Comparisons of Dose-Volume Histograms for Proton-Beam versus 3-D Conformal X-Ray Therapy in Patients with Stage I Non-Small Cell Lung Cancer

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Purpose: Dose-volume histograms (DVHs) were reviewed to determine if there is an advantage of the two modalities when treating patients with non-small cell lung cancer (NSCLC).
Patients and Methods: 24 stage I NSCLC patients who underwent proton-beam therapy (PBT) from June 2003 to May 2007 were included in this study. Based on the same clinical target volumes (CTVs), treatment planning was made to cover CTV within 90% isodose lines. Each patient was evaluated by two sets of DVHs, one for PBT and the other for three-dimensional conformal X-ray therapy (3D-CRT).
Results: For all patients, the 95% isodose line covered 86.4% of the CTV for PBT, and 43.2% for 3D-CRT. PBT was associated with significantly lower mean doses to the ipsilateral lung, total lung, heart, esophagus, and spinal cord than 3D-CRT. PBT offered reduced radiation doses to the lung when evaluated in terms of percentage lung volumes receiving $\geq$ 5 Gy (V_5), $\geq$ 10 Gy (V_{10}), and $\geq$ 20 Gy (V_{20}) when compared to 3D-CRT.
Conclusion: PBT is advantageous over 3D-CRT in reducing doses to the lung, heart, esophagus, and spinal cord in treating stage I NSCLC.

Key Words: Dose-volume histograms · Proton-beam therapy · Three-dimensional conformal radiotherapy · Stage I non-small cell lung cancer

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Vergleich von Dosis-Volumen-Histogrammen für Protonenstrahlen versus 3-D konforme Röntgenstrahltherapie bei Patienten mit nichtkleinzelligem Lungenkarzinom im Stadium I

Ziel: Dosis-Volumen-Histogramme (DVHs) wurden untersucht, um die Vorteile der beiden Modalitäten bei der Behandlung von Patienten mit nichtkleinzelligem Lungenkarzinom (NSCLC) im Stadium I zu ermitteln.
Patienten und Methodik: Die Studie umfasste 24 Patienten mit NSCLC Stadium I, die im Zeitraum von Juni 2003 bis Mai 2007 mit Protonenstrahltherapie („proton beam therapy" [PBT]) behandelt wurden. Auf der Basis gleicher klinischer Zielvolumina (CTVs) wurde jeder Patient mit zwei Gruppen von DVHs beurteilt: einer für die PBT und einer für dreidimensionale konforme Röntgenstrahltherapie (3D-CRT).
Ergebnisse: Bei allen Patienten wurden die CTVs von 90% der Isodosislinien sowohl bei PBT als auch bei 3D-CRT abgedeckt, während 95% der Isodosislinien bei PBT 86,4% und bei 3D-CRT 43,2% der CTVs abdeckten. Die PBT war mit einer signifikant niedrigeren mittleren Strahlendosis für die ipsilaterale Lunge, die gesamte Lunge, das Herz, die Speiseröhre und das Rückenmark assoziiert als die 3D-CRT. Die PBT bot reduzierte Strahlenbelastungen der Lunge, wenn der Prozentsatz des Lungenvolumens bewertet wurde, welches im Vergleich zur 3D-CRT einer Strahlenbelastung von $\geq$ 5 Gy (V_5), $\geq$ 10 Gy (V_{10}) und $\geq$ 20 Gy (V_{20}) ausgesetzt war.
Schlussfolgerung: Die PBT bietet gegenüber der 3D-CRT Vorteile bei der Reduktion der Strahlendosis für die umliegenden Organe und ist die Behandlung der Wahl insbesondere bei in der Nähe des Mediastinums liegenden Tumoren.

