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Original article

# Carbon-ion re-irradiation for recurrences after initial treatment of stage I non-small cell lung cancer with carbon-ion radiotherapy

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ABSTRACT

*Purpose:* To investigate carbon-ion radiotherapy (CIRT) for in-field recurrence of stage I non-small cell lung cancer (NSCLC) initially treated with CIRT.

*Materials and methods:* From January 2007 to March 2014, patients initially treated for stage I NSCLC with CIRT and relapsed in-field were candidates. Overall survival (OS) rate, local control (LC) rate, progressive free survival (PFS) rate, dose to the lungs and skin, and adverse effects were analyzed.

*Results:* Twenty-nine patients were eligible. Median age at re-irradiation was 74 years (range 53–90). Median observation period from the first day of re-irradiation was 29 months (4–88 months). Median prescribed dose was 46.0 Gy (RBE) as initial treatment and 66.0 Gy (RBE) in 12 fractions as re-irradiation. Two-year OS, LC, and PFS rates after re-irradiation were 69.0% (95% CI: 50.3–83.0), 66.9% (95% CI: 47.5–81.9), and 51.7% (95% CI: 34.1–68.9). Median skin maximum dose was 53.8 Gy (RBE) (range 4.4–103.1) and median of mean lung dose was 7.3 Gy (RBE) (range 2.6–14.0). There were no severer than grade 2 adverse effects except one (3.4%) grade 3 bacterial pneumonia, which was not considered radiation-induced.

*Conclusion:* CIRT for stage I NSCLC local recurrence is an acceptable definitive re-treatment.



Re-irradiation has been controversial as to whether it should be implemented. Excess exposure sometimes causes severe adverse phenomena, and a few reports have indicated that some re-irradiation cases were related to death [1–4]. However, candidates under consideration for re-irradiation tend to have few other choices. Re-irradiation has played a central role in palliative care for a long time, but the role of re-irradiation has changed not only for palliation but also for definitive supplementary treatments in line with the developments and advances of irradiation technologies [5–7]. Especially, stereotactic body radiotherapy (SBRT) is considered preferable for the precise irradiation of a limited lesion [3].

Carbon-ion radiotherapy (CIRT) provides local treatment with its high dose concentration [8], and positive results are strongly expected. However, it will take a long time to fully investigate CIRT re-irradiation because only a small number of institutions are currently performing CIRT. In addition to this difficulty in accumulating data regarding CIRT re-irradiation, the problem of analyzing re-irradiation arises from the wide variety of clinical conditions. This means that evaluating and/or arranging between studies concerning re-irradiation is difficult because it is almost impossible to equalize the conditions of clinical status such as interval of re-irradiation, re-staging, and schedule of dose/fractionation [9]. In other words, as re-irradiation analysis is potentially inhomogeneous, any investigation into re-irradiation should be based on some specific purpose or goal.

In this study, we focused on local recurrences of stage I non-small cell lung cancer (NSCLC) cases that had initially been treated with CIRT. This article aims to describe the analysis with respect to treatment outcome and toxicity of CIRT for stage I NSCLC recurrence initially treated with CIRT.

## Materials and methods

According to our institute database up to January 2016, we have treated 29 patients with in-field recurrences, who had initially CIRT-treated peripheral stage I NSCLC before April 2014. Patients with lymph node recurrence and/or distant metastasis were excluded, so the targets of this study were located peripherally. Written informed consent as approved by the local institutional

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review board, conducted in accordance with the ethical standards provided by the Declaration of Helsinki, was obtained from all participants. The re-irradiation trial mainly aimed to confirm adverse effects regarding CIRT, and the study was a retrospective analysis.

### *Initial treatments*

All patients were treated in accordance with our protocols and motion management for stage I NSCLC [10–12]. With single-fraction treatment, the prescribed dose was escalated from 34.0 Gy (RBE) to 48.0 Gy (RBE). In the 4-fraction treatment, T1 tumors were treated with 52.8 Gy (RBE) and T2 tumors with 60.0 Gy (RBE). For treatment in 9 fractions, the prescribed dose was 61.2 Gy (RBE). The dose was prescribed to an isocenter. Clinical staging was based on the Union for International Cancer Control tumor-node-metastasis classification version 6.

### *Recurrence confirmation*

After an initial CIRT, patients were routinely followed up with a chest CT and tumor markers every 3 or 6 months, based on clinical trials for stage I NCSLC [11,13]. When a new mass emerged or the remnant in the lungs seemed to become larger with an increase in tumor markers, [$^{11}$C]-acetate or [$^{18}$F]-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scanning was carried out. Those patients with high accumulation (maximum standardized uptake values [SUVmax] > 5) on PET/CT and/or higher accumulation on PET/CT late phases were considered as positive, distinguishing them from inflammations. Further, if possible, biopsies under bronchoscopy or CT guide were performed for histological confirmation.

