WITHDRAWN: Correlation between DVH parameters and lung function changes before and after radiotherapy and the occurrence of radiation-induced lung injury (RILI)

Sha Sha
shasha11@tom.com

Jiaozhou Central Hospital

Research

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EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background: The purpose of the study was to explore the correlation between DVH parameters and lung function changes before and after radiotherapy and the occurrence of radiation-induced lung injury (RILI), and to evaluate its value in predicting the risk of RILI.

Methods: 120 patients with advanced non-small cell lung cancer who had been diagnosed in Jiaozhou Central Hospital of Qingdao City in the past three years and received chest conformal (intensity modulated) radiation therapy were selected. Before radiotherapy, irradiation of 45-50 Gy, and 1 month after the end of radiotherapy, the patients were tested for lung function, and the ventilation and diffusion function of the patients were tested using the Japanese CHESTAC-8800 lung function tester. The evaluation of radiation lung injury was based on the RTOG acute radiation lung injury classification standard, and the observation end point was ≥2 grade RILI.

Results: A total of 34 patients with ≥2 grade RILI among 120 patients in this study, including 23 cases of grade 2 and 11 cases of grade 3, the incidence rate was 28.33%. The difference between FVC, FEV1, FEV1 / FVC, DLCO, V5, V10, V15 before radiotherapy, 45-50 Gy, and 1 month after the end of radiotherapy were statistically significant (P <0.05). Univariate analysis showed that lung function, V5, V10, and V15 before radiotherapy were related factors for RILI (P <0.05). Multivariate logistic analysis showed that the risk of RILI was 1.855 times that of patients with higher FEV1 / FVC before radiation therapy (OR = 1.855, 95% CI = 1.199-1.946, P = 0.037), patients with V10 ≥50% were 3.673 times higher than patients with V10 <50% (OR = 3.673, 95% CI = 1.548-7.582, P = 0.039).

Conclusions: V10≥50% and FEV1 / FVC are high-risk factors for RILI before radiotherapy, which has certain value in predicting the risk of RILI.

Background

As the number of elderly people in our country continues to increase, the incidence of elderly lung cancer increases year by year[1–3]. Lung cancer has become a current global malignant tumor that seriously threatens human health and life safety[4, 5]. Among them, non-small cell lung cancer accounts for 80% of lung cancer, and the incidence and mortality are relatively high, which has aroused widespread concern among clinicians[6–8]. Locally advanced non-small cell lung cancer refers to stage IIIa and IIIb lesions that have not been found to have distant metastases, accounting for 30–40% of non-small cell lung cancer, of which about 80% cannot be surgically removed[9–11]. Simultaneous radiotherapy and chemotherapy for non-small cell lung cancer that is not suitable for surgery has become the current standard treatment mode[12]. The emergence of radiation-induced lung injury (RILI) not only poses a great threat to the patient's prognosis and quality of life, but also hinders the clinical application of effective radiation dose, which ultimately leads to the failure of local tumor control[13, 14].

Postoperative radiotherapy is a necessary treatment, but it is easy to cause radiation pneumonia[15]. Volume parameters such as V5, V10, and V15 are commonly used indicators to predict radiation pneumonitis, but recent studies have found that the occurrence of radiation pneumonitis is also related to the lung function before radiotherapy[16, 17]. The incidence of chest cancer treated with radiotherapy and chemotherapy is 40–60%[18, 19]. Due to its high incidence, insidious onset, delayed onset, and no targeted treatment, once diagnosed, it is often impossible to reverse the condition. This makes research simple and easy to predict indicators attract attention, in order to evaluate the risk of lung injury before and early treatment. At the same time, effective interventions can be implemented early to prevent or avoid the occurrence of RILI[20]. The occurrence of RILI is the result of multiple factors. This study retrospectively analyzed the occurrence of RILI in 120 patients with locally advanced non-small cell lung cancer after receiving three-dimensional conformal radiotherapy to explore related factors affecting the occurrence of RILI and provide a reference for further optimizing the 3D-CRT plan for locally advanced non-small cell lung cancer.

