Safety and Efficacy of Carbon-ion Radiotherapy Alone for Stage III Non-small Cell Lung Cancer

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Abstract. *Background/Aim:* We evaluated the efficacy and safety of carbon-ion radiotherapy (CIRT) alone for Stage III non-small-cell lung cancer (NSCLC). *Patients and Methods:* Data of 65 patients (median age=73 years) with Stage III NSCLC who underwent CIRT alone in the QST Hospital, Chiba, Japan, between 1997 and 2015 were retrospectively analysed. The median dose was 72.0 Gy (relative biological effectiveness). *Results:* The median follow-up was 27.6 months (range=1.6-207.7 months). Two-year local control, progression-free survival (PFS), and overall survival (OS) rates were 73.9%, 38.6%, and 54.9%, respectively. Overall, 1 (2%), 4 (6%), and 1 (2%) patient developed Grade 4 (mediastinal haemorrhage), Grade 3 (radiation pneumonitis), and Grade 3 (bronchial fistula) toxicities, respectively. On univariate analysis, clinical T and N stage and CIRT timing were significant predictors of PFS and OS; clinical target volume was a significant predictor of PFS. *Conclusion:* CIRT alone is effective with acceptable toxicity for Stage III NSCLC.

Chemoradiotherapy using a platinum preparation is the standard treatment of choice for unresectable Stage IIIA and Stage IIIB non-small cell lung cancer (NSCLC). Several studies have evaluated the use of platinum-based concurrent chemoradiotherapy for patients with Stage III NSCLC, and the median overall survival (OS) was 22.0-28.7 months (1-3). Moreover, the anti-programmed death ligand 1 antibody durvalumab has been effective as consolidation therapy after platinum-based concurrent chemoradiotherapy for Stage III NSCLC (4). However, despite the survival benefits, concurrent

chemoradiotherapy and consolidation therapy induced severe esophagitis, pneumonitis, and hematologic toxicity; therefore, it is sometimes not indicated for elderly patients and patients with severe comorbidities (5, 6). Accordingly, more effective and low-burden local therapy is desired.

Carbon-ion radiotherapy (CIRT) involves high linear energy transfer with good dose-localizing properties; it is being gradually used across Europe and Asia (7), as CIRT delivers a high dose of radiation to the target tissue, while avoiding the adjacent critical organs-at-risk. Consequently, CIRT can clinically achieve high local control (LC) rates with relatively low toxicity (8-10). Regarding the use of CIRT for locally advanced lung cancer, the 2-year LC and OS rates were 81.8% and 62.2%, respectively, and no Grade ≥ 3 toxicities were observed in a multicentre study of 64 patients with Stage II and III NSCLC (9). In another study, the 2-year LC and OS rates after CIRT alone for 141 patients with Stage II and III NSCLC were 80.3% and 58.7%, respectively (10). In addition, 6 patients (4.2%) and 1 patient (0.7%) experienced Grade 3 and Grade 4 toxicities, respectively, and none experienced Grade 5 toxicities. Thus, these clinical outcomes indicated that CIRT alone may be a promising treatment option for Stage II and III NSCLC. However, these studies evaluated the usefulness of CIRT for Stage II and III lung cancer together (8-10), and no previous study has evaluated the outcomes with a focus on Stage III NSCLC. In addition, the efficacy of chemoradiotherapy and consolidation therapy with durvalumab has already been demonstrated for stage III NSCLC. Therefore, in the current study, we retrospectively analysed the clinical outcomes of CIRT alone in 65 patients with Stage III NSCLC.

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Key Words: Carbon-ion radiotherapy, non-small-cell lung cancer, effectiveness, stage III, toxicity.

Patients and Methods

Study design. This study was approved by the Institutional Review Board of our institution and conducted in accordance with the Declaration of Helsinki. In this retrospective analysis, we used the data of 24 patients with Stage III NSCLC from our institutional prospective phase I/II study for Stage II and III NSCLC as well as

those of 41 patients with Stage III NSCLC who were ineligible for the phase I/II study and who received the same treatment for the same period (10). The selection criteria for this retrospective analysis were as follows: i) histologically or clinically diagnosed Stage IIIA or B NSCLC per the 7th Edition of the UICC TNM Classification, ii) Eastern Cooperative Oncology Group performance status score of 0-2, iii) measurable tumours, iv) patients who had unresectable tumours or those refused surgery, v) patients who received definitive treatment, vi) patients who had no other active cancers, and vii) no history of radiotherapy to the concerned region. The exclusion criteria included lung tumours with suspected invasion to the trachea, great vessels, heart, or carina. The histology or cytology was confirmed in 59 patients (90.8%) *via* bronchoscopic biopsy, computed tomography (CT)-guided biopsy, or sputum cytology.

