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Clinical outcomes of carbon-ion radiotherapy for locally advanced non-small-cell lung cancer

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The efficacy and safety of carbon-ion radiotherapy (CIRT) for locally advanced non-small-cell lung cancer (LA-NSCLC) remain unclear. We reported the clinical outcomes of CIRT for LA-NSCLC. Data for 141 eligible patients who received CIRT between 1995 and 2015 were retrospectively analyzed. Local control (LC), locoregional control (LRC), progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. The median age was 75.0 years. Overall, 21 (14.9%), 57 (40.4%), 43 (30.5%) and 20 (14.2%) patients had T1, T2, T3 and T4 disease, respectively. Moreover, 51 (36.2%), 45 (31.9%), 40 (28.4%) and 5 (3.5%) patients had N0, N1, N2 and N3 disease, respectively. Furthermore, 34 (24.1%), 42 (29.8%), 45 (31.9%) and 20 (14.2%) patients had stages IIA, IIB, IIIA and IIIB disease, respectively. Overall, 62 (44.0%), 60 (42.6%), 8 (5.7%) and 11 (7.8%) patients had adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and others, respectively. The median dose was 72.0 Gy (relative biological effectiveness). No patient received concurrent chemotherapy. Median follow-up periods were 29.3 (1.6-207.7) and 40.0 (10.7-207.7) months for all patients and survivors, respectively. Two-year LC, PFS and OS rates were 80.3%, 40.2% and 58.7%, respectively. Overall, 1 (0.7%), 5 (3.5%) and 1 (0.7%) patient developed Grades 4 (mediastinal hemorrhage), 3 (radiation pneumonitis) and 3 (bronchial fistula) toxicities, respectively. Multivariate analysis showed adenocarcinoma and N2/3 classification as significant poor prognosticators of PFS. CIRT is an effective treatment with acceptable toxicity for LA-NSCLC, especially for elderly patients or patients with severe comorbidities who cannot be treated with surgery or chemoradiotherapy.

KEYWORDS
carbon-ion radiotherapy, effectiveness, elderly patients, locally advanced non-small-cell lung cancer, radiation therapy

1 | INTRODUCTION

Primary lung cancer is one of the most common cancers in the world and is the second most common cancer in the USA.[1,2] The most frequent type is non-small-cell lung cancer (NSCLC), which accounts approximately for 80% of all cases of lung cancer. The standard treatment for locally advanced NSCLC (LA-NSCLC) consists of surgery, chemotherapy and/or radiotherapy. For inoperable patients, in

several studies, platinum-based concurrent chemoradiotherapy was performed for patients with LA-NSCLC, and the 2-year high overall survival (OS) rate was approximately 50%-60%.[3-5] However, in contrast to its survival benefit, concurrent chemoradiotherapy induces severe hematologic toxicity, infection, esophagitis and pneumonitis; therefore, chemoradiotherapy is sometimes a heavy burden in elderly patients or patients with severe comorbidities.[6-8] As an alternative treatment option, radiotherapy alone or low-dose carboplatin-based concurrent chemotherapy is sometimes introduced to patients, but such patients have a 2-year OS rate of approximately 5%-40%, with a poor prognosis.[9,10]

Carbon-ion radiotherapy (CIRT) is a high linear energy transfer radiotherapy that is being widely used across Europe and Asia. CIRT has good dose-localizing properties.[11] Therefore, it can deliver a higher dose to the target volume than conventional photon radiotherapy while avoiding the adjacent critical organs at risk, such as the lung, esophagus, trachea and heart. In fact, CIRT can clinically achieve high local control (LC) rates with low toxicity.[12-15] From our institute, 2 published studies have been reported. Takahashi et al.[12] demonstrated that the 2-year LC and OS rates of CIRT alone in 62 patients with LA-NSCLC were 93.1% and 51.9%, respectively, with 2 (3.2%) patients experiencing Grade 3 toxicities and none experiencing Grade ≥4 toxicities. Moreover, Karube et al.[13] conducted a multicenter study on CIRT in 64 patients with LA-NSCLC. The 2-year LC and OS rates were 81.8% and 62.2%, respectively; and no Grade ≥3 toxicities were observed. These clinical outcomes indicated that CIRT may be a promising treatment option for LA-NSCLC.