Schlüsselwörter: Dosis-Volumen-Histogramme · Protonstrahltherapie · Dreidimensionale konforme Röntgenstrahltherapie · Nichtkleinzelliges Lungenkarzinom Stadium I

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Introduction

Lung cancer is the leading cause of cancer death for men and the third for women in Japan [2, 16, 17, 20]. As for stage I non-small cell lung cancer (NSCLC), surgical resection results in 60–70% 5-year overall survival rates [4, 9]. However, about 20% of these patients opt for another therapy because of coexisting illnesses or refusal of surgery. Conventional radiotherapy offers only 5–27% 5-year survival rates for the same group of patients [6, 14]. However, several studies have confirmed advantage of radiation dose escalation in patients with lung cancer [11, 22], and biologically equivalent doses > 100 Gy given by three-dimensional conformal radiotherapy (3D-CRT) or stereotactic body radiotherapy (SBRT) can achieve a high local control rate without jeopardizing the lung, spinal cord, heart, or esophagus [5, 19]. Recently, these therapies have become standard treatments for stage I NSCLC, and the survival rate is reported to be promising [5, 19, 30].

Our proton-beam therapy (PBT) studies [10, 26] have shown that it is an effective approach for patients with early stage NSCLC. In this study, two sets of dose distributions, PBT versus 3D-CRT, were evaluated.

Patients and Methods

From June 2003 through May 2007, 24 patients with stage I NSCLC located in the peripheral lung were treated at the Proton Medical Research Center, University of Tsukuba, Japan (Table 1).

Treatment Planning

The treatment-planning system made for PBT (Hitachi Co. Ltd, Tokyo, Japan) can calculate dose distributions both for PBT and 4-MV X-ray therapy with a pencil-beam algorithm. Clinical target volume (CTV) corresponded to the gross tumor volume with a 5-mm margin on the system display. Planning target volume (PTV) was defined as CTV plus 5–10 mm around the CTV, and an additional 5-mm margin was added in the caudal direction to compensate respiratory movements. The number of PBT ports used was determined to be two to four (mean, 2.4) by physician's preference. Using a respiratory gating system (AnzaiMedical Co., Ltd, Tokyo, Japan), proton beam irradiation was applied at the end of expiration. The treatment-planning system provided information necessary for a ridge filter, a range shifter, shapes of a collimator, and a bolus. 3D-CRT treatment planning based on 4-MV X-rays was carried out using the same system. Since the second build-up effects occur in the lung tumor, lower-energy X-ray theoretically increases the surface of the lung tumor [23]. In addition, a Japanese frame is relatively small compared to that of Europeans or Americans. Then, 4-MV X-ray might be desirable. Simulation 3D-CRT using five to seven coplanar ports (mean, 6.5) covered the same CTV and PTV.

A total dose of 66 GyE in ten fractions at the isocenter was prescribed to cover 90% CTV with adequate margin for both treatment plans. Irradiated volumes and doses to the normal lung, spinal cord, heart, and esophagus were outlined slice by slice on the treatment-planning system, and were evaluated by dose-volume histogram analyses. The treatment-planning system provided mean doses to the ipsilateral lung, total lung, heart, esophagus, spinal cord, percent volumes of the lung receiving ≥ 5 Gy (V_5), ≥ 10 Gy (V_{10}), and ≥ 20 Gy (V_{20}), and 90% and 95% isodose line coverage for PBT and 3D-CRT.

Table 1. Patients' characteristics (n = 24). CTV: clinical target volume.

Tabelle 1. Patientencharakteristik (n = 24). CTV: klinisches Zielvolumen.

Gender (n)	
• Male	17
• Female	7
Age (years)	70 (51–83)
Clincal stage (n)	
• T1 N0 M0	16
• T2 N0 M0	8
Performance status	
• 0	16
• 1	7
• 2	1
Calculated irradiated field size[a] (mm)	24 (10–42)
Histology (n)	
• Adenocarcinoma	16
• Squamous cell carcinoma	6
• Large cell carcinoma	1
• Low differentiated carcinoma	1
Reasons for nonsurgical treatment (n)	
• Pulmonary disease	9
• Cardiovascular disease	3
• Mental disease	1
• Patient refusal	11

[a]calculated by the following equation: $(6 \times CTV/\pi)^{1/3}$

Table 2. Dose-volume histogram: proton versus photon. CTV: clinical target volume.

