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Observational Study**Multiple regression analysis of risk factors related to radiation pneumonia**

Shi LL *et al.* Risk factors related to radiation pneumonia

Ling-Ling Shi, Jiang-Hua Yang, Hong-Fa Yao

Abstract**BACKGROUND**

To carry out multiple regression analysis of the influencing factors of radiation pneumonia.

AIM

To carry out multiple regression analysis on the influencing factors of radiation pneumonia.

METHODS

Records of 234 patients receiving chest radiotherapy in Huzhou Central Hospital (Huzhou, Zhejiang Province, China) from January 2018 to February 2021 were collected and divided into two groups based on the presence of the radiation pneumonia diagnosis. Among them, 93 patients with radiation pneumonia were set as the study group and 141 patients without radiation pneumonia were set as the control group. General characteristics, and radiation and imaging examination data of both groups were collected and compared. Due to the statistical significance observed, multiple regression analysis was performed on age, tumor type, chemotherapy history, forced

vital capacity (FVC), forced expiratory volume in the first second (FEV1), carbon monoxide diffusion volume (DLCO), FEV1/FVC, planned target area (PTV), mean lung dose (MLD), total number of radiation fields, percentage of lung tissue in total lung volume (vdose), probability of normal tissue complications (NTCP) and other factors.

RESULTS

The proportion of patients aged ≥ 60 years, with the diagnosis of lung cancer and a history of chemotherapy in the study group was higher than that in the control group ($P < 0.05$); FEV1, DLCO and FEV1/FVC in the study group were lower than in the control group ($P < 0.05$), while PTV, MLD, total field number, vdose and NTCP were higher than in the control group ($P < 0.05$). Logistic regression analysis showed that age, lung cancer diagnosis, chemotherapy history, FEV1, FEV1/FVC, PTV, MLD, total number of radiation fields, vdose and NTCP were all risk factors of radiation pneumonia.

CONCLUSION

We identified patient age, type of lung cancer, history of chemotherapy, lung function and radiotherapy parameters as risk factors of radiation pneumonia. Comprehensive evaluation and examination should be carried out before radiotherapy to effectively prevent radiation pneumonia.

Key Words: Radiation pneumonia; Influencing factors; Radiotherapy; Multiple regression analysis

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Core Tip: Radiotherapy is a common treatment method for malignant tumors. However, it is associated with a high risk of radiation pneumonia. Therefore, the early

prevention of radiation pneumonia is very important. We retrospectively compared medical records and analyzed the relevant clinical data of 234 patients with and without radiation pneumonia to demonstrate that the risk factors of radiation pneumonia include patient age, lung cancer diagnosis, history of chemotherapy, lung function and radiotherapy parameters. Comprehensive evaluation and examination for each patient should be carried out before radiotherapy to effectively prevent radiation pneumonia.

INTRODUCTION

Radiotherapy is a common treatment method for malignant tumors. About 70.0% of patients with malignant tumors need radiotherapy at a certain stage of the disease^[1,2]. However, radiotherapy in patients with breast cancer, lung cancer, esophageal cancer and other chest malignant tumors is associated with a higher risk of radiation pneumonitis^[3,4]. In the process of treatment, radiation can directly damage the vascular endothelial cells and parenchymal cells of the lung, cause inflammatory changes, promote the continuous activation of stromal cells, and lead to irreversible pulmonary fibrosis injury^[5]. It may not only affect the smooth implementation of the treatment plan and reduce treatment efficacy, but also increases pain and seriously reduces quality of life of cancer patients^[6,7]. Radiation pneumonia is a common complication of radiotherapy for thoracic tumors, and is mainly caused by radiation-induced damage to the pulmonary vascular endothelial cells and parenchymal cells. It can develop into chronic inflammation and cause pulmonary fibrosis^[8]. Radiation pneumonia symptoms include low fever, irritating dry cough, dyspnea, and even respiratory distress and respiratory failure^[9]. While corticosteroid treatment that is often given to patients with radiation pneumonia can improve the symptoms, it is associated with a risk of pulmonary fibrosis^[10]. Therefore, early prevention of radiation pneumonia, based on the clinical continuous comprehensive analysis of associated risk factors and the formulation of targeted preventative methods, is crucial. The current study retrospectively compares medical records of 234 patients with and without radiation pneumonia, treated in Huzhou Central Hospital, and analyzes the relevant clinical data.

