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Research Article

Factors that Influence the Need to Start Adaptive Radiotherapy

Nouran Muhammed Roby,[1] Mohamed Hassan,[2] Mohamed A. Aboelkasem,[2] Maha Kamaleldin,[2] Ahmed S. Ali[2]

[1]Clinical Oncology Department, Ahmed Maher Teaching Hospital, Cairo, Egypt
[2]Kasr El-Aini Center of Clinical Oncology and Nuclear Medicine, Cairo University, Cairo, Egypt

Address correspondence to Nouran Muhammed Roby (nouran.elroby@gmail.com).

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ABSTRACT

Introduction: Adaptive radiotherapy (ART) is an essential approach to account for anatomical and biological uncertainties. Adaptive radiotherapy is, however, time-consuming, and it is unclear which patients are eligible or when is the best time to start ART. **Methods:** This prospective study was conducted at Kasr El-Aini Center of Clinical Oncology and Nuclear Medicine, Cairo, Egypt from January 2019 to December 2020. Thirty patients with pathologically proven, limited-stage small cell or stage I-II non–small cell lung cancer who were either not fit for or refused surgery or had stage III disease were recruited and underwent treatment planning to receive 60 Gy on a conventional 3D conformal radiation schedule with platinum-based chemotherapy. All patients underwent computed tomography (CT) planning within 2 and 4 weeks of starting radiation therapy to assess the need for adaptation. Pulmonary function test and echocardiography findings were assessed at the end of treatment and at 3 and 6 months after treatment, and were compared to the baseline. **Results:** We found a significant reduction in mean value of the planning target volume (PTV) in the CT scans at the second (331 cm^3) and fourth (257 cm^3) weeks of treatment as compared to baseline (342 cm^3) (p-value < 0.0001). Adaptation decreased the dose to the organ at risk with statistical significance and with improvement of the target coverage. At week 2 of radiotherapy, the need for adaptation was correlated to the conformity index ($p = 0.0473$), esophageal V35 ($p = 0.0488$), esophageal V50 ($p = 0.0295$), and its mean dose ($p = 0.0087$). At week 4 it was correlated to forced expiratory volume in 1 second (FEV1) ($p = 0.0303$), ratio between the forced expiratory volume in 1 second and the forced vital capacity (FEV1/FVC) ($p = 0.0024$), and echocardiography ($p = 0.0183$). **Conclusions:** Conformity index and esophageal dose constraints can predict the need for adaptation at week 2, whereas baseline pulmonary function parameters and echocardiography can predict the need for adaptation at week 4 of radiotherapy.

Keywords: adaptation, radiotherapy, lung

INTRODUCTION

Owing to developments in radiation therapy delivery technology, lung cancer treatment is rapidly evolving.[1] Lung cancer radiotherapy is very challenging, as large margins (such as the internal target volume and setup margin to account for organ movement and setup errors) are provided to account for the various sources of systematic and random errors, such as breathing motion within a fraction, baseline change between and within fractions, organ motion, and demarcation. Using 4D computed tomography (4D-CT) and daily setup to target the tumor, much effort has been made to reduce these inaccuracies.[2] Owing to anatomical or physiologic changes in relation to the initial simulation, adaptive radiotherapy (ART) enables the revision of a treatment plan with the aim of enhancing the dosage distribution to the patient.[3] Three types of contemporary ART exist: offline, internet, and real-time adaptation. Offline adaptation is the process of revising the patient's treatment strategy following the administration of one or more treatment fractions. It frequently entails re-simulation, recontouring, and re-planning in the same way the original treatment strategy was developed. Online adaptation, which uses plan modifications just prior to the delivery of the fraction and frequently entails recontouring and re-planning on an image-guided radiotherapy–derived imaging dataset, is a fast-emerging field. Based on real-time imaging to gate the treatment beam or track the target using the multileaf collimator, real-time adaptation automatically modifies the treatment plan during the fraction of treatment.[4] All forms of ART represent a burden to personnel and patients: the patient's treatment course will be interrupted and all the procedures will have to be repeated; a radiation oncologist will have to repeat the contouring and review and approve the adapted plan; and a physicist will have to generate a new plan and perform quality assurance.[5] The advantages of higher dosimetric coverage of the tumor and dose sparing to the organs at risk (OARs) may allow dose escalation for better local control, and therefore exceed the burden experienced by personnel.[4] Unfortunately, there are no guidelines regarding which patients should be selected for adaptation, when to perform adaptation, how to perform adaptation, and the benefits of adaptation when it comes to the use of ART for lung cancer.[6]

We conducted our study to determine the factors affecting the need for adaptation.

