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Research

Segmental bronchi radiation dose affected the progression of radiation pneumonitis in lung cancer patients

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Abstract

Objective To evaluate the association between the segmental bronchi radiation dose and radiation pneumonitis (RP) in patients with lung cancer who underwent radiotherapy.

Methods A total of 135 patients with lung cancer who were treated with radiation therapy between December 2014 and December 2015 were enrolled in the study. RP was defined and graded according to the criteria of the Radiation Therapy Oncology Group. The radiation dose to the segmental bronchi, along with clinical, and other dosimetric factors were recorded. Logistic regression analysis was used to evaluate the association between the related factors and RP.

Results Among the 135 enrolled patients, 24 (17.8%) developed grade 3 radiation pneumonitis or higher. Study found that RP was associated with the following factors: patient age, complications with chronic obstructive pulmonary disease, concurrent chemotherapy, percentage of lung volume receiving more than 30 Gy (V30), whole lung volume, and the segmental bronchi maximum and mean dose. Logistic regression analysis showed that the maximum dose of the segmental bronchi, whole lung volume, and V30 were independent risk factors for RP. According to the receiver operating characteristic curve, the maximum dose constraint of the segmental bronchi during radiotherapy is estimated at 23.85 Gy.

Conclusion The segmental bronchi radiation dose should be considered as a normal tissue constraint, in addition to whole lung volume and V30 in radiotherapy for patients with lung cancer to decrease the incidence of RP.

Keywords Radiation pneumonitis · Segmental bronchi · Lung cancer · Radiation · Risk factor

1 Introduction

In recent years, the incidence and mortality rate of thoracic tumors have gradually increased [1, 2]. Radiotherapy is one of the primary treatments used for patients with lung cancer, particularly for those with unresectable tumors [3, 4], and has achieved good results; however, it can also cause radiotherapy-related complications, such as radiation pneumonitis (RP) and radiation esophagitis. Acute RP is a common dose-limiting complication after radiotherapy for lung cancer [5, 6]; it limits the radiation dose that can be administered to the tumor and significantly affects the quality of life and overall survival of patients. Therefore, reducing the occurrence of RP has important clinical value [7, 8].

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Previous studies have identified safe radiotherapy strategies based on the dosimetric limitations recommended by the National Comprehensive Cancer Network (NCCN) guidelines [9]. However, severe RP still occurs in clinical practice, significantly affecting patients' quality of life. Therefore, it is necessary to identify risk factors other than the currently known parameters. According to the current NCCN guidelines, the constraints for lung dosimetric metrics include the volume of normal lung tissue irradiated with 5 Gy, 20 Gy, and 30 Gy isodose lines (V5, V20, and V30, respectively) and the mean lung dose [10–12]. Segmental bronchi are located in the third and fourth layers of pulmonary bronchi, and segmental bronchi can easily lead to segmental pneumonia after being damaged by radiation and other factors [13]. However, few reports have been published about the constraints on segmental bronchi dose [14].

To evaluate the role of the radiation dose to the segmental bronchi in RP, this study retrospectively analyzed the clinical data of patients with lung cancer who underwent radiation therapy in our cancer center from 2014 to 2015. Moreover, we assessed the correlation between the segmental bronchi dose and acute RP in patients with lung cancer. The results of this study may aid in optimizing radiotherapy strategies to reduce RP.

2 Methods and materials

2.1 Patient selection and characteristics

The data were retrospectively collected and analyzed. Patients (N = 135) who were diagnosed with lung cancer were enrolled from December 2014 to December 2015 at the Department of Oncology at the First Affiliated Hospital of Yangtze University. Patients with pre-existing lung diseases other than chronic obstructive pulmonary disease (COPD) were excluded. The lung function of the patients, as detected by Spirometry, was normal before radiation therapy, and their Eastern Cooperative Oncology Group (ECOG) scores were 0–2. The patient population included 128 males and 7 females, with a median age of 61 years. There were 37 patients with COPD, 95 patients with a previous history of chemotherapy, 23 patients with a history of concurrent chemoradiotherapy. Additionally, 28 patients were clinical stage II, 74 as stage III, and 33 as stage IV. This study was performed in line with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients and approval was granted by the Ethics Committee of the Hubei Cancer Hospital.