### *Re-irradiation treatments*

Eligibility criteria were 1) initially treated peripheral stage I NSCLC with CIRT, 2) in-field recurrence, and 3) keeping performance status of 0 to 1.

Since the gross tumor was generally difficult to recognize because most of the targets were surrounded by remnants or fibrosis caused by radiation pneumonia, we used PET/CT with clinical judgments for contouring the clinical target volume (CTV). The planning target volume (PTV) was generated by adding 5 mm to CTV in all directions.

Planning CT was acquired with custom immobilized devices. Beam directions were basically the same as for the initial treatment. For obtaining the beam angles, patients were axially rotated with a couch between +20° and −20° angles in supine, prone, or both positions if needed. A respiratory gating system was used for both acquiring the planning CT and irradiation at the peak exhalation phase to minimize respiratory motion of targets [14].

The number of fractions for CIRT re-irradiation was set at 12. The prescribed dose was started at 54.0 Gy (RBE), and then was escalated gradually to 57.6, 60.0, 66.0, and 72.0 Gy (RBE) while confirming the absence of severe side effects. The dose was prescribed to an isocenter.

### *Evaluation of adverse effects*

We defined acute from late phases at 90 days after finishing irradiation. The main concerns regarding side effects were lung reaction, skin, and musculoskeletal symptoms. Evaluations of side effects were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [15].

### *Accumulated dose evaluation*

Accumulated dose on lungs and skin was evaluated. The region of interest of skin was defined as 3 mm from the surface. Initial dose distribution data were exported to the second planning CT. Fusion of planning CT was based on bone match of ribs and vertebrae. Fusion and accumulated dose distribution were calculated by the commercial software MIM Maestro (MIM Software Inc., Cleveland, OH, USA). These accumulated doses were simple assumptions of the 2 plans and, for easier comparison, we showed the biological effective dose (BED) as a reference. We used $\alpha = 0.764\ \mathrm{Gy}^{-1}$ and $\beta = 0.0615\ \mathrm{Gy}^{-2}$ based on the published report [16]. We evaluated skin maximum dose (Dmax), mean lung dose (MLD), percentage of lung receiving at least 5 Gy (RBE) (Lung-V5), Lung-V10, and Lung-V20.

### *Statistical analysis*

Survival outcomes were evaluated by Kaplan–Meier method. JMP® 11.2.0 (SAS Institute Inc., Cary, NC, USA) software was used for the Kaplan–Meier method and calculating the one-sided 95% confidence interval (CI).

## Results

The patients consisted of 22 males and 7 females. For their initial treatments, 17 patients were treated with single-fraction CIRT with a prescribed dose ranging from 34.0 Gy (RBE) to 48.0 Gy (RBE), 4 patients were treated with 52.8 Gy (RBE) in 4 fractions, 7 patients were treated with 60.0 Gy (RBE) in 4 fractions, and one patient was treated with 61.2 Gy (RBE) in 9 fractions. Median age at re-irradiation was 74 years (range 53–90). The median interval between initial and second treatments was 20 months (range 8–99). In the order of dose escalations of 54.0, 57.6, 60.0, 66.0, and 72.0 Gy (RBE), 3, 5, 5, 9, and 7 patients were re-treated, respectively. Histology was initially diagnosed as 19 adenocarcinomas, 9 squamous cell carcinomas, and one NSCLC. Recurrences were judged from 18 biopsies, and 11 image diagnoses with ascent of tumor markers. The patient characteristics and the prescription of the initial and second dose/fractionations are shown in Tables 1 and 2.

The median observation period between the first day of re-irradiation and the last follow-up was 29 months (range 4–88). Two-year overall survival (OS), local control (LC), and progressive free survival (PFS) rates after re-irradiation were 69.0% (95% CI: 50.3–83.0), 66.9% (95% CI: 47.5–81.9), and 51.7% (95% CI: 34.1–68.9) (Fig. 1).

Among the 29 patients, 18 patients died, 10 patients had in-field relapses, 2 patients had lymph nodes recurrences, and none had any distant metastases. The causes of death were 9 lung cancers, 2 pneumonitis, one blood infusion reaction not related to lung cancer, one colon cancer, one heart failure by hypertrophic myocardiopathy, one natural death without cancer, one intestinal perforation, one drowning while taking a bath, and one unknown reason (the patient's family answered our mail-in survey in terms of the date of death but refused to divulge the cause).

As for lung reactions, one patient (3.4%) had grade 3 pneumonia in the acute phase of re-irradiation, diagnosed as bacterial pneumonia, and the patient recovered after administration of intravenous antibiotics. Others had less than grade 1 lung reactions. In the late phase, grade 2 lung reaction was observed in 2 patients (6.9%), and there was no greater than grade 2 lung reaction. Regarding skin reaction, in both acute and late phases of re-irradiation, grade 2 was observed in 2 patients (6.9%). Only 2 patients (6.9%) complained of grade 1 pain in irradiated soft tissue. As for other clinical status, 2 patients (6.9%) had grade 2

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