SAKAE and Hideyuki SAKURAI

Departments of Radiation Oncology and Proton Medical Research Center, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki, 305-8575, Japan
*Corresponding author. Proton Medical Research Center, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki, 305-8575, Japan. Tel: +81-29-853-7100; Fax: +81-29-853-7102; Email: ohno@pmrc.tsukuba.ac.jp

(Received 17 June 2014; revised 18 August 2014; accepted 19 August 2014)

The purpose of this study was to compare the parameters of the dose–volume histogram (DVH) between proton beam therapy (PBT) and X-ray conformal radiotherapy (XCRT) for locally advanced non-small-cell lung cancer (NSCLC), according to the tumor conditions. A total of 35 patients having NSCLC treated with PBT were enrolled in this analysis. The numbers of TNM stage and lymph node status were IIB ($n = 3$), IIIA ($n = 15$) and IIIB ($n = 17$), and N0 ($n = 2$), N1 ($n = 4$), N2 ($n = 17$) and N3 ($n = 12$), respectively. Plans for XCRT were simulated based on the same CT, and the same clinical target volume (CTV) was used based on the actual PBT plan. The treatment dose was 74 Gy-equivalent dose (GyE) for the primary site and 66 GyE for positive lymph nodes. The parameters were then calculated according to the normal lung dose, and the irradiation volumes of the doses (Vx) were compared. We also evaluated the feasibility of both plans according to criteria: V5 ≥ 42%, V20 ≥ 25%, mean lung dose ≥ 20 Gy. The mean normal lung dose and V5 to V50 were significantly lower in PBT than in XCRT. The differences were greater with the more advanced nodal status and with the larger CTV. Furthermore, 45.7% of the X-ray plans were classified as inadequate according to the criteria, whereas 17.1% of the proton plans were considered unsuitable. The number of inadequate X-ray plans increased in cases with advanced nodal stage. This study indicated that some patients who cannot receive photon radiotherapy may be able to be treated using PBT.

Keywords: proton therapy; locally advanced NSCLC; dose escalation; DVH

INTRODUCTION

Radiotherapy plays an important role in the treatment of locally advanced, unresectable non-small-cell lung cancer (NSCLC). In order to achieve the maximum survival benefit with radiotherapy, the dose–response relationship and its combination with chemotherapy has been investigated since the 1980s. Several successful dose-escalation studies with concurrent chemotherapy have been undertaken worldwide and have led to improved tumor control and survival at doses above 70 Gy [1–8]. However, the Phase III study by RTOG showed no survival benefit with a dose of 74 Gy compared with 60 Gy [9]. While Cox *et al.* reported that pulmonary or cardiopulmonary effects of radiotherapy could affect the outcome, the reason for this was unclear [10]. Meanwhile, Chang *et al.* successfully administered chemo-proton therapy for unresectable Stage III NSCLC with a dose of 74 GyE, and reported a median survival time of 29.4 months [11]. We consider that PBT will be key to safe dose escalation for locally advanced NSCLC due to the sharp energy peak, called the Bragg peak.

The dosimetric comparison of protons and photon radiotherapy for early stage NSCLC has been widely discussed, and some reports of early-stage NSCLC have shown that PBT also significantly reduces the normal lung dose [12–17]. However, there have been few investigations of the differences in dose distribution for advanced NSCLC [17, 18].

In this report, we simulated proton therapy using a high radiation dose at 74 GyE for unresectable locally advanced NSCLC and compared the parameters of the dose–volume histograms (DVHs) for PBT and photon conformal radiotherapy

(XCRT), based upon the tumor condition, i.e. stage, lymph node status, and target volume.

MATERIALS AND METHODS

Patient characteristics

A total of 35 cases of inoperable locally advanced Stage IIB and III NSCLC were enrolled in this analysis. The TNM stage was Stage IIB in three patients, IIIA in 15, and IIIB in 17. The nodal stage was N0, N1, N2 and N3 in 2, 4, 17 and 12 patients, according to the TNM classification of malignant tumors, sixth edition. The tumor was located in the upper lobe in 24 patients and in the middle and lower lobe in 11 patients. All patients were treated with proton beams of 155–250 MeV generated using a synchrotron accelerator (Hitachi Inc., Ibaraki, Japan) at the Proton Medical Research Center. This study was approved by our institutional review board, and written informed consent was obtained from all patients.

Treatment planning

For treatment planning, chest CT images were obtained in 5-mm thick slices, with the patient in a body cast in the treatment position (Engineering System Co., Matsumoto, Japan), during the end-expiratory phase using a respiratory-gated system (DAR-3000, Shimadzu, Kyoto, Japan). The dose calculation for PBT and XCRT was performed using the same CT series for each patient with the pencil beam method for PBT (proton treatment planning software ver. 2, Hitachi Inc., Ibaraki, Japan) and with superposition on for XCRT (Xio ver. 4, Elekta, Stockholm, Sweden). Proton beams of 155–250 MeV and X-ray irradiation of 10 MV were used in the treatment plans. The treatment planning system for PBT automatically estimated the conditions required for beam delivery, which include a ridge filter, a range shifter, a collimator and bolus. The beam delivery system created a homogeneous dose distribution at the prescription dose using the spread-out Bragg peak of the proton beams. The concept of dose delivery, for both the target and normal tissues, was exactly the same for PBT as for XCRT; the daily fractionation dose was 2 Gy, and the primary site and positive lymph nodes were irradiated at 74 Gy and 66 Gy, respectively.

We defined the clinical target volume (CTV) as the primary tumor and clinically positive lymph nodes. Prophylactic lymph nodes were not included in the CTV. Clinically positive lymph nodes were defined as nodes ≥1 cm as visualized on a CT scan or as PET-positive lymph nodes. CTV-p was defined as the primary tumor alone. The planned target volume (PTV) and PTV-p encompassed the CTV and CTV-p, respectively, with a 5–10-mm margin in all directions and an additional 5-mm margin in the caudal direction (to compensate for respiratory motion), and the coverage of PTVs was provided for by more than 95% prescribed doses. To ensure this coverage, we set up ~5-mm distal and proximal margins for PTVs at PBT. The total normal lung volume was the total lung volume reduced by the tumor volume (gross tumor volume: GTV) and atelectasis. The median CTV was 228.5 cm^3 (range: 34.4–555.5 cm^3), and the median total normal lung volume was 3426.4 cm^3 (range: 1219–5179 cm^3).