Methods

Recruitment of research objects

A total of 120 patients with advanced non-small cell lung cancer who had been diagnosed in Jiaozhou Central Hospital of Qingdao City in the past three years (2017–2019) and undergoing chest conformal (modulated intensity) radiotherapy were selected. This study was approved by the Ethics Committee of Jiaozhou Central Hospital. All patients gave informed written consent to participate in the study. Before radiotherapy, irradiation of 45–50 Gy, and 1 month after the end of radiotherapy, the patients were tested for lung function, and the ventilation and diffusion function of the patients were tested using the Japanese CHESTAC-8800 lung function tester. Including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), forced expiratory volume in 1 second and forced vital capacity ratio (FEV1 / FVC) and carbon monoxide dispersion (DLCO). DVH parameters include V5, V10, and V15. The evaluation of radiation lung injury was based on the RTOG acute radiation lung injury classification standard, and the observation end point was ≥ 2 grade RILI.

Treatment method

The patient took the supine position, fixed the position with a vacuum air cushion, and performed a chest enhancement scan under the US GE16 slice spiral CT simulator. Scanning range: from the level of the cricothyroid membrane to the lower edge of the costal diaphragm angle 3 cm, both are 5 mm layer spacing. Import the scanned image into the VENUSTPS treatment planning system and perform 3D reconstruction. The outline of the target area is strictly implemented in accordance with the relevant provisions of the ICRU No. 50 and No. 62 report tumors. GTV: CT image shows the tumor area and enlarged lymph nodes (the long diameter of lymph nodes ≥ 1 cm). CTV: On the basis of GTV, the vertical direction is expanded by 10 to 15 mm, and the surrounding directions are each released 5 to 6 mm (squamous cell carcinoma 5 mm, adenocarcinoma 6 mm). The outline of CTV should be noted and appropriately modified according to specific anatomical limits (such as lung tissue, spinal cord, vertebral body, etc.).

PTV: Based on CTV, all directions are expanded by 5 mm. The VENUS TPS planning system designs a radiotherapy plan and optimizes the treatment plan using a dose-volume histogram to ensure that 95% of the isodose line covers PTV. The limit for organs at risk is: the exposure dose of 1/3 volume of the heart does not exceed 50 Gy, and the exposure dose of 2/3 volume does not exceed 45 Gy. The maximum dose of spinal cord irradiation does not exceed 45 Gy. According to the specific situation of the patient, the prescribed radiation dose is determined to be 50-70Gy, divided dose 200 cGy / time, 1 time / d, 5 times / week, a total of 5–7 weeks of radiotherapy is completed. Chest-enhanced CT was reexamined from radiotherapy to DT30 40 Gy. At the same time, according to the patient's situation to decide whether to chemotherapy, more than chemotherapy before radiotherapy, usually based on platinum-based chemotherapy.

Determination of lung function and DVH parameters

In this study, patients with abnormal lung function group means that the measured value / predicted value of lung function and ventilation function index is less than 70%, and lung function tests are routinely performed within 1 week before radiotherapy. When FEV1 / FVC < 70%, it can be diagnosed as obstructed airway and restricted airflow in the lungs, that is, chronic obstructive pulmonary disease. In the study, the dose-volume histogram in each patient's radiation treatment plan was read to obtain the dosimetric parameters such as V5, V10, V20, and V30 required for the study.

Diagnostic criteria for radioactive damage

In the first year after the end of radiotherapy, general conditions, lung function and chest CT examinations were performed every 1 month to evaluate the efficacy and the occurrence of RILI. The classification of radiation injury is strictly based on the classification standard of acute radiation injury developed by the American Radiation Oncology Collaborative Group (RTOG). In this study, patients with RILI who occurred ≥ 2 grades were included in the occurrence group. The specific grading standards are as follows, level 1: paroxysmal mild cough or shortness of breath during activity. Level 2: Continuous or repeated coughing, which can be relieved by treatment with narcotic antitussive drugs, or shortness of breath and difficulty in breathing after light activity (forced). Level 3: Use narcotic antitussive drugs to treat severe cough that cannot be controlled or relieved, or shortness of breath at rest, or confirmed by imaging examination. Clinically, symptomatic treatment such as intermittent oxygen inhalation and corticosteroids is needed. Level 4: It has been accompanied by severe respiratory dysfunction or pulmonary insufficiency, and clinical symptomatic treatment such as continuous oxygen inhalation or assisted ventilation is required.

Statistical analysis

SPSS 23.0 statistical software was used to process the data. The measurement data is expressed as mean ± SD, using *t* test. Count data is expressed as a rate (%), using χ^2 test. Chi-square test was used for univariate analysis, and Logistic regression model for multivariate logistic analysis. Inspection level α = 0.05. P < 0.05 indicates that the difference is statistically significant.

