CLINICAL CURATIVE EFFECT OF CYTOKINES COMBINED WITH DOSE-VOLUME HISTOGRAM PARAMETERS AND FEATURES IN PREDICTING RADIATION-INDUCED LUNG INJURY FOR NON-SMALL CELL LUNG CANCER

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ABSTRACT

Objective*: This study aimed to investigate the clinical features of patients with non-small cell lung cancer (NSCLC), the levels of interleukin-1 (IL-1), interleukinn-6 (IL-6), and tumor necrosis factor-α (TNF-α) in plasma before and after radiotherapy.*

Methods*: The correlation between dose-volume histogram (DVH) parameters and radiation-induced lung injury (RILI) was also studied. The clinical data of 200 patients with locally advanced NSCLC who received three-dimensional conformal radiotherapy (3D-CRT) in the hospital were retrospectively studied. These patients were divided into an occurrence group and a non-occurrence group. Enzyme-linked immunosorbent assay (ELISA) was adopted for detecting IL-1, IL-6, and TNF-α in plasma before and during radiotherapy.* V_5, V_{10}, V_{15}, V_{20}, *and mean lung dose (MLD) parameters were obtained from DVH, then the correlations between cytokines and DVH parameters as well as RILI were analyzed.*

Result*: The incidence of RILI was 30.5%, and the incidence of RILI with abnormal lung function before radiotherapy was 49.1%, which was higher than 25.5% in patients with normal lung function. IL-6 level in patients with RILI before radiotherapy was higher than that in the non-occurrence group. The* V_5, V_{10}, *and MLD in patients with RILI were higher than those in the non-occurrence group.*

Conclusion*: Multivariate analysis showed that IL-6,* V_5, *and* V_{10} *were independent risk factors for RILI before radiotherapy. The IL-6 level combined with* V_5 *and* V_{10} *had a good predictive effect on RILI in patients with NSCLC before radiotherapy.*

Keywords: *Cytokines, Dose-Volume Histogram Parameters, Non-Small Cell Lung Cancer, Radiation-Induced Lung Injury, Predictive Value.*

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Introduction

The major treatment method for malignant tumors is radiotherapy nowadays(1). According to statistics, 65%-75% of malignant tumor patients have received radiotherapy(2). With the development of chemotherapy equipment and technology, the normal-tissue complication probability around the tumor has been very low, but the complications caused by radiotherapy can’t be avoided. Radiation-induced lung injury (RILI) is one of the most common complications during radiotherapy for thoracic tumors(3). After a certain dose of radiation to the lung tissue, there is lung injury change histologically, which is often manifested as pulmonary interstitial congestion and edema as well as increased intra-alveolar exudation(4). The probability of RILI is more than 8% after three-dimensional conformal radiotherapy (3D-CRT)(5), and the onset often shows a lag effect. These seriously affect the curative effect on patients, and in severe cases, threaten the life of patients(6). Therefore, it has an important clinical significance for the prediction of RILI.

The occurrence of RILI is the result of a variety of factors, such as the patient's own age, gender, smoking, and basic lung function(7). It is also related to the dose-volume histogram (DVH) parameters(8). Patients with poor basic lung function are more likely to develop RILI than patients with normal lungs at the same radiotherapy dose volume.

DVH is the most effective tool for evaluating 3D-CRT. It simply and clearly shows the relationship of the dose and volume between the gross target volume (GTV) and normal tissues. The relationship between the radiation resistance and the volume exposed to normal tissues and organs has also been specifically described in DVH. The metrological parameters V_5, V_{10}, V_{15}, V_{20}, and mean lung dose (MLD) developed by DVH can be taken as important reference indicators for optimizing treatment plans(9,10). Scholars have utilized DVH parameters to predict RILI in recent years, but its predictive effect is limited because DVH evaluates both lungs as homogeneous organs. It is considered to reduce the exposure volume of both lungs when formulating precise radiotherapy plans, so as to reduce the normal-tissue complication probability; but the heterogeneity of lung function in individual patients does not be taken into account(11,12).