Tabelle 2. Dosis-Volumen-Histogramm: Proton versus Photon. CTV: klinisches Zielvolumen.

	Proton	Photon	p-value
Lung			
• Total lung dose (Gy)	2.6 ± 0.9	4.6 ± 1.2	p < 0.001
• Ipsilateral lung dose (Gy)	5.6 ± 1.8	8.6 ± 2.1	p < 0.001
• V_5 (%)	10.2 ± 3.3	25.7 ± 5.0	p < 0.001
• V_{10} (%)	8.5 ± 3.0	14.5 ± 3.3	p < 0.001
• V_{20} (%)	5.3 ± 2.0	7.4 ± 2.2	p < 0.001
Esophagus (Gy)	0.0 ± 0.1	2.7 ± 2.1	p < 0.001
Heart (Gy)	0.1 ± 0.3	3.5 ± 3.0	p < 0.001
Spinal cord (Gy)	0.1 ± 0.3	1.8 ± 1.3	p < 0.001
CTV covered by 90% isodose line (%)	99.0 ± 1.3	99.0 ± 0.4	p = 0.57
CTV covered by 95% isodose line (%)	86.4 ± 12.5	43.2 ± 33.0	p < 0.001

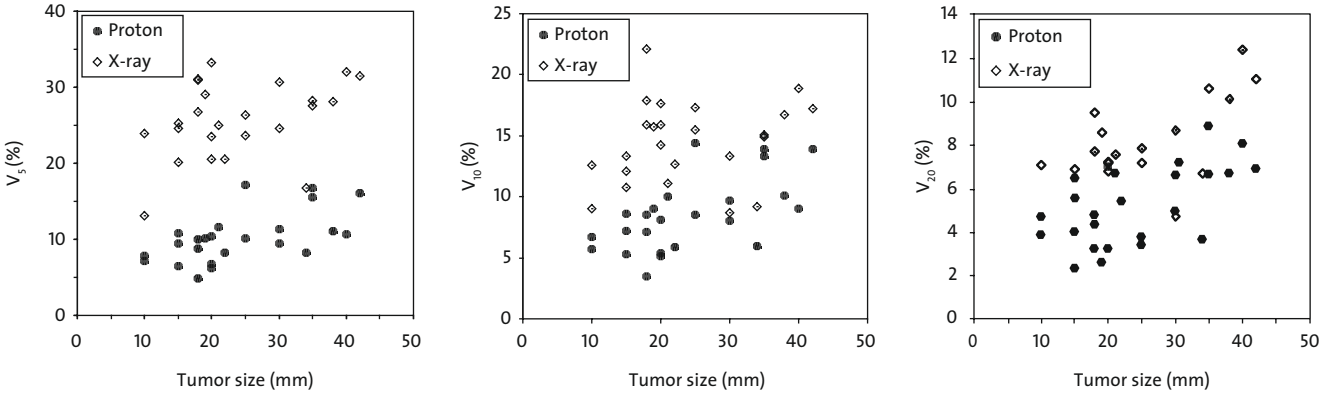

Figure 1. V_5, V_{10} and V_{20} were plotted referring to calculated field size. PBT appears more beneficial over 3D-CRT in terms of V_5 more than V_{10} or V_{20} and V_{10} more than V_{20}. PBT appears beneficial for the lung which has limited functions.

Abbildung 1. V_5, V_{10} und V_{20} wurden unter Bezugnahme auf die berechnete Feldgröße eingetragen. Die PBT scheint hinsichtlich einer V_5 von mehr als V_{10} oder V_{20} und V_{10} von mehr als V_{20} vorteilhafter als die 3D-CRT zu sein. Die PBT scheint für Lungen mit eingeschränkter Funktion von Vorteil zu sein.

Data obtained were analyzed using an SPSS program (Version 11.0, Chicago, IL, USA), and statistical differences were tested by t-test.

