

# Carbon-ion radiotherapy for patients with advanced stage non–small-cell lung cancer at multicenters

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## ABSTRACT

Carbon-ion radiation therapy (CIRT) for advanced non–small-cell lung cancer (NSCLC) has not been well studied to date. This paper aimed to analyze a retrospective multicenter survey for detecting problems with the use of CIRT for Stage II and III NSCLC (7th UICC TNM Staging System). Inclusion was restricted to patients with Stage II and III NSCLC who received CIRT from November 2003 to December 2014. We gathered the data from three CIRT operating centers on July 2015. Patients with radiotherapy history, patients with cancers other than lung cancer, and those receiving palliative therapies were excluded. The patient characteristics, prescribed dose/fraction, survival rates, and adverse effects were analyzed. The total number of patients was 64 (male: 49, female: 15). Of these, 53 patients were medically inoperable. The median age was 76 years (range 46–91), and the median follow-up period was 18.5 months (range 3.2–121.5). The clinical staging consisted of 10 Stage IIA, 30 Stage IIB, 23 Stage IIIA and 1 Stage IIIB. The median prescribed dose was 72.0 Gy (RBE) (range 52.8–72.0) in 16 fractions (range 4–16). The 2-year overall survival, progression-free survival, and local control rates were 62.2% [confidence interval (CI): 47.5–76.9], 42.3% (CI: 28.8–55.8) and 81.8% (CI: 69.9–94.0), respectively. There were no higher than Grade 2 adverse effects observed. CIRT for inoperable Stage II and III NSCLC could be implemented without severe adverse effects, but the clinical staging (including lymph node status) was inhomogeneous. In addition, the prescribed dose and fractionation were not standardized. Further data accumulation and a multiple centers prospective trial for evaluating clinical stage–based results are required.

**KEYWORDS:** carbon-ion radiotherapy, non–small-cell lung cancer, multicenter survey, retrospective study

## INTRODUCTION

Lung cancer is one of the most common cancers; in the USA, lung cancer has been identified as the second-most common cancer, and heads the list of causes of cancer-related death in both males and females [1]. As for the lethality of non–small-cell lung cancer (NSCLC), the 5-year overall survival rate of untreated lung cancer (only of stage I) has been reported as 17% [2]. In addition to its high malignancy, some patients are judged

inoperable because of the difficulty of resection and/or their medical complications.

Although several randomized trials and meta-analyses have indicated that concurrent chemoradiotherapy is suitable treatment for inoperable NSCLC, the prognosis remains poor [3–7]. Other treatment modalities have been investigated: e.g. a clinical trial using carbon-ion radiotherapy (CIRT) was initiated in 2000, from which Takahashi *et al.* reported a single-center dose-escalation study of

inoperable, locally advanced NSCLC using CIRT [8]; however, comprehensive understanding of the use of CIRT for advanced stage NSCLC has not yet been attained.

The aim of this paper was to accumulate multiple-center data and to analyze the current indications for the use of CIRT in advanced NSCLC.

## MATERIALS AND METHODS

The subjects of this study received CIRT between November 2003 and December 2014. We retrospectively searched the database of three Japanese CIRT operating institutes in July 2015. These institutes obtained written informed consent for use of the data from all participants, and each Ethics Committee approved each trial. Clinical staging was based on the Union for International Cancer Control tumor-node-metastasis classification version 7 [9]. The eligibility criteria of this study were: (i) Stage II or III NSCLC was diagnosed from both biopsy and image analysis, (ii) inoperable, or refusal of surgery, (iii) definitive treatments, (iv) no other active cancers, (v) no history of radiotherapy to the concerned region, and (vi) performance status maintained at 0–2. The performance status was based on the criteria of the Eastern Cooperative Oncology Group [10]. Those patients with Stage I NSCLC were excluded because a clinical trial for Stage I NSCLC was already running, and those with Stage IV disease were excluded because metastases were not considered controllable with local treatments. Whether cancers were operable or not was judged by the doctors who introduced the patients to the CIRT institute.

Details of the carbon-ion radiation therapy and treatment planning have been reported elsewhere [8, 11]. The parameters analyzed were: age, sex, clinical stage, surgery tolerance, histology, prescribed dose/fractionations, overall survival rate, local control rate, progression-free survival rate, and adverse effects. Adverse effects were evaluated for the acute and late phases, which were separated by the 90 days after the first day of CIRT. Survival outcomes were evaluated using the Kaplan–Meier method. JMP® 11.2.0 (SAS Institute Inc., Cary, NC, USA) software was used for calculating the Kaplan–Meier survival probability estimates.

According to the carbon-ion radiation dose definition, radiation dose by carbon ions is conventionally expressed in Gray equivalents (GyE). GyE values are obtained by multiplying the carbon physical dose (Gy) by the relative biological effectiveness (RBE) factor [12].