For PBT, both 66 GyE and an additional 8 GyE were delivered via two to three ports in the optimal direction to maintain a tolerable spinal dose (~40 GyE) to PTV and PTV-p, respectively. For XCRT, an initial 44 Gy dose was delivered via the anterior and posterior ports for PTV, and 22 Gy was then irradiated using oblique fields to avoid the spinal cord. Finally, we applied a booster dose at 8 Gy to PTV-p. A typical treatment plan of XCRT and PBT is shown in Fig. 1.

Analysis

The DVH of the lung was calculated during planning for both PBT and XCRT, and the relationship between tumor factor (TNM stage, T stage, N stage, CTV) and dosimetric factors (i.e. mean lung dose (MLD) and the percentage volume of the whole lung receiving more than a certain dose (Vx)) were analyzed by a two-sample *t*-test and the correlation coefficient. We also evaluated the feasibility of the plans according to the criteria reported for the increasing risk of radiation pneumonitis, as follows: V5 ≥ 42% [19], V20 ≥ 25% [20], MLD ≥ 20 Gy [21].

All statistical analyses were performed using statistical software (SPSS, IBM Inc., NY, USA), and *P*-values < 0.05 were considered statistically significant.

RESULTS

Mean lung dose

The relationship between the MLD and lymph node status or stage is shown in Fig. 2. The average MLD for N0–1, N2, N3 in PBT and XCRT was 7.80 Gy vs 12.25 Gy ($P = 0.01$), 10.41 Gy vs 14.17 Gy ($P < 0.001$), and 12.20 Gy vs 18.00 Gy ($P < 0.001$), and the average MLD for Stage IIB, IIIA and IIIB was 9.05 Gy vs 11.61 Gy ($P = 0.07$), 9.70 Gy vs 13.68 Gy ($P < 0.001$) and 11.62 Gy vs 17.08 Gy ($P < 0.001$), respectively. The MLD in the PBT was significantly lower than that of XCRT for all stages and nodal status. The CTV volume was also a significant factor affecting MLD (coefficient factor (r) = 0.376, $P = 0.013$) (Fig. 3). The larger the CTV, the greater the difference in MLD between the PBT and the XCRT plans.

Lung volume receiving more than a certain dose (Vx)

The results of V5, V10, V20, V30, V40 and V50 in accordance with nodal stages are shown in Fig. 4. The irradiated normal lung volume increased significantly with the advanced nodal stage. Furthermore, in Fig. 4, both lines in

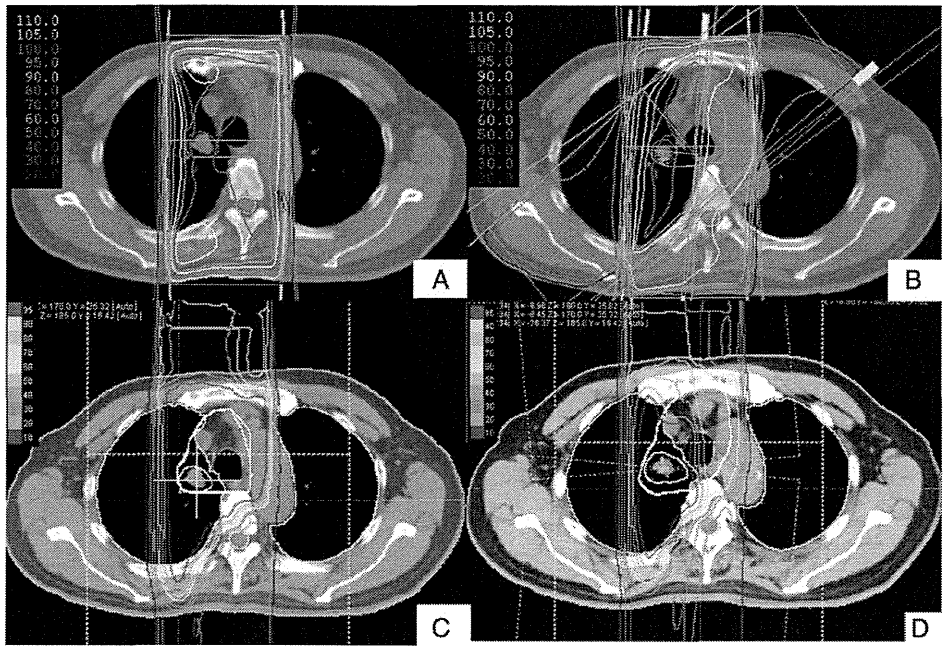


Fig. 1. Comparison of dose distributions for T1N3M0 lung cancer between XCRT (A/B) and PBT (C/D). (**A**) An initial 44 Gy of XCRT was delivered via the anterior and posterior ports. Note the difference in dose to the spinal cord between XCRT and PBT. (**B**) Sum plan of XCRT. After 44 Gy, an oblique field was needed to avoid the spinal cord in XCRT. (**C**) In PBT, a reduction of the dose to the spinal cord to less than 50% allows using the anterior and posterior ports until 66 GyE to the CTV1. (**D**) Sum plan of PBT.

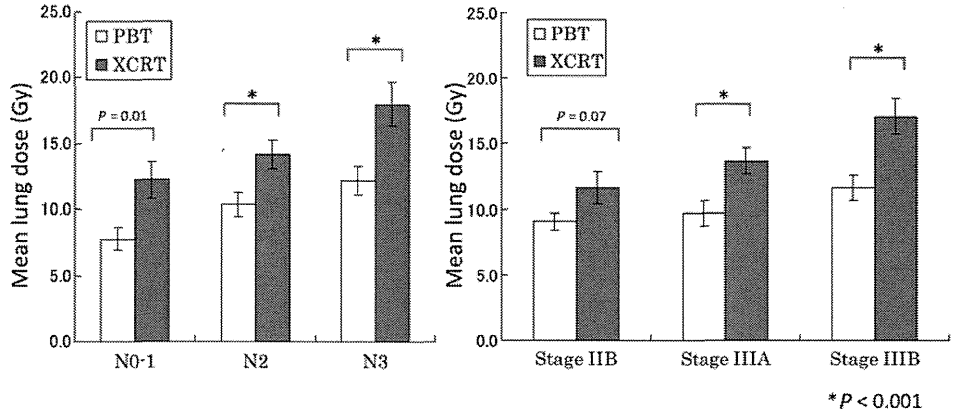


Fig. 2. The relationship between the mean lung dose and N stage for each modality of PBT and XCRT.

the PBT and XCRT appear to be nearly parallel in the N0 to N2 patients, but not in the N3 patients. This means that the differences in the lung doses between the XCRT and PBT are greater in the N3 patients compared with the N0–2 patients, especially for the dose to the lower to middle lung lobes. The irradiated normal lung volume also increased significantly with the advanced TNM stage (Fig. 5). The correlation between CTV and the differences in Vx (Vx in XCRT – Vx in PBT) was also observed in V30–V50 ($P = 0.391$, 0.454, 0.266, 0.046, 0.019 and 0.030 for V5, V10, V20, V30, V40 and V50, respectively). Thus, the differences between PBT and XCRT were observed, and while the differences were greater at lower doses, the correlation of Vx differences with CTV was stronger for larger doses; i.e. V30–V50.

