Dosimetric Analysis Between Carbon Ion Radiotherapy and Stereotactic Body Radiotherapy in Stage I Lung Cancer

TAKESHI EBARA[1], HIROFUMI SHIMADA[2], HIDEMASA KAWAMURA[2], KATSUYUKI SHIRAI[3], JUN-ICHI SAITO[3], MOTOHIRO KAWASHIMA[2], MUTSUMI TASHIRO[2], TATSUYA OHNO[2], TATSUAKI KANAI[2] and TAKASHI NAKANO[3]

[1]*Department of Radiation Oncology, Gunma Prefectural Cancer Center, Gunma, Japan;*
[2]*Gunma University Heavy Ion Medical Center, Gunma University, Gunma, Japan;*
[3]*Department of Radiation Oncology, Gunma University, Graduate School of Medicine, Gunma, Japan*

Abstract. *Aim: To evaluate dosimetric differences between carbon ion radiotherapy (C-ion RT) and stereotactic body radiotherapy (SBRT) for stage I non-small cell lung cancer (NSCLC). Patients and Methods: Thirteen stage I NSCLC cases were planned with C-ion RT and SBRT. Prescription of the dose and fractionation (fr) for stage IA and IB in C-ion RT were 52.8 Gy (RBE)/4fr and 60.0 Gy (RBE)/4fr, respectively and those in SBRT were 52.8 Gy/4fr and 60.0 Gy/4fr, respectively. Results: The conformity index (CI) for planning target volume of C-ion RT was significantly lower than that of SBRT. The normal lung doses in C-ion RT were significantly lower those that in SBRT. In particularly, for a larger tumor, C-ion RT was lower CI and normal lung dose than SBRT. Conclusion: C-ion RT has an advantage in both target conformity and sparing of normal lung in stage I NSCLC.*

The application of radiotherapy (RT) is based on the fundamental principle of achieving precise dose localization in the target lesion while causing minimal damage to surrounding normal tissues. Particle therapy with carbon ions or protons as well as stereotactic body radiation therapy (SBRT) appears to be effective for patients with stage I non-small cell lung cancer (NSCLC) (1-5). Particle therapy has a better dose distribution compared to photons. The physical advantage of particle therapy is that it can deliver similar or higher doses to the tumor while reducing doses to the surrounding normal tissues. This characteristic could prove beneficial in lung cancer patients with compromised pulmonary function.

Correspondence to: Takeshi Ebara, Department of Radiation Oncology, Gunma, Prefectural Cancer Center, 617-1 Takabayashinishi Ota, 373-8550 Gunma, Japan. Tel: +81 276380771, Fax: +81 276380614, e-mail: evashun1999@yahoo.co.jp

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Carbon ions and protons share the similar physical property of having a Bragg peak. However, there are several differences between them. For example, carbon ions show less lateral scatter than protons and distal fall-off of protons is steeper than that of carbon ions. In addition, a carbon-ion beam has high linear energy transfer (LET). Low-LET radiations such as photon and proton are less effective to hypoxic tumor cells and differences in radiosensitivity related to the cell cycle of tumor. In contrast, high-LET radiations can be effective because of the reduction of the oxygen enhancement ratio and differences in radiosensitivity related to the cell cycle of tumor (6).

Several studies have demonstrated that proton therapy (PT) was more advantageous than SBRT in reducing doses to the lung and delivering similar or higher doses to planning target volume (PTV) in treating stage I NSCLC (7-10). On the other hand, there is no report addressing the dosimetric comparisons between carbon ion radiotherapy (C-ion RT) and SBRT. Therefore, the purpose of the present study was to clarify the dosimetric differences between C-ion RT and SBRT for stage I NSCLC patients.

Patients and Methods

Patients. Data from 13 stage I consecutive cases (7 cases of stage IA and 6 cases of IB) of NSCLC were analyzed. All of them had actually undergone photon radiation therapy at our hospital.

Treatment planning. Computed tomography (CT) images for actual SBRT were used for this virtual plan study. CT scans were obtained under normal quiet breathing with 1.25-2.50-mm thickness and interval in supine position. The gross tumor volume (GTV) was delineated on serial CT images. The clinical target volume (CTV) was defined as the GTV with an 8-mm margin in all directions within lung parenchyma. The PTV was defined as the CTV with a 2-mm margin in all directions. The dose prescription for stage IA and IB in C-ion RT were 52.8 Gy (RBE) and 60.0 Gy (RBE) in 4 fractions, respectively and those in SBRT were 52.8 Gy and 60.0 Gy in 4fractions, respectively. The unit about Gy (RBE) has been described previously (11,12). The prescribed point was defined