2.2 Follow-up

Patients usually receive clinical evaluation every 3 to 6 months in the first year, including non-enhanced chest CT scan, which is performed semiannually for the following 4 years and annually thereafter. Recent radiological or clinical follow-up provided data on local control and side effects [15]. All the procedures were performed in accordance with the hospital's ethical guidelines.

2.3 Methods of radiation therapy

Patients were immobilized in the supine position with whole body vacuum cushions or a thermoplastic mask system. Siemens CT machine was used to simulate the treatment positioning. The simulated CT scan was performed with a slice thickness of 5 mm, capturing a range from the upper boundary to the cricoid and extending down to the adrenal gland, typically encompassing the entire lung.

The CT images were transmitted to the Varian Eclipse V8.6 (Varian Medical Systems, Palo Alto, CA, USA) treatment planning system. Target volumes were defined and manually contoured, according to the International Commission on Radiation Units and Measurements (ICRU) Reports No. 62 [16], delineating normal organs at risk, such as both of the lungs, spinal cord, heart, and esophagus. In addition, the clinical target or planned target volumes was excluded from the lung contour for evaluation.

All patients underwent radiation therapy with a dose of more than 50 Gy at 1.8–2.0 Gy per fraction delivered in five fractions per week [17]. Three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) were adopted using 6 MV photons that were generated from a linear accelerator. The dose constraints for the organs at risk were adapted from Bentzen et al. [18]. In addition, the segmental bronchi were contoured based on the anatomical structure visible on the lung window of CT simulation images. The proximal bifurcation of the segmental bronchi, located 2 cm outside the planned target volume, was delineated as shown in Fig. 1. Three consecutive layers were contoured from the opening of each segmental bronchus.

2.4 Statistical analysis

A multivariate logistic regression model and manual reverse stepwise elimination technique were used to determine the dosimetric predictors of toxicity. This method includes all dosimetric variables that are statistically significant in univariate analysis. The iterative process of variable removal continues until all remaining variables reach the significance threshold, which is set to a P-value of 0.5. At the same time as calculating the variance inflation factor (VIF), reverse stepwise regression was performed to address the issue of collinearity. Subsequently, we used post estimated marginal means and analyzed the interaction between predicted margins to determine the maximum dose at which the predicted likelihood of developing grade > 2 pneumonia remained below 20%. This leads to the generation of dose probability curves for further analysis. So, a prediction probability of 20% was applied that is consistent with the cut-off value used in QUANTEC. In addition, multivariate analysis (MVA) was conducted for each dosimetric parameter, and each predictor was combined with key clinical variables such as performance status and disease stage of the ECOG into its own individual model.

3 Results

3.1 Correlation between clinical characteristics and radiation pneumonitis

All patients were followed up for more than 6 months, with a median follow-up time of 8 months (6–12 months). As shown in Table 1, 24 patients (17.8%) experienced RP of grade 3 or higher and 111patients (82.2%) experienced RP of grade 2 or below. Age, COPD, and concurrent chemoradiotherapy were related to the occurrence of acute grade 3 or higher RP (19 patients > 60 years old [19/79, 24.1%] vs. 5 ≤ 60 years old [5/56, 8.9%]; 11 with COPD [11/37, 29.7%] vs. 13 without COPD [13/98, 13.3%]; 9 with a history of concurrent chemotherapy [9/23, 39.1%] vs. 15 without a history of concurrent chemotherapy [15/112, 13.4%]). The differences between these characteristics were all statistically significant ($P < 0.05$).

3.2 Correlation between lung radiotherapy dosimetry factors and radiation pneumonitis

As shown in Table 2, the mean prescription dose of the radiation treatment was 56.7 Gy in patients with grade 3 RP or higher but 55 Gy in those with grade 2 or below. The mean volumes of V5, V10, V20 and the mean lung dose of patients of grade 3 RP or higher were 40.7, 32.6, 20.7, and 11.3 Gy, respectively. However, the corresponding values for patients with RP of grade 2 or below were 38.2, 29.5, 18.7, and 9.9 Gy. No significant differences in these values were found between the two groups ($P > 0.05$).