METHODS

The research protocol was approved by the research ethics committee and the scientific research committee of the Department of Clinical Oncology, Faculty of Medicine, Cairo University, and by the Faculty of Medicine Research Ethics Committee (approval number I-120318).

This prospective phase II feasibility study was conducted at Kasr Al-Aini Center of Clinical Oncology and Nuclear Medicine, Cairo, Egypt between January 2019 and December 2020.

The study included 30 patients older than 18 years with pathologically proven, limited-stage small cell or stage I-II non–small cell lung cancer who were not fit for or refused surgery or had stage III disease according to the American Joint Committee on Cancer (AJCC) staging, 8th edition.

All patients received definitive radiotherapy at a dose of 60 Gy in 30 fractions over a period of 6 weeks with 2 Gy per fraction. For stage III non–small cell lung cancer and limited-stage lung cancer, patients received platinum-based chemotherapy as induction then concurrent, sequential, or concurrent treatment only. All target volumes were delineated according to EORTC (European Organization for Research and Treatment of Cancer) recommendations[7] and OARs were delineated if within the beam pass, according to the atlas for organs at risk in thoracic radiotherapy.[8]

After 10 and 20 fractions, patients underwent CT planning with the same reference point and as in the previous steps, target volumes and OARs were delineated. A plan was generated and accepted according to the previously mentioned criteria. New plans were compared to the baseline; when a dosimetric or geometric deviation from the original plan was detected, adaptive treatment was adopted by using the most recent plan. Criteria for adaptation were decided according to the following: geometric criteria for deviation were targeted to match structure distances exceeding 10 mm from those measured in the original planning CT. Dosimetric criteria for deviation were planning target volume (PTV) or OAR constraints exceeding the acceptance criteria. For patients requiring adaptive planning, changes in tumor volume and lung were assessed for their effect on the need for adaptive planning. Lung changes were defined as follows: pleural effusion as a well-defined, smooth, basal density change greater than 1 cm; atelectasis as well defined, often smooth, and triangular density changes in relation to the tumor area; and pneumonia or pneumonitis as diffuse density changes in the lung tissue not specifically related to the tumor area.

Patients were assessed by using echocardiography (ejection fraction expressed as percentage) and pulmonary function test (FEV1, FVC, and FEV1/FVC were expressed as a percentage of the predicted value) at baseline then at the end of radiotherapy, and at 3 months and 6 months after radiotherapy.

Statistical Analysis

Statistical analysis was performed by using MedCalc Statistical Software for Windows version 19.6 (MedCalc Software Ltd, Ostend, Belgium; www.medcalc.org). The Shapiro-Wilk test was used for testing normal distribution. The Krusal-Wallis test was used for comparing abnormally distributed variables between more than two groups, and *p*-value was considered significant if $p < 0.05$.

RESULTS

Patient Characteristics

The median age of the patients was 58 years (range, 45–73). Most were male (26 [86.7%]) with only four female patients (13.3%). Seven (23.3%) were nonsmokers, 3 (10%) were ex-smokers, and 20 (66.7%) were smokers. Twelve patients (40%) had hypertension, and only four (13.3%) had diabetes. Most of the patients had hemoptysis (73.3%) (Table 1).