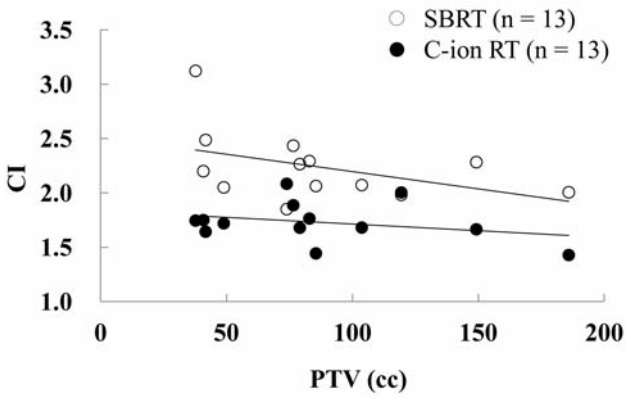

Figure 1. *Scatter diagrams comparing PTV with CI for C-ion RT and SBRT. PTV; Planning target volume, CI; conformity index, C-ion RT; carbon ion radiotherapy, SBRT; stereotactic body radiotherapy.*

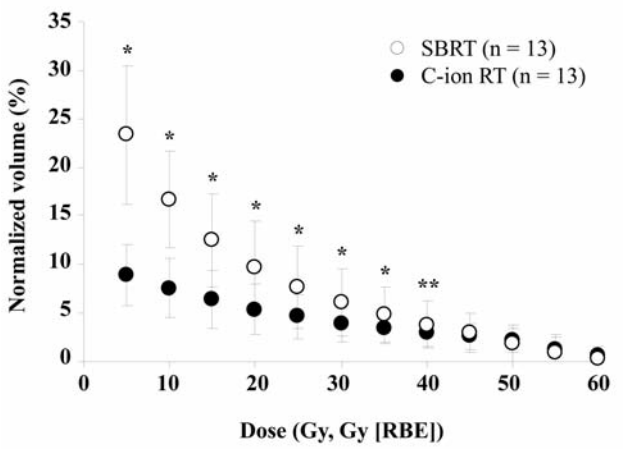

Figure 2. *The relative volumes of normal lung receiving more than a threshold dose. The differences between C-ion RT and SBRT increased with decreasing received dose. Data are presented as the mean±SD. *p<0.001, **p<0.005.*

in the center of the PTV. The same CT images and contours were used for generating the C-ion RT and SBRT. All plans were calculated with heterogeneity correction.

C-ion RT plans were designed using the XiO-N system (ELEKTA, Stockholm, Kingdom of Sweden and Mitsubishi Electric, Tokyo, Japan). The XiO-N system consists of XiO (ELEKTA)-based platform, external dose engine, k2 Dose, and connection and source data management tool (Mitsubishi Electric) and provided information necessary for a ridge filter, a range shifter, shapes of the multileaf collimator and a range compensator (RCs) bolus. The leaf margin was normally adjusted to 5-6 mm on the iso-center plane to cover the PTV with 95% of a prescribed dose. A smearing margin to the RCs to smear out the dose was added. The number of C-ion RT ports was determined to be 2 to 4 by physician's preference. The details of planning have been described previously (13).

SBRT plans were designed using the XiO 4.30 (ELEKTA) system. The shapes of beams were manually optimized using the multileaf collimation with 6 to 8 non-coplanar 4 or 6 MV photon beams. The individual field weights were also arranged in order to cover the PTV at least 80 % of the prescribed dose and minimize the organ at risk (OAR) dose.

The following dosimetric parameters were assessed; homogeneity index (HI; maximum dose/minimum dose in target) and conformity index (CI; volume receiving the minimum target dose/target volume) for the PTV. Mean normal lung dose (MLD) and Vd were evaluated by the dose-volume histogram of normal lung. Vd was defined as the relative volumes of normal lung receiving more than a threshold dose (d). For example, V20 meant the percentage of normal lung volume irradiated to 20 Gy or more. The threshold dose employed were 5–60 Gy in increments of 5 Gy. Normal lung volume was defined as the bilateral lung volume minus GTV. Maximum and mean doses to spinal cord, esophagus, trachea and heart were also evaluated.

Statistical analysis. All dosimetric data were compared with a paired two-tailed Student's *t*-test. Statistical analyses were performed using the StatView J-5.0 Japanese version software package (HULINKS, Inc. Tokyo, Japan). Differences with a *p*-value of <0.05 were considered significant.