Patients with RP of grade 3 RP or higher had a mean lung volume of 2921.6 cm^3, lung V30 of 14.7%, and 8.1 Gy mean dose for the segmental bronchi with 29.8 Gy maximum dose to it. By contrast, patients with RP of grade 2 or below had a mean lung volume of 3368.9 cm^3, lung V30 of 11.7%, with segmental bronchi mean and maximum dose of 5.6 Gy, and 19.3 Gy, respectively. These differences were statistically significant ($P < 0.05$).

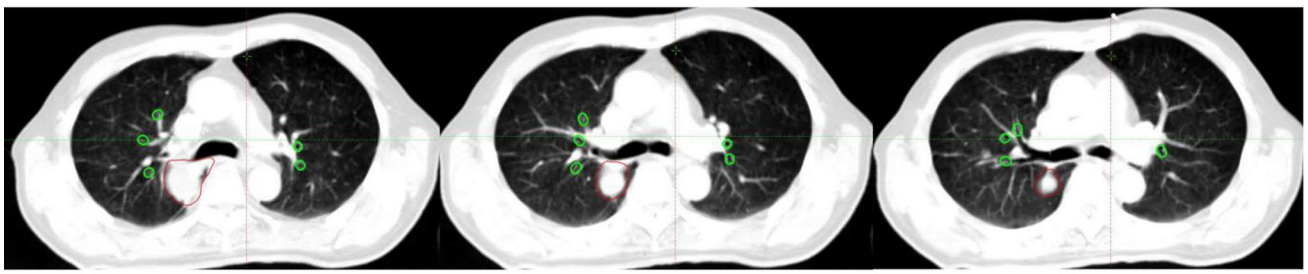

Fig. 1 The contouring of the segmental bronchi in the treatment planning system with the different anatomical levels. The green outline indicates the segmental bronchi. The red outline indicates the gross tumor volume

Table 1 Differences in clinical characteristics of patients with lung cancer who underwent radiotherapy

Factors	Radiation pneumonitis		χ^2	*P* value
	≤ Grade 2 (n)	≥ Grade 3 (n)		
Number of patients	111	24		
ECOG scores				
0	78	13	3.22	0.80
1	32	10		
2	1	1		
Gender				
Male	107	21	1.62	0.19
Female	4	3		
Age (y)				
≤ 60	51	5	5.13	0.03*
> 60	60	19		
COPD				
Yes	26	11	4.98	0.03*
No	85	13		
Stage				
II	24	4	0.30	0.91
III	60	14		
IV	27	6		
Chemotherapy history			1.08	0.46
Yes	76	19		
No	35	5		
Concurrent chemoradiotherapy			6.98	0.006**
Yes	14	9		
No	97	15		
Treatment technique			0.13	0.79
3D-CRT	65	15		
IMRT	46	9		

3D-CRT three-dimensional conformal radiotherapy, *COPD* chronic obstructive pulmonary disease, *ECOG* Eastern Cooperative Oncology Group, *IMRT* intensity-modulated radiotherapy. Associations between RP grade and various clinicopathological parameters, * $P < 0.05$, ** $P < 0.05$

Table 2 Differences in lung radiotherapy dosimetry factors by radiation pneumonitis severity

Dosimetry factors	≤ Grade 2	≥ Grade 3	*P* value
Treatment prescription dose (Gy)	55 ± 6.3	56.7 ± 6.6	0.30
Lung volume (cm^3)	3368.9 ± 977.4	2921.6 ± 762.4	0.04*
V5 (%)[a]	38.2 ± 13.6	40.7 ± 12	0.45
V10 (%)[a]	29.5 ± 10.2	32.6 ± 7.3	0.19
V20 (%)[a]	18.7 ± 7.4	20.7 ± 4.1	0.23
V30 (%)[a]	11.7 ± 6.2	14.7 ± 3.7	0.03*
Mean lung dose (Gy)	9.9 ± 3.7	11.3 ± 2.5	0.10
D_{max} of segmental bronchi (Gy)	19.3 ± 14.2	29.8 ± 20.4	0.01*
D_{mean} of segmental bronchi (Gy)	5.6 ± 4.2	8.1 ± 5.4	0.03*