Carbon-ion radiotherapy. Patients were immobilized using an individually tailored immobilization device (Moldcare; Alcare, Tokyo, Japan; Shellfitter; Kuraray, Osaka, Japan), and CT images were obtained with the patient in the supine or prone position by using respiratory sensors to monitor the respiratory phase.

The gross tumour volume was contoured as a primary lung lesion and metastatic lymph nodes on CT images (8, 10). The clinical target volume (CTV) was defined as the primary lesion with a 10-mm margin and any prophylactic lymph nodes (ipsilateral hilar and/or mediastinal lymph nodes). For N0 cases, prophylactic irradiation to the lymph nodes was omitted. In cases where the CTV was close to the organs-at-risk, the CTV was reduced. The planning target volume (PTV) was defined as the CTV plus a 5-mm safety margin to account for positioning errors. Three-dimensional treatment planning was performed using the in-house HIPLAN software (NIRS, Chiba, Japan) until May 2012 and XiO-N (ELEKTA, Stockholm, Sweden; Mitsubishi Electric, Tokyo, Japan) from April 2012 onwards. The total dose was administered to the isocentre, and it enclosed the PTV conformably, with the 95% isodose line. The prescribed dose ranged from 64.0 to 76.0 Gy [relative biological effectiveness (RBE)] in 16 fractions, 4 days per week. The results of our dose escalation study have been previously reported (8). Accordingly, the recommended dose was fixed at 72 Gy (RBE) in 16 fractions. Subsequently, this dose was used for all patients (n=48, 73.8%). For patients with lymph node metastasis, prophylactic irradiation to the lymph nodes was performed at a median dose of 49.5 Gy (RBE) (8, 10, 11). The following irradiation dose constraints were applied: 60 Gy (RBE) to the main bronchus, 50 Gy (RBE) to the oesophagus, and 30 Gy (RBE) to the spinal cord. Irradiation was performed in 2-5 fields with 250 or 290 MeV carbon ions (10). During each course of irradiation, the patient's position was confirmed by using a computer-aided online positioning system.

Regarding chemotherapy, 18 patients received neoadjuvant chemotherapy. Among these 18 patients, 16 underwent platinum-based induction chemotherapy and 1 patient underwent gefitinib; the history regarding chemotherapy was unclear in 1 patient. None of the 65 patients received concurrent or adjuvant chemotherapy.

Follow-up. After treatment, follow-up was performed at 1, 3, 6, 9, and 12 months, and every 3-6 months after 12 months if serious complications had not occurred. During each follow-up, chest CT, chest radiography, and a blood test were performed. If necessary, brain magnetic resonance imaging or positron emission tomography (PET) was performed.

Table I. Patient and tumour characteristics.

Characteristics	Value or number (%)
Age	
Median, years (range)	73 (40-88)
Gender	
Male	52 (80)
Female	13 (20)
PS score	
0	28 (43)
1	33 (51)
2	4 (6)
Smoking status	
Current or previous	51 (78)
Never	14 (22)
Interstitial pneumonia	
Present	3 (5)
Absent	62 (95)
Treatment status	
Initial treatment	48 (74)
Recurrence or residual cancer after surgery or chemotherapy	17 (26)
Location of the primary tumour	
Upper lobe	53 (82)
Middle lobe	2 (3)
Lower lobe	10 (15)
Resection status	
Resectable	11 (17)
Unresectable	54 (83)
Clinical T stage	
1	10 (15)
2	22 (34)
3	13 (20)
4	20 (31)
Clinical N stage	
0	13 (20)
1	7 (11)
2	40 (62)
3	5 (8)
Clinical stage	
IIIA	45 (69)
IIIB	20 (31)
Histology of the primary lung cancer	
Adenocarcinoma	28 (43)
Squamous cell carcinoma	23 (35)
Large cell carcinoma	5 (8)
Non-small-cell carcinoma	3 (5)
Unknown	6 (9)
Irradiation field	
Primary lesion	11 (17)
Primary lesion and the hilar lymph nodes	3 (5)
Primary lesion and the mediastinal lymph node	51 (78)
Total dose	
Median (range, Gy RBE)	72 (64-76)
CTV	
Median (range, ml)	423 (60-1476)
VC	
Median (range, ml)	2840 (1100-5570)
FEV1	
Median (range, ml)	1830 (590-4400)
FEV1/FVC	
Median (range, %)	73.3 (38.2-87.0)
%DLCO	
Median (range, %)	72.2 (25.4-237.0)

PS, Performance status; RBE, relative biological effectiveness; CTV, clinical target volume; VC, vital capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; %DLCO, percent of diffusing capacity for carbon monoxide.

