RESEARCH ARTICLE

Adaptive carbon ion radiotherapy for locally advanced non-small cell lung cancer: Organ-sparing potential and target coverage

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Abstract

Background: The dose distribution of carbon ion radiotherapy (CIRT) for locally advanced non-small cell lung cancer (LANSCLC) is highly sensitive to anatomical changes.

Purpose: To demonstrate the dosimetric benefits of adaptive CIRT for LANSCLC and compare the differences between patients with and without adaptive plans based on dosimetry and clinical effect factors.

Materials and methods: Of the 98 patients with LANSCLC receiving CIRT, 31 patients underwent replanning following re-evaluations that revealed changes that would have compromised the dose coverage of the target volume or violated dose constraints. Dosimetric parameters and clinical factors were compared between patients with and without adaptive plans. Multivariate analysis identified factors influencing the adaptive planning.

Results: The median number of fractions delivered using adaptive plans was eight (range: 2-18). Adaptive plans ensured target coverage, and the maximum spinal cord dose was significantly decreased ($p = 0.02$). The median reduction in the maximum spinal cord dose was 10.4 Gy (relative biological effectiveness). Patients with adaptive plans had larger tumor volumes ($p < 0.001$); the median initial internal gross tumor volumes (iGTVs) of patients with adaptive and nonadaptive plans were 125.9 and 49.79 cm^3, respectively. Tumor volumes of patients with adaptive plans were altered to a greater extent ($p < 0.001$); the median absolute percentage of volume changes in patients in the adaptive and in nonadaptive groups were 20.76% and 3.63%, respectively, while the median movements of iGTV centers were 5.75 and 2.44 mm, respectively. Binary logistic regression analysis revealed that the iGTV volume change and iGTV center movements were significantly different between the groups.

Conclusions: An adaptive plan can effectively ensure target area coverage and protect normal tissues, especially in patients with large tumor volumes and substantial changes. iGTV volume changes and iGTV center movements are the main factors influencing adaptive planning. Weekly simulation computed tomography scans are necessary for treatment evaluation in patients with LANSCLC treated with CIRT.

KEYWORDS
adaptive therapy, carbon ion therapy, locally advanced non-small cell lung cancer

1 | INTRODUCTION

Non-small cell lung cancer (NSCLC) is one of the leading causes of mortality worldwide, and approximately 30% of patients are diagnosed at stage III of the disease, which is often unresectable.[1–3] The standard of care for patients with unresectable locally advanced NSCLC (LANSCLC) is platinum-based doublet chemotherapy concurrent with radiotherapy and durvalumab consolidation therapy.[4–10] During radiation therapy, changes in tumor volume can reduce target area coverage. Adaptive radiotherapy (ART) based on tumor volume changes can ensure adequate target coverage while reducing the dose delivered to normal tissue. The low toxicity and the low marginal failure rate of ART make this modality a positive option for future radiotherapy.[11–15] Adaptation of radiotherapy plans for tumor shrinkage, once or twice during the treatment course, significantly reduces the median lung dose, which permits clinically relevant escalation of the irradiation dose.[16]

Owing to the physical dosimetric advantage of the carbon ion beam, the radiation dose of normal tissue can be greatly reduced, and the spread-out Bragg peak can generate a uniformly irradiated high-dose region in the target area, followed by a sharp decrease. The radiation damage caused by carbon ions is two to three times greater than that of X-rays and can break the DNA double strand of tumor cells, resulting in death of the irradiated tumor cells. It is also extremely effective for certain tumors that are resistant to photon and proton rays; therefore, the additional biological advantages of carbon ions are beneficial in the treatment of tumors. In the treatment of LANSCLC, carbon ion radiotherapy (CIRT) provides a higher uniform target dose and lower normal tissue doses than photon radiotherapy.[17–19] CIRT with pencil beam scanning has been used to treat patients with NSCLC.[20] However, the dose distribution of carbon ion beams is highly sensitive to lung density changes. During the treatment course, changes in tumor volume and location could affect the target coverage and normal tissue doses, thus necessitating ART.