D_{max} maximum dose, D_{mean} mean dose, *RP* radiation pneumonitis

[a]V5, V10, V20, and V30 represent the percentage of lung volume receiving more than 5 Gy, 10 Gy, 20 Gy, and 30 Gy. Associations between RP grade and various treatment parameters, * $P < 0.05$, ** $P < 0.05$

Table 3 Factors influencing the risk ratio of radiation pneumonitis

Factors	Regression coefficient	Wald	*P* value	OR	95% CI
Age	0.008	0.041	0.84	1.0	0.93–1.09
With COPD	1.35	2.38	0.12	3.89	0.69–21.8
Chemoradiotherapy	0.92	1.14	0.28	2.5	0.47–13.5
Lung volume (cm^3)	− 0.23	7.07	0.01*	0.85	0.72–0.98
D_{max} of segmental bronchi	0.027	3.86	0.035*	1.13	1.07–1.29
D_{mean} of segmental bronchi	0.041	0.13	0.72	1.04	0.83–1.3
V30	0.13	4.47	0.035*	1.14	1.0–1.29

CI confidence interval, *COPD* chronic obstructive pulmonary disease, D_{max} maximum dose, D_{mean} mean dose, *OR* odds ratio, *V30* percentage of lung volume receiving more than 30 Gy. Associations between RP and various risk factors, * $P < 0.05$, ** $P < 0.05$

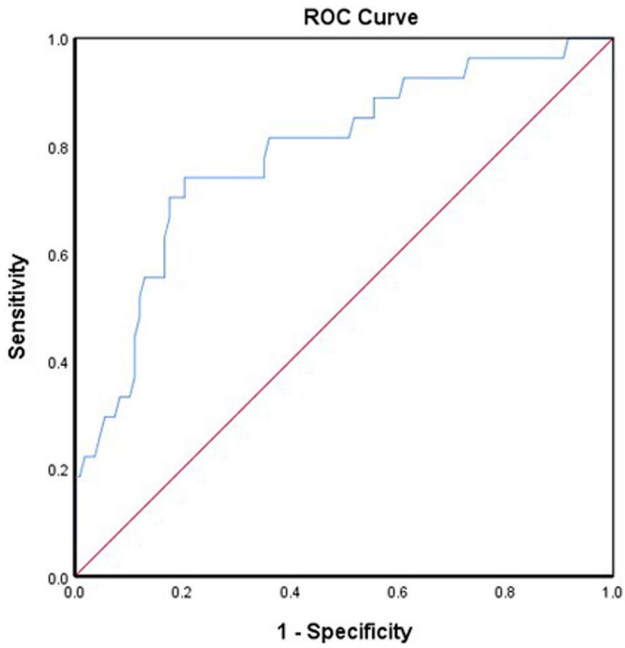

Fig. 2 Optimum cutoff value of the segmental bronchi maximum dose (23.85 Gy) by calculating area under the receiver operating characteristic (ROC) curve to prevent radiation pneumonitis

3.3 Factors influencing the risk ratio of radiation pneumonitis

Results of the logistic regression analysis (Table 3) showed that the maximum dose of the segmental bronchi, total lung volume, and V30 were independent risk factors for predicting RP ($P < 0.05$). The corresponding risk ratios were 1.13 (95% confidence interval [CI] 1.07–1.29), 0.85 (95% CI 0.72–0.98), and 1.14 (95% CI 1.00–1.29), respectively. Therefore, these risk factors significantly increased the incidence of RP grade 3 or higher.

3.4 Receiver operating characteristic curve of the maximum dose of the segmental bronchi

A receiver operating characteristic curve was plotted to verify the optimum cutoff value for the maximum dose of the segmental bronchi. The results showed that the area under this curve was 0.78 (95% CI 0.58–0.88) (Fig. 2). Thus, the optimum cutoff value of the maximum dose of the segmental bronchi was 23.85 Gy (sensitivity, 81%; specificity, 73%).