Disease Characteristics

As regards disease staging, 19 patients (63.4%) had T3 or T4 disease with mean tumor size of 64.3 mm and 20 patients (66.4%) had node-positive disease with mean tumor size of 8.3 mm. Most patients (83.3%) had stage III disease; 18 patients (60%) had tumor located in the left lung, whereas 12 (40%) had tumor located in the right lung. Most tumors were in the lower lobe (53.3%). The

Table 1. Patients and tumor characteristics

Variable	***n* (%)**
Patient Characteristics	
ECOG	
1	29 (96.7)
2	1 (3.3)
Sex	
Female	4 (13.3)
Male	26 (86.7)
Smoking	
Nonsmoker	7 (23.3)
Smoker	20 (66.7)
Ex-smoker	3 (10.0)
Comorbidities	
Hypertension	12 (40.0)
Diabetes	4 (13.3)
Complaint	
Cough	8 (26.7)
Chest pain	20 (66.7)
Hemoptysis	22 (73.3)
Tumor Characteristics	
T stage	
T1,2	11 (36.6)
T3,4	19 (63.4)
N stage	
N0	10 (33.3)
N+	20 (66.4)
Stage	
I and II	5 (16.7)
III	25 (83.3)
Site	
Upper lobe	8 (26.7)
Middle lobe	6 (20.0)
Lower lobe	16 (53.3)
Pathology	
Adenocarcinoma	16 (53.3)
Others	14 (46.7)

ECOG: Eastern Cooperative Oncology Group.

most common histology was adenocarcinoma in 53.3% of cases (Table 1).

Treatment Adaptation

Patients were evaluated by CT scan for the need for adaptation during the second and fourth weeks after the start of radiotherapy. In the second week, as in the fourth week, 20 patients needed adaptation.

Dosimetric deviation was observed in five patients (25%) at 2 weeks and in two patients (10%) at 4 weeks, and geometric deviation was observed in 15 (75%) and 18 (90%) patients at 2 and 4 weeks, respectively.

A significant change was recorded in the mean value of the PTV-T as it was 342.7 cm^3 at baseline, 331 cm^3 at week 2, and 257 cm^3 at week 4 with p-value < 0.0001; no significant changes in other tumor or nodal dosimetric parameters that translated into significant reduction in the whole OARs constraints were recorded during the second and fourth week when compared to baseline.

Lung changes were evaluated at weeks 2 and 4 in the CT scans performed. They were observed in four (13.3%), eight (26.7%), and four (13.3%) patients at baseline, at week 2, and at week 4, respectively. The most common change observed was atelectasis at week 2 as it was present in six patients (20%) (Fig. 1).

We attempted to find a correlation between the need for adaptation at week 2 and the different baseline variables. We found positive correlations with planning target volume-tumor (PTV-T) conformity index (> 1.46; $p = 0.0473$), esophagus V35 ($> 3.6\%$; $p = 0.0488$), esophagus V50 ($> 0.85\%$; $p = 0.0295$), and esophagus mean dose (> 15.3 Gy; $p = 0.0087$). We failed to establish a correlation with age, performance status, sex, comorbidities, T stage, N stage, side and site of tumor, tumor size, organ function (pulmonary function tests and echocardiography), other dosimetric parameters, geometric deviation parameters, or lung changes (Table 2; Fig. 2).

The correlation between the need for adaptation at week 4, compared to week 2, was negative for conformity index for the tumor and all esophagus dosimetric parameters and positive for baseline FEV1 ($< 69\%$; $p = 0.0303$), FEV1/FVC ($\geq 70\%$; $p = 0.0024$), and echocardiography ejection fraction (Table 3).

Our study included a small number of patients as most of the patients either presented with stage IV disease or had poor performance status (ECOG > 2). We did not assess diffusing lung capacity for carbon monoxide (DLCO), as it is not available in the chest department,