Results

The median of GTV was 21.0 cc with a range of 4.0-66.2 cc and that of PTV was 79.1 cc with a range of 37.7-185.8 cc. The CI for PTV of C-ion RT and SBRT were 1.73±0.19 and 2.24±0.32, respectively ($p<0.01$). Figure 1 shows scatter diagrams comparing PTV with CI for C-ion RT and SBRT. Larger differences in the CI were seen with smaller PTV while C-ion RT was lower CI to larger PTV. The HI for PTV of C-ion RT and SBRT were 1.27±0.10 and 1.30±0.08, respectively (not significant). Figure 2 depicts relative volumes of normal lung receiving more than the threshold dose. V5 through V40 with increments of 5 Gy in C-ion RT were significantly lower than that in SBRT. The MLD of C-ion RT and SBRT were 2.86±1.22 Gy and 5.99±2.04 Gy, respectively ($p<0.001$). Figures 3 shows scatter diagrams comparing PTV with V5, V10, V15, V20 and MLD for C-ion RT and SBRT. The Vd and MLD of C-ion RT were lower than those of SBRT, although those for both C-ion RT and SBRT increased with enlargement of PTV. The outcomes for dosimetric parameters for normal tissues are summarized in Table I. Except for the maximum dose for the trachea, all parameters of C-ion RT were significantly smaller than that of SBRT.

Figure 4 illustrates a representative case of stage IB. C-ion RT showed that the 95% isodose line covered the PTV while SBRT showed that the 80 to 90% isodose line covered the PTV. Moreover the dose distribution outside PTV of C-ion RT is steeper than that of SBRT. In C-ion RT

Table I. *Summary of dosimetric parameters for normal tissues*.

	Maximum dose		*p*-Value	Mean dose		*p*-Value
	C-ion RT (cGy (RBE))	SBRT (cGy)		C-ion RT (cGyE (RBE))	SBRT (cGy)	
Spinal cord	2.3±2.3	12.2±7.8	0.001	0.2±0.2	2.2±1.3	0.001
Esophagus	4.1±6.9	14.4±13.3	<0.01	0.2±0.1	3.1±3.0	0.01
Trachea	19.5±24.0	21.2±22.8	NS	0.6±0.8	3.4±3.5	<0.05
Heart	7.8±19.0	15.7±19.7	<0.05	0.3±0.7	4.9±6.6	<0.05

C-ion RT: Carbon ion radiation therapy, SBRT: Stereotactic body radiotherapy. Mean±standard deviation, RBE: relative biological effectiveness.

the 50% isodose line fits to PTV and the 20% isodose line covers the half area of ipsilateral lung, while in SBRT the 50% isodose line covers the half of ipsilateral lung and the 20% isodose line covers almost all the ipsilateral lung on the iso-center plane.

Discussion

The present study revealed that C-ion RT presented a more conformal dose distribution than SBRT and significantly reduced doses to the normal tissues compared to SBRT. The characteristic carbon-ion beam, that is distal fall-off the Bragg peak and less lateral scatter than photon, realizes conformal dose distribution and sparing normal tissues. The HI for PTV showed no significant difference in C-ion RT and SBRT. Because SBRT planned to cover the almost PTV by 90 % of the prescribed dose, the dose in PTV resulted in homogeneous distribution.

There are many studies addressing the dosimetric factors to predict radiation pneumonitis (RP) in lung cancer treated with SBRT. Takeda *et al*. showed that V15 was a significant factor differentiating between grade 0-1 and grade 2 RP (14). Barriger *et al*. reported that development of symptomatic RP correlated with V20 (15). Matsuo *et al*. demonstrated that V25 was a significant factor associated with RP (16). Barriger and Borst revealed significant dose–response relationship between the risk of RP and MLD (15,17). All of these dosimetric factors were significantly low in C-ion RT compared to SBRT. Low dose parameter such as a V5, in which there was large difference between C-ion RT and SBRT has not reported the predictive value for PR after SBRT. However, the data from three-dimensional conformal radiation therapy and intensity-modulated radiation therapy for thoracic malignancies suggested that delivery of a small dose of radiation as low as 5 Gy to a large lung volume is not safe (18, 19). A small dose of radiation to a large volume of lung could be much worse than a large dose to a small volume in functional lung damage. This fact is important for candidates for radiation therapy because they have pulmonary comorbidities. Additionally, large PTV and higher CI are also reported to be significant risk factors for RP after SBRT (16, 20). C-ion RT which is keeping normal lung dose and CI at low levels could be fit for large PTV.