Feasibility of the plan

Table 1 summarizes the number of inadequate plans for photon radiotherapy and PBT. According to the criteria of V5 ≥ 42% [19], V20 ≥ 25% [20] and MLD ≥ 20 Gy([21],

45.7% of the XCRT plans were classified as inadequate, whereas only 17.1% of the proton plans were not suitable. The number of inadequate XCRT plans increased accordingly with the advanced nodal stage.

DISCUSSION

Radiation pneumonitis is a significant concern during radiotherapy for patients with lung cancer. The risk of radiation pneumonitis correlates closely with the volume dose of the normal lung. Tsujino *et al.* found that V20 correlated significantly with the incidence of radiation pneumonitis. They reported that the incidence of severe radiation pneumonitis was significantly higher in patients with V20 ≥ 25% [20]. Marks *et al.* analyzed the findings of previous studies and suggested that an MLD of 20–23 Gy with conventional fractions was appropriate to limit the risk of radiation pneumonitis to ≤ 20% [21]. Furthermore, Wang *et al.* analyzed patients with NSCLC that were treated with concurrent chemoradiotherapy and showed a significantly lower frequency of Grade 3 or worse radiation pneumonitis for patients with V5 ≤ 42% compared with those patients with V5 > 42% [19]. Therefore, radiotherapy can be more difficult for larger tumors, with increasing risk of radiation pneumonitis in the treatment of locally advanced NSCLC.

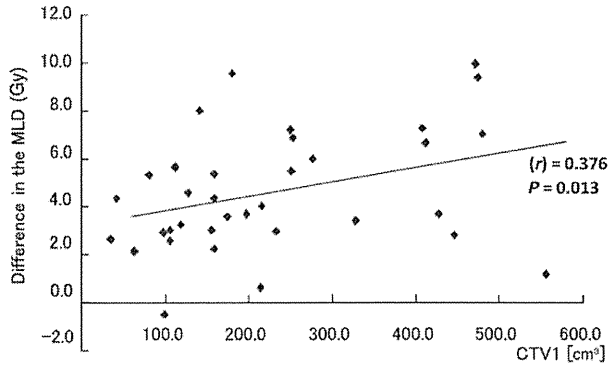


Fig. 3. The correlation between CTV1 and the reduction in MLD. Difference in MLD = MLD (XCRT) – MLD (PBT).

Chemoradiotherapy is now standard treatment for unresectable locally advanced NSCLC. However, the feasible doses for concurrent chemoradiotherapy remain controversial. Even though a Phase III study (RTOG 0617) was not able to show any survival benefit by dose escalation, the toxicities were considered tolerable, and survival was improved in many prospective studies [1–3, 8].

Meanwhile, proton beams are now popular for various cancers because of their excellent dose localization, and they can be applied to many patients with a variety of malignancies. Some authors have reported favorable results for PBT for advanced NSCLC [22–24]. Chang *et al.* reported that the median survival for patients with Stage III NSCLC was 29.4 months with concurrent chemo–proton therapy using a dose of 74 GyE, with no Grade 4 non-hematologic toxicities [22]. Oshiro *et al.* reported that while the median survival was 21.3 months, Grade ≥ 3 lung toxicities were observed in three patients, and no severe esophagitis was observed in the standalone PBT for 57 patients with Stage III NSCLC [24]. These results suggest that PBT has a great potential for producing a survival benefit with less toxicities, which may be a

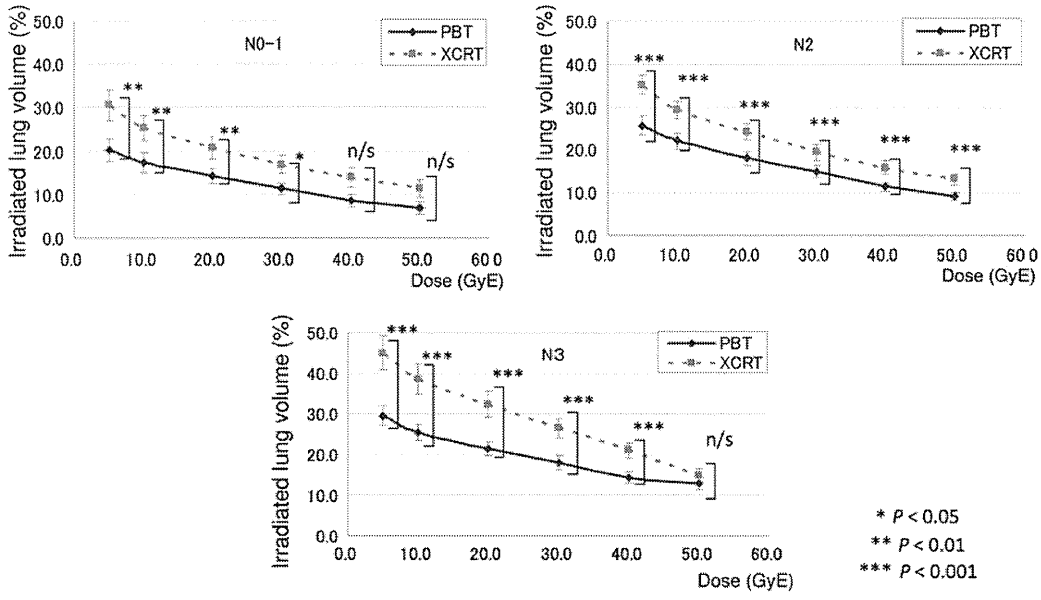


Fig. 4. The relationship between V5–50 and N stage for each modality of PBT and XCRT.