Studies have found that cytokines, such as interleukin-1 (IL-1)(13), interleukin-6 (IL-6(14), transforming growth factor (TGF-β1)(15), angiotensin-converting enzyme(16), and tumor necrosis factor (TNF-α)(17), can effectively predict RILI. The identification of certain cytokines for predicting the risk of RILI can maximize the benefit to patients and minimize the occurrence of RILI during clinical radiotherapy. However, there is not a recognized mathematical model currently that can predict the occurrence of radiation pneumonitis, and there are few methods combined with DVH parameters. The combination of DVH parameters with biological factors can make predictions of RILI more comprehensive and accurate. Since patients with non-small cell lung cancer (NSCLC) have the highest incidence of RILI during radiotherapy, and the treatment methods are mature and standardized, the NSCLC was taken as the research object in this research. This was intended to explore the predictive effect of cytokines combined with DVH parameters on RILI.

Material and methods

General clinical data

The subjects of this study were patients with locally advanced NSCLC who underwent 3D-CRT in the Second Affiliated Hospital of Xingtai Medical College from October 2015 to October 2019, whose clinical data were retrospectively analyzed. The clinical data included a detailed collection of routine medical history, physical examination information, surgical history, chemotherapy history, chemotherapy regimens and cycles, chest X-ray, chest computerized tomography (CT), electrocardiogram, blood routine, blood biochemistry, liver and kidney function, pulmonary function test, and immune function. The standard score of Karnofsky Performance Status (KPS) was taken to evaluate the general condition of patients.

Inclusion criteria were as follows. Patients were diagnosed with thoracic tumors by pathology and imaging. They received radiotherapy for the first time. Their KPS scores were ≥ 70. They had no serious heart disease and no history of thoracic surgery. They had radiation resistance. The estimated survival time was ≥ 3 months. Patients or families signed the informed consent form for radiotherapy.

The following exclusion criteria were implemented. The patients got a KPS score of < 70. They could not accept and tolerate radiotherapy. Imaging showed severe pulmonary infection and pulmonary fibrosis. They suffered from heart disease. They failed to adhere to the radiotherapy plan or total radiation dose as DT < 50 Gy. They had received radiotherapy in the past, and they were the stage IV patients.

Methods for radiation therapy

For radiotherapy, the patients were supine on the positioning bed, and the body position was fixed with a negative-pressure vacuum air cushion. As the previous CT films were referred to, the Philips CT Big Bore analog positioning machine was used for positioning and lining. The spiral GE Revolution ACTs 16-slice spiral CT machine was used for chest enhanced scanning, with a slice thickness of 5 mm. The scanned images were imported into the planning system for three-dimensional reconstruction, to delineate the GTV of the gross tumor target area. On the basis of the GTV, the upper and lower directions were expanded by 10-15 mm, and the surrounding directions were expanded by 5-6 mm (5 mm for squamous cell carcinoma and 6 mm for adenocarcinoma). The obtained was just the clinical target volume (CTV). On the basis of the CTV, it was expanded by 5 mm in all directions, which was the plan target volume (PTV). 5 coplanar irradiation fields were set, and DVH was utilized to optimize the treatment plan, so as to ensure that the 95% isodose line covered PTV. According to the specific conditions of the patients, the prescribed irradiation dose was 45-50 Gy, and the single irradiation dose was DT 2.0 Gy, once a day, 5 times a week.

For chemotherapy, platinum-based regimens were chosen. Chemotherapy was usually given before radiotherapy.

Detection of plasma cytokines

3 mL of venous blood was collected from 200 patients on an empty stomach in the morning before radiotherapy and during radiotherapy (at an irradiation of 45-50 Gy). It was stored in non-anticoagulant tubes, left standing at 4 °C for 30 min, and then centrifuged at room temperature at 2500 r/min for 15 min. 1.5mL of serum was obtained and put into an Eppendorf centrifuge tube, then placed in a -80 °C low-temperature refrigerator for freezing. IL-1, IL-6, and TNF-α were detected by enzyme-linked immunosorbent assay (ELISA).

Determination of lung function and DVH parameters

A pulmonary function test was performed within 1 week before radiotherapy. For the indicators of ventilation function, it was regarded as abnormal lung function when the measured value/predicted value < 70% or the measured value/predicted value of small airway resistance > 150%. The DVH parameters, including V^5, V^{10}, V^{15}, V^{20}, MLD, and other posologic parameters, were retrieved from the radiotherapy planning system of the hospital.