Although reduced doses to spinal cord, esophagus, trachea and heart were statistically significant, the absolute differences were small and with unknown clinical significance. Tolerance doses of spinal cord, esophagus and trachea were well-established and it is not difficult to establish lower tolerance doses in SBRT. On the other hand, a clear quantitative dose and/or volume dependence for most radiation-induced heart disease has not yet been shown (21). Recently, rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy, with no apparent threshold (22). Doses to the heart must be carefully managed because patients with stage I NSCLC are expected to be long-term survivors.

Several treatment planning studies have shown that PT demonstrates a superior conformality and a reduced dose to adjacent normal tissue or critical structures compared to SBRT (7-10). There might be no significant dosimetric difference between C-ion RT and PT for stage I NSCLC. However, the carbon-ion beam has high LET for which the relative biological effectiveness (RBE) can be as high as 2.0-3.5 (6). The tumors with low radioresponsiveness against low-LET radiations (photon and proton) are assumed to have a high proportion of hypoxic cells, poor re-oxygenation pattern and high intrinsic repair capacity. A large tumor such a T2 showed a higher local recurrence rate and worse survival than a T1 tumor. The tumor diameter was a significant factor in all failures (local, regional or distant metastases) after SBRT for stage I NSCLC (23). This can possibly be explained by the increased percentage of more radioresistant and aggressive cells in large tumors, which include larger populations of low radioresponsive cells against low LET. Thereby, it is also assumed that large tumors could benefit from C-ion RT in terms of biology.