MATERIALS AND METHODS

Patients

Records of 234 patients (126 males and 108 females) who underwent radiotherapy in Huzhou Central Hospital (Huzhou, Zhejiang Province, China) from January 2018 to February 2021 were collected.

Inclusion criteria

(1) Receiving intensity modulated conformal radiotherapy for the first time; (2) Complete radiotherapy process; (3) Complete medical records and a follow-up time > 6 mo; (4) Kappa functional status score ≥ 70 ; and (5) Patients are aware of the study and cooperate with informed consent.

Exclusion criteria

(1) Radiotherapy for other parts at the same time; (2) Interruption of radiotherapy; (3) Suffering from severe basic lung diseases, such as pulmonary fibrosis; and (4) History of lung surgery.

The Medical Ethics Association of Huzhou Central Hospital approved the study and obtained the informed consent from all enrolled patients (approval number: HZFY-L21035478, date: 2021-08-28).

Diagnostic criteria for radiation pneumonia^[11,12]

(1) Lung irradiation dose > 8Gy; (2) Within 1-6 mo after irradiation; (3) Chest tightness, low fever, irritating dry cough, dyspnea and other symptoms; (4) Physical examination showed decrease in respiratory sound, dry and wet rales could be heard, and the skin at the radiation field had signs of erythema and pigmentation; (5) Laboratory examination showed increased or decreased leukocyte count; blood gas analysis showed increased carbon dioxide partial pressure and decreased blood oxygen partial pressure; (6) Pulmonary function examination showed that carbon monoxide diffusion volume

(DLCO) and ventilation/blood flow ratio decreased, or there was no abnormality; and (7) Chest computed tomography (CT) showed flake ground glass shadow, consolidation shadow and fiber strip shadow in the irradiated lung field.

Observation indexes

(1) Gender, age, smoking history, tumor type, tumour, node, metastasis (TNM) stage, chemotherapy, and operation data of the two groups were collected and recorded; and (2) On the end day of radiotherapy, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and DLCO of the two groups were measured by a pulmonary function instrument, and the FEV1/FVC values were calculated. Concurrently, planned target area (PTV), mean lung dose (MLD), total number of radiation fields, percentage of lung tissue in total lung volume (vdose) and the probability of normal tissue complications (NTCP) were recorded.

Statistical analysis

General data and laboratory indexes of the two groups were compared. Data were processed by Spss 22.0 (IBM, Chicago, IL, United States), [n (%)] was used to represent the non-grade count data, and the test method was χ^2 ; (mean \pm SD) is used to represent the measurement data. T -test was used for normal distribution and rank sum test was used for non-normal distribution. The risk factors were analyzed by multivariate logistic regression. $P < 0.05$ was considered statistically significant.

A Kattan-style nomogram was prepared as a graphical representation of the logistic regression model used to predict radiation pneumonia. The position and the length of the scale for each independent variable was based on its respective beta-coefficient calibrated against the Points scale at the top^[13].

Decision curve analysis was performed to calculate a clinical “net benefit” for the radiation treatment. Net benefit was calculated across a range of threshold probabilities (minimum probability of disease at which treatment would be warranted) as described in^[14]. Prediction by all independent variables in the model were also plotted separately,

with continuous variables transformed based on probability. The independent variables in the regression model were assessed for multicollinearity and any variables with a variance inflation factor of 10 or higher were removed. This allowed for a less complex and more applicable decision curve analysis, by limiting the variables that a physician would need to take into consideration when assessing net benefit.

⁹ **RESULTS**

A total of 234 patients (126 males and 108 females) met the inclusion criteria; 93 patients with radiation pneumonia within 6 mo after radiotherapy were set as the study group. Radiation pneumonia diagnosis was established as described above and confirmed by the chest CT (Figure 1). The remaining 141 patients without radiation pneumonia within 6 mo were set as the control group. The proportion of patients aged ≥ 60 years, with a diagnosis of lung cancer, previous chemotherapy history and operation was higher in the study group than that in the control group ($P < 0.05$). There was no significant difference between the two groups in gender, smoking history, TNM stage, chemotherapy history and operation ($P > 0.05$) (Table 1).

FEV1, DLCO and FEV1/FVC in the study group were lower than those in the control group ($P < 0.05$), while PTV, MLD, total field number, vdose and NTCP were higher than those in the control group ($P < 0.05$) (Table 2).