Observation indicators

The patients were observed according to the evaluation criteria for acute radiation injury of the Radiation Therapy Oncology Group (RTOG)[18]. Dry cough, fever, dyspnea, and pulmonary rales developed within 3 months of radiotherapy. Imaging examination showed that flaked shadows merged into large, dense, fuzzy shadows in the irradiated lung fields, and there were also faint reticular shadows. The occurrence of RILI was shown in Table 1a. For the degree of pulmonary fibrosis, CT showed ground-glass degeneration and fibrous shadows across the lung lobes consistent with the those in irradiation area after radiotherapy. The lung markings increased and thickened with blurred edges, which were presented in Table 1b.

Methods for data processing

SPSS 24.0 was applied for statistical analysis of the data. The measurement data conforming to the normal distribution were expressed as mean ± standard deviation, and the comparisons between groups were by t-test. The continuous measurement data that were not normally distributed were expressed by M (P_{25}, P_{75}), and the paired nonparametric Wilcoxon test was utilized for the comparisons with the groups. The enumeration data were expressed as the rate (%), and the chi-square test was used for comparisons between groups. Logistic regression analysis was used for multivariate analysis, and a PI prediction model was established. P<0.05 was regarded as as a statistically significant difference.

Grades	Symptoms
0	Normal with no change
1	Slight cough or shortness of breath on exertion
2	Persistent cough that is relieved with narcotic antitussives, or dyspnea on light activity (exertion)
3	Severe cough that can't be controlled by taking narcotic antitussives, shortness of breath at rest, or requiring intermittent oxygen inhalation and corticosteroid therapy confirmed by imaging data
4	Accompanied with severe respiratory insufficiency, requiring treatment such as continuous oxygen inhalation or assisted ventilation

Table 1 a: RTOG grading criteria for acute radiation pneumonitis and lung injury.

Grades	Symptoms
1	Asymptomatic or mildly dry cough
2	Moderate pulmonary fibrosis or pneumonia (severe cough)
3	Severe fibrosis, with dense images under CT scanning of pneumonia
4	Respiratory dysfunction, requiring continuous oxygen inhalation

Table 1 b: Scoring criteria for radiation pulmonary fibrosis.

Experimental results

The occurrence of RILI

200 patients were enrolled in the experiment and were followed up until March 31, 2021. The longest was 11 months, the shortest was 7 months, and the median time was 9 months from the start of radiotherapy. 3 months after the start of radiotherapy, a radiation pneumonitis evaluation was made.

Grades	Acute RILI	Incidence
0	141	70.5%
1	43	21.5%
2	31	15.5%
3	17	8.5%
4	8	4.0%
Total	200	100%

Table 2 a: RTOG evaluation results of patients.

There were 99 cases of acute RILI in total, including 43 cases of grade 1, 31 cases of grade 2, 17 cases of grade 3, and 8 cases of grade 4. The RILI more severe than grade 2 occurred in 56 cases, with an incidence of 28.0%. 141 cases were in grade 0 with no occurrence, accounting for 70.5%, which were displayed in Table 2a and Figure 1a. 37 patients developed radiation fibrosis, accounting for 18.5%. As shown in Table 2b and Figure 1b, 3 patients died due to other sudden physical diseases 1 month and 3 months after radiotherapy, respectively. 7 patients got radiation esophagitis, which were not included in the analysis results, as improved after symptomatic treatment.

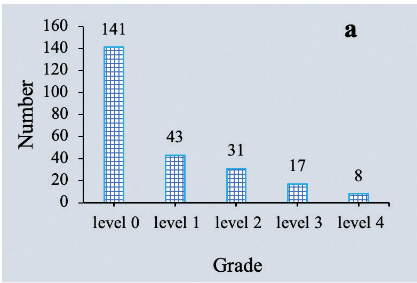

Figure 1 a: The distribution of the number of patients in each grade by RTOG evaluation.

