Dosimetric comparison of carbon ion and X-ray radiotherapy for Stage IIIA non–small cell lung cancer

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ABSTRACT

The present study compared the dose–volume histograms of patients with Stage IIIA non–small cell lung cancer (NSCLC) treated with carbon ion radiotherapy with those of patients treated with X-ray radiotherapy. Patients with Stage IIIA NSCLC (n = 10 patients for each approach) were enrolled. Both radiotherapy plans were calculated with the same targets and organs at risk on the same CT. The treatment plan for the prophylactic lymph node and primary tumor (PTV1) delivered 40 Gy for X-ray radiotherapy and 40 Gy (relative biological effectiveness; RBE) for carbon ion radiotherapy. The total doses for the primary tumor and clinically positive lymph nodes (PTV2) were 60 Gy for X-ray radiotherapy and 60 Gy (RBE) for carbon ion radiotherapy. The homogeneity indexes for PTV1 and PTV2 were superior for carbon ion radiotherapy in comparison with X-ray radiotherapy (PTV1, 0.57 vs 0.65, P = 0.009; PTV2, 0.07 vs 0.16, P = 0.005). The normal lung mean dose, V5, V10 and V20 for carbon ion radiotherapy were 7.7 Gy (RBE), 21.4%, 19.7% and 17.0%, respectively, whereas the corresponding doses for X-ray radiotherapy were 11.9 Gy, 34.9%, 26.6% and 20.8%, respectively. Maximum spinal cord dose, esophageal maximum dose and V50, and bone V10, V30 and V50 were lower with carbon ion radiotherapy than with X-ray radiotherapy. The present study indicates that carbon ion radiotherapy provides a more homogeneous target dose and a lower dose to organs at risk than X-ray radiotherapy for Stage IIIA non–small cell lung cancer.

KEYWORDS: carbon ion, locally advanced NSCLC, dosimetry analysis, DVH, lung cancer

INTRODUCTION

Combined treatment with radiotherapy and chemotherapy is a standard treatment for patients with unresectable locally advanced non–small cell lung cancer (NSCLC). The 5-year overall survival rate for locally advanced NSCLC treated with combined radiotherapy and chemotherapy is 15–20%, and the local relapse rate is ~30% [1–3]. Although an X-ray radiotherapy dose escalation study has been conducted to assess clinical outcomes with increased doses of radiation, the efficacy of this approach remains unclear [4]. The RTOG0617 study, which compared high-dose and standard-dose radiotherapies for Stage IIIA and IIIB NSCLC, showed that patients treated with high-dose radiotherapy had a worse clinical outcome than those treated with standard doses [5].

A carbon ion beam has a Bragg peak and a sharp penumbra, which confers a higher conformal dose distribution than X-rays [6], and it is effective in combating X-ray–resistant tumors. Carbon ion radiotherapy is clinically effective against X-ray–resistant tumors, such as chordoma, sarcoma, and non-squamous head and neck tumors [7]. In Stage I NSCLC, the 5-year local control rate of patients treated with carbon ion radiotherapy is 95% for T1 tumors and 80% for T2 tumors. In addition, carbon ion radiotherapy for lung cancer is a safe treatment for elderly people and patients with
poor pulmonary function [8, 9]. A comparison of the dose–volume histograms (DVHs) of carbon ion radiotherapy with those of stereotactic body radiotherapy in Stage I NSCLC showed that carbon ion radiotherapy has better target conformity and spares normal tissues of the lung, spinal cord, heart, esophagus and trachea [10]. A proton beam also has a Bragg peak. Several studies have shown that proton beam radiotherapy can deliver a high dose to tumors while reducing the dose to surrounding normal organs [11–15].

A prospective non-randomized Phase I/II study of carbon ion radiotherapy for patients with inoperable Stage IIA–IIIA NSCLC was reported. The majority of patients (49 of 62) were N0 or N1 patients, and the rest (13 of 62) were single-station N2 patients. They received a total dose of 68–76 Gray equivalents (GyE) in 16 fractions without concurrent chemotherapy. Two-year local control and overall survival rates in the 62 patients were 93.1% and 51.9%, respectively. The rate of Grade 3 or greater toxicity was 3.2%. The authors concluded that this result was superior to that of X-ray chemotherapy. The rate of Grade 3 or greater toxicity was 3.2%. The authors concluded that this result was superior to that of X-ray chemotherapy. Two-year survival rates in the 62 patients were 93.1% and 51.9%, respectively. The rate of Grade 3 or greater toxicity was 3.2%.