However, the efficacy and safety of CIRT are not clearly understood, with only 2 published studies having reported on a small number of patients with LA-NSCLC.[12,13] In this study, we retrospectively analyzed the clinical outcomes in 141 patients treated for LA-NSCLC with CIRT.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was approved by the Institutional Review Board of our institution. Research was conducted in accordance with the Helsinki Declaration. This study was a retrospective evaluation of 141 patients from a previously reported prospective phase I/II study of 72 patients and a retrospective study of 69 patients who were deemed ineligible for the phase I/II study at our institution. The details of the prospective phase I/II study were previously reported.[12] The eligibility criteria for this study conducted between June 1995 and November 2015 at our institution were as follows: (i) histologically or clinically diagnosed LA-NSCLC stages IIA to IIIB (the UICC's TNM 7th Classification);[16] (ii) Eastern Cooperative Oncology Group performance status of 0-2; (iii) measurable tumors; (iv) inoperable or refusal of surgery; (v) definitive treatments; (vi) no other active cancers; and (vii) no history of radiotherapy to the concerned region. Exclusion criteria included lung tumors with suspected invasion to the trachea, great vessels, heart or carina. Consequently, data for 141 patients who met the inclusion criteria were analyzed. The histology or cytology was confirmed in 133 (94.3%) patients by bronchoscopic biopsy, computed tomography (CT)-guided biopsy or sputum cytology.

Acute toxicity was defined as that occurring within 3 months of the commencement of CIRT. Acute and late toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0).[17]

2.2 | Carbon-ion radiotherapy

Patients were fixed using an individually tailored immobilization device (Moldcare; Alcare, Tokyo, Japan; Shellfitter; Kuraray, Osaka, Japan), and CT images were taken in the supine or prone position using respiratory sensors to monitor the respiratory phase.[12,13]

Primary lung lesion and metastatic lymph nodes were contoured as the gross tumor volume (GTV) on CT images. The primary lesions with a 10-mm margin and any prophylactic lymph nodes (ipsilateral hilar and/or mediastinal lymph nodes) were defined as the clinical target volume (CTV). For N0 cases, prophylactic lymph node irradiation was omitted. Planning target volume (PTV) was defined as the CTV+ 5-mm safety margin. In cases where the CTV was close to the organs at risk, the CTV was reduced.

The prescribed dose ranged from 54.0 to 76.0 Gy (relative biological effectiveness [RBE]) in 12-16 fractions, 4 days per week. A dose escalation study was conducted in the cradle of our study and has been previously reported.[12] Consequently, the recommended dose was fixed at 72 Gy (RBE) in 16 fractions. Subsequently, this dose was adopted for all patients (n = 89, 63.1%). The total dose was applied to the isocenter, and it enclosed the PTV conformably, with the 95% isodose line. With lymph node metastasis, prophylactic lymph nodes were irradiated at a median dose of 49.5 Gy (RBE).[12,18] The following irradiation dose constraints were applied: main bronchus, 60 Gy (RBE); esophagus, 50 Gy (RBE); and spinal cord, 30 Gy (RBE). Irradiation was performed in 2-5 fields with 250 or 290 MeV carbon ions.

Regarding chemotherapy, 24 patients received neoadjuvant chemotherapy. Of these patients, 5 patients underwent induction chemotherapy to shrink their tumors. A total of 18 patients first received chemotherapy alone based on the decision made by their previous doctors. However, their treatment plans were changed to CIRT because their therapeutic responses to chemotherapy were subtherapeutic or because the patients wished to change treatment regimen. For 1 patient, the chemotherapy history was unclear. None of the 141 patients received concurrent or adjuvant chemotherapy.