Grades	Incidence of chronic pulmonary fibrosis	Incidence
1	20	10.0%
2	15	7.5%
3	2	1.0%
4	0	-

Table 2 b: Assessment results of radiation fibrosis in patients..

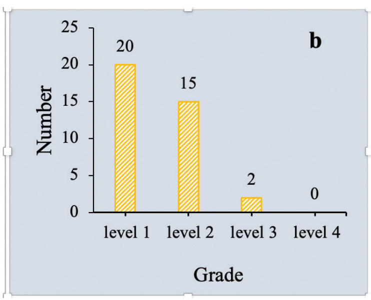

Figure 1 b: The distribution of the number of patients in each grade of radiation pulmonary fibrosis.

The correlation between clinical features and RILI

As listed in Table 3, the incidence of RILI in patients with abnormal lung function was 49.1% before radiotherapy, which was significantly higher than 25.5% in patients with normal lung function, suggesting a difference of statistical significance (P<0.01). For gender, age, pathological type, tumor location, order of radiotherapy and chemotherapy, treatment of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), and total dose of radiotherapy, no significant difference was found in the incidence of RILI in patients with NSCLC (P>0.05).

Clinical features	Number of cases	Occurrence [n (%)]	Non-occurrence [n (%)]	χ^2	*P*
Gender				1.261	0.315
Male	112	37 (33.0%)	75 (67.0%)		
Female	88	24 (27.3%)	64 (72.7%)		
Age				0.432	0.124
< 70	156	45 (28.8%)	111 (71.2%)		
≥ 70	44	19 (43.2%)	25 (56.8%)		
Pathological type				0.134	0.312
Squamous cell carcinoma	92	26 (28.3%)	66 (71.7%)		
adenocarcinoma	108	32 (29.7%)	76 (70.3%)		
Tumor location				2.861	0.133
Central	92	34 (37.0%)	58 (63.0%)		
Peripheral	108	28 (25.9%)	80 (74.1%)		
Lung function before treatment				3.776	0.005
normal	94	24 (25.5%)	70 (74.5%)		
abnormal	106	52 (49.1%)	54 (50.9%)		
Order of treatment				0.123	0.217
Simultaneous treatment	75	21 (28.0%)	54 (72.0%)		
Conversion therapy	125	47 (37.6%)	78 (62.4%)		
EGFR-TKI treatment				2.16	0.121
YES	77	23 (29.9%)	54 (70.1%)		
NO	123	43 (35.0%)	80 (65.0%)		
Total dose (Gy)				1.553	0.861
< 60	86	27 (31.4%)	59 (68.6%)		
≥ 60	114	36 (31.6%)	78 (68.4%)		

Table 3: Correlation between clinical features of patients with NSCLC and incidence of RILI.

The correlation between cytokine levels and the occurrence of RILI

As shown in Table 4, the level of IL-6 in patients with RILI was higher than that in patients without occurrence before radiotherapy, with a statistically significant difference (P<0.05). The levels of IL-1, TNF-α, and IL-6 were all increased after treatment compared to the non-occurrence group, but there was not a statistical difference (P>0.05). No statistical difference was also found in comparisons between groups (P>0.05).

Items	Occurrence (n=61)	Non-occurrence (n=139)	*Z*	*P*
Before treatment IL-1	3.52 (2.14, 5.18)	3.29 (1.87, 6.12)	0.154	0.238
Under treatment IL-1	5.31 (3.75, 7.15)	5.17 (2.17, 10.64)	1.184	0.071
Before treatment IL-6	9.76 (6.13, 11.46)	8.48 (3.34, 15.75)	2.891	0.016
Under treatment IL-6	15.48 (11.83, 20.27)	14.96 (5.15, 21.91)	0.371	0.059
Before treatment TNF-α	23.55 (12.36, 30.61)	18.61 (11.31, 28.62)	0.661	0.167
Under treatment TNF-α	36.25 (14.51, 65.18)	28.43 (15.76, 39.63)	1.032	0.411

Table 4: Comparison of plasma levels of IL-1, IL-6, and TNF-α in patients with and without RILI [(ng/mL), M (P_{25}, $P_{75)}$].