Adaptive planning in photon therapy can help improve the delivery of a target dose, protect normal tissues, and reduce radiotoxicity in patients with NSCLC.[15,21–23] By creating look-up tables to predict the theoretical dosimetric advantage under normal lung dose constraints, they found that ART provided the optimal dosimetric effect at around the 15th administration of radiation therapy.[13,14] For patients with NSCLC, adaptive planning in proton therapy have acceptable toxicity and are used to treat larger tumors with a capacity for greater shrinkage.[24] However, for higher energy carbon ions, there have been no reports regarding the use of ART for NSCLC. Therefore, the main aim of this study was to validate the potential benefits of carbon ion ART, to identify the characteristics of patients that are the most suitable for adaptive planning, and to determine the appropriate timing of adaption.

More specifically, this study aimed to evaluate the dosimetric advantages of an adaptive plan and compare the differences between patients with and without adaptive plans based on dosimetry and clinical effect factors. The study focuses on the more forward-looking ART in particle radiotherapy and the innovative implementation of adaptive CIRT for patients with LANSCLC, which provides some degree of theoretical and practical significance for clinical treatment.

2 | MATERIALS AND METHODS

2.1 | Patients

In this study, 98 patients with LANSCLC who received CIRT at Shanghai Proton and Heavy Ion Center were selected, 31 of whom had an initial confirmation plan that failed to meet the criteria and required adaptive planning. The inclusion criteria in this study were as follows: patients with pathologically confirmed LANSCLC (IIB-IIIC, 7th edition of the American Joint Committee on Cancer staging manual) who were deemed medically inoperable or who declined surgery and were treated with CIRT; Karnofsky Performance Status (KPS) score ≥80; weekly simulation computed tomography (CT) scans during treatment; and tumor motion assessed pretreatment. This retrospective study design was approved by the Ethics Review Board of The Shanghai Proton and Heavy Ion Center.

2.2 | Simulation CT and target definition

A vacuum bag was used to place the patient in a supine or prone position based on the location of the radiation target. For patients who were treated under free-breathing or respiratory gating conditions, a thermoplastic mask was used to fix the position and restrict breathing-related movement. For patients treated in free respiratory or active respiratory control mode, a simulation CT scan was performed in the same breathing mode. CT scans were performed from the mandible to the kidneys and adrenal glands, including the tumor lesions, the entire lung, the entire neck, and all the organs and tissues through which radiation may pass.

The gross tumor volume (GTV) was contoured based on the CT images under the pulmonary or mediastinal window based on our protocol, including the primary tumors and the metastatic hilar and mediastinal lymph nodes. Patients with respiratory gating were scanned using four-dimensional simulation CT. Ten phases of the whole respiratory cycle were reconstructed, and the GTV outlined in each phase was combined into the internal gross tumor volume (iGTV). The clinical target

volume (CTV) was defined as an extension from the GTV/iGTV of 0.6-0.8 cm. Range uncertainty and setting errors were calculated when creating the planning target volume (PTV). In most cases, the PTV was the CTV plus 0.5-0.7 cm for the lateral margin and 0.7-1.5 cm for the beam ward edge.[20]

2.3 | Treatment planning

Details of CIRT and treatment planning techniques have been reported previously.[20] All CIRT planning was performed using the Syngo treatment planning system (Siemens, Erlangen, Germany). The CIRT plans were designed using two to four beams (beam energy 85-430 MeV) with the pencil beam scanning technique. The radiation dose was expressed in Gy (relative biological effectiveness [RBE]), which is defined as the measured carbon physical dose (Gy) multiplied by the clinical RBE. The target coverage required at least 99% of the iGTV/GTV at 95% of the prescription dose. The median prescription dose was 75 (range: 60-83.6) Gy (RBE); dose and fractions used included 6-6.5 Gy (RBE) $\times$ 10 Fx and 3-4 Gy (RBE) $\times$ 16-23 Fx, respectively. All treatment plans were designed to meet strict guidelines for protecting the organs at risk (OARs) (Supporting Information S1), including the lungs, spinal cord, esophagus, trachea, bronchial tree, and heart.[25–29]