Taking the above statistically significant factors (age, tumor type, chemotherapy history, FEV1, DLCO, FEV1/FVC, PTV, MLD, total number of radiation fields, vdose, NTCP) as independent variables and the diagnosis of radiation pneumonia as a dependent variable, logistic regression analysis was carried out. It was found that age ≥ 60 years old, lung cancer diagnosis, chemotherapy history, FEV1, DLCO, FEV1/FVC, PTV, MLD, total number of radiation fields and NTCP were risk factors of radiation pneumonia (Table 3).

Based on the logistic regression analysis, a nomogram was proposed to predict an individual patient's probability of radiation pneumonia (Figure 2). When the position of the totaled points on the total points scale lines up with the linear and probability-based

predictor scales, 0 (linear) and 0.5 (probability), respectively, indicate the risk of radiation pneumonia. As shown in Figure 2, age, lung cancer diagnosis, history of chemotherapy, FEV1, DLCO, FEV1/FVC, PTV, MLD, and a total number of radiation fields have a greater capacity for providing points in the nomogram and can serve as indicators of the risk of radiation pneumonia.

Decision curve analysis was then created (Figure 3), with two standard plots, showing the benefit of assuming the patient will not develop radiation pneumonia ("Treat None") and the benefit of assuming the patient will develop radiation pneumonia ("Treat All"), respectively. Differences in the predictive power of variables were plotted within these standard plots to predict the risk of radiation pneumonia.

DISCUSSION

This study analyzed the risk factors of radiation pneumonia. We found that these factors include age, diagnosis of lung cancer, history of chemotherapy, lung function and radiotherapy parameters.

With increased age, tolerance of radiotherapy in patients decreases and the risk of radiation pneumonitis increases. Vogelius and Bentzen^[15] conducted a meta-analysis to assess the impact of various clinical risk factors on the incidence rate of symptomatic radiation pneumonitis. Age was one of the significant risk factors for radiation pneumonitis (OR = 1.7, $P < 0.0001$). With the increase in age, all body functions of radiotherapy patients were reduced. Additionally, there may be underlying pulmonary diseases, making elderly patients more sensitive to radiation damage, increasing the damage to lung tissue caused by radiotherapy and increasing the risk of radiation pneumonia^[16]. The onset of lung cancer is obscure, as there are generally no specific symptoms in the early stage. Therefore, most patients are diagnosed at the middle and late stages when the lung tissue has already suffered a certain degree of damage. This often requires clinical increase of the radiation dose to efficiently kill tumor cells, resulting in further lung tissue damage and subsequently, radiation pneumonia.

Consistent with our findings, Zhang *et al*^[17] also showed that lung disease and tumor that is located in the middle or lower lobe, are risk factors for radiation pneumonia.

Chemotherapy is a commonly used method to treat cancer. However, increased toxicity and side effects of chemotherapy, coupled with the impact of increased tumor consumption, can lead to malnutrition. Subsequently, this can lead to a decline in epidemic immunity function, the dysfunction of respiratory muscles that may affect effective cough, and eventually, an increased risk of radiation pneumonia^[18]. Palma *et al*^[19] retrospectively analyzed data of 836 patients with non-small cell lung cancer who received radiotherapy and chemotherapy in Europe, North America and Asia. In recursive partition analysis (RPA), it was found that patients over 65 years old after carboplatin/paclitaxel chemotherapy had the highest risk of radiation pneumonia (> 50%).

Relevant studies have shown that poor pulmonary function reduces the tolerance of lung tissue to radiation, and leads to the reduction of the safety threshold of radiotherapy parameters, and, subsequently, radiation pneumonia^[20-22].

Increase in radiotherapy parameters such as PTV, MLD, total number of radiation fields, vdose and NTCP is indicative of the increase in radiation dose, the radiation range and the degree of damage to the lung tissue that are caused by radiotherapy. Accordingly, the possibility of radiation pneumonia increases. Lu *et al*^[23] showed significant differences in PTV, MLD, total MLD, and V5, V10, V20, and V40 (percentage of lung volumes exceeding 5, 10, 20, and 40 Gy) in patients with radiation and non-radiation pneumonia. In addition, PTV > 145 cm³, total MLD ≥ 4.7gy, V5 ≥ 26.8%, V10 > 12% and V20 ≥ 5.8 were associated with radiation pneumonitis risk. These published findings are consistent with results of our study that shows that radiotherapy parameters are independent risk factors of radiation pneumonia. Although our logistic regression analysis showed that vdose was not a statistically significant risk factor ($P = 0.133$), subsequent decision curve analysis demonstrated a very high net benefit across the threshold probability, approximating that of the full model.