The correlation between DVH parameters and the occurrence of RILI

As displayed in Table 5 and Figure 2, the levels of V_5, V_{10}, and MLD in patients with RILI were all higher than those in the non-occurrence group, showing differences of statistical significance (P<0.01, P<0.05, and P<0.05, respectively). The levels of V_{15} and V_{20} in patients with RILI were also higher than those in the non-occurrence group, but the differences were not statistically significant (P>0.05).

Groups	Occurrence (n=61)	Non-occurrence (n=139)	*t*	*P*
V_5 (%)	64.15 ± 21.41	52.64 ± 16.39	2.141	0.001
V_{10} (%)	51.13 ± 17.84	46.13 ± 14.71	1.515	0.004
V_{15} (%)	48.10 ± 14.73	36.70 ± 10.83	1.894	0.103
V_{20} (%)	34.14 ± 11.23	27.57 ± 7.68	0.953	0.286
MLD (Gy)	21.67 ± 6.96	14.73 ± 5.11	0.715	0.021

Table 5: Comparison of DVH parameters in patients with and without RILI.

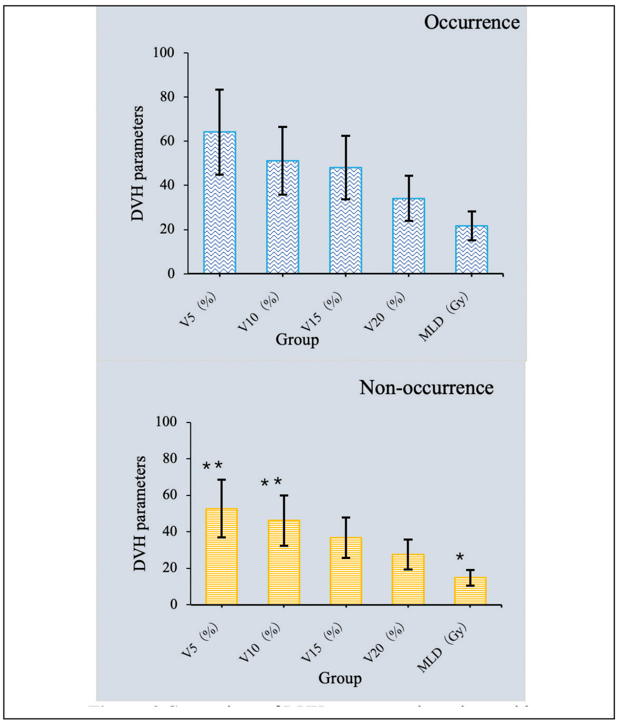

Figure 2: Comparison of DVH parameters in patients with and without RILI.

*Note: *represented P<0.05 in comparison in each group between the occurrence and non-occurrence of RILI, so the differences were considered to be statistically significant. **represented P<0.01 with differences of statistical significance in each group.*

Analysis of influencing factors for RILI

The clinical factors, radio-physical factors, and cytokines of statistical significance were analyzed in a multivariate Logistic regression model. V_5, V_{10}, and IL-6 levels before treatment were the main factors affecting RILI, which were presented in Table 6. The prediction model could be expressed as PI = h0(t)exp (2.145X1+1.417X2+1.538X3, where X was the predictive factor and covariate of radiation pneumonia.

Factors	β	SE	*P*	RR	95% CI	
					upper limit	lower limit
V_5	2.145	0.135	0.041	1.451	1.412	5.161
V_{10}	1.417	1.234	0.014	1.723	2.161	10.25
Before treat-ment IL-6	1.538	1.523	0.002	1.241	1.015	3.516

Table 6: Multivariate Logistic regression analysis of occurrence of RILI.

Discussion

About 13%-37% of patients who undergo chest radiotherapy will develop RILI. The onset process is slow and insidious, and it has great potential risks. Generally, RILI will occur from 50 days to 2 years after radiotherapy. This research also proved that the median time to RILI in 200 patients with NSCLC was 85 days; 56 patients got RILI with grade 2 and above, accounting for 28%. Since RILI is often irreversible with high incidence, how to predict and prevent RILI is particularly important(19). There are many factors affecting the occurrence and development of RILI, mainly including radiobiological factors, radio-physical factors, and clinical factors. At present, most studies are limited to the correlation between certain factors and RILI, showing many deficiencies. Therefore, multivariate analysis and prediction can often achieve predictive effects with high accuracy.