2.4 | Adaptive planning

CT scans were conducted for every patient before the first treatment and every week during treatment. The structures on the original planned CT were aligned to the new simulation CT, and the physician modified and confirmed the target areas and OARs on the new simulation CT images. The original plan for the latest simulation CT was recalculated to create a confirmation plan. Adaptive planning was initiated when the quality of the confirmation plan did not meet the clinical requirements. When an adaptive plan for patients was required, more than 99% of the iGTV/GTV was required to be surrounded by 95% of the prescribed doses, and the normal tissue dose was reduced to as low as the dose of the original plan. The adaptive plans delivered the same fraction dose to the tumor as the confirmation plan should have to ensure that the prescribed dose was delivered as a result of biological dose accumulation. Moreover, most of the replanning to generate an adaptive plan was optimized to meet the clinical requirements based on the original beam settings, and some adaptive plans were completely replanned in cases where the original beam settings were no longer appropriate. The simulation CT continued to be conducted every week during the follow-up treatment.

Based on these assessments, an adaptive plan was developed for the 31 patients whose confirmation plan failed to meet the criteria. To evaluate the dosimetric effects of these adaptive changes, we compared the iGTV/GTV coverages and the dose–volume histograms of normal tissues between the confirmation plan (the original plan recalculated using the simulation CT) and the adaptive plan (the new plan calculated using the simulation CT). The conformal index (CI) and homogeneity index (HI) were determined for the iGTV/GTV, maximum spinal cord dose, mean and maximum esophagus doses, maximum bronchial tree dose, heart volume receiving 40 Gy (RBE) (V40), mean heart dose, mean lung dose, and lung V5, V10, and V20 values.

The closer the HI value of the target volume is to 1, the more uniform the dose distribution is in the target area. The HI is described as follows:

$$HI = D5/D95 \tag{1}$$

D5 and D95 are defined as the doses received at 5% and 95% of the target volume, respectively. CI is calculated according to the following formula:

$$CI = \frac{V^2_{T,R_x}}{V_T \times V_{R_x}} \tag{2}$$

$V_{(T, RX)}$ is the target volume receiving the prescription dose, V_T is the target volume, and V_{Rx} is the body volume receiving the prescription dose. It can be deduced from the equation that conformity improves as the CI value approaches 1.

In addition, the original planning CT and simulation CT were fused in MIM Maestro (MIM Software, Cleveland, OH), and the three-dimensional coordinates of the central point of the target area were recorded as ($X0$, $Y0$, $Z0$) and ($X1$, $Y1$, $Z1$), respectively. Thereafter, the relative distance of the target area center points was calculated as follows:

$$L = \sqrt{(X1 - X0)^2 + (Y1 - Y0)^2 + (Z1 - Z0)^2} \tag{3}$$

2.5 | Statistical analysis

The characteristics of patients with adaptive plans were compared with those with nonadaptive plans using the Mann–Whitney U test (comparison between groups of continuous data) and chi-square test (comparison between groups of categorical data), and p-values of <0.05 were considered significant. Binary logistic regression analysis was used to analyze the correlation between tumor characteristics and ART. All analyses were performed using SPSS Statistics version 21 (Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics

From July 2016 to June 2020, 98 patients with LANSCLC were treated with CIRT. During treatment, 31 cases (31.6%) were replanned after evaluating the feasibility of the original plan in a CT review, whereas 67 cases (68.4%) had no change to the original plan. Patients who received the adaptive plan included a larger proportion of smokers, those with larger tumors with greater iGTV volume change and centroid shift during treatment, and those who received smaller fraction doses, compared to those who received a nonadaptive plan. The patient and disease characteristics are summarized in Table 1.