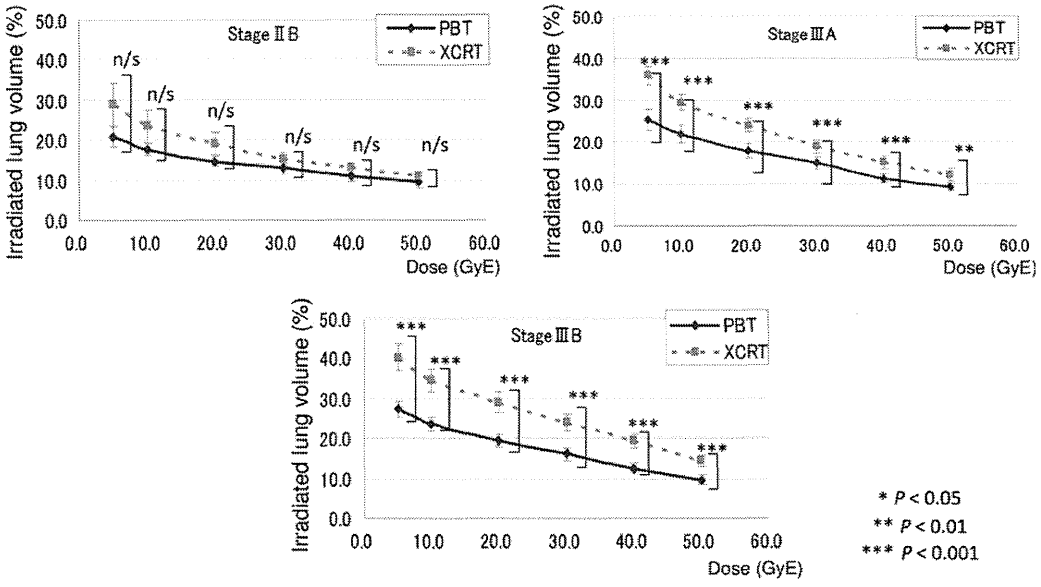


Fig. 5. The relationship between V5–50 and TNM stage for each modality of PBT and XCRT.

Table 1. The numbers of inadequate plan in XCRT and PBT according to the criteria of V5 ≥ 42% [19], V20 ≥ 25% [20] and MLD ≥ 20 Gy [21]

Group	XCRT	PBT	*P-value*
All ($n = 35$)	16 (45.7%)	6 (17.1%)	0.01
N0–1 ($n = 6$)	1 (16.7%)	0 (0.0%)	
N2 ($n = 17$)	5 (29.4%)	2 (11.8%)	
N3 ($n = 12$)	10 (83.3%)	4 (33.3%)	0.013

result of its excellent dose localization, as noted above. To the best of our knowledge, there have only been two reports suggesting dosimetric advantages for PBT in advanced NSCLC. Chang *et al.* compared dose distribution in XCRT (63 Gy) with PBT (74 GyE) plans and reported that V5, V10 and V20 were significant lower in PBT plans. Stuschke *et al.* compared intensity-modulated proton therapy (IMPT), photon intensity-modulated radiotherapy (IMXT) and tomotherapy in six patients and found that MLD and V10 and V20 were lowest for the IMPT plans [18]. Our study also showed dosimetric advantages of proton compared with photon radiotherapy in the treatment of advanced NSCLC, especially for more advanced lymph node stages, and some patients who received PBT could not be treated with photon radiotherapy. Furthermore, a significant correlation was revealed between the CTV and MLD, V30, V40 and V50 in our study, which suggested that PBT is more advantageous for a larger CTV to reduce doses to the normal lung, especially for critical doses >20 Gy. Thus, PBT appears to be more advantageous for patients with more advanced NSCLC, and can provide treatment opportunities for some patients with fewer options.

However, there are some limitations to our study. While DVHs were investigated in the initial plan, some plans were changed practically as a consequence of tumor shrinking. Furthermore, the calculation algorithm differed between PBT and photon radiotherapy in this study. Our results reflect a practical propensity for a dose–volume relationship, but comparison of adoptive plans after refinement (using a Monte Carlo algorithm) will be necessary for precise analysis in the future.

In conclusion, PBT can reduce the normal lung dose compared with XCRT, especially in the advanced nodal stage, and more locally advanced patients can be treated by this modality using PBT.

FUNDING

This research was partly supported by the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program) initiated by the Council for Science and Technology Policy (CSTP). This work was also supported in part by a Grant-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan. Funding to pay the Open Access publication charges for this article was provided by Proton Medical Research Center, University of Tsukuba.

REFERENCES

1. Socinski MA, Rosenman JG, Halle J *et al.* Dose-escalating conformal thoracic radiation therapy with induction and

concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: a modified phase I/II trial. *Cancer* 2001;**92**:1213–23.
2. Socinski MA, Morris DE, Halle JS *et al.* Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: a dose-escalation phase I trial. *J Clin Oncol* 2004;**22**: 4341–50.
3. 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**:348–56.
4. Socinski MA, Blackstock AW, Bogart 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.
5. Cox JD, Azarnia N, Byhardt RW *et al.* A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. *J Clin Oncol* 1990;**8**:1543–55.
6. Blackstock AW, Ho C, Butler J *et al.* Phase Ia/Ib chemoradiation trial of gemcitabine and dose-escalated thoracic radiation in patients with stage III A/B non-small cell lung cancer. *J Thorac Oncol* 2006;**1**:434–40.
7. Hayman JA, Martel MK, Ten Haken RK *et al.* Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. *J Clin Oncol* 2001;**19**:127–36.
8. Vokes EE, Herndon JE, II, Crawford J *et al.* Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002;**20**:4191–8.
9. Bradley JD, Komaki R, Masters G *et al.* A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/– cetuximab for stage IIIa/IIIb non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617. In: *53rd Annual Meeting of the American Society of Radiation Oncology, Miami, FL., October 2–6, 2011.*
10. Cox JD. Are the results of RTOG 0617 mysterious? *Int J Radiat Oncol Biol Phys* 2012;**82**:1042–4.
11. Chang JY, Komaki R, Lu C *et al.* Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer* 2011;**117**:4707–13.
12. Hoppe BS, Huh S, Flampouri S *et al.* Double-scattered proton-based stereotactic body radiotherapy for stage I lung cancer: a dosimetric comparison with photon-based stereotactic body radiotherapy. *Radiother Oncol* 2010;**97**:425–30.
13. Seco J, Panahandeh HR, Westover K *et al.* Treatment of non-small cell lung cancer patients with proton beam-based stereotactic body radiotherapy: dosimetric comparison with photon plans highlights importance of range uncertainty. *Int J Radiat Oncol Biol Phys* 2012;**83**:354–61.
14. Macdonald OK, Kruse JJ, Miller JM *et al.* Proton beam radiotherapy versus three-dimensional conformal stereotactic body radiotherapy in primary peripheral, early-stage non-small-cell lung carcinoma: a comparative dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2009;**75**:950–8.
15. Register SP, Zhang X, Mohan R *et al.* Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;**80**:1015–22.
16. Westover KD, Seco J, Adams JA *et al.* Proton SBRT for medically inoperable stage I NSCLC. *J Thorac Oncol* 2012;**7**: 1021–5.
17. 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**:1087–96.
18. Stuschke M, Kaiser A, Pottgen C *et al.* Potentials of robust intensity modulated scanning proton plans for locally advanced lung cancer in comparison to intensity modulated photon plans. *Radiother Oncol* 2012;**104**:45–51.
19. Wang S, Liao Z, Wei X *et al.* Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). *Int J Radiat Oncol Biol Phys* 2006;**66**:1399–407.
20. Tsujino K, Hirota S, Endo M *et al.* Predictive value of dose–volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys* 2003;**55**:110–5.
21. Marks LB, Bentzen SM, Deasy JO *et al.* Radiation dose–volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;**76**:S70–6.
22. Chang JY, Komaki R, Lu C *et al.* Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer* **117**: 4707–13.
23. Nichols RC, Huh SN, Henderson RH *et al.* Proton radiation therapy offers reduced normal lung and bone marrow exposure for patients receiving dose-escalated radiation therapy for unresectable stage iii non-small-cell lung cancer: a dosimetric study. *Clin Lung Cancer* 2011;**12**:252–7.
24. Oshiro Y, Mizumoto M, Okumura T *et al.* Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol* **7**:370–5.