Proton-Beam Therapy

Proton beams with a maximum energy of 250 MeV (PROBEAT, Hitachi Co. Ltd., Tokyo, Japan) employing passive scattering were spread out by the ridge filter, adjusted in the distal margin by a range shifter, tailored by a compensator, shaped by a collimator, and conformally covered the PTV while sparing the adjacent normal tissue.

Results

The calculated data for the 24 patients in PBT and 3D-CRT are shown in Table 2. The 90% isodose line covered > 99% of the CTVs both in PBT and 3D-CRT treatment plans, while the 95% isodose line covered 86.4% of the CTV in PBT and 43.2% in 3D-CRT ($p < 0.001$). After a total dose of 66 GyE for all 24 patients, mean doses from PBT to the ipsilateral lung, total lung, heart, esophagus, and spinal cord were 5.6, 2.6, 0.1, 0.0, and 0.1 GyE, respectively, whereas those from 3D-CRT were 8.6, 4.6, 3.5, 2.7, and 1.8 GyE, respectively ($p < 0.001$). As for assessing the exposure to the lung, V_5, V_{10}, and V_{20} values were 10.2%, 8.5%, and 5.3%, respectively, for PBT, whereas they were 25.7%, 14.5%, and 7.4%, respectively, for 3D-CRT ($p < 0.001$). Figure 1 shows V_5, V_{10}, and V_{20} data corresponding to the average tumor diameter, indicating that PBT reduces doses to the normal lung.

Discussion

Regarding lung toxicities, Graham et al. [8] have shown that V_{20} is a predictor of radiation pneumonitis in NSCLC patients treated by photon radiotherapy which includes 3D-CRT. Wang et al. [28] have reported a correlation between V_5, V_{10} and lung toxicity. Georg et al. [7] reported that only small dosimetric differences between PBT and X-ray were found, but V_2 and V_4 of PBT were statistically significantly better than those of 3D-CRT. Our results show that PBT significantly reduces the mean doses to the ipsilateral and total lung, V_5, V_{10}, and V_{20} when compared to 3D-CRT ($p < 0.001$) while effectively covering the CTV (Table 2). Although severe toxicities were rare when treated with PBT, stereotactic radiotherapy or 3D-CRT [3, 13, 15, 27], a reduction in irradiated lung volumes is critical in patients with chronic obstructive lung diseases.

In regard to relatively large tumors, Timmerman et al. [27] have reported that a CTV of > 10 ml has an eightfold risk of high-grade toxicity compared with smaller tumors when using X-ray therapy. Our study failed to show the benefit of PBT when treating large tumors, however, Chang et al. [3] reported that PBT reduced dose to normal tissue compared with X-ray in patients with stage III NSCLC. The V_{20} is the percentage of the total lung volume irradiated in excess of the maximal tolerance dose which may be lower if there is chronic lung disease. PBT appears beneficial over 3D-CRT when compared with V_{10} or V_5.

PBT holds advantage over 3D-CRT [1] when treating a tumor located close to critical organs, such as heart, esophagus, and spinal cord, since the major feature of PBT is the depth dose distribution. Timmerman et al. [27] have shown that patients with central tumor locations have an elevenfold increase in risk of experiencing severe toxicity compared with those with more peripheral ones. Onimaru et al. [18] have reported a grade 5 radiation-induced esophageal ulcer after receiving a dose of 48 Gy in eight fractions.

Concurrent chemoradiotherapy has become the standard in stage III NSCLC patients with good performance status [12, 21], however, > 50% of patients suffer from grade 3 or higher acute toxic effects, and 10–15% of patients develop grade 3

or higher chronic toxic effects, because antineoplastic agents may enhance the risk of radiation toxicity [24, 25, 29]. It is apparent that smaller-volume irradiation reduces the incidence of these high-grade toxicities.

Conclusion

This study has shown that PBT significantly reduces the doses to the lung, heart, esophagus, and spinal cord, compared with optimal 3D-CRT when treating stage I NSCLC. This advantage, however, is not obvious when treating a large tumor. These results need to be confirmed by further investigations.

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