3.2 | Adaptive planning characteristics

The 31 patients required 43 adaptive planning sessions during radiotherapy due to large changes in tumor volume and position. Ten patients required two replans, seven of whom had tumors whose volumes increased and then decreased during the course of treatment, triggering separate replans. The other three patients' tumor volumes continued to decrease during the course of treatment, triggering replanning twice. One patient required three replans, which were triggered by a change in the tumor location due to mediastinal shift; interestingly, in that case, the tumor had returned to its original position at the time of treatment.

The median number of fractions delivered using an adaptive plan was eight (range: 2-18), and the median number of replanning sessions per patient was one (range: 1-3). The median initial iGTV/GTV, the absolute value of median iGTV/GTV percentage change, and the median movement of the iGTV/GTV center are shown in Table 2. The mean volume change in iGTV/GTV of patients with adaptive planning was 1.16% per day.

After dosimetric assessment of all 43 adaptive plans, 40 (93%) replans were required due to insufficient iGTV/GTV coverage, 19 (44.2%) replans were needed due to radiation doses exceeding safe levels in normal tissues (2 maximum esophagus doses, 1 lung V20 dose, 11 maximum spinal cord doses, and 7 maximum bronchial tree doses), and 16 (37.2%) replans were necessary due to both insufficient target coverage and normal tissue overdose. An example of adaptive planning is shown in Figure 1; in that case, the patient was evaluated in the confirmation plan for inadequate coverage of the target area and high-dose irradiation of the spinal cord, and a corrected dose distribution was achieved by replanning. Without adaptive planning, the V95% of the iGTV/GTV would be reduced to 55.81% and the maximum dose to the spinal cord would be 91.67 Gy (RBE).

3.3 | Target coverage of adaptive planning

An adaptive plan can effectively ensure target area coverage (Table 3). Replanning improved the average iGTV V95% values by 23.55% over the confirmation plans, and the average iGTV V99% values improved by 29.66%. The target coverage was significantly higher after replanning than that of the confirmation plan ($p < 0.001$; Figure 2a). The CIs and HIs had also been significantly improved, which means that replanning improved the target conformity and uniformity ($p < 0.001$).

There were no significant differences in D5, D95, V95, V99, CI, and HI between the replan and the original plan.

3.4 | Normal tissue doses for adaptive planning

Compared to the confirmation plan, the lung V5 and V10, the mean heart dose, and the maximum esophagus, spinal cord, and main bronchial tree doses were lower in the replan (Table 4). This was especially true for the spinal cord (Figure 2b), where the median reduction in maximum spinal cord dose was 10.4 Gy (RBE) ($p = 0.02$).

In comparison to the original plan, the lung V5 and V10 values, the mean and maximum esophagus doses, and the maximum spinal cord dose were lower in the replan; however, the differences were subtle and not statistically significant.

3.5 | Multivariate analysis

The univariate analysis showed that certain parameters, including the initial iGTV volume, iGTV volume change, movement of the iGTV center, fraction dose, smoking, and chemotherapy were significantly different between patients who received an adaptive plan and those who did not. These factors were included in a binary logistic regression analysis, and the results showed that only iGTV volume change and movement of the iGTV center had a significant impact on the dose distribution to the extent that adaptive planning may be required ($p < 0.05$).

4 | DISCUSSION

To explore the characteristics of patients who require adaptive CIRT for LANSCLC, we reviewed all the data of patients with LANSCLC at our center, including patients receiving either adaptive or nonadaptive plans. During radiation therapy for lung cancer, uncertainty in patient positioning, respiratory motion, anatomical changes, and