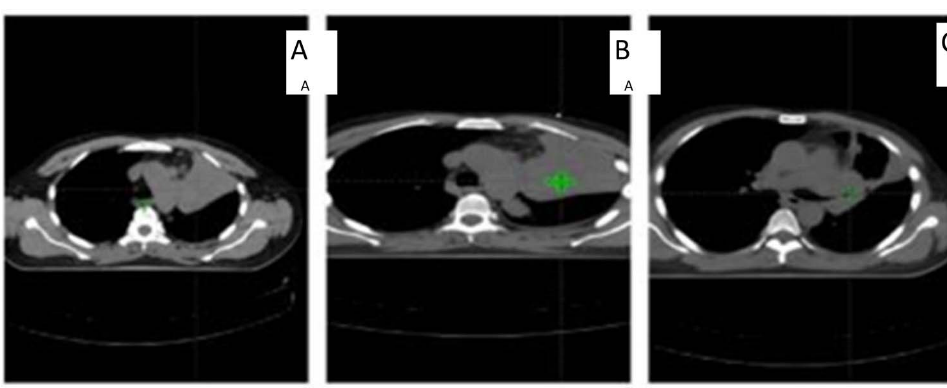

Figure 1. Change in tumor volume: (A) baseline (170 cm^3); (B) at 2 weeks (210 cm^3); and (C) at 4 weeks (130 cm^3).

Table 2. Factors predicting the need for adaptation at week 2

Variable	Parameter	Adaptation needed (N = 20), n (%)	Adaptation not need (N = 10), n (%)	p-Value	Correlation Coefficient
PTV-T CI	≥ 1.46	19 (95)	8 (80)	0.0473	0.969
	< 1.46	1 (5)	2 (20)		
Esophagus mean dose, Gy	≥ 15.3	18 (90)	6 (60)	0.0087	0.933
	< 15.3	2 (10)	4 (40)		
Esophagus V35, %	≥ 3.6	18 (90)	7 (70)	0.0488	0.925
	< 3.6	2 (10)	3 (30)		
Esophagus V50, %	≥ 0.85	17 (85)	5 (50)	0.0295	1.612
	< 0.85	3 (15)	5 (50)		

PTV-T CI: Planning target volume-tumor conformity index.

whereas most studies did so and reported a decline in DLCO more so than in FEV1 following lung radiotherapy.[9]

DISCUSSION

We conducted our prospective phase II study including 30 patients to investigate the factors that may predict the need for adaptation in patients with lung cancer and we concluded that adaptation improved the tumor coverage and spared the OARs (see supplemental material, available online).

The median age of the patients was 58 years (range, 45–73), which is below the median age globally[10]; adenocarcinoma histology was present in 53.3% of cases, and its incidence globally is 63.3%.[11]

Regarding the evaluation of pulmonary function, the mean percentage of the predicted FEV1 at baseline was 70%, FVC was 80%, and FEV1/FVC was 78%, results comparable to those of Grambozov et al,[12] who reported the same percentage for the FEV1 at baseline; however, these values were lower than those reported by Takemoto et al[13] whose patients had mean percentage of the predicted FEV1 at baseline of 80.9% and FVC of 92%, as they included patients with stage I and II disease only.

All patients underwent CT planning at the second and fourth week from the start of radiotherapy to assess the need for adaptation. In contrast, Hoegen et al[14] used daily cone beam CT (CBCT) and included only 10 patients in their study. Schmidt et al[15] used only one 4D-CT scan at mid treatment to investigate possible anatomical changes during the treatment course, whereas Møller et al[16] used CBCTs of fractions 1, 6, 11, 16, 21, 26, and 31, which were evaluated in Offline Review. Berkovic et al[16] also found that a single adaptation is beneficial at 15 fractions and 20 fractions for concurrent chemoradiation and sequential chemoradiation, respectively.

Criteria for adaptation were either geometric or dosimetric deviation. Geometric criteria for deviation were targeted