Results

The general characteristics of research objects

In the 120 patients in this study, there were 34 cases with ≥ 2 grade RILI, including 23 cases with grade 2 and 11 cases with grade 3, with an incidence rate of 28.33%. Nine cases occurred during radiotherapy, and the remaining 25 cases occurred within 1 month after radiotherapy. There was no grade 4 RILI in the whole group. The median age was 57.9 years old (31–76 years old). There were 79 males and 41 females, 70 cases of squamous cell carcinoma and 50 cases of adenocarcinoma, 57 cases in stage a and 63 cases in stage b. The primary tumor location was 60 cases in each of central type and peripheral type. There were 77 cases with smoking history. There was no statistical difference in the comparison of general characteristics between the RILI-occurring group and the non-occurring RILI group ($P > 0.05$). The statistical analysis results are shown in Table 1.

Table 1
Comparison of the general characteristics of the two groups

Variables	RILI group (n = 34)	Non-RILI group (n = 86)	χ^2	*P*
Gender			0.477	0.49
Male	24	55		
Female	10	31		
Age (yrs)			0.946	0.331
< 65	21	61		
≥ 65	13	25		
Pathological type			0.005	0.945
Squamous cell carcinoma	20	50		
Adenocarcinoma	14	36		
Clinical stage			0.563	0.453
a	18	39		
b	16	47		
Primary tumor location			0.657	0.418
Central type	15	45		
Peripheral type	19	41		
Has a history of smoking			0.119	0.73
Yes	21	56		
No	13	30		

Comparison of lung function and DVH parameters in different treatment stages

The V5, V10 and V15 of the RILI-occurring group were higher than those of the corresponding non-occurring group, and the DVH parameters were statistically different between the two groups ($P < 0.05$). The statistical analysis results are shown in Table 2.

Table 2
Comparison of DVH parameters in different treatment stages

Different treatment stages	DVH parameters	RILI group (n = 34)	Non-RILI group (n = 86)	*t*	*P*
Before radiation	V5 (%)	58.87 ± 5.91	46.18 ± 6.75	9.597	< 0.001
	V10 (%)	43.14 ± 6.17	33.57 ± 6.58	7.306	< 0.001
	V15 (%)	33.76 ± 5.01	25.49 ± 6.88	7.291	< 0.001
Radiation (45–50 Gy exposure)	V5 (%)	57.96 ± 5.39	44.41 ± 5.85	11.669	< 0.001
	V10 (%)	41.91 ± 6.19	31.99 ± 5.86	8.195	< 0.001
	V15 (%)	33.84 ± 4.61	25.96 ± 4.68	8.349	< 0.001
1 month after radiation	V5 (%)	51.01 ± 4.09	39.87 ± 5.01	11.516	< 0.001
	V10 (%)	34.04 ± 4.91	28.03 ± 4.70	6.241	< 0.001
	V15 (%)	26.84 ± 4.31	22.37 ± 4.69	4.801	< 0.001

Taking the median of each DVH parameter in patients with RILI as the cut-off point, the DVH parameters in this study were grouped accordingly. The analysis results showed that the incidence of the DVH parameter RILI was significantly different among different groups ($P < 0.05$). The incidence of RILI at different stages of treatment during before radiotherapy (Table 3), radiotherapy (Table 4) and 1 month after the radiotherapy (Table 5) in the two groups of subjects was in V5 ≥ 75% group, V10 ≥ 50% group, and V15 ≥ 25% group, FVC < 70% group, FEV1 < 70% group, FEV1/FVC < 70% group and DLCO < 70% group. The differences between every groups were statistically significant ($P < 0.05$).

Table 3
Comparison of lung function and DVH parameters before radiotherapy between the two groups

Parameters	RILI group (n = 34)	Non-RILI group (n = 86)	χ^2	*P*
FVC			7.749	0.021
< 70%	4	3		
70–80%	15	23		
> 80%	15	60		
FEV1			8.532	0.014
< 70%	3	2		
70–80%	17	25		
> 80%	14	59		
FEV1/FVC			37.135	< 0.001
< 70%	2	5		
70–80%	26	16		
> 80%	6	65		
DLCO			23.546	< 0.001
< 70%	2	11		
70–80%	24	20		
> 80%	8	55		
V5			8.405	0.004
< 75%	23	77		
≥ 75%	11	9		
V10			5.124	0.024
< 50%	21	70		
≥ 50%	13	16		
V15			4.028	0.045
< 25%	25	76		
≥ 25%	9	10		