Journal of Radiation Research, 2014, 55, 959–965
doi: 10.1093/jrr/rru034 Advance Access Publication 25 May 2014

High-dose concurrent chemo–proton therapy for Stage III NSCLC: preliminary results of a Phase II study

Yoshiko OSHIRO[1], Toshiyuki OKUMURA[1], Koichi KURISHIMA[2], Shinsuke HOMMA[2], Masashi MIZUMOTO[1], Hitoshi ISHIKAWA[1], Masataka ONIZUKA[3], Mitsuaki SAKAI[3], Yukinobu GOTO[3], Nobuyuki HIZAWA[2], Yukio SATO[3] and Hideyuki SAKURAI[1,*]

[1]Department of Radiation Oncology, University of Tsukuba, Tsukuba, Ibaraki, Japan
[2]Department of Respiratory Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
[3]Department of Respiratory Surgery, University of Tsukuba, Tsukuba, Ibaraki, Japan
*Corresponding author. Tel: +81-298-537-100; Fax: +81-298-537-102; Email: hsakurai@pmrc.tsukuba.ac.jp

(Received 6 January 2014; revised 17 March 2014; accepted 1 April 2014)

The aim of this report is to present the preliminary results of a Phase II study of high-dose (74 Gy RBE) proton beam therapy (PBT) with concurrent chemotherapy for unresectable locally advanced non-small-cell lung cancer (NSCLC). Patients were treated with PBT and chemotherapy with monthly cisplatin (on Day 1) and vinorelbine (on Days 1 and 8). The treatment doses were 74 Gy RBE for the primary site and 66 Gy RBE for the lymph nodes without elective lymph nodes. Adapted planning was made during the treatment. A total of 15 patients with Stage III NSCLC (IIIA: 4, IIIB: 11) were evaluated in this study. The median follow-up period was 21.7 months. None of the patients experienced Grade 4 or 5 non-hematologic toxicities. Acute pneumonitis was observed in three patients (Grade 1 in one, and Grade 3 in two), but Grade 3 pneumonitis was considered to be non-proton-related. Grade 3 acute esophagitis and dermatitis were observed in one and two patients, respectively. Severe ($\geq$ Grade 3) leukocytopenia, neutropenia and thrombocytopenia were observed in 10 patients, seven patients and one patient, respectively. Late radiation Grades 2 and 3 pneumonitis was observed in one patient each. Six patients (40%) experienced local recurrence at the primary site and were treated with 74 Gy RBE. Disease progression was observed in 11 patients. The mean survival time was 26.7 months. We concluded that high-dose PBT with concurrent chemotherapy is safe to use in the treatment of unresectable Stage III NSCLC.

Keywords: proton therapy; radiotherapy; lung cancer; Phase II study; chemo–proton therapy

INTRODUCTION

The prognosis of unresectable advanced non-small-cell lung cancer (NSCLC) remains poor despite advances in radiotherapy and medication. Concurrent chemoradiotherapy is the first treatment choice for unresectable advanced NSCLC. In the 2000s, dose escalation studies were encouraged, and doses > 70 Gy were delivered with concurrent chemotherapy [1–6]. The prognoses were favorable in many Phase I/II studies, with median survivals of > 20 months and toxicities that appeared tolerable [3–6]. However, in the Phase III study, there was no apparent survival benefit [7]. While the reason was unclear, cardiopulmonary toxicities were suspected as potential contributors [8]. Proton beam therapy (PBT) has been utilized in advanced lung cancer [9–11]. Proton beams can reduce the doses for normal lung tissues because of the penetration energy peak, the 'Bragg peak'. Therefore, we hypothesized that high-dose PBT with concurrent chemotherapy might be well tolerated and lead to favorable results. We initiated a Phase II study in 2010 to evaluate the safety and efficacy of high-dose PBT with concurrent chemotherapy for unresectable or medically inoperable advanced NSCLC. Herein, we report the preliminary results.

MATERIALS AND METHODS

Patients

This Phase II study was approved by the ethics board of Tsukuba University, and written informed consent was obtained from each patient. Patients with unresectable or

medically inoperable, histologically or cytologically confirmed Stage II and Stage III NSCLC (according to the TNM classification of malignant tumors, 7th edition) were enrolled between February 2010 and January 2013. Disease in all cases was staged using computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, and bone scintigram one month prior to enrollment. 2-[18F]-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) was not essential in this study. Other eligibility criteria included age between 20 and 70 years, performance status (PS) of 0–1, adequate principal organ function with serum white blood cell count (WBCs) ≥ 3000/μl, neutrophil cells (NTRs) ≥ 1500/μl, platelets (PLTs) ≥ 100 000/μl, hemoglobin (Hb) ≥ 9.0 g/dl, serum creatinine (Cre) ≤ 1.2 mg/dl, creatinine clearance (Ccr) ≥ 60 ml/min (according to the Cockcroft–Gault equation), serum alanine aminotransferase (ALT) < 100 U/l, aspartate amino transferase (AST) < 100 U/l, total bilirubin (T-Bil) < 1.5 mg/dl, forced expiratory volume after 1.0 s (FEV1.0) ≥ 0.75 l, and arterial oxygen pressure (PaO_2) ≥ 60 Torr.

Patients with contralateral hilar lymph node metastasis, intrapulmonary metastasis in the same lobe, obvious interstitial pneumonitis on imaging, or uncontrollable hypertension and diabetes were excluded. Patients who had undergone thoracic radiotherapy or chemotherapy in the past five years, patients with lung cancer within the past two years and those with a malignant tumor at another site were also excluded.