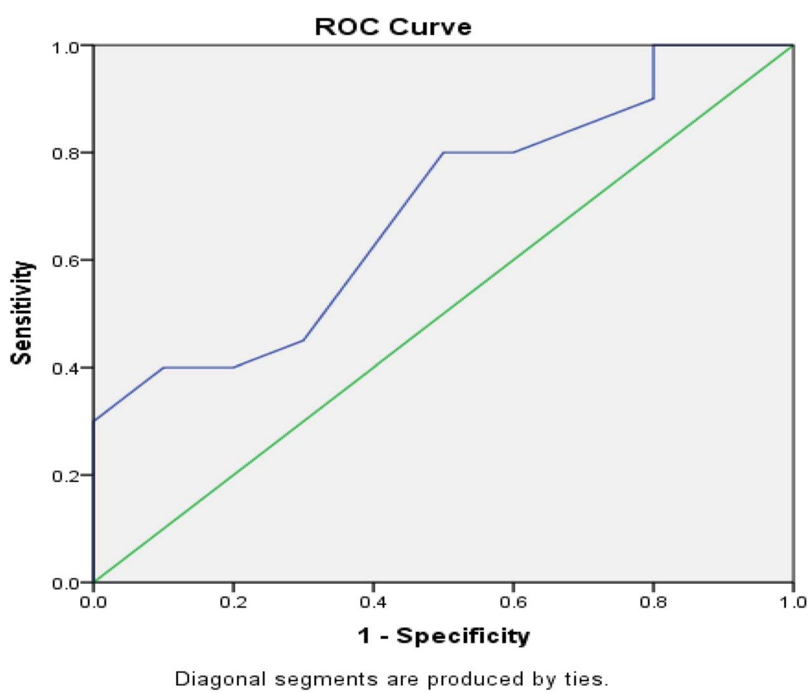

Figure 2. ROC curve showing predictability of PTV–conformity index to plan adaptation at 2 weeks.
PTV: planning target volume; ROC: receiver operating characteristic curve.

Table 3. Factors predicting the need for adaptation at week 4

Organ Function	Adaptation needed (N = 20), n (%)	Adaptation not needed (N = 9), n (%)	p-Value	Correlation Coefficient
Pulmonary function tests				
FEV1				
$> 69\%$	10 (50)	7 (77.8)	0.0303	−.0499
$\leq 69\%$	10 (50)	2 (22.2)		
FEV1/FVC				
$\geq 70\%$	18 (90)	8 (88.9)	0.0024	0.408
$< 70\%$	2 (10)	1 (11.1)		
Echocardiography				
EF				
$\leq 57\%$	4 (20)	2 (22.2)	0.0183	−0.094
$> 57\%$	16 (80)	7 (77.8)		

EF: Ejection fraction; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity.

to match structure distances exceeding 10 mm from those measured in the original planning CT, and dosimetric deviation was determined when target or OARs constraints exceeded the acceptance criteria. Møller et al [2] considered the geometric deviation to be more than 5 mm.

We used spinal canal and carina as match structures to assess the geometric deviation. In clinical practice, some radio-oncologists take bone tissues (eg, vertebrae, ribs) as surrogates of lung tumor, whereas others perform image-guided lung radiotherapy by matching soft tissues (eg, tumor, carina) directly.[18–20]

However, the optimal surrogate of lung tumors is unknown; Li et al[21] established that the "bronchi" and "carina" are the optimal surrogates for central lung targets, whereas "rib" and "vertebrae" are the optimal surrogates for peripheral lung targets for manual matching of online and planned tumors.

Half of the patients (50%) underwent plan adaptation twice, 13 patients (43.3%) underwent adaptation once, and two patients (6.7%) continued with the baseline plan.

Geometric deviation (tumor location or volume change) was observed more frequently than dosimetric deviation (geometric deviation was observed in 15 [75%] and 18 [90%] patients at 2 and 4 weeks, respectively, whereas dosimetric deviation was observed in five patients [25%] at 2 weeks and in two patients [10%] at 4 weeks). These results are comparable to those of Bjaanæs and colleagues,[22] whereas many other studies reported lower frequencies (range, 27–60%).[24,25]

We have shown a statistically significant reduction in the volume of tumor in the CT scans performed at weeks 2 and 4 of treatment, compared to baseline ($p = 0.005$), similarly to Schmidt et al[15], who demonstrated that tumor volumes were highly correlated ($p < 0.001$); however, in their study a single 4D-CT scan (CT2) was acquired halfway through the treatment course to investigate possible anatomical changes during the treatment course.