Based on the results of our logistic regression analysis, we were able to generate a nomogram, incorporating factors, such as age, lung cancer diagnosis, history of chemotherapy, lung function and radiotherapy parameters. The range of data for each independent variable corresponded with the length of its scale and the extent that they span to right on the Points scale indicated their relative importance in the prediction model. The total points summed for each variable for a given patient indicated the probability of radiation pneumonia on the prediction scale at the bottom. Our results also demonstrate that independent variables that are significant predictors in the regression models have a greater capacity for providing points in the nomogram. Together with the decision curve analysis, performed in our study, these results may help a physician to decide on whether the benefit of the radiation treatment outweighs the potential risk of developing radiation pneumonia. These tools, therefore, can be a useful guide in clinical practice, to evaluate the risk of radiation pneumonia for a given patient based on their individual variables.

Limitation of study

This study includes a small sample size of 98 patients who have received radiotherapy in Huzhou Central Hospital within the past year, and there are few observation indexes, which may affect the accuracy of the results. Therefore, further multi-center and large-scale studies are needed, with increased sample size and a number of observation indexes to analyze the risk factors of radiation pneumonitis more comprehensively.

CONCLUSION

The occurrence of radiation pneumonia is affected by many factors. Before radiotherapy, clinicians should fully consider all the influencing factors for each patient individually and formulate a scientific and reasonable radiotherapy plan to avoid the occurrence of radiation pneumonia as much as possible while ensuring the treatment effect. The results of this study show that the risk factors of radiation pneumonia

include patient age, lung cancer diagnosis, chemotherapy, lung function, radiotherapy parameters. We created nomogram and decision curve analysis to provide the clinicians with tools to evaluate the risk of radiation pneumonia for a given patient based on the identified risk factors.

ARTICLE HIGHLIGHTS

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Research background

Radiotherapy is a common treatment method for malignant thoracic tumors. However, it is associated with complications, such as radiation pneumonia that is mainly caused by the radiation-induced damage to the pulmonary vascular endothelial cells and parenchymal cells. It can develop into chronic inflammation and pulmonary fibrosis and may reduce the effectiveness of the treatment and impact the quality of life of cancer patients.

Research motivation

Early prevention of radiation pneumonia is very important. Clinical continuous comprehensive analysis of associated risk factors and the formulation of targeted preventative methods may reduce the incidence of this complication.

Research objectives

The purpose of our study was to carry out multiple regression analysis on the influencing factors of radiation pneumonia.

Research methods

Records of patients receiving chest radiotherapy between January 2018 to February 2021 were collected and divided into two groups according to whether radiation pneumonia was diagnosed. Multiple regression analysis was performed on age, tumor type, chemotherapy history, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), DLCO, FEV1/FVC, planned target area (PTV), mean lung dose (MLD),

total number of radiation fields, percentage of lung tissue in total lung volume (vdose), probability of normal tissue complications (NTCP) and other factors.

Research results

The proportion of patients with age ≥ 60 years, lung cancer diagnosis and a history of chemotherapy in the study group was higher than that in the control group ($P < 0.05$); FEV1, DLCO and FEV1/FVC in the study group were lower than the control group ($P < 0.05$), while PTV, MLD, total field number, vdose and NTCP were higher than the control group ($P < 0.05$). Logistic regression analysis showed that age, lung cancer diagnosis, chemotherapy history, FEV1, FEV1/FVC, PTV, MLD, total number of radiation fields, vdose and NTCP were all risk factors of radiation pneumonia.

Research conclusions

The risk factors of radiation pneumonia include patient age, lung cancer diagnosis, history of chemotherapy, lung function, and radiotherapy parameters.

Research perspectives

A comprehensive evaluation and examination should be carried out before beginning the radiotherapy treatment. Clinicians should fully consider all the influencing factors based on the individual situation of each patient, to design a scientific and reasonable radiotherapy plan.

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