TABLE 1 Characteristics of the patient population

Characteristics	Patients with adaptive plans (*n* = 31)	Patients with nonadaptive plans (*n* = 67)	*p*-value
Age, years			
Median (range)	69 (47-81)	66 (46-83)	0.211
Sex, *n* (%)			
Male	27 (87.1%)	53 (79.1%)	0.342
Female	4 (12.9%)	14 (20.9%)	0.342
Pathology, *n* (%)			
SCC	18 (58.1%)	35 (52.2%)	0.590
Adeno	9 (29.0%)	22 (32.8%)	0.707
Non-small cell, NOS	4 (12.9%)	10 (14.9%)	1.000
Stage,[a] *n* (%)			
IIB	5 (16.0%)	22 (32.8%)	0.085
IIIA	14 (45.2%)	20 (29.9%)	0.139
IIIB	10 (32.3%)	22 (32.8%)	0.955
IIIC	2 (6.5%)	3 (4.5%)	1.000
Tumor location, *n* (%)			
Left lower lobe	4 (12.9%)	7 (10.4%)	0.989
Left upper lobe	11 (35.5%)	18 (26.9%)	0.485
Right lower lobe	4 (12.9%)	7 (10.4%)	0.989
Right upper lobe	12 (38.7%)	28 (41.8%)	0.773
Middle lobe	0	7 (10.4%)	0.148
Smoker, *n* (%)	29 (93.6%)	50 (74.6%)	0.028
Pack years			
Median (range)	45 (0-120)	30 (0-195)	0.100
Weight change[b] (kg)			
Median (range)	1.8 (0.9-11.2)	2.1 (0.6-11.2)	0.456
Prescription dose, Gy (RBE)			
Median (range)	72.6 (62.1-82.8)	78.7 (60.0-83.6)	0.022
Fraction dose, Gy (RBE)			
Median (range)	3.3 (2.7-4.0)	3.6 (3.0-6.5)	<0.001
Chemotherapy,[c] *n* (%)	21.0 (67.7%)	55 (82.1%)	0.035
Chemotherapy[c] cycle			
Median (range)	2 (0-6)	3 (0-8)	0.053
Body position, *n* (%)			
Supine	18 (58.1%)	37 (55.2%)	0.792
Prone	13 (41.9%)	30 (44.8%)	0.792
Atelectasis, *n* (%)	13 (41.9%)	26 (38.8%)	0.768
Breath control, *n* (%)			
Gating	25 (80.6%)	56 (83.6%)	0.721
FB	3 (9.7%)	9 (13.4%)	0.365
ABC	3 (9.7%)	2 (3.0%)	0.845
Tumor characteristics			
Primary volume (cm^3)	125.90 (28.08-326.90)	49.79 (1.67-444.52)	<0.001

(Continues)

TABLE 1 (Continued)

Characteristics	Patients with adaptive plans (*n* = 31)	Patients with nonadaptive plans (*n* = 67)	*p*-value
Percent change in volume[d] (%)	20.76[e] (6.30-114.20)	3.63[b] (0.25-20.63)	<0.001
Movement of center (mm)	5.75[e] (1.38-14.10)	2.44[b] (0.63-6.54)	<0.001

p-values were calculated using the Mann–Whitney U test and chi-square test.

Abbreviations: ABC, active breathing control; Adeno, adenocarcinoma; AJCC, American Joint Committee on Cancer; FB, free breathing; NOS, not otherwise specified; RBE, relative biological effectiveness; SCC, squamous cell carcinoma.