2.3 | Follow-up

After treatment, follow-up observations were 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 observation, chest CT, chest X-ray and a blood test were performed. If necessary,

TABLE 1 Characteristics of 141 patients treated with carbon-ion radiotherapy

Factors	Value or number (%)
Age	
Median, years (range)	75.0 (40.0-88.0)
Sex	
Male	108 (76.6)
Female	33 (23.4)
PS	
0	54 (38.3)
1	80 (56.7)
2	7 (5.0)
Smoking status	
Current or previous	26 (31.2)
Never	115 (81.6)
Interstitial pneumonia	
Yes	6 (4.3)
No	135 (95.7)
Treatment status	
Initial treatment	115 (81.6)
Recurrence or residual cancer after surgery or chemotherapy	26 (18.4)
Location of primary tumor	
Upper lobe	98 (69.5)
Middle lobe	4 (2.8)
Lower lobe	39 (27.7)
Operability	
Yes	30 (21.3)
No	111 (78.7)
Clinical T classification	
1	21 (14.9)
2	57 (40.4)
3	43 (30.5)
4	20 (14.2)
Clinical N classification	
0	51 (36.2)
1	45 (31.9)
2	40 (28.4)
3	5 (3.5)
Clinical stage	
IIA	34 (24.1)
IIB	42 (29.8)
IIIA	45 (31.9)
IIIB	20 (14.2)
Histology of primary lung cancer	
Adenocarcinoma	62 (44.0)
Squamous cell carcinoma	60 (42.6)
Large cell carcinoma	8 (5.7)
Non-small-cell carcinoma	3 (2.1)
Unknown	8 (5.7)
Total dose	
Median (Gy RBE) (range)	72.0 (54.0-76.0)
CTV	
Median (mL) (range)	320.0 (57.7-1475.5)

CTV, clinical target volume; PS, performance status; RBE, relative biological effectiveness.

brain magnetic resonance imaging or positron emission tomography (PET) was performed.

2.4 | Statistical analyses

Local control, locoregional control (LRC), progression-free survival (PFS) and OS were calculated using the Kaplan-Meier method. LC was defined as the time interval between irradiation commencement date and the local tumor regrowth in the PTV date or the last follow-up. LRC was defined as the time interval between the irradiation commencement date and the local or regional relapse date or the last follow-up. PFS was defined as the time interval between the irradiation commencement date and the date of disease progression at any site, death from any cause, or the last follow-up. OS was defined as the time interval between the irradiation commencement date and death, or the last follow-up.

To determine the prognostic factors of PFS and OS, univariate analysis was performed using the log-rank test. The patients were divided into subgroups according to the median values of age, total dose, the CTV, and the CIRT treatment timing (before or after January 2005). Multivariate analysis was performed using the Cox proportional hazards model. A 2-tailed $P < .05$ was considered statistically significant. All statistical analyses were conducted using JMP statistical software (version 14.0; SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

Two patients discontinued CIRT at 67.5 Gy (RBE) in 15 fractions and 71.25 Gy (RBE) in 15 fractions due to radiation pneumonitis and exacerbation of interstitial pneumonitis, respectively; therefore, 139 patients completed CIRT. The characteristics of the patients are summarized in Table 1. The median follow-up period was 29.3 months (1.6-207.7) for all patients and 40.0 months (10.7-207.7) for survivors. The median age was 75.0 years. Overall, 21 (14.9%), 57 (40.4%), 43 (30.5%) and 20 (14.2%) patients had T1, T2, T3 and T4 disease, respectively. Moreover, 51 (36.2%), 45 (31.9%), 40 (28.4%)