Proton beam therapy

For treatment planning, chest CT images were obtained in 5-mm thick slices in the treatment position, with a respiratory-gated system during the end-expiratory phase. The gross target volume (GTV) was defined as the primary tumor and clinically positive lymph nodes. The clinical target volume (CTV)-1 encompassed the primary tumor and the locoregional lymph nodes where clinically positive lymph nodes existed. Prophylactic lymph nodes were not included. Clinically positive lymph nodes were defined as nodes ≥ 1 cm on a CT scan or as PET-positive lymph nodes. The planned target volume (PTV)-1 covered the CTV-1 with a 7–10-mm margin in all directions and an additional 5-mm margin in the caudal direction to compensate for respiratory motion. CTV-2 was defined as only the primary tumor, and PTV-2 was settled as well. The treatment doses of 74 Gy RBE in 37 fractions and 66 Gy RBE in 33 fractions were delivered to PTV-2 and PTV-1, respectively. The targets were delineated as maximal contour on the lung and mediastinum window. The RBE of the proton beam was assigned a value of 1.1 [12]. Adapted planning was made with reduction in tumor volume.

Treatment beams were delivered during the end-expiratory phase using a respiratory gating system controlled by a laser range finder that monitors the movement of the patient's body surface. The patient's body was immobilized using a custom-shaped body cast (ESFORM, Engineering System Co., Matsumoto). Prior to each treatment, the patient's position was confirmed by fluoroscopy.

The termination criteria of PBT were as follows: WBCs < 1000/μl, NTRs < 500/μl, PLTs < 5000, fever ≥ 38° C. PBT was stopped when radiation pneumonitis was observed, and the patients were withdrawn from this study when PBT could not be reinitiated within 14 d, or disease progression was observed.

Chemotherapy

All patients received monthly concurrent cisplatin (CDDP) and vinorelbine (VNR) as intravenous infusions during PBT. CDDP was administered at 80 mg/m^2 on Day 1 and VNR was administered at 20 mg/m^2 on Days 1 and 8. The two courses of chemotherapy were administered during PBT. While neoadjuvant (induction) chemotherapy was not allowed, adjuvant (consolidation) was allowed in this study.

The discontinuance criteria of VNR on Day 8 were as follows: WBCs < 3000/μl, NTRs < 1500/μl, PLTs < 100 000/μl, infectious fever up ≥ 38°, ALT ≥ 100 U/l, AST ≥ 100 U/l, T-Bil ≥ 1.5 mg/dl, and non-hematologic toxicity ≥ Grade 3.

The continuance criteria for the second course were: WBCs ≥ 3000/μl, NTRs ≥ 1500/μl, PLTs ≥ 100 000/μl, Cre ≤ 1.2 mg/dl, Ccr ≥ 60 ml/min, ALT < 100 U/l, AST < 100 U/l, T-Bil < 1.5 mg/dl and PS ≤ 1. The second course of CDDP and VNR was reduced to 60 mg/m^2 and 15 mg/m^2, respectively, when VNR was skipped during the first course, or toxicities were observed during the first course, as follows: WBCs < 1000/μl, NTRs < 500/μl, PLTs < 25 000/μl, Cre > 1.6 mg/dl and non-hematologic toxicity ≥ Grade 3. Chemotherapy was stopped when the tumor progressed, severe (≥ Grade 3) toxicities of pneumonitis, kidney, liver or peripheral nerve were observed, if the second course could not be initiated within 14 d of the scheduled date, or if the patient refused chemotherapy.

Follow-up

Patients were evaluated at least weekly during treatment, and every 2–3 months after the PBT for 1 year, and 3–6 months, thereafter. Acute and late toxicities were defined as evaluated and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3 [13]. Acute toxicities were defined as occurring during and within 6 months after the chemo–proton therapy, and late toxicities were defined as those appeared 6 months after the completion of chemo–proton therapy. The survival and recurrence were calculated from the date of the start of chemoradiotherapy.

The response rate was evaluated and classified into complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD), according to the modifications of the Response Evaluation Criteria in Solid Tumors (RECIST) [14]. Local recurrence was defined as an increase in tumor size > 20%, or significant positive accumulation on the PET imaging.

Statistical analysis

The primary endpoint was toxicity, and the secondary endpoints were overall survival, progression-free survival, local control rate and response rate. The survival was analysed using the Kaplan–Meier method (SPSS, IBM Inc., NY, USA).

RESULTS

A total of 17 patients were enrolled in this study, and two patients were withdrawn. Obstructive pneumonia could not be controlled in one patient, and the chemotherapy agents were changed before the start of treatment. The other patient could not continue with the PBT because of the Great East Japan Earthquake, and photon radiotherapy was used as an alternative. Therefore, 15 patients were evaluated in this study.

The characteristics of the 15 patients are presented in Table 1. Four and 11 patients had Stage IIIA and III B disease, respectively, and all patients had unresectable NSCLC. The median CTV volume was 191.3 cm^3.

At the time of analysis, nine patients were alive. The median follow-up period for the survivors was 21.7 months (range: 7–39 months). The mean survival time was 26.7 months (95% confidence interval (CI): 19.5–33.9 months), and the 2-year overall survival time was 51% (95% CI: 21.7–80.3%) (Fig. 1). The median progression-free survival was 10.2 months (95% CI: 8.0–12.4 months), and the 1- and 2-year progression-free survival rates were 24.2% (95% CI: 1.0–48%) and 16.1% (95% CI: 0–36.6%), respectively (Fig. 2). The acute toxicities are presented in Table 2. Among the non-hematologic acute toxicities, Grade 3 pneumonitis was observed in two patients and was diagnosed as infectious pneumonia and obstructive pneumonia on the basis of clinical course and image findings. No severe radiation pneumonitis was observed. Grade 3 esophagitis and skin reactions were observed in one and two patients, respectively. Among the hematologic toxicities, severe ($\geq$ Grade 3) leukocytopenia, neutropenia and thrombocytopenia were observed in 10 patients, 7 patients and 1 patient, respectively. In particular, Grade 4 neutropenia was observed in four patients (26.7%). The full doses of the first and second courses of chemotherapy were completed in 13 (87%) and eight (53%) patients, respectively.

Late toxicities were evaluated in 13 patients. One patient experienced Grade 3 radiation pneumonitis, and another patient experienced Grade 2 radiation pneumonitis. Grade 1 vasculitis and skin atrophy were also observed in one patient each.