[a]AJCC staging v7.
[b]During treatment.
[c]Before treatment.
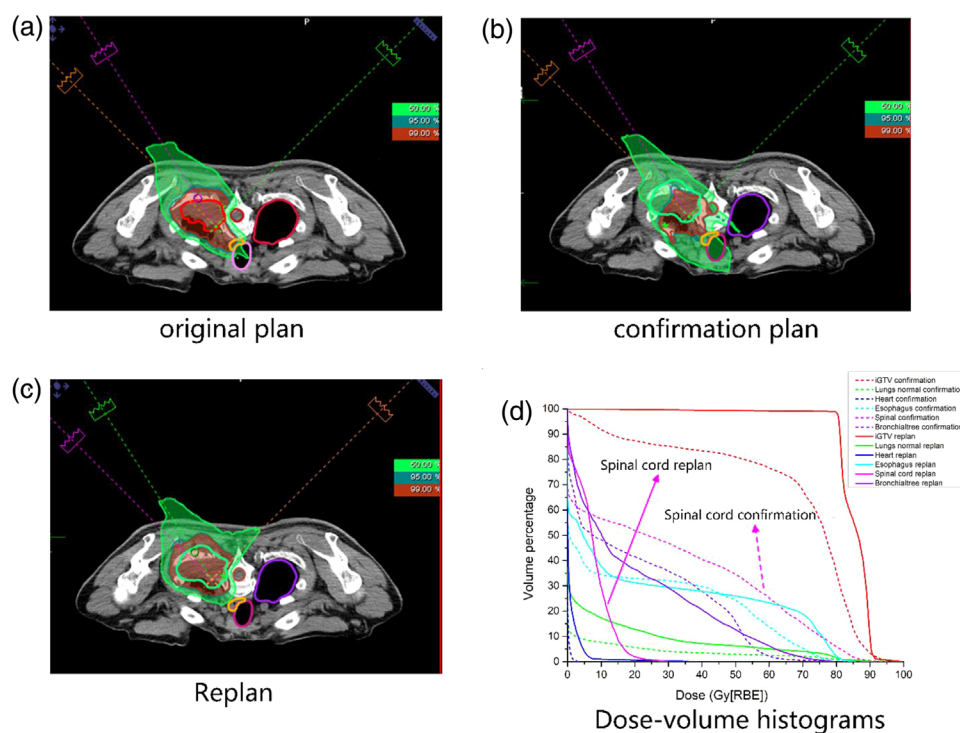[d]Absolute value.
[e]At first replanning.

FIGURE 1 (a-c) Dose distributions in a cross-section of patients with the original plan, confirmation plan, and replan. (d) Dose–volume histograms reveal notable differences in iGTV coverage and organs at risk, especially the spinal cord, between the confirmation plan and replan. iGTV, internal gross tumor volume; RBE, relative biological effectiveness

tumor regression responses can influence the dose distribution,[11] leading to incorrect target area definitions. Lung atelectasis, tumor progression, and pleural effusion[30–34] may also result in suboptimal coverage of the target area or an overdose to normal tissues. In addition to dosimetry and tumor anatomical changes during treatment, other factors, such as tumor pathology, tumor location, smoking, body weight changes, respiratory control, treatment posture, history of chemotherapy, prescription dose, and atelectasis were included in this study. The multivariate analysis revealed that the iGTV volume change and movement of the iGTV center had a

significant impact on dose distribution to the extent that adaptive planning may be warranted.