Table 4
Comparison of lung function and DVH parameters in radiotherapy (radiation 45–50 Gy) between the two groups

Parameters	RILI group (n = 34)	Non-RILI group (n = 86)	χ^2	*P*
FVC			7.557	0.023
< 70%	4	3		
70–80%	14	21		
> 80%	16	62		
FEV1			7.715	0.021
< 70%	3	2		
70–80%	16	24		
> 80%	15	60		
FEV1/FVC			32.366	< 0.001
< 70%	2	5		
70–80%	24	15		
> 80%	8	66		
DLCO			18.524	< 0.001
< 70%	2	10		
70–80%	21	18		
> 80%	11	58		
V5			5.549	0.018
< 75%	24	76		
≥ 75%	10	10		
V10			4.453	0.035
< 50%	22	71		
≥ 50%	12	15		
V15			6.564	0.01
< 25%	24	77		
≥ 25%	10	9		

Table 5
Comparison of lung function and DVH parameters 1 month after the radiotherapy in the two groups

Parameters	RILI group (n = 34)	Non-RILI group (n = 86)	χ^2	*P*
FVC			6.126	0.047
< 70%	3	3		
70–80%	14	20		
> 80%	17	63		
FEV1			7.614	0.022
< 70%	2	1		
70–80%	16	23		
> 80%	16	62		
FEV1/FVC			24.84	< 0.001
< 70%	2	3		
70–80%	20	13		
> 80%	12	70		
DLCO			13.057	< 0.001
< 70%	1	6		
70–80%	18	17		
> 80%	15	63		
V5			4.896	0.027
< 75%	25	77		
≥ 75%	9	9		
V10			4.525	0.033
< 50%	23	73		
≥ 50%	11	13		
V15			5.906	0.015
< 25%	25	78		
≥ 25%	9	8		

Analysis of related influencing factors of RILI in two groups of patients

The variables with single factor analysis $P < 0.1$ in this study were included in the multivariate logistic regression model. The analysis found that the factors closely related to the occurrence of RILI were FEV1 / FVC and V10 ≥ 50% before radiotherapy, and the OR (95% CI) values were 1.855 and 3.673, respectively. The results suggest that FEV1 / FVC and V10 ≥ 50% before radiotherapy are independent risk factors associated with RILI. The risk of RILI in patients with higher FEV1 / FVC before radiotherapy was 1.855 times that of relatively lower patients ($OR = 1.855$, 95% $CI = 1.199–1.946$, $P = 0.037$). Patients with V10 ≥ 50% were 3.673 times higher than patients with V10 < 50% ($OR = 3.673$, 95% $CI = 1.548–7.582$, $P = 0.039$). The statistical analysis results are shown in Table 6.

Table 6
Analysis of related influencing factors of RILI in two groups of patients

Variables	*B*	*Wald*	*OR*	*P*	*95%CI*
FEV1/FVC	0.032	3.794	1.855	0.037	1.199–1.946
V10 ≥ 50%	1.305	3.102	3.673	0.039	1.548–7.582

Discussion

At present, the incidence of lung cancer is showing a rapid upward trend in the world, and the mortality rate ranks first in malignant tumors in the world[21, 22]. Lung cancer has become the first cause of death from malignant tumors in China, accounting for 22.7% of all malignant tumor deaths[23, 24]. Synchronous radiotherapy and chemotherapy for non-small cell lung cancer that is not suitable for surgery has become the current standard treatment mode, and RILI is a common complication of lung cancer radiotherapy[25, 26]. RILI not only poses a great threat to the patient's prognosis and quality of life, but also hinders the clinical application of effective radiation dose[27, 28]. It is one of the dose limiting factors of chest radiotherapy and an important factor affecting the failure of local tumor control[29].

Radiotherapy is one of the main methods for the treatment of lung cancer, but due to serious complications of radiation pneumonitis, the dose of radiotherapy has decreased and the local recurrence rate has increased[30]. With the emergence of three-dimensional conformal radiotherapy and three-dimensional conformal intensity-modulated radiotherapy, the incidence of radiation pneumonitis has decreased compared with the previous. However, the data show that radiation pneumonitis with clinical symptoms occurred 7% -32%, severe radiation pneumonitis occurred 2.6% -18.0%, and death occurred 0–2%[31–33]. The occurrence of radiation pneumonitis reduces the patient's quality of life and even endangers the patient's life.