The maximum irradiation field size at our carbon ion radiotherapy facility is 15 cm × 15 cm under the multileaf collimator in fully opened condition [18]. The patients who could not be treated with single field were excluded. Half of the tumors were in the right lung and half in the left lung. The clinical stage of the patients was T1–3N2M0 (n = 9) and T3N1M0 (n = 1) (Table 1). The present study was approved by the institutional review board of our hospital (No. 1309).

### MATERIALS AND METHODS

#### Patients

Ten patients with Stage IIA NSCLC were enrolled. All patients were treated with X-ray radiotherapy in our institute during 2008–2012. Those patients were treated with X-ray radiotherapy in our institute during 2008–2012. The maximum irradiation field size at our carbon ion radiotherapy facility is 15 cm × 15 cm under the multileaf collimator in fully opened condition [18]. The patients who could not be treated with single field were excluded. Half of the tumors were in the right lung and half in the left lung. The clinical stage of the patients was T1–3N2M0 (n = 9) and T3N1M0 (n = 1) (Table 1). The present study was approved by the institutional review board of our hospital (No. 1309).

#### Table 1. Pretreatment patient characteristics

| No. | TNM     | Primary tumor location | Size of primary tumor (cm) | IASLC lymph node station | Maximal nodal size (cm) and location (s) |
|-----|---------|------------------------|-----------------------------|--------------------------|----------------------------------------|
| 1   | T1bN2M0 | Left upper             | 2.8                         | #4, #6, #11, #10         | 5.0 (#4)                              |
| 2   | T3N2M0  | Right upper            | 3.3                         | #4, #6, #10–11           | 5.4 (#6)                              |
| 3   | T2aN2M0 | Right upper            | 4.8                         | #4, #10, #11             | 3.8 (#4)                              |
| 4   | T2aN2M0 | Right upper            | 3.2                         | #2, #4                   | 3.5 (#2)                              |
| 5   | T1bN2M0 | Left upper             | 3.0                         | #3a, #6                  | 7.6 (#6)                              |
| 6   | T2bN2M0 | Right upper            | 5.5                         | #4, #7, #10, #11         | 6.1 (#4)                              |
| 7   | T2bN2M0 | Left upper             | 6.8                         | #5, #6                   | 1.0 (#5)                              |
| 8   | T1bN2M0 | Left upper             | 2.6                         | #5, #10                  | 1.8 (#10)                             |
| 9   | T3N1M0  | Right upper            | 5.2                         | #11                      | 5.2 (contiguous with primary)         |
| 10  | T1bN2M0 | Left upper             | 2.4                         | #4                      | 1.0 (#4)                              |

IASLC = International Association for the Study of Lung Cancer.

### Treatment planning

For treatment planning, free breathing computed tomography (CT) images were obtained from 2.5-mm thickness slices. The gross tumor volume (GTV) included the primary tumor and clinically positive lymph nodes. Clinically positive lymph nodes were defined as nodes ≥1 cm on CT images or positron emission tomography–positive lymph nodes. The clinical target volume (CTV) included the GTV and prophylactic lymph nodes, which were defined as the ipsilateral hilum and mediastinal nodal areas using the lymph node map of the International Association for the Study of Lung Cancer [19]. The planning target volume (PTV) 1 was defined as the CTV plus a 5–10-mm margin in all directions, while taking into consideration organ motion and set-up errors. PTV2 did not include prophylactic lymph nodal areas. PTV2 was defined as the GTV plus a 5–10-mm margin in all directions, while taking into consideration organ motion and set-up errors. Lungs, spinal cord, esophagus and ‘trachea and proximal bronchial tree (trachea & PBT)’ were contoured as organs at risk (OARs), using the RTOG 1106 Atlas [20]. Bone (ribs, clavicles and vertebrae) were autocontoured using MIM Maestro (ver. 6.3; MIM Software Inc., Cleveland, USA) as an OAR. The same target volumes and OARs were used in carbon ion and X-ray radiotherapy treatment planning. PTV1 received a dose of 40 Gy/Gy (relative biological effectiveness; RBE). PTV2 received an additional dose of 20 Gy/Gy (RBE). The total dose for PTV2 was 60 Gy/Gy (RBE). The dose was administered to the PTV’s isocenter. The dose of carbon ion radiotherapy is expressed as Gy (RBE),
which is defined as the physical dose (Gy) multiplied by the RBE of the carbon ions. GyE has the same meaning. GyE has been previously reformulated as Gy (RBE) \[21, 22\]. The normal lung dose (MLD) and V5, 10, 20, 30, 40 and 50 were evaluated from the DVH of normal lung. We also evaluated: maximum spinal cord dose; esophageal maximum dose and V50; bone V10, V30 and V50; and trachea & PBT V40 and V50.