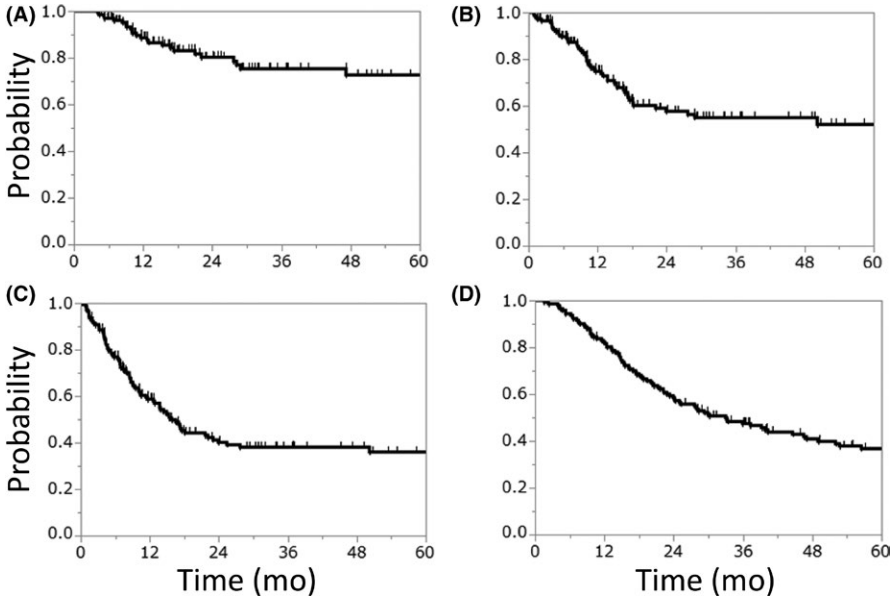

FIGURE 1 Local control rate (A), locoregional control rate (B), progression-free survival rate (C) and overall survival rate (D)

TABLE 2 Toxicity

Grade	2 (%)	3 (%)	4 (%)	Total (%)
Acute				
Dermatitis	19 (13.5)	0	0	19 (13.5)
Esophagitis	5 (3.5)	0	0	5 (3.5)
Late				
Pneumonitis	10 (7.1)	5 (3.5)	0	15 (10.6)
Brachial plexopathy	2 (1.4)	0	0	2 (1.4)
Pneumothorax	2 (1.4)	0	0	2 (1.4)
Chest wall pain	1 (.7)	0	0	1 (.7)
Bronchial fistula	0	1 (.7)	0	1 (.7)
Mediastinal hemorrhage	0	0	1 (.7)	1 (.7)

and 5 (3.5%) patients had N0, N1, N2 and N3 disease, respectively. Furthermore, 34 (24.1%), 42 (29.8%), 45 (31.9%) and 20 (14.2%) patients had stages IIA, IIB, IIIA and IIIB disease, respectively. Overall, 62 (44.0%), 60 (42.6%), 8 (5.7%) and 3 (2.1%) patients had adenocarcinoma, squamous cell carcinoma, large cell carcinoma and non-small-cell carcinoma, respectively, while 8 (5.7%) were clinically diagnosed as having primary lung cancer.

3.2 | Local control and survival

By the end of follow-up, 58 and 49 patients had either died of cancer or unrelated causes, while 34 patients survived. The 2-year and 3-year LC rates were 80.3% (95% confidence interval [CI]: 71.1%-87.1%) and 75.4% (95% CI: 65.1%-83.4%), respectively (Figure 1A). The 2-year and 3-year LRC rates were 57.7% (95% CI: 48.0%-66.8%) and 54.9% (95% CI: 45.0%-64.4%), respectively (Figure 1B). The 2-year and 3-year PFS rates were 40.2% (95% CI: 31.7%-49.3%) and 38.1% (95% CI: 29.7%-47.3%), respectively (Figure 1C). The 2-year and 3-year OS rates were 58.7% (95% CI: 50.3%-66.5%) and 47.5% (95% CI: 39.3%-55.8%), respectively (Figure 1D). The median PFS and OS durations were 11.6 and 29.3 months, respectively.

Next, we focused on elderly patients older than 70 years (n = 91). The median PFS and OS were 12.6 and 27.8 months, respectively. By categorizing the elderly patients into those with stages II or III LA-NSCLC, the median PFS and OS were 16.2 and 30.4 months or 10.2 and 24.1 months, respectively.

At the time of first relapse, 14 local recurrences, 32 regional recurrences (regional lymph nodes or/and satellite nodes in the ipsilateral lung) and 47 distant metastases were detected.

3.3 | Toxicities

In total, 1 (.7%) patient developed Grade 4 mediastinal hemorrhage, 5 (3.5%) developed Grade 3 radiation pneumonitis and 1 (.7%) developed Grade 3 bronchial fistula (Table 2).