## RESULTS

The total number of patients was 64: 49 males and 15 females. The median age was 76 (range 46–91). The median observation period was 18.5 months (range 3.2–121.5). The number of patients in the various clinical stages were Stage IIA: 10, Stage IIB: 30, Stage IIIA 23 and Stage IIIB: 1. The histology diagnosed: 31 adenocarcinomas, 27 squamous cell carcinomas, 2 NSCLCs and 4 unknown cancers. Three patients maintained performance status (PS) 0, 55 patients PS 1, and 6 patients PS 2. Eleven patients were judged as operable and 53 inoperable by the introducing doctors. The median dose and median fractionation were 72.0 Gy (RBE) (range 52.8–72.0) and 16 fractions (range 4–16), respectively. The median planning target volume (PTV) was 186.8 ml (range 28.1–1475.5 ml). The 2-year overall

survival, progression-free survival and local control rates were 62.2% [95% confidence interval (CI): 47.5–76.9], 42.3% (95% CI: 28.8–55.8) and 81.8% (95% CI: 69.9–94.0), respectively. By dividing the patients into those with N0 diseases and those with N1/N2 diseases, the 2-year overall survival rates were 67.8% (95% CI: 45.2–84.3) and 62.2% (95% CI: 36.2–75.5), respectively; there was no significant difference ( $P = 0.42$ , log-rank). No higher than Grade 2 adverse effects were observed. An acute Grade 2 lung reaction was observed in three patients, a Grade 2 lung reaction in 4 patients, an acute Grade 2 skin reaction in 3 patients, and Grade 2 chest wall pain in 1 patient. The patient characteristics are summarized in Table 1.

Institution A treated 8 Stage IIA patients, 13 Stage IIB patients, 14 Stage IIIA patients and one Stage IIIB patient. With respect to N status, there were 14 patients with N0 disease, 15 with N1 disease and 7 with N2 disease. None of the patients were judged to be operable. All patients were treated with 72.0 Gy (RBE) in 16 fractions. The median PTV was 179.9 ml (range 50.3–1475.5 ml).

**Table 1. Patient characteristics**

Male/female	49/15
Median age (range)	76 (46–91)
PS 0/1/2	3/55/6
Staging	
IIA	10
IIB	30
IIIA	23
IIIB	1
Histology	
Adenocarcinoma	31
Squamous cell carcinoma	27
Non-small-cell carcinoma	2
Lung cancer (indiscriminate)	4
Operable/inoperable	11/53
Median planning target volume (range) (ml)	186.8 (28.1–1475.5)
Median prescribed dose (range) (Gy (RBE))	72.0 (52.8–72.0)
Median number of fractionation (range)	16 (4–16)
Grade 2 adverse effects	
Acute lung	3 (4.7%)
Late lung	4 (6.3%)
Acute skin	3 (4.7%)
Chest wall pain	1 (1.6%)
No higher than Grade 2 adverse effects.	

Institution B treated 17 Stage IIB patients and 9 Stage IIIA patients. With respect to N status, 19 patients with N0 disease and 7 patients with N2 disease were treated. Of the 26 patients, 15 patients were judged to be inoperable, and 11 patients rejected surgery. With regard to dose/fractionation, one patient was treated with 52.8 Gy (RBE) in 4 fractions, 11 patients were treated with 60.0 Gy (RBE) in 4 fractions, 13 patients were treated with 64.0 Gy (RBE) in 16 fractions, and 1 patient was treated with 70.4 Gy (RBE) in 16 fractions. The median PTV was 247.0 ml (range 28.1–1171.5 ml). Institution C treated 2 Stage IIA patients (T2aN1M0 and T2bN0M0), both of whom were judged to be inoperable and were treated with 64.0 Gy (RBE) in 16 fractions. The median PTV was 88.5 ml (range 60.0–117.0 ml). The patient characteristics for each of the three institutes are shown in Table 2.

**DISCUSSION**

We retrospectively investigated the clinical outcomes of CIRT for patients with Stage II and III NSCLC at three CIRT operating centers. Although the three institutes have treated Stage II and III NSCLC based on a perspective dogma, no higher than Grade 2 adverse effects were observed.

Like other reports about advanced stage NSCLC, there were inhomogeneous groups of clinical staging in this study. The clinical strategies differed between the three institutes, as follows. At Institute A, none of the patients with N3 disease were treated, but one patient with Stage IIIB (T4N2M0) was considered treatable. On the other hand, Institute C treated only Stage II patients with N1 disease, and did not treat patients with Stage III disease; Institute B did not treat patients with N1 disease. In addition, the different clinical targets were connected to prescribed doses and fractionations, and there was no communality among the three institutes.