Figure 1. Local control rate (a), progression-free survival rate (b) and overall survival rate (c).

Acute and late toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0).

Statistical analysis. Local control (LC), progression-free survival (PFS), and OS were calculated using the Kaplan-Meier method. All the parameters were defined as intervals starting from the date of re-irradiation commencement. LC was defined till the date of local tumour regrowth in the PTV or the last follow-up. PFS was defined till the date of disease progression at any site, death from any cause, or the last follow-up. OS was defined till death or the last follow-up.

Univariate analysis was performed using the generalized Wilcoxon test to determine the prognostic factors of LC, PFS, and OS. The patients were divided into subgroups according to the median values of age, total dose, the CTV, the CIRT treatment timing (before or after January 2005), vital capacity (VC), forced expiratory volume in the first second (FEV1), the ratio of the FEV1 to the forced vital capacity (FVC), and percent predicted diffusing capacity for carbon monoxide (%DLCO). A two-tailed p -value < 0.05 was considered statistically significant. All statistical analyses were conducted using JMP statistical software (version 14.0; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. CIRT was discontinued in 2 patients, owing to radiation pneumonitis in 1 patient after receiving 67.5 Gy (RBE) in 15 fractions and owing to exacerbation of interstitial pneumonitis in 1 patient after receiving 71.25 Gy (RBE) in 15 fractions. Consequently, 63 patients (97%) completed CIRT alone.

The patient and tumour characteristics are summarized in Table I. The median patient age was 73 years. Overall, 10 (15%), 22 (34%), 13 (20%), and 20 (31%) patients had T1, T2, T3, and T4 disease, respectively. Moreover, 13 (20%), 7 (11%), 40 (62%), and 5 (8%) patients had N0, N1, N2, and N3 disease, respectively. Furthermore, 45 (69%) patients had Stage IIIA NSCLC and 20 (31%) had Stage IIIB NSCLC.

Local control and survival. The median follow-up period was 27.6 months (range=1.6-207.7 months) for all patients and 51.4 months for survivors. At the end of the follow-up,

Table II. Toxicities observed in patients with Stage III non-small cell lung cancer after carbon-ion radiotherapy.

Grade	2 n (%)	3 n (%)	4 n (%)	Total n (%)
Dermatitis	10 (15)	0	0	10 (15)
Esophagitis	3 (5)	0	0	3 (5)
Pneumonitis	7 (11)	4 (6)	0	11 (17)
Brachial plexopathy	2 (3)	0	0	2 (3)
Pneumothorax	1 (2)	0	0	1 (2)
Chest wall pain	1 (2)	0	0	1 (2)
Bronchial fistula	0	1 (2)	0	1 (2)
Mediastinal haemorrhage	0	0	1 (2)	1 (2)

16 patients survived, 31 died of cancer, and 18 died of unrelated causes. At the first relapse, local recurrence was observed in 7 patients, regional recurrence in 10 (in the regional lymph nodes or/and satellite nodes in the ipsilateral lung), and distant metastases in 24.

The median PFS and OS were 10.1 and 27.6 months, respectively. The 2-year and 3-year PFS rates were 38.6% (95% confidence interval [CI]=27.0%-51.7%) and 32.8% (95% CI=21.9%-46.1%), respectively (Figure 1b). The 2-year and 3-year OS rates were 54.9% (95% CI=42.7%-66.6%) and 42.0% (95% CI=30.5%-54.4%), respectively (Figure 1c). The 2-year and 3-year LC rates were 73.9% (95% CI=58.2%-85.2%) and 70.2% (95% CI=53.8%-82.7%), respectively (Figure 1a).

Toxicities. No patient developed Grade ≥ 3 acute toxicity (Table II). Regarding late toxicities, 1 patient (2%) developed Grade 4 mediastinal haemorrhage, 4 (6%) developed Grade 3 radiation pneumonitis, and 1 (2%) developed Grade 3 bronchial fistula. The information about the patient with Grade 4 mediastinal haemorrhage was reported previously (11).