In clinical factors, some scholars believe that concurrent chemoradiotherapy, chronic obstructive pulmonary disease, abnormal pulmonary function before radiotherapy, and low KPS score may increase the risk of RILI(20,21). In this research, the clinical features of patients were analyzed, from which the abnormal lung function before radiotherapy was related to the occurrence of RILI with statistically significant differences (P<0.05). But no correlation was discovered after multivariate Logistic regression analysis. The sample size obtained was relatively small, most of them were middle-aged and elderly people, and many people had some basic lung diseases, so the influence of some factors was not fully reflected.

In radiobiological factors, inflammatory cytokines (such as ET-1, IL-1, IL-6, and TNF-α) related to pulmonary inflammatory responses are often associated with manifestations of lymphocytic alveolitis. These are also the main pathological changes of RILI, so many researchers turn their attention to inflammatory factors. Some researchers have found that the increase in plasma ET-1 concentration during and after radiotherapy is closely related to the occurrence of RILI[22]. The dynamic changes of TNF-α and IL-6 before and during radiotherapy were consistent with the pathological time period of acute lung injury. The higher plasma IL-6 level before radiotherapy is an independent risk factor for RILI[23]. This work also gained the same findings. During the treatment, the levels of various cytokines (IL-1, IL-6, and TNF-α) in the plasma were significantly increased compared with those before radiotherapy when the radiation was 45-50 Gy. The plasma IL-6 level before radiotherapy was higher in the occurrence group than that in the non-occurrence group, with a statistically significant difference ($P<0.05$).

It was verified that those with high IL-6 level before radiotherapy were more prone to RILI.

In radio-physical factors, the normal lung dose-volume is closely related to the severity of RILI. With the improvement of treatment technologies, especially the wide application of 3D-CRT in radiotherapy, the normal and appropriate dose can be controlled before radiotherapy. Therefore, the incidence of RILI can be greatly reduced, and the tumor control rate can be effectively improved. Studies have revealed that lung V_{20}, V_{30}, and MLD are closely related to the occurrence of RILI[24, 25]. Although radiologists have effectively controlled the dose, some patients still suffer from RILI when using a high dose, making the research of low-dose treatment more and more important.

Studies have shown that the volume of the lung low-dose area such as V5-V15, especially V5, has an important impact on the occurrence of RILI. V5 is an independent influencing factor for radiation pneumonitis of grade ≥ 3. V5 is associated with the occurrence of radiation pneumonitis of grade 2 or higher, with a V5 threshold of 65%. V5> 60% becomes an independent risk factor for radiation pneumonitis of grade 3[26]. This research showed that the lung low-dose areas V_5, V_{10}, and MLD of patients with RILI were higher than those without RILI, and the differences were statistically significant ($P<0.05$). It was suggested that all of V_5, V_{10}, and MLD could affect the occurrence of RILI. Since the dose to both lungs was limited when making a treatment plan, and there was a distinct correlation with DVH parameters, other physical parameters could not be completely ruled out to be involved in the occurrence of RILI. The biological factor IL-6 was combined with DVH parameters V_5 and V_{10} in this work. The results of the multivariate analysis demonstrated that high plasma IL-6 level, V_5, and V_{10} before radiotherapy were independent risk factors for RILI.

Conclusion

To sum up, RILI was caused by a variety of factors. It was known that the high level of plasma IL-6 before radiotherapy and the parameters of V_5 and V_{10} in the low-dose area were the high-risk factors for the occurrence of RILI. The IL-6 level was combined with V5 and V10 parameters before radiotherapy, which was expected to be an indicator for predicting RILI. This work provided clinical data and a reference for clinical treatment, but it was limited by the number of samples, age composition, and other factors, which led to deficiencies. It needed further clinical research for whether an accurate mathematical prediction model could be proposed through the combined application of clinical factors, biological factors, and physical factors. If it came true, patients with NSCLC who were prone to RILI could be found before treatment, so that the damage caused during radiotherapy could be prevented and avoided in advance.

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