**Statistical analysis**

The results were compared using the Wilcoxon matched-pair signed-rank test for non-normally distributed data. The threshold for statistical significance was set to \(P < 0.05\). Statistical analysis was performed using IBM SPSS Statistics 21.0 software (IBM, Armonk, NY, USA).

**RESULTS**

**Dose delivery to PTVs**

Table 2 shows the DVHs of the PTVs. There was no difference between the two treatments in D95% for PTV1, which included prophylactic lymph nodes. Carbon ion radiotherapy had a lower D2% and a higher D98% for PTV1 than X-ray radiotherapy. The HI for PTV1 using carbon ion radiotherapy was superior to that using X-ray radiotherapy (0.57 vs 0.65, \(P = 0.009\)). There was no difference between the two plans with respect to the D50% for PTV2 \([60.0 \text{ Gy (RBE)} \text{ vs } 60.1 \text{ Gy}, P = 0.959\]). The D95% for PTV2 using carbon ion radiotherapy was superior to that using X-ray radiotherapy \([58.2 \text{ Gy (RBE)} \text{ vs } 55.6 \text{ Gy}, P = 0.005\]). The HI for PTV2 using carbon ion radiotherapy was also superior to that using X-ray radiotherapy (0.07 vs 0.16, \(P = 0.005\)).

**Dose delivery to organs at risk**

The results of the lung doses V5, V10, V20, V30, V40 and V50 are shown in Fig. 2. All indexes of irradiated normal lung volume were significantly lower with carbon ion radiotherapy. The mean lung dose of carbon ion radiotherapy was lower than that of X-ray radiotherapy \([7.7 \pm 1.7 \text{ Gy (RBE)} \text{ vs } 11.9 \pm 1.7 \text{ Gy}, P = 0.005\]). The other dose–volume measurements for OARs are shown in Table 3. Maximum spinal cord dose, esophageal V50, bone V10, V30 and V50, and trachea & PBT V50 were lower with carbon ion radiotherapy than with X-ray radiotherapy. There was no significant difference in trachea & PBT V40 between the two radiotherapies.

**DISCUSSION**

The present study showed that the HIs for PTVs treated with carbon ion radiotherapy were superior to those treated with X-ray radiotherapy (Table 2). Carbon ion radiotherapy delivered lower doses to the OARs, including lung, spinal cord, esophagus, bones, and trachea & PBT, than did X-ray radiotherapy (Fig. 2 and Table 3).

Despite standard concomitant X-ray radiotherapy with chemotherapy, the incidence of local recurrence for Stage III NSCLC is about one-third \([1, 2]\). To improve the local recurrence rate, a randomized dose escalation study comparing high-dose (74 Gy) with
standard-dose (60 Gy) radiotherapy was performed. Median overall survival was shorter in the high-dose group (20.3 vs 27.8 months) than in the standard-dose group. There were more treatment-related deaths in the high-dose group (comparison: eight vs three patients) [5]. In conventional X-ray radiotherapy, it is difficult to deliver a sufficient dose to peripheral portions of the tumor because NSCLC is surrounded by lung tissue, which has a low electron density. There is increased transmission of X-rays and the lateral scatter of electrons out of the beam pathway can lead to an increased penumbra width in low-density tissue compared with in water-density tissue. A larger leaf margin is needed to deliver a sufficient dose to the PTV, and this leads to higher lung doses and increased radiation pneumonitis [25]. This is one reason why dose escalation with X-rays is difficult. In the present study, carbon ion radiotherapy provided a higher minimum dose to PTVs and resulted in a HI for PTV2 that was half that of X-ray radiotherapy (Table 2). Half of the HI means that the gap between the maximum and minimum doses was halved, suggesting that carbon ion radiotherapy can deliver a homogeneous dose distribution to tumors, even if they are surrounded by lung tissue.