Table III. Univariate analysis of local control, progression-free survival, and overall survival.

Factors	No of patients	Local control	Progression-free survival	Overall survival
		<i>p</i> -Value	<i>p</i> -Value	<i>p</i> -Value
Age		0.620	0.552	0.421
≥73 years	30			
<73 years	35			
Gender		0.381	0.558	0.734
Male	52			
Female	13			
Smoking status		0.127	0.080	0.141
Current or previous	51			
Never	14			
Neoadjuvant chemotherapy		0.165	0.772	0.951
Administered	18			
Not administered	47			
Location of the primary tumour		0.818	0.182	0.205
Upper or Middle lobe	55			
Lower lobe	10			
Resection status		0.726	0.294	0.438
Resectable	11			
Unresectable	54			
Clinical T stage		0.248	<0.001	0.002
T1-2	32			
T3-4	33			
Clinical N stage		0.189	0.017	0.008
N0	13			
N1-3	52			
Clinical stage		0.520	0.232	0.352
IIIA	45			
IIIB	20			
Histology of the primary lung cancer		0.997	0.098	0.312
Adenocarcinoma	28			
Squamous cell carcinoma	23			
Others	14			
Total dose		0.687	0.845	0.941
<72 Gy RBE	11			
≥72 Gy RBE	54			
CTV at re-irradiation		0.193	0.057	0.101
<423 ml	32			
≥423 ml	33			
Timing of CIRT		0.139	0.050	0.038
Before January 2005	31			
After January 2005	34			
VC		0.262	0.367	0.356
≥2840 cm ³	33			
<2840 cm ³	32			
FEV1		0.228	0.366	0.436
≥1830 cm ³	32			
<1830 cm ³	33			
FEV1/FVC		0.684	0.532	0.657
≥73.3%	33			
<73.3%	32			
%DLCO		0.885	0.628	0.196
≥72.2%	33			
<72.2%	32			

RBE, Relative biological effectiveness; CTV, clinical target volume; CIRT, carbon-ion radiotherapy; VC, vital capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; %DLCO, percent of diffusing capacity for carbon monoxide.

Figure 2. Progression-free survival rate (a) and overall survival rate (b) according to the T stage.

Figure 3. Progression-free survival rate (a) and overall survival rate (b) according to the N stage.

Prognostic factors. The results of univariate analyses to identify potential prognostic factors are shown in Table III. On univariate analysis, the clinical T stage, clinical N stage, and the timing of CIRT (before or after January 2005) were significant predictors of PFS and OS, and CTV was a significant predictor of PFS. The 2-year PFS and OS rates of patients with T1-2 disease *versus* those with T3-4 disease were 19.8% *versus* 56.2% and 34.4% *versus* 75.2%, respectively (Figure 2). The 2-year PFS and OS rates of patients with N0 disease *versus* those with N1-3 disease were 61.5% *versus* 33.2% and 100% *versus* 43.4%, respectively (Figure 3). Considering the timing of CIRT, the 2-year PFS and OS rates before *vs* after January 2005 were 34.6% *versus* 41.1% and 41.9% *versus* 66.8%, respectively (Figure 4). The 2-year PFS rates of patients with CTV <423 ml *versus* those with CTV ≥423 ml were 41.8% *versus* 35.5% (Figure 5).

Discussion

To the best of our knowledge, the current study is the first to evaluate the efficacy and safety of CIRT alone only for Stage III NSCLC. Our findings demonstrated that CIRT

alone resulted in high LC and moderate survival with acceptable toxicity, and that the T stage, N stage, and the timing of CIRT were significant predictors of PFS and OS. In studies that evaluated the efficacy and safety of platinum-based concurrent chemoradiotherapy for patients with Stage III NSCLC, the median PFS and OS were 9.5-13.3 months and 22.0-28.7 months, respectively (1-3). In addition, another phase III trial compared the anti-programmed death ligand 1 antibody durvalumab as consolidation therapy after concurrent chemoradiotherapy for Stage III NSCLC with a placebo (4). In that study, PFS was significantly longer after durvalumab treatment (median PFS=16.8 months) than after placebo treatment (median PFS=5.6 months), although analysis of the OS was not planned at the time of the interim analysis. In another study, proton beam radiotherapy and concurrent chemotherapy were administered for Stage III NSCLC; the median PFS and OS were 12.9 months and 26.5 months, respectively (12). The present study revealed that the median PFS and OS for Stage III NSCLC were 10.1 months and 27.6 months, respectively. Our findings indicate that CIRT alone is as efficacious as photon or proton concurrent chemoradiotherapy when we consider the fact

Figure 4. Progression-free survival rate (a) and overall survival rate (b) according to the timing of CIRT. CIRT, Carbon-ion radiotherapy.

that the median age of the patients in the present study (73 years) was higher than the median age of the patients in the above-mentioned chemoradiotherapy studies (63-64 years), durvalumab study (64 years), or proton study (70 years).