The patient with Grade 4 mediastinal hemorrhage was diagnosed with locally advanced lung cancer (ycT4N2M0, Stage IIIB). T4 classification was diagnosed as an invasion to the mediastinum. The

TABLE 3 Univariate analysis of progression free survival and OS rates

Factors	Number of patients	PFS *P*-value	OS *P*-value
Age			
≥75 years old	72	.127	.123
<75	69		
Gender			
Male	108	.155	.357
Female	33		
Smoking status			
Current or previous	115	.229	.635
Never	26		
Neoadjuvant chemotherapy			
Yes	24	.349	.345
No	117		
Location of primary tumor			
Upper or middle lobe	102	.388	.060
Lower lobe	39		
Operability			
Yes	30	.751	.990
No	111		
Clinical T classification			
1	21	.101	.062
2	57		
3	43		
4	20		
Clinical N classification			
0	51	.006*	.027*
1	45		
2	40		
3	5		
Clinical stage			
IIA	34	.347	.481
IIB	42		
IIIA	45		
IIIB	20		
Histology of primary lung cancer			
Adenocarcinoma	62	.002*	.458
Squamous cell carcinoma	60		
Others	19		
Total dose			
<72 Gy RBE	28	.730	.257
≥72 Gy RBE	113		
CTV at re-irradiation			
<320 mL	71	.288	.054
≥320 mL	70		
The timing of CIRT			
The earlier timing	70	.287	.016*
The later timing	71		

*Represents the statistic significance ($P < 0.05$).
CIRT, carbon-ion radiotherapy; CTV, clinical target volume; OS, overall survival; PFS, progression free survival; RBE, relative biological effectiveness.

primary tumor was adjacent to the aortic arch but did not invade the aortic arch. After induction chemotherapy with platinum-based agents and other drugs, including bevacizumab, the patient received initial CIRT at 72.0 Gy (RBE) in 16 fractions. After that treatment, the disease did not recur. Thirty-three months later, a false aneurysm was detected around the aortic arch, adjacent to the initial site of the primary tumor. Two months later, mediastinal hemorrhage due to the rupture of the false aneurysm occurred, and an indwelling arterial stent was inserted. Consequently, the patient was cured.

Of the 6 patients with interstitial pneumonia, 2 developed Grade 3 radiation pneumonitis. No other toxicities of Grade ≥2 were observed.

We focused on the elderly patients older than 70 years (Table S1); 4 (4.4%) developed Grade 3 radiation pneumonitis and 1 (1.1%) developed Grade 3 bronchial fistula.

3.4 | Prognostic factors

Univariate and multivariate analyses were performed to identify potential prognostic factors of PFS and OS among the different subgroups (Table 3). On the basis of the significant *P*-values from the univariate analysis, multivariate analysis was performed. The results revealed that N classification ($P = .009$) and histology ($P < .001$) were significant predictors of PFS and that the timing of CIRT ($P = .012$) was a significant predictor of OS (Table 4). Furthermore, the 2-year PFS rates of N0-1 vs N2-3 patients were 44.8% vs 29.3% (Figure 2A). The 2-year PFS rates of patients with adenocarcinoma vs the other histology were 23.6% vs 53.5% (Figure 2B).

Associations between stage and outcomes were also evaluated. Although no significant difference was identified, 2-year PFS and OS rate of stages II or III were 40.0% and 61.8% or 40.6% and 54.9%, respectively.

4 | DISCUSSION

Definitive treatment for LA-NSCLC is generally chosen as surgery or chemoradiotherapy. However, for elderly patients or those who have severe comorbidities, surgery or photon chemoradiotherapy is a heavy burden. The outcomes of the alternative treatment including radiotherapy alone remain poor. Therefore, new approaches,

TABLE 4 Multivariate analysis of progression free survival and overall survival rate

Factors	PFS		OS	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
N classification N2-3 vs N0-1	1.912 (1.183-3.027)	.009*	1.408 (.915-2.120)	.117
Histology AD vs others	2.282 (1.460-3.595)	<.001*	1.078 (.726-1.587)	.706
The timing of CIRT the former part vs the latter part	1.329 (.853-2.073)	.208	1.683 (1.121-2.555)	.012*

*Represents the statistic significance ($P < 0.05$).