The tumor response upon completion of PBT was PR in 6 and SD in 9. Disease progression was observed in 11 patients during the follow-up period. The first progression site was local in six patients, bone metastasis in two patients, and brain, intrapulmonary and lymph nodes outside the irradiation field in one patient each. All of the local recurrences occurred in the primary tumors, not in the lymph nodes. The course of each patient is shown in Table 3.

Table 1. Patient characteristics

Age	
Median (range)	60 (40–68)
Sex	
Male	13
Female	2
Stage	
II	0
IIIA	4
IIIB	11
Pathology	
Adenocarcinoma	7
Squamous cell carcinoma	5
Non-small-cell carcinoma	2
Adenoidcystic carcinoma	1
Clinical target volume	
Median (range) (cc)	191.3 (33.1–817.3)
Status	
Alive	9
Dead	6
Local recurrence	
Yes	6
No	9

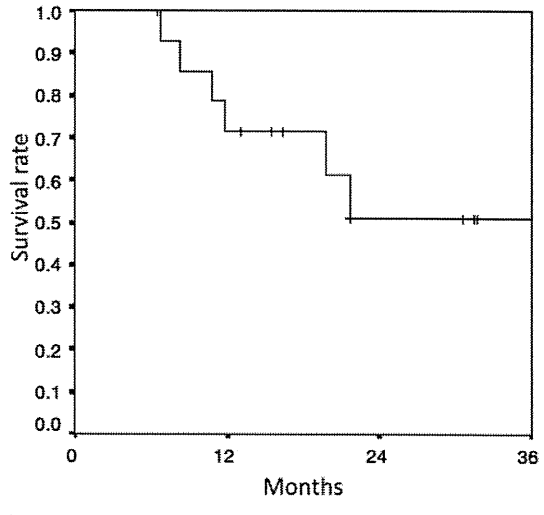


Fig. 1. Overall survival of patients.

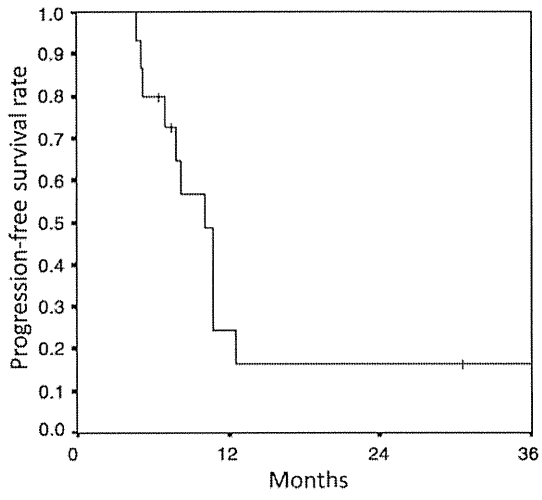


Fig. 2. Progression-free survival of patients.

Table 2. Acute toxicities

	Toxicity grade					
	0	**1**	**2**	**3**	**4**	**5**
Bone Marrow						
Leukocytopenia	1	2	2	10	0	0
Neutropenia	2	1	5	3	4	0
Hemoglobin reduction	1	12	2	0	0	0
Thrombocytopenia	13	1	0	1	0	0
Lung						
Cough	14	1	0	0	0	0
Pneumonitis	12	1	0	2[a]	0	0
Dyspnea	14	1	0	0	0	0
Gastrointestinal						
Appetite loss	13	2	0	0	0	0
Nausea	14	1	0	0	0	0
Esophagitis	7	3	4	1	0	0
Weight loss	14	0	1	0	0	0
Other						
Dermatitis	4	4	5	2	0	0
Hyperbilirubinemia	14	1	0	0	0	0
Singultation	14	1	0	0	0	0

[a]Infectious pneumonitis and obstructive pneumonia were suspected according to imaging and clinical course.

DISCUSSION

Dose escalation with concurrent chemoradiotherapy for advanced NSCLC is controversial. The median survival time was 16–26 months in Phase I/II studies of high-dose radiotherapy in combination with concurrent chemotherapy [1–6]. However, in a Phase III study, the one-year survival rate was 70.4% in the 74 Gy arm, which was much inferior to the 60 Gy arm (80%) [7]. The reason for the negative results in the Phase III study is not clear. However, Cox *et al.* suggested the contribution of cardiopulmonary toxicities [8].

Excellent dose localization of proton beams can reduce normal tissue doses. Roelofs *et al.* suggested that PBT gave the lowest dose to organs at risk (lung, esophagus, spinal cord and heart) compared with 3D conformal radiotherapy and intensity-modulated radiotherapy, while maintaining doses of 70 Gy to the target [15]. Nichols *et al.* evaluated the dose distribution in eight patients with Stage III disease and found that PBT led to about a 30% reduction of the normal lung volume receiving 20 Gy (V_{20}) in all patients [16]. Therefore, reduction of the toxicity is anticipated by the use of proton beams, even though high doses are delivered to the tumor. However, there have been few reports of high-dose chemo–proton therapy [17, 18]. Recently, Chang *et al.* reported a Phase II study with high-dose chemo–proton therapy using 74 Gy RBE and weekly carboplatine and paclitaxel. In this study, the median survival period was 29.4 months and the toxicities were considered acceptable [17].

In our series, CDDP and VNR were used as a chemotherapy regimen, according to the studies by the Cancer and Leukemia Group B (CALGB) [19] and Sekine *et al.* [20]. In the Phase II study by CALGB, gemcitabine (GEM), PTX and VNR were compared as additional agents used with CDDP for concurrent chemoradiotherapy at a dose of 66 Gy. There was a significant difference in median survival time (MST) between the three agents. However, esophagitis and platelet depletion and granulocytopenia occurred frequently in the GEM and PTX groups, respectively [19]. Sekine *et al.* reported the MST of 30.4 months for unresectable Stage III NSCLC treated concurrently with 60 Gy of photon radiotherapy and CDDP and VNR chemotherapy [20]. Therefore, we conducted chemoradiotherapy with CDDP and VNR, as performed previously (unpublished data), and continued this regimen. We found that radio-toxicities were relatively mild and well tolerated using PBT of 74 Gy with CDDP and VNR. However, nearly half of the patients were unable to complete chemotherapy, and myelosuppression occurred frequently under this chemotherapy regimen.