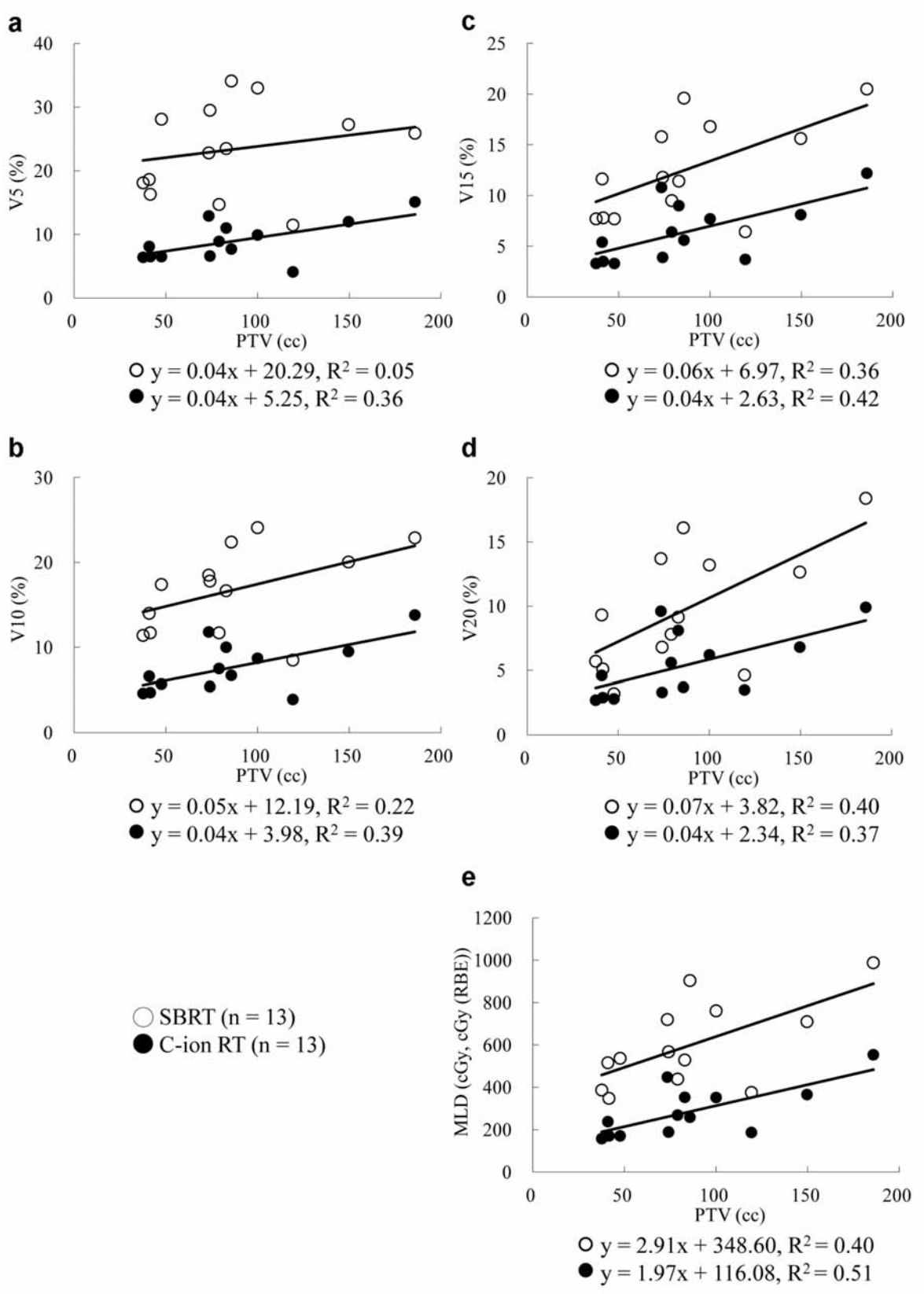

Figure 3. *(a)-(e). Scatter diagrams comparing PTV with V5, V10, V15, V20 and mean normal lung dose (MLD) for C-ion RT and SBRT.*

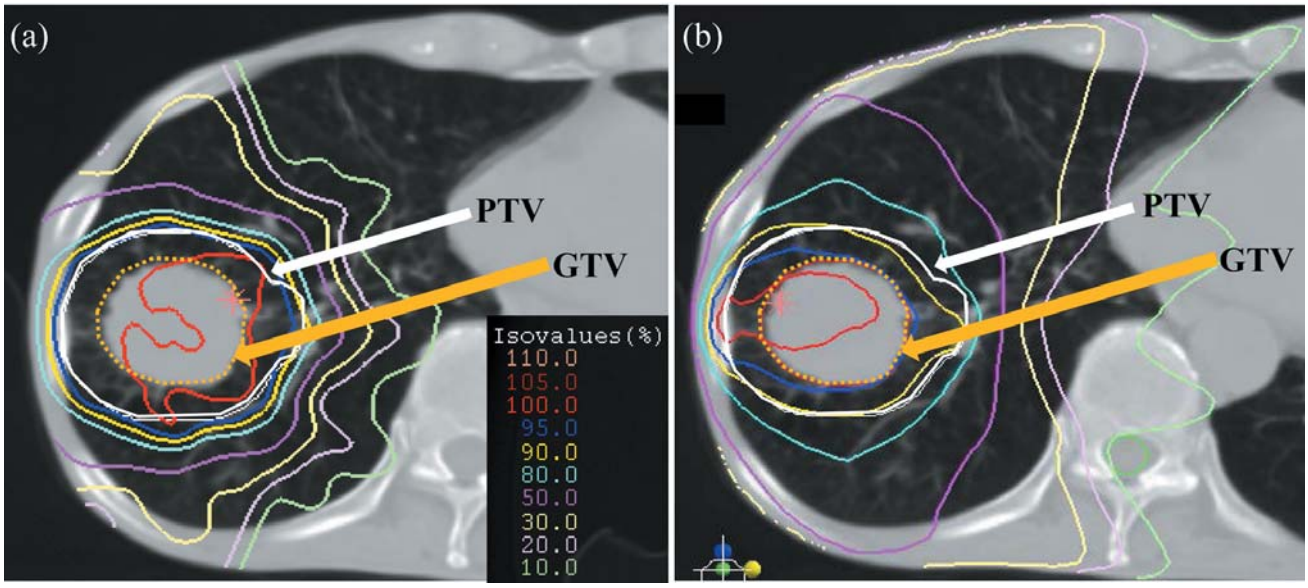

Figure 4. *(a)-(b). (a); C-ion RT, (b); SBRT). Representative case of stage IB. Color-corded dose distribution is shown with percent isodose lines.*

Finally, the limitations of the present study must be addressed. The influence of respiratory movements could not be evaluated in the present study. Because the carbon-ion beam is sensitive to geometric uncertainties and in hypodense tissue such as the lung parenchyma where the beam attenuation is low, respiratory movements are more important for the carbon-ion beam than for a photon. Strictly speaking, the tumor moves in the gating phase, although the carbon-ion beam is usually delivered under respiratory-gated movements. Because the depth dose distribution for carbon ion beam is sensitive to change in tissue density along its pathlength, intrafraction movements perturbs the carbon ion beam distribution (24). In addition, since the carbon-ion beam ports in our facility were fixed to be either horizontal or vertical, the patient was usually rolled to concentrate the dose to the target. Simulation CTs for C-ion RTs are scanned in each position because the anatomic organ location can change due to the position. However, the simulation CTs for the present study were obtained in the supine position only. Namely, the anatomic organ location changes due to the CT positions were not considered for the present study.

In conclusion, C-ion RT with 2, 3, or 4 beams provides an advantage in both target conformity and sparing of normal lung tissues compared with SBRT in peripheral stage I NSCLC. C-ion RT appears to have an advantage over SBRT especially for larger tumors.

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