However, survival rates in this study were not inferior to those for NSCLC in recent reports about chemoradiotherapy [13–14]. In addition, the insignificant difference in the overall survival rate between N0 disease and N1/N2 disease was a pleasing finding. It was expected that N1/N2 disease should be inferior to N0 disease in terms of survival rate, so this finding implies an effectiveness of CIRT for advanced NSCLC. Given the fact that 83% of the patients were inoperable in this research, the improved survival of patients with N1/N2 disease might be attributable to CIRT.

One of the limitations of this study was an inhomogeneous clinical grouping by institutes. In addition, the number of patients was very small for an 11-year span. One of the reasons for this was the limited availability of CIRT. Also, there has been no evidence supporting the use of CIRT for advanced NSCLC, so general practitioners found it difficult to recommend CIRT for patients. Although Takahashi *et al.* [8] recently showed a benefit for inoperable NSCLC patients, a Phase III clinical trial has not yet commenced. One concern with advanced NSCLC treatments is how much and which prophylactic regions to treat—there was no consensus among the institutes. That is why there was a wide range in the PTV treated. As the lymph node map for lung cancer has depicted [15], a consensus about treating lymph node areas is required in order to determine the criteria for implementing refined clinical trials. Since the number of institutions undertaking CIRT has recently increased,

**Table 2. Patient characteristics by institutes**

Institution A	
Stage	
IIA	8
IIB	13
IIIA	14
IIIB	1
N staging	
N0	14
N1	15
N2	7
Median planning target volume (range) (ml)	179.9 (50.3–1475.5)
Prescribed dose/fractionation	
72.0 Gy (RBE)/16 fractions	36
Institution B	
Stage	
IIB	17
IIIA	9
N staging	
N0	14
N1	15
N2	7
Median planning target volume (range) (ml)	179.9 (50.3–1475.5)
Prescribed dose/fractionation	
52.8 Gy (RBE)/4 fractions	1
60.0 Gy (RBE)/4 fractions	11
64.0 Gy (RBE)/16 fractions	13
70.4 Gy (RBE)/16 fractions	1
Institution C	
Stage	
IIA	2
N staging	
N0	1
N1	1
Median planning target volume (range) (ml)	88.5 (60.0–117.0)
Prescribed dose/fractionation	
64.0 Gy (RBE)/16 fractions	2

further research (such as a prospective multicenter clinical trial) is expected.

In addition to the expectation of clinical trials, we are interested in adjuvant therapies, i.e. whether chemotherapy is necessary or not, whether chemotherapy should be used before CIRT or concurrent with CIRT, interaction with current medicines (programmed cell death 1 inhibitor, etc.). Several trials are being considered, seeking to further improve treatment for advanced NSCLC.

### CONCLUSION

We report on current evidence regarding the use of CIRT for inoperable Stage II and III NSCLC at multicenters using CIRT, and how CIRT can be implemented without severe adverse effects; however, the clinical staging, including lymph node status, was inhomogeneous. In addition, the prescribed doses and fractionation were not standardized. Further data accumulation and a multiple-centers prospective trial are awaited for evaluating clinical staging-based results.

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### CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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### REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5–29.
2. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. *Chest* 2007;132:193–9.
3. Sause W, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000;117:358–64.
4. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95–01 Study. *J Clin Oncol* 2005;23:5910–7.
5. Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–83.
6. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011;103:1452–60.
7. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–9.
8. Takahashi W, Nakajima M, Yamamoto N, et al. A prospective nonrandomized phase I/II study of carbon ion radiotherapy in a favorable subset of locally advanced non-small cell lung cancer (NSCLC). *Cancer* 2015;121:1321–7.
9. Marshall HM, Leong SC, Bowman RV, et al. The science behind the 7th edition Tumour, Node, Metastasis staging system for lung cancer. *Respirology* 2012;17:247–60.
10. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
11. Shirai K, Kawashima M, Saitoh JI, et al. Clinical outcomes using carbon-ion radiotherapy and dose-volume histogram comparison between carbon-ion radiotherapy and photon therapy for T2b-4N0M0 non-small cell lung cancer-A pilot study. *PLoS One*. 2017;12:e0175589.
12. Kanai T, Endo M, Minohara S, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. *Int J Radiat Oncol Biol Phys* 1999;44:201–10.
13. Walraven I, van den Heuvel M, van Diessen J, et al. Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. *Radiother Oncol* 2016;118:442–6.
14. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187–99.
15. Lynch R, Pitson G, Ball D, et al. Computed tomographic atlas for the new international lymph node map for lung cancer: a radiation oncologist perspective. *Pract Radiat Oncol* 2013;3:54–66.