Mean lung dose was reduced from 14 Gy at baseline to 12 Gy by the fourth week of radiotherapy with significance statistically, similarly to the study of Møller et al[23] who reported a significant decrease in mean lung dose reduced from 14.6 Gy to 12.6 Gy on average. On the other hand, Berkovic et al[16] demonstrated that one single adaptation after 15 or 20 fractions may be sufficient to significantly reduce mean heart dose, mean esophagus dose, and spinal cord dose; these findings are comparable to those of our study, which concluded that there was significant reduction in the heart (V30: $p = 0.038$; V25: $p = 0.018$; mean: $p = 0.009$), esophagus (V35: $p = 0.003$; V50: $p = 0.04$; V60: $p = 0.03$; mean: $p = 0.002$), and spinal cord (Dmax $p = 0.04$) constraints over the course of the radiotherapy.

In contrast, Hoegan et al[14] demonstrated that some doses to OARs other than the lung (namely mean esophagus and mean heart dose) could be decreased by ART, but not significantly.

Lung changes were observed in 13.3% of patients at baseline; these changes were 26.7% and 13.7% at 2 weeks and 4 weeks of treatment, respectively, but we failed to establish a correlation with the need for adaptation, whereas Møller et al[2] concluded that among the 23% of patients who had lung changes, 13% would benefit from adaptation.

At the second week of radiotherapy, need for adaptation was correlated to the conformity index ($p = 0.0473$), esophageal V35 ($p = 0.0488$), esophageal V50 ($p = 0.0295$), and its mean dose ($p = 0.0087$), whereas at week 4 it was correlated to FEV1 ($p = 0.0303$), FEV1/FVC ($p = 0.0024$), and echocardiography ($p = 0.0183$).

There was significant improvement in the mean value of the predicted FEV1, FVC, and FEV1/FVC in pulmonary function tests (PFTs) s and mean ejection fraction (EF)in echocardiography at 6 months compared to baseline, but there was a decline at the end of treatment and 3 months after treatment in the mean value of predicted FEV1, FVC, and FEV1/FVC in PFTs. Guerra et al[25] reported that the FEV1/FVC showed an increase and decrease after radiation. Park et al[26] reported similar results and showed that PFT declined until 6 months and then stabilized 1 year after radiotherapy. This is most probably due to late effect of radiotherapy to the lung.

CONCLUSION

Adaptive plans to compensate for the continuous change in tumor volume or position lead to improvement in tumor coverage and sparing of the OARs. PTV-T conformity index, esophagus V35, esophagus V50, and esophagus mean dose can predict the need for adaptation at 2 weeks from the start of radiotherapy and at 4 weeks. Baseline FEV1, FEV1/FVC, and echocardiography ejection fraction are the predictive factors for adaptation.

SUPPLEMENTAL MATERIAL

Supplemental materials are available online with the article.