There are two manifestations of RILI, divided into two stages, namely acute radiation pneumonia and radiation pulmonary fibrosis[14, 34]. Early research believed that these two stages were a gradual process, that is, radiation pulmonary fibrosis was gradually evolved and developed from radiation pneumonia[28]. Typical radiation pneumonia generally occurs during radiotherapy or 1 to 3 months after radiotherapy. Congestion and edema of the lung tissue, increased exudation of alveolar fibrin, and thickening of the lung interstitial. Its clinical manifestation is almost no different from that of general pneumonia. Its particularity is that it is not caused by pathogenic microorganism infection, so it is often called radiation lung disease. Once diagnosed, it is often irreversible, and the clinical manifestations are mainly dry cough, less sputum, chest tightness, and chest pain[35]. Wet rales can be heard in the lung field where the lesion is occurring, and the breath sounds are rough. Severe cases will be accompanied by varying degrees of dyspnea, low fever, and normal blood leukocytes, which are not effective after antibacterial treatment[36]. The incidence of radiation-induced pulmonary fibrosis is more than 6 months after radiotherapy, and the fibrosis of the alveolar septum is accompanied by atrophy of the alveoli. Replaced and filled by fibrous connective tissue, the lung function is severely damaged and eventually leads to dyspnea and death. The percussion of the lung field where the lesion occurred showed dullness, the breathing sound was low or the fine wet rales were heard.

The results of univariate analysis in this study showed that lung function before radiotherapy was associated with RILI. RILI is mostly a latent and hidden development process. RILI with symptoms occurs in 13–37% of patients undergoing chest radiotherapy. The incidence of RILI in this study is 26%, which is consistent with it. At present, the research related to the clinical factors affecting RILI is more controversial. Some researchers believe that low KPS score[37], smoking[38], chronic obstructive pulmonary disease (COPD) [10], lung function status before radiotherapy[39], lower lung lobe tumors[40], and concurrent radiotherapy and chemotherapy can increase the risk of RILI.

So far, the academic community has not formed a unified opinion on whether the basic lung function before radiotherapy is closely related to the occurrence of radiation pneumonia. Some researchers believe that before radiotherapy, there is no direct correlation between basic pulmonary diseases such as COPD and radiation pneumonia[10]. However, some studies have pointed out that the state of lung function before radiotherapy is the main factor affecting the occurrence of RILI, even its independent risk factor[41]. The results of this study showed that patients with higher FEV1/FVC before radiation therapy had 1.855 times the risk of RILI than those with relatively lower patients. The results of the study suggest that FEV1/FVC is an independent risk factor affecting the occurrence of RILI before radiotherapy. Vdose (eg V5, V10, V15) refers to the volume of lung tissue that is irradiated above a certain dose (5 Gy, 10 Gy, 15 Gy), as a percentage of the total lung volume. Graham et al [42] research confirmed that V20 is the only independent factor that affects the occurrence of RILI. Kim et al [43] reported that V20, V30, V50 and MLD are related to the occurrence of RILI. This study also found that all DVH parameters are involved in the occurrence of RILI. Among them, multivariate analysis confirmed that V15 is the only independent factor that affects the occurrence of RILI. And V15 ≥ 25% may be an independent predictor of dosimetric occurrence of RILI.

Conclusions

In conclusion, the plasma levels of cytokines before and after radiotherapy changed in this study. Among the cytokines, only FEV1 / FVC and V10 ≥ 50% before radiotherapy were found to be independent risk factors related to RILI. Each DVH parameter in the RILI-occurring group was higher than that in the corresponding non-occurring group. Among them, V15 was an independent high-risk factor affecting the occurrence of RILI, and V15 ≥ 25% may be an independent dosimetric predictor of RILI. Before the end of radiotherapy, for the susceptible patients with risk factors, reasonably change or adjust the late radiotherapy plan to minimize the risk of RILI.

List of Abbreviations

RILI: radiation-induced lung injury

FVC: forced vital capacity

FEV1: forced expiratory volume in 1 second

FEV1 / FVC: forced expiratory volume in 1 second and forced vital capacity ratio

DLCO: carbon monoxide dispersion

RTOG: Radiation Oncology Collaborative Group

COPD: chronic obstructive pulmonary disease

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.This study is approved by the Ethics Committee of Jiaozhou Central Hospital. Written informed consent was obtained.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors read and approved the final manuscript.

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