Radiation pneumonitis, which is occasionally fatal, is one of the major toxicities of lung cancer chemoradiotherapy. Radiation pneumonitis is predicted by DVH parameters. Tsujino et al. showed that normal lung V20 was an important factor. The 6-month cumulative incidences of radiation pneumonitis of Grade 2 or greater were 8.7%, 18.3%, 51% and 85% in patients with a V20 of <20%, 21–25%, 26–30% and >31%, respectively. A small difference in the V20 of only a few percent can have a huge impact clinically [26]. This study showed that the absolute difference in normal lung V20 between carbon ion and X-ray radiotherapies was 3.8%. According to Marks et al., the mean lung dose is a concise and effective index for predicting radiation pneumonitis. If their estimations are used together with the data of the present study, the incidence of radiation pneumonitis would be 5.2% for carbon ion radiotherapy and 8.5% for X-ray radiotherapy [27]. Wang et al. reported that V5 is a more useful index than other indexes, including MLD and V10–V65, for lung [28]. The V5 for carbon radiotherapy was 13.5% lower than that of X-ray radiotherapy.

Radiation esophagitis has become more problematic in the recent chemoradiotherapy era. One randomized Phase III trial of X-ray radiotherapy with chemotherapy for NSCLC showed that Grade 3 or greater esophagitis occurs in 14% of patients treated with cisplatin and docetaxel, and in 6% of patients treated with mitomycin, vindesine and cisplatin [29]. Past studies of the association between radiation esophagitis and DVH parameters reported that the mean dose and V50 to the esophagus could be used to predict the occurrence of radiation esophagitis [30]. Esophageal mean

| Table 2. Comparison of PTV1 and PTV2 doses delivered by X-ray radiotherapy (XRT) with those delivered by carbon-ion beam radiotherapy (CIRT) |
|-------------------------------------------------|-------------------|-------------------|-----|
| PTV1                                            | XRT (mean ± SD)   | CIRT (mean ± SD)  | P  |
| D95 (Gy, Gy [RBE])                             | 39.0 ± 1.6        | 39.2 ± 0.4        | 0.241 |
| Homogeneity index                              | 0.65 ± 0.05       | 0.57 ± 0.02       | 0.009 |
| D2 (Gy, Gy [RBE])                              | 62.8 ± 1.3        | 60.9 ± 0.8        | 0.007 |
| D98 (Gy, Gy [RBE])                             | 37.4 ± 1.4        | 38.6 ± 0.4        | 0.022 |
| D50 (Gy, Gy [RBE])                             | 55.0 ± 5.5        | 49.4 ± 5.2        | 0.005 |
| PTV2                                            | XRT (mean ± SD)   | CIRT (mean ± SD)  | P  |
| D95 (Gy, Gy [RBE])                             | 55.6 ± 1.2        | 58.2 ± 0.5        | 0.005 |
| Homogeneity index                              | 0.16 ± 0.02       | 0.07 ± 0.02       | 0.005 |
| D2 (Gy, Gy [RBE])                              | 62.8 ± 1.8        | 61.3 ± 1.0        | 0.013 |
| D98 (Gy, Gy [RBE])                             | 53.8 ± 1.6        | 57.2 ± 0.7        | 0.005 |
| D50 (Gy, Gy [RBE])                             | 60.1 ± 1.0        | 60.0 ± 0.3        | 0.959 |

PTV = planning target volume, SD = standard deviation.

Fig. 2. The lung dose (V5–50) for X-ray radiotherapy (XRT) and carbon ion radiotherapy (CIRT). A single asterisk indicates P < 0.05.
Table 3. Doses delivered to spinal cord, esophagus, bone, trachea, and the proximal bronchial tree by X-ray radiotherapy (XRT) and carbon-ion beam radiotherapy (CIRT)