During treatment, images were obtained and evaluated weekly using simulation CTs. The original treatment plan was modified following re-evaluation in 31 of the 98 patients, resulting in a 23.56% increase in the mean value of the target V95% in the replan compared to the confirmation plan. This indicates that nearly one third of the patients with LANSCLC treated with CIRT required adaptive planning for more precise radiotherapy. If there had been no replanning, the target coverage would have been poor and would not have met the treatment
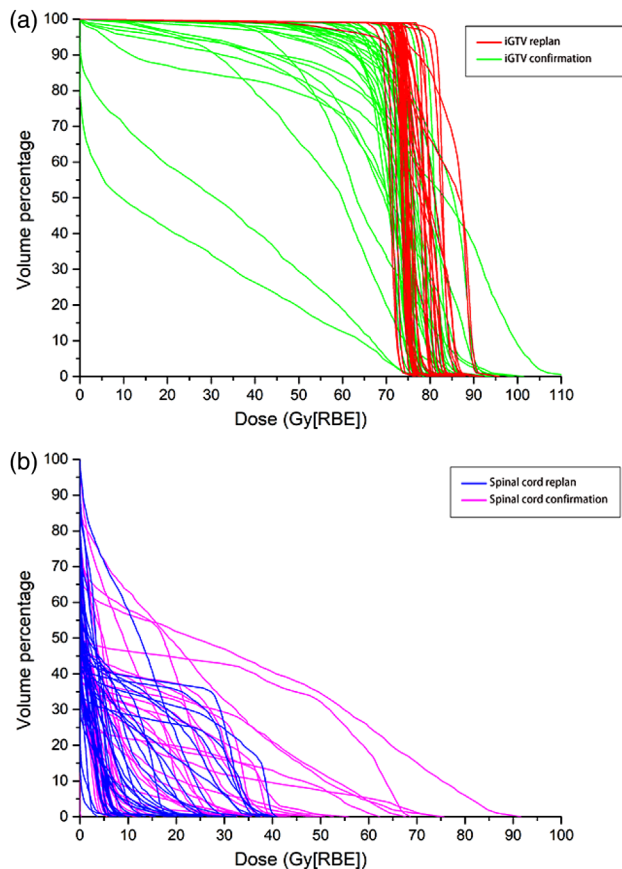
FIGURE 2 (a) Dose–volume histograms reveal notable differences in iGTV coverage between the confirmation plans and replans of the 43 adaptive planning sessions. The iGTV prescription dose is normalized to 72.6 Gy (RBE). The DVH of some plans extended to a prominently high dose due to the influence of simultaneous integrated boosting. (b) Dose–volume histograms reveal notable differences in the spinal cord between the confirmation plans and replans of 43 adaptive planning sessions. iGTV, internal gross tumor volume; RBE, relative biological effectiveness

TABLE 2 Tumor (iGTV/GTV) characteristics for patients with adaptive planning

iGTV/GTV ($n = 43$)	Median (range)
Primary volume (cm^3)	144.10 (28.08-491.56)
Percent change[a] (%)	19.2 (3.2-114.2)
Movement of center (mm)	
Total distance	5.63 (1.28-14.10)
Superior	2.53 (0.11-12.71)
Inferior	3.29 (0.29-6.26)
Right	1.54 (0.04-7.53)
Left	2.51 (0.04-12.87)
Posterior	2.32 (0.61-10.97)
Anterior	2.38 (0.07-7.50)

Abbreviations: iGTV, internal gross tumor volume; GTV, gross tumor volume.
[a]Absolute value.

TABLE 3 Differences in target coverages between confirmation plan and replan

	Confirmation plan ($n = 43$)	Replan ($n = 43$)	*p*-value
D5 (Gy [RBE])	80.08 ± 0.84	76.15 ± 1.90	0.203
D95 (Gy [RBE])	52.93 ± 3.38	71.09 ± 1.92	<0.001
V95% (%)	76.06 ± 3.64	99.61 ± 0.16	<0.001
V99% (%)	63.96 ± 3.94	93.62 ± 2.37	<0.001
HI	6.55 ± 3.20	1.07 ± 0.01	<0.001
CI	0.29 ± 0.03	0.52 ± 0.04	<0.001

p-values were calculated using the Mann–Whitney U test.
Abbreviations: CI, conformal index; HI, homogeneity index; RBE, relative biological effectiveness.

standard. The dosimetric parameters demonstrated that replanning ensured target area coverage, and the radiation doses of normal tissues were also reduced, especially the maximum spinal cord dose. The mean lung

TABLE 4 Differences in normal tissue dose–volume histograms between confirmation plan and replan

	Confirmation plan ($n = 43$)		Replan ($n = 43$)		*p*-value
	Median	Range	Median	Range	
Lungs V5 (%)	28.48	8.28-45.77	26.55	11.34-51.73	0.935
Lungs V10 (%)	23.99	6.12-36.61	21.95	9.02-40.58	0.859
Lungs V20 (%)	18.83	3.33-30.71	17.56	0.73-32.25	0.498
MLD (Gy [RBE])	10.59	2.21-16.02	10.23	2.21-16.29	0.753
Heart V40 (%)	4.79	0-54.52	5.05	0-14.75	0.941
MHD (Gy [RBE])	6.06	0.10-44.43	5.71	0.18-14.08	0.870
MED (Gy [RBE])	14.51	0.97-42.77	17.64	1.33-49.15	0.935
Dmax of Eso (Gy [RBE])	71.83	7.32-93.12	70.67	21.24-84.14	0.577
Dmax of SC (Gy [RBE])	31.82	0.24-91.66	21.39	3.67-40.87	0.020
Dmax of MBT (Gy [RBE])	78.87	1.35-92.45	77.70	21.48-91.51	0.371