4 Discussion

RP is a common adverse event of thoracic tumor radiotherapy with an incidence rate of 8–37.2% [6, 10, 19]. This adverse event seriously limits the radiation dose prescribed for lung cancer, affecting the local control rate of patients undergoing radiotherapy. However, in clinical practice, there is a possibility of reirradiation with reduced tumor volume after conventional radiotherapy [20, 21]. Thus, radiotherapy for patients with lung cancer requires careful consideration to prevent RP, especially grade 3 or higher [22].

Currently, when evaluating a radiotherapy strategy in clinical practice, the dose volume histogram is used to determine the lung dose. The primary parameters include V5, V10, V20, and V30, as well as the mean lung dose [9, 23]. However, few research reports have focused on the dose constraints of the segmental bronchi [14]. The segmental bronchi are the tertiary bronchi below the lung lobe bronchi that are connected downward to the bronchioles [24]. This study showed that the maximum and mean doses of the segmental bronchi are closely related to the occurrence of grade 3 RP or higher, and as the dose of the segment bronchi increases, the risk of severe RP grows, suggesting dose as a potential independent risk factor for RP. Therefore, dose constraints on the segmental bronchi during radiotherapy may reduce the occurrence of severe RP.

According to the receiver operating characteristic curve, the maximum dose constraint of the segmental bronchi during radiotherapy is estimated at 23.85 Gy. However, the definition of a safe dose range requires further clinical studies with larger sample sizes. It has been speculated that the possible mechanism is associated with mucous membrane edema and fibrosis of the segmental bronchi caused by the irradiation. This leads to narrowing of the segmental bronchi and affects the discharge of alveolar secretions [14].

The other dosimetric factors closely related to RP incidence in this study were total lung volume and lung V30. The results of the multiple regression analysis suggested that the larger the lung volume, the lower the risk of severe RP, whereas the larger the lung V30, the higher the risk of RP. Clinical factors such as age, the presence of COPD, and a history of chemotherapy in combination with radiotherapy for the occurrence of RP of grade 3 or higher. Patients over 60 years old had a greater risk of severe RP than the younger patients. If a patient had COPD or concurrent chemoradiotherapy, the risk of RP increased by radiotherapy. Therefore, the effect of the above factors should be considered when using radiotherapy for thoracic tumors. These results are consistent with previous research finding on this topic [10, 25].

In summary, the risk factors related to RP in patients with lung cancer radiotherapy should be fully evaluated to avoid the occurrence of RP. In particular, the dose constraints of the maximum and mean dose of the segmental bronchi should be considered when determining the treatment constraints for lung cancer radiation therapy. However, this study has some limitations, such as a retrospective design, single center study, and limited sample size. In addition, some certain variables (such as comorbidities or treatment details) cannot be controlled due to data limitations, explicitly acknowledging this will provide a more comprehensive scope of research. These may all limit its generalizability. Therefore, in the future, strategies to address this limitation may be proposed, such as conducting multicenter prospective trials to validate the determined dose thresholds, conducting multicenter studies or validating in larger, different cohorts to increase the rigor of the research. This may update guidelines for segmental bronchial dose limitation in radiation therapy plans, highlighting the clinical impact potential of this study.

Author contributions Gai Liang experimental design, financial support, data analysis and interpretation, manuscript writing; RuiJie Chang, Qu Zhang, Yan Luo and Yi Peng data collection, analysis and interpretation; Bo Luo study conception and experimental design, data analysis and interpretation, manuscript writing and final approval of the manuscript. All authors reviewed the manuscript.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The research was ethically approved by the Ethics Committee of the Hubei Cancer Hospital. Prior to participation, all participants were duly informed of their rights and responsibilities and provided explicit written consent. The study was conducted in agreement with the guidelines governing research involving human participants, as outlined by the Ethics Committee of the Hubei Cancer Hospital.

Competing interests The authors declare no competing interests.

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