|                      | XRT (mean ± SD) | CIRT (mean ± SD) | P value |
|----------------------|----------------|------------------|---------|
| Spinal cord          |                |                  |         |
| Dmax (Gy, Gy [RBE])  | 44.6 ± 2.2     | 28.2 ± 3.7       | 0.005   |
| Esophagus            |                |                  |         |
| Mean dose (Gy, Gy [RBE]) | 21.7 ± 4.5    | 18.5 ± 2.9       | 0.005   |
| V50 (%)              | 10.5 ± 10.7    | 3.6 ± 6.0        | 0.012   |
| Bone                 |                |                  |         |
| V10 (cm³)            | 298 ± 31       | 252 ± 27         | 0.005   |
| V30 (cm³)            | 234 ± 28       | 79 ± 22          | 0.005   |
| V50 (cm³)            | 57 ± 19        | 6 ± 4            | 0.005   |
| Trachea and PBT      |                |                  |         |
| V40 (%)              | 53.8 ± 11.5    | 49.6 ± 6.4       | 0.636   |
| V50 (%)              | 27.7 ± 9.9     | 18.6 ± 9.5       | 0.005   |

PBT = Proximal Bronchial Tree, SD = standard deviation.

dose and V50 were significantly lower with carbon ion radiotherapy than with X-ray radiotherapy.

The reduction in the radiation dose to bone might contribute to lower incidences of bone fracture and bone marrow suppression. According to a report about the association between insufficiency fractures and irradiation dose, a dose of 50.4 Gy or greater was found to be a risk factor for fracture [31]. The present study showed that the volume irradiated to more than 50 Gy/Gy (RBE) was 89% lower with carbon ion radiotherapy than with X-ray radiotherapy.

Irradiating the trachea & PBT poses greater risks, since stereotactic radiotherapy for NSCLC has been shown to induce fatal central-airway necrosis in patients receiving a high-dose fraction [32]. The maximum dose constraints for irradiation of trachea & PBT are described in the NCCN guidelines for stereotactic radiotherapy, but are not described for conventional fractionated radiotherapy [33]. Miller et al. reported an incidence of bronchial stenosis of 4% for unresectable NSCLC patients receiving 74 Gy and 25% for those receiving 86 Gy, when X-ray radiotherapy was performed on a twice-daily basis [34]. Carbon ion radiotherapy reduced the volume irradiated at 50 Gy/Gy (RBE) or greater by about one third.

The dose constraints for carbon ion radiotherapy have not been clarified in a clinical setting. A Phase I/II clinical trial of preoperative carbon ion radiotherapy for esophageal carcinoma delivered a total dose of 28.8–36.8 GyE in eight fractions to the PTV, including the esophagus and metastatic lymph nodes. There was only one case (3.2%) where a dose of 35.2 GyE resulted in Grade 3 toxicity corresponding to postoperative acute respiratory distress syndrome [35]. A clinical study of carbon ion radiotherapy for patients with inoperable Stage IIA–IIIA NSCLC used the following OAR constraints: spinal cord, 30 GyE; esophagus, 50 GyE; and mainstem bronchus, 60 GyE. No patient receiving a total dose of 68–72 GyE exhibited Grade 3 or greater toxicity, and only two patients (10.5%) receiving 78 GyE in 16 fractions exhibited Grade 3 toxicity [16]. Although these constraints might be useful for ensuring safety in the deliverance of carbon ion radiotherapy, further clinical research is needed to analyze the association between dose-volume and toxicity.

There are three limitations in the present study. First, the study only included Stage IIIA lung cancers of the upper lobe. Thus, our results cannot be applied to all locally advanced NSCLC. The second is prophylactic lymph node irradiation. Although traditional radiation therapy for patients with locally advanced NSCLC results in the irradiation of the prophylactic lymph node region, some recent dose-escalation studies have applied techniques that do not result in the irradiation of this region. The optimal irradiation area is still unclear. The third is the evaluation of the respiratory movement. The effects of tissue density on the beam pathway are more likely to change the dose distribution during particle therapy than during X-ray radiotherapy. The impact of respiratory movement can be reduced clinically by performing breathing-synchronized irradiation. However, eliminating the effect completely is difficult.

In conclusion, carbon ion radiotherapy irradiated targets with greater homogeneity and at lower doses to OARs, such as the lungs, spinal cord, esophagus, bone, and trachea & PBT, than X-ray radiotherapy. According to these results, carbon ion radiotherapy for locally advanced NSCLC may result in lower doses to OARs while preserving the target dose. Alternatively, carbon ion radiotherapy could be used to increase the target dose while maintaining the OAR dose. Clinical trials to validate the safety and efficacy of carbon ion radiotherapy for locally advanced NSCLC are warranted.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

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