Regarding Grade ≥ 3 toxicity, hematological toxicity is the most frequent complication after concurrent chemoradiotherapy and consolidation therapy for Stage III NSCLC. In fact, $>50\%$ of patients treated with concurrent chemoradiotherapy developed Grade ≥ 3 leukopenia, anaemia, and/or thrombocytopenia (1-3). In contrast, in the current study, none of the patients treated with CIRT experienced any hematological toxicity, because CIRT results in minimal irradiation to the bone marrow. Among non-hematological toxicities, radiation pneumonitis and esophagitis are major complications (1-3). After photon chemoradiotherapy, the incidence of Grade ≥ 3 pneumonitis and esophagitis was 4.1%-10% and 7%-14%, respectively (1-3). Moreover, Grade 3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab; the most common adverse event was pneumonia (4.4%). Furthermore, after proton beam concurrent chemotherapy for Stage II or III NSCLC, the incidence of Grade ≥ 3 pneumonitis and esophagitis was 10.5%-12% and 6%-12%, respectively (12-14). In contrast, in the current study using CIRT alone, Grade 3 radiation pneumonitis occurred in only 6% of all patients and none of the patients developed Grade ≥ 4 radiation pneumonitis and Grade ≥ 3 esophagitis. Thus, our findings indicate that, considering Grade ≥ 3 toxicity, CIRT alone may be safer than photon chemoradiotherapy and consolidation therapy or proton chemoradiotherapy.

On univariate analysis, we found that the T1-2 classification, N1-3 classification, and the former part about the timing of CIRT were significant poor prognostic factors of PFS and OS, and that CTV ≥ 423 ml was a significant poor prognostic factor of PFS. Similar to the findings of previous studies (8, 10), the N stage and timing of CIRT were identified as poor prognostic factors. The result that the prognosis of patients with T1-2 disease is poorer than that of patients with T3-4 disease may have arisen from the

Figure 5. Progression-free survival rate according to the CTV. CTV, Clinical target volume.

difference of the metastatic potential between T1-2 and T3-4 disease. According to the TNM classification, Stage III includes T3N1-3 and T4N0-3 but only T1-2N2-3. In other words, the T1-2 tumours in our study were more progressive lung cancers than the T3-4 tumours considering the presence of metastatic lymph nodes. Moreover, patients with T1-2 disease in our study seemed to have more indolent distant metastasis than the patients with T3-4 disease did, especially before January 2005 considering the timing of CIRT. In fact, stage migration was noted because minimal metastasis was partially detected owing to the improvement in the imaging diagnostic technology such as PET and CT (15, 16). Before January 2005, considering the timing of CIRT, PFS and OS of patients with T1-2 disease were significantly poorer than those of patients with T3-4 disease, but after January 2005, there was no significant difference in PFS and OS between patients with T1-2 disease and patients with T3-4 disease (Figure 6). This is probably because recent imaging techniques have excluded patients who have minimal distant metastases, especially many patients with T1-2N2-3 disease.

Figure 6. Progression-free survival rate (a) and overall survival rate (b) according to the T stage of patients with Stage III non-small-cell lung cancer who underwent CIRT before January 2005; progression-free survival rate (c) and overall survival rate (d) according to the T stage of patients with Stage III non-small-cell lung cancer who received CIRT after January 2005. CIRT, carbon-ion radiotherapy.

The current study had several limitations. First, the study was a single-centre retrospective analysis with a small sample size (N=65). Therefore, selection bias may exist. Second, the late toxicity might be underestimated, because the median follow-up duration (27.6 months) was not sufficient. Finally, the total doses varied [64-76 Gy (RBE) in 16 fractions]. Therefore, further large-scale multicentre prospective trials are needed.

In conclusion, CIRT alone is an effective treatment with acceptable toxicity for Stage III NSCLC and is a reasonable treatment option, especially for patients with Stage III lung cancer with N0 classification or T3-4 classification.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

AM designed the study with support from YN and HK, and wrote the initial draft of the manuscript. YN and HK contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript.

All Authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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