p-values were calculated using the Mann–Whitney U test.
*Abbreviation*s: Dmax, maximum dose; Eso, esophagus; MBT, main bronchial tree; MED, mean esophagus dose; MHD, mean heart dose; MLD, mean lung dose; RBE, relative biological effectiveness; SC, spinal cord; V5/V10/V20, volume of the normal lung that received at least 5/10/20 Gy (RBE).

dose; lung V5, V10, V20 values; and maximum doses for the esophagus, spinal cord, and bronchial tree were reduced after replanning. However, the mean esophagus dose was increased, possibly because the esophagus was closer to the target area in some patients, and the increase in target coverage led to an increase in the mean esophagus dose, without exceeding the dose limit.

Our results indicate that there are significant differences in the initial iGTV, iGTV volume change, and movement of the iGTV center between patients receiving adaptive and nonadaptive plans. The adaptive plan tended to be used for patients with larger initial iGTV and larger anatomical changes. This is consistent with the reported results of adaptive photon radiotherapy[12–14] and adaptive proton radiotherapy[24] for LANSCLC. Our findings suggest that patients with LANSCLC undergoing carbon irradiation should be considered for adaptive planning when the absolute value of the iGTV percentage change exceeds 20% or when the iGTV center point is shifted by more than 5.00 mm. However, recalculation of the evaluation CT is required when significant anatomical changes of the tumor are observed during treatment, to ensure that the target area is appropriately covered, and that the dose parameters meet the requirements for treatment continuation. Interestingly, the patients who required adaptive planning received smaller fraction doses. The total number of fractions for the two groups were 21.84 ± 0.24 and 20.78 ± 0.28 for the adaptive and nonadaptive groups, respectively, and the data revealed a correlation between the total treatment duration and the need for adaptation. Of course, a longer treatment duration itself implies a greater likelihood of tumor changes during treatment.

A delay between a patient's CT image acquisition and the completion of the treatment planning is inevitable. During this period, tumors progress in some patients, and the CT scans following a patient's admission to the hospital may show greater tumor changes. Following the alignment of the new CT with the planned CT, we generated a confirmation plan to verify that the dose lines met the treatment standards. A daily change of 0.2-4.1% of the iGTV was observed, which is consistent with the tumor shrinkage data in adaptive photon radiotherapy.[13,14,32,35] Therefore, patients with LANSCLC receiving CIRT were recommended to undergo weekly simulation CT scans and were re-evaluated during their treatment period.

Our adaptive plan can effectively ensure target area coverage while protecting normal tissues. However, this study has several limitations. First, we only analyzed the dosimetric advantages of the adaptive plans and tumor changes in patients receiving adaptive plans. Second, ART increases the burden in terms of workload for the institution and increases the time and effort required by the clinicians and physicists. Last but not least, a fast and reliable deformable alignment tool is essential for fast ART. Further studies must be undertaken to analyze all other tumor features and dosimetric parameters on CT, with a goal of ensuring that patients receive the best treatment without significantly increasing the pressure on the medical system.

5 | CONCLUSIONS

An adaptive plan can effectively ensure target area coverage and protect normal tissues, especially for large tumor with substantial changes in their anatomical structure. The parameters, iGTV volume change, and iGTV center movement are the main factors affecting adaptive planning. We recommend that patients with LANSCLC undergo weekly simulation CT scans for treatment evaluation. The methods developed here could help guide future prospective trials using adaptive CIRT for patients with LANSCLC.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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