Meanwhile, local recurrence in the primary lesion was observed in six patients (40%) in our series. This occurred more often than the finding of 5% reported by Hoppe *et al.* [18] and of 20.5% reported by Chang *et al.* [17], and this may be due to the fact that the tumors were large and at an advanced stage (IIIB disease in the most patients) in our study with a mean CTV of 191.3 cm^3 (almost twice the CTV reported by Chang *et al.* (median: 101.3 cm^3)). Of the 19 patients in the study by Hoppe *et al.*, 16 had Stage IIIA disease [18]. In addition, Chang *et al.* set CTVs as the GTVs (defined as maximum image verified across all phases of the

Table 3. Clinical course of each patient

No.	Stage	CTV (cm^3)	#1 CDDP + VNR	#2 CDDP + VNR	Local effects	Adjuvant (#3, 4) chemo	Local recurrence	Progression	Treatment for recurrences	Overall survival (M)	Cause of death
1	IIIB	222.2	VNR skip	Reduced	SD	No	Yes	Local	chemo	19.8	Cancer
2	IIIB	65.7	Full	skip	SD	Yes	No	None	-	38.8	Alive
3	IIIA	93.9	Full	Reduced	PR	No	Yes	Marginal & Local	none	21.7	Cancer
4	IIIA	478.8	Full	skip	PR	No	Yes	Local	chemo	11.8	Cancer
5	IIIB	537.1	VNR skip	Reduced	SD	No	Yes	Local	none	10.8	Cancer
6	IIIB	155.8	Full	Reduced	PR	No	No	None	-	30.5	Alive
7	IIIB	192.6	Full	Full	PR	Yes	No	Lymph nodes	chemo, RT[#]	21.7	Alive
8	IIIB	167.1	Full	Full	PR	Yes	No	Brain	chemo RT	31.4	Alive
9	IIIB	376.2	Full	Full	SD	Yes	Yes	Local	chemo RT	31.7	Alive
10	IIIB	190.0	Full	Full	SD	Yes	No	Bone	RT	6.7	Cancer
11	IIIA	185.1	Full	Full	SD	Yes	No	None	-	8.2	CVD[‖]
12	IIIB	817.3	Full	Reduced	SD	No	No	Intrapulmonary	chemo	13.1	Alive
13	IIIB	389.7	Full	VNR skip	PR	Yes	Yes	Local	chemo	15.5	Alive
14	IIIB	33.1	Full	Full	SD	Yes	No	Bone	chemo	16.3	Alive
15	IIIA	170.7	Full	Full	SD	No	No	None	-	6.5	Alive

CTV = clinical target volume, CDDP = cisplatin, VNR = vinorelbine, SD = stable disease, PR = partial response, chemo = chemotherapy including molecularly targeted drug, RT = radiotherapy, CVD = cerebrovascular disease.

4D CT) plus 8 mm margins [17]. Tumor size may have been assessed differently because additional uniform CTV margins were not added to the GTVs on the CT images obtained at the expiratory phase in our study. In five of the six patients who experienced local recurrence the CTV was > 222 cm^3. The one patient with a CTV of 99 cm^3 exhibited marginal recurrence. In contrast, there was no in-field lymph node recurrence, even though 66 Gy RBE was delivered in this region. Therefore, it would appear that while 66 Gy RBE was sufficient to control lymph nodes, there are limitations to its ability to control large tumors, even with the high dose of 74 Gy RBE.

Because of the short follow-up period, survival has not been assessed to date. However, the current mean survival time of 26.7 months is comparable with previous reports of Phase I/II high-dose concurrent chemoradiotherapy. Most of our patients experienced disease progression, and many received adjuvant therapy, including chemotherapy, molecular-targeted agents, and photon radiotherapy. We consider that improvements in survival for advanced NSCLC could be achieved by multimodality therapy, and our study suggests that 74 Gy RBE of PBT with concurrent CDDP and VNR is safe and useful in the multimodality therapy for unresectable NSCLC.

FUNDING

This work was supported in part by Grants-in-Aid for Scientific Research (B) (24390286) from the Ministry of Education, Science, Sports and Culture of Japan. Funding to pay the Open Access publication charges for this article was provided by Grants-in-Aid for Scientific Research (B) (24390286) from the Ministry of Education, Science, Sports and Culture of Japan.

REFERENCES

1. Blackstock AW, Ho C, Butler J *et al.* Phase Ia/Ib chemo-radiation trial of gemcitabine and dose-escalated thoracic radiation in patients with stage III A/B non-small cell lung cancer. *J Thorac Oncol* 2006;**1**:434–40.
2. Hayman JA, Martel MK, Ten Haken RK *et al.* Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. *J Clin Oncol* 2001;**19**:127–36.
3. Socinski MA, Morris DE, Halle JS *et al.* Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: a dose-escalation phase I trial. *J Clin Oncol* 2004;**22**: 4341–50.
4. Socinski MA, Rosenman JG, Halle J *et al.* Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B non-small cell lung carcinoma: a modified phase I/II trial. *Cancer* 2001;**92**:1213–23.
5. Socinski MA, Blackstock AW, Bogart 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. 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**:348–56.
7. Bradley JD, Paulus R, Komaki R *et al.* A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy ± cetuximab for stage IIIA/IIIB non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617. *Abstracts of the Fifty-third Annual Meeting of the American Society for Radiation Oncology*, Miami, 2011.
8. Cox JD. Are the results of RTOG 0617 mysterious? *Int J Radiat Oncol Biol Phys* 2012;**82**:1042–4.
9. Shioyama Y, Tokuuye K, Okumura T *et al.* Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;**56**:7–13.
10. Oshiro Y, Mizumoto M, Okumura T *et al.* Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol* 2012;**7**:370–5.
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* 2010;**81**:979–84.
12. Paganetti H, Niemierko A, Ancukiewicz M *et al.* Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys* 2002;**53**:407–21.
13. Trotti A, Colevas AD, Setser A *et al.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;**13**: 176–81.
14. James K, Eisenhauer E, Christian M *et al.* Measuring response in solid tumors: unidimensional versus bidimensional measurement. *J Natl Cancer Inst* 1999;**91**:523–8.
15. Roelofs E, Engelsman M, Rasch C *et al.* Results of a multicentric *in silico* clinical trial (ROCOCO): comparing radiotherapy with photons and protons for non-small cell lung cancer. *J Thorac Oncol* 2012;**7**:165–76.
16. Nichols RC, Huh SN, Henderson RH *et al.* Proton radiation therapy offers reduced normal lung and bone marrow exposure for patients receiving dose-escalated radiation therapy for unresectable stage III non-small-cell lung cancer: a dosimetric study. *Clin Lung Cancer* 2011;**12**:252–7.
17. Chang JY, Komaki R, Lu C *et al.* Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer* 2011;**117**: 4707–13.
18. Hoppe BS, Flampouri S, Henderson RH *et al.* Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: technique and early results. *Clin Lung Cancer* 2012;**13**:352–8.
19. Vokes EE, Herndon JE, II, Crawford J *et al.* Randomized phase II study of cisplatin with gemcitabine or paclitaxel or