References

1. Piperdi H, Portal D, Neibart SS, et al. Adaptive radiation therapy in the treatment of lung cancer: an overview of the current state of the field. *Front Oncol* 2021;11:770382.
2. Møller DS, Khalil AA, Knap MM, Hoffmann L. Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. *Radiother Oncol*. 2014;110:517–522.
3. Yan D, Vicini F, Wong J, Martinez A. Adaptive radiation therapy. *Phys Med Biol*. 1997;42:123–132.
4. Glide-Hurst CK, Lee P, Yock AD, et al. Adaptive radiation therapy (ART) strategies and technical considerations: a state of the ART review From NRG Oncology. *Int J Radiat Oncol Biol Phys*. 2021;109:1054–1075.
5. Sonke JJ, Belderbos J. Adaptive radiotherapy for lung cancer. *Semin Radiat Oncol*. 2010;20:94–106.
6. Berkovic P, Paelinck L, Gulyban A, et al. Adaptive radiotherapy for locally advanced non-small cell lung cancer: dosimetric gain and treatment outcome prediction. *Acta Oncol*. 2017;56:1656–1659.
7. De Ruysscher D, Faivre-Finn C, Moeller D, et al. Lung group and the radiation oncology group of the European Organization for Research and Treatment of Cancer (EORTC). EORTC recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiother Oncol* 2017;124:1–10.
8. Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys*. 2011;81:1442–1457.
9. Niezink AGH, de Jong RA, Muijs CT, et al. Pulmonary function changes after radiotherapy for lung or esophageal cancer: a systematic review focusing on dose-volume parameters. *Oncologist*. 2017;22:1257–1264.
10. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.
11. Galvez-Nino M, Ruiz R, Pinto JA, et al., Lung cancer in the young. *Lung* 2020;198:195–200.
12. Grambozov B, Wolf F, Kaiser J, et al., Pulmonary function decreases moderately after accelerated high-dose irradiation for stage III non-small cell lung cancer. *Thorac Cancer* 2020;11:369–378.
13. Takemoto S, Shibamoto Y, Hashizume C, et al. Changes in pulmonary function and their correlation with dose-volume parameters in patients undergoing stereotactic body radiotherapy for lung cancer. *J Radiat Res* 2021;62:338–345.
14. Hoegen P, Lang C, Akbaba S, et al. Cone-beam-CT guided adaptive radiotherapy for locally advanced non-small cell lung cancer enables quality assurance and superior sparing of healthy lung. *Front Oncol*. 2020;10:564857.
15. Schmidt ML, Hoffmann L, Kandi M, et al. Dosimetric impact of respiratory motion, interfraction baseline shifts, and anatomical changes in radiotherapy of non-small cell lung cancer. *Acta Oncol*. 2013;52:1490–1496.
16. Berkovic P, Paelinck L, Lievens Y, et al. Adaptive radiotherapy for locally advanced non-small cell lung cancer, can we predict when and for whom? *Acta Oncol*. 2015;54:1438–1444.
17. Guckenberger M, Meyer J, Wilbert J, et al. Intra-fractional uncertainties in cone-beam CT based image-guided radiotherapy (IGRT) of pulmonary tumors. *Radiother Oncol*. 2007;83:57–64.
18. Wang YY, Fu XL, Xu ZY, et al. Quality assurance program for a kilovoltage cone-beam CT Guided Radiation Therapy System. *Int J Radiat Oncol Biol Phys* 2007;69: S719–S720.
19. Bissonnette JP, Franks KN, Purdie TG, et al. Quantifying interfraction and intrafraction tumor motion in lung stereotactic body radiotherapy using respiration-correlated cone beam computed tomography. *Int J Radiat Oncol Biol Phys* 2009;75:688–695.
20. Boda-Heggemann J, Fleckenstein J, Lohr F, et al. Multiple breath-hold CBCT for online image guided radiotherapy of lung tumors: simulation with a dynamic phantom and first patient data. *Radiother Oncol*. 2011;98:309–316.
21. Li HS, Kong LL, Zhang J, et al. Evaluation of the geometric accuracy of anatomic landmarks as surrogates for intrapulmonary tumors in image-guided radiotherapy. *Asian Pac J Cancer Prev*. 2012;13:2393–2398.
22. Bjaanæs MM, Sande EPS, Loe Ø, et al. Improved adaptive radiotherapy to adjust for anatomical alterations during curative treatment for locally advanced lung cancer. *Phys Imaging Radiat Oncol*. 2021;18:51–54.
23. Møller DS, Holt MI, Alber M, et al. Adaptive radiotherapy for advanced lung cancer ensures target coverage and decreases lung dose. *Radiother Oncol*. 2016;121:32–38.
24. Elsayad K, Kriz J, Reinartz G, et al. Cone-beam CT-guided radiotherapy in the management of lung cancer: Diagnostic and therapeutic value. *Strahlenther Onkol*. 2016;192:83–91.
25. Lopez Guerra JL, Gomez DR, Zhuang Y, et al., Changes in pulmonary function after three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or proton beam therapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2012;83:e537–e543.
26. Park YH, Kim JS. Predictors of radiation pneumonitis and pulmonary function changes after concurrent chemoradiotherapy of non-small cell lung cancer. *Radiat Oncol J*. 2013;31:34–40.