AD, adenocarcinoma; CI, confidence interval; CIRT, carbon-ion radiotherapy; OS, overall survival; PFS, progression free survival.

such as CIRT, are required for more effective and safe treatment. To date, only 2 studies of relatively small numbers of patients in terms of CIRT for LA-NSCLC have been published.[12,13] To the best of our knowledge, our study has reported the largest number of patients in evaluating the efficacy and toxicity of CIRT in LA-NSCLC. Our findings demonstrated that CIRT is effective and has an acceptable toxicity and that CIRT has become the reasonable treatment option, especially for elderly patients or patients with severe comorbidities who cannot be treated with surgery or chemoradiotherapy.

Bradley et al.[4] performed the Radiation Therapy Oncology Group 0617 trial of photon chemoradiotherapy for stage III LA-NSCLC and showed that the median PFS, median OS, 2-year PFS and OS rates in patients who received 60 Gy irradiation plus concurrent chemotherapy were 11.8 months, 28.7 months, 30.7% and 57.6%, respectively. Yamamoto et al.[5] conducted a multicenter phase III trial of photon chemoradiotherapy for stage III LA-NSCLC. They showed that median PFS and median OS of patients who received cisplatin plus paclitaxel chemoradiotherapy were 9.5 and 22.0 months, respectively. Meanwhile, using CIRT, Takahashi et al. and Karube et al. treated 62 and 64 patients with stages II/III LA-NSCLC, respectively.[12,13] They illustrated that the 2-year PFS and OS rates were 42.3% and 51.9%-62.2%, respectively. The present study revealed that the median PFS, median OS, 2-year PFS and OS for stages II/III LA-NSCLC were 11.6 months, 29.3 months, 40.2% and 58.7%, respectively. By grouping their patients into stages II or III, the corresponding values for patients with stage III were 10.1 months, 27.6 months, 40.6% and 54.9%, respectively. These findings may indicate that CIRT is approximately comparable to photon chemoradiotherapy.

In the present study, 1 (.7%) patient developed Grade 4 mediastinal hemorrhage from the aortic arch, to which the primary tumor was very close. This patient had received bevacizumab for 3 months before CIRT. Spigel et al.[19] reported that photon chemoradiotherapy, including bevacizumab, was associated with a relatively high incidence of tracheoesophageal fistulae formation in patients with primary lung cancer. The authors hypothesized that bevacizumab, an angiogenesis inhibitor, delays the healing of antecedent mucosal injury from chemoradiotherapy, leading to severe tracheoesophageal mucosal injury. This hypothesis may be applicable to our Grade 4 mediastinal hemorrhage case. Considering that the wall of the aortic arch, which was irradiated within the high dose area, was injured, bevacizumab delayed the healing of the wall injury. Consequently, a false aneurysm, which developed around the aortic arch, was ruptured. In addition, the other study reported that bevacizumab and high dose re-irradiation with CIRT to the trachea might increase the risk of tracheal necrosis.[20] These results suggest a warning about the increased risk of rupture with bevacizumab and high dose irradiation with CIRT to the great vessel. We treated the other 4 patients who received adjuvant chemotherapy including bevacizumab, and, fortunately, no great vessel toxicity occurred.

Regarding severe toxicity, hematologic toxicity is the most frequent in photon chemoradiotherapy for LA-NSCLC; in contrast, concerning non-hematologic toxicity, radiation pneumonitis and esophagitis are generally considered as major risks.[4] Some studies have shown, using photon chemoradiotherapy, that Grade ≥3 pneumonitis and esophagitis were .7%-11% and 7%-20%, respectively.[4,5,21] Meanwhile, our study using CIRT showed that Grade 3 radiation pneumonitis was observed in only 3.5% of all patients. None of our patients developed Grade ≥3 esophagitis or any hematologic toxicity. Our findings suggest that, with respect to Grade ≥3 toxicity, CIRT is superior to photon chemoradiotherapy.

Concerning the standard treatment for the elderly patients with LA-NSCLC, whether chemotherapy should be added to radiotherapy or not is controversial.[8] Some studies reported an improvement in survival with the addition of chemotherapy to radiation but they also had an increase in severe toxicity.[9,22,23] In fact, Atagi et al.[9] conducted a randomized, controlled, phase 3 trial using radiotherapy with or without low-dose carboplatin in elderly patients (>70 years old) with stage III LA-NSCLC. The median PFS and OS for chemoradiotherapy or radiotherapy alone groups were 8.9 and 22.4 months, or 6.8 and 16.9 months, respectively. As expected, patients in the chemoradiotherapy group suffered more Grade 3 to 4 hematologic toxicity and Grade 3 infections than those in the radiotherapy alone group. As expected, the former group developed Grades 3-4 leucopenia (63.5%), Grades 3-4 thrombocytopenia (29.2%), Grade 3 infection (12.5%) and Grades 3-4 lung toxicities (7.5%). Meanwhile, our results illustrated that the median PFS and OS in the elderly patients with stage III LA-NSCLC were 10.6 and 24.1 months, respectively, and that 5 (5.5%)

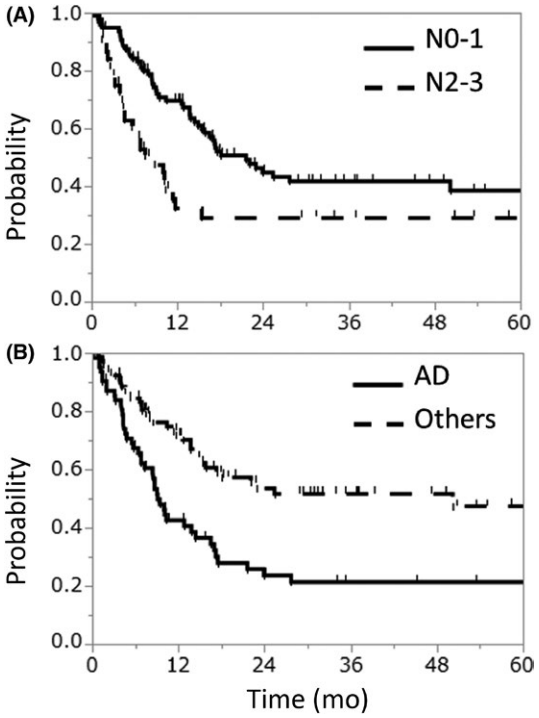

FIGURE 2 Progression-free survival rate according to N classification (A) and histology (B). AD, adenocarcinoma

patients developed Grade 3 lung toxicities. No patients developed hematologic toxicity and infection. These results indicated that CIRT is approximately comparable in efficacy to photon concurrent chemoradiotherapy in elderly patients but with less toxicity. Recently, the risk factors, including the lung volume receiving ≥30 Gy (RBE) for Grade ≥2 radiation pneumonitis after CIRT, were reported.[18] In future, we may be able to reduce the incidence of severe radiation pneumonitis as risk factors.

In the multivariate analysis, we found that N2-3 classification ($P = .009$) and adenocarcinoma ($P < .001$) were significant poor prognostic factors of PFS. This may have arisen from the fact that these factors often cause regional lymph nodes outside the irradiated field, or distant metastasis. In addition, OS in patients who were treated in the earlier part of the timing of CIRT (i.e. before January 2005) were significantly poor ($P = .012$) compared to those whose timing occurred later. The reason for this is not clear; however, this may have arisen due to the lack of PET-CT for disease staging. From 2005, almost all patients with LA-NSCLC had PET-CT done, and consequently, we were able to assess for distant metastasis and metastatic lymph nodes more accurately.[24]

Our study had several limitations. First, our study is a single-center retrospective analysis. Second, our results might have underestimated the late toxicity because the median follow-up duration (29.3 months) of all 141 patients was not sufficient. Finally, the total doses and fractionation varied (54-76 Gy (RBE) in 12-16 fractions). Therefore, further large-scale multicenter prospective trials are warranted.

In conclusion, CIRT is an effective treatment option with acceptable toxicity for LA-NSCLC, especially for elderly patients or patients with severe comorbidities who cannot be treated with surgery or chemoradiotherapy. CIRT demonstrated comparable efficacy to photon chemoradiotherapy but with less toxicity.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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