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Research article

Analysis of related factors of radiation pneumonia caused by precise radiotherapy of esophageal cancer based on random forest algorithm

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Abstract: The precise radiotherapy of esophageal cancer may cause different degrees of radiation damage for lung tissues and cause radioactive pneumonia. However, the occurrence of radioactive pneumonia is related to many factors. To further clarify the correlation between the occurrence of radioactive pneumonia and related factors, a random forest model was used to build a risk prediction model for patients with esophageal cancer undergoing radiotherapy. In this study, we retrospectively reviewed 118 patients with esophageal cancer confirmed by pathology in our hospital. The health characteristics and related parameters of all patients were analyzed, and the predictive effect of radiation pneumonia was discussed using the random forest algorithm. After treatment, 71 patients developed radioactive pneumonia (60.17%). In univariate analyses, age, planning target volume length, Karnofsky performance score (KPS), pulmonary emphysema, with or without chemotherapy, and the ratio of planning target volume to planning gross tumor volume (PTV/PGTV) in mediastinum were significantly associated with radioactive pneumonia ($P < 0.05$ for each comparison). Multivariate analysis revealed that with or without pulmonary emphysema (OR = 7.491, $P = 0.001$), PTV/PGTV (OR = 0.205, $P = 0.007$), and KPS (OR = 0.251, $P = 0.011$) were independent predictors for radiation pneumonia. The results concluded that the analysis of radiation pneumonia-related factors based on the random forest algorithm could build a mathematical prediction model for the easily obtained data. This algorithm also could effectively analyze the risk factors of radiation pneumonia and formulate the appropriate treatment plan for esophageal cancer.

Keywords: esophageal cancer; radiation pneumonia; radiation therapy; random forest

1. Introduction

Esophageal carcinoma has the characteristics of low cure rate and high recurrence rate, and radiation therapy is still the primary treatment for it so far [1,2]. Due to the particular tumor location and narrow target area, the radiotherapy was carried out from both sides of the chest, so radiotherapy complications, especially for radiation pneumonia, were frequent [3].

Radiation pneumonia is a common side effect after radiotherapy for lung cancer, with a reported incidence of 10 to 30%, and the fatal toxicity can also reach 2% [4]. Multiple health factors may be related to the occurrence of radiation pneumonia [5]. This pneumonia develops with irritating cough or dry cough, accompanied by shortness of breath and chest pain, low heat even high fever in some patients. Even worse, it could develop into radiation-induced pulmonary fibrosis, which can't be reversed [6]. The symptoms of radiation pneumonia are unclear or not obvious in some special patients, leading to a delay in the diagnosis. A fatal radiation pneumonia course can result from the appropriate disrupt management.

So far, scholars have not given up the research on the influencing factors of radiation pneumonia. Ullah et al. [7] believed that the elderly age is a factor of reduced radiation tolerance, and that women have a higher risk of radiation pneumonia than men. Giuranno et al. [8] thought that there was a strong correlation between emphysema and radiation pneumonia. Li et al. [9] found that inhibition or deletion of NLRP3 can specifically alleviate the mouse lung inflammation caused by radiation and lipopolysaccharide treatment. Although the clinical factors containing age, radiation technology, and tumor location have been correlated with radiation pneumonia occurrence [10], the risk factors for radiation pneumonia are unclear. Random forest algorithms can build a mathematical model of data and effectively analyze the influencing factors of radiation pneumonia through the model to guide the treatment. Therefore, the purpose of this study is to apply the random forest algorithm to show the effective clinical prediction of lung injury factors after radiotherapy of esophageal cancer and establish a prediction model to identify the risk factors related to radiation pneumonia. This will improve esophageal cancer, reduce the complications of radiation pneumonia, and have important clinical significance. In the second section, we discuss applying the random forest algorithm to the risk factors of radiation pneumonia. In the third section, the prediction results of risk factors of radiation pneumonia by random forest algorithm were given, and the results are statistically analyzed. In the fourth section, the results were integrated and analyzed, and the conclusions were given.

2. Materials and methods

2.1. Patients

Between January 2016 and January 2018, 118 patients of our hospital with esophageal cancer who had received thoracic radiotherapy were included in this study. The Ethics Committee of Second Affiliated Hospital of Anhui Medical University approved this study and has been registered at www.chictr.org.cn. The reference number for the ethics approval is PJ-YX2018-050. All participants understood and signed the informed consent form before entering the study.

The inclusion criteria were: 1) No apparent external invasion: the tumor showed no noticeable chest and back pain, and CT showed no invasion of adjacent tissues and organs such as the aorta or tracheobronchial tree; 2) silence with paralysis; 3) the lesion was relatively short, the initial site of the tumor was 23–28 cm from the incisor, and the length of the esophageal lesion under barium X-ray was 4–7 cm; 4) No other severe complications except radiation pneumonia; 5) No radiation contraindication; 6) availability of laboratory data for all desired time points and written informed consent obtained; 7) definite pathological or cytological diagnosis.

Data on all the health and tumor characteristics were collected (Table 1).

Table 1. Clinical and treatment characteristics.

Characteristic	Patients (n)	Proportion or median (range)
Sex		
Male	85	72.03
Female	33	27.97
Age		
≤ 75	51	43.22
> 75	67	56.78
Tumor Location		
Upper lobe	29	24.58
Middle lobe	50	42.37
lower lobe	39	33.05
PTV		
≥ 12 cm^3	66	58.41
< 12 cm^3	47	41.59
KPS score		
> 90	36	30.51
< 90	82	69.49
Current smoker		
Yes	55	46.61
NO	63	53.39
Diabetes mellitus		
Yes	19	16.10
NO	99	83.90
High blood pressure		
Yes	46	38.98
NO	72	61.02
Pulmonary emphysema		
Yes	39	33.05
NO	79	66.95
Chemotherapy		
Yes	47	40.17
NO	70	59.83

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Characteristic	Patients (n)	Proportion or median (range)
Classification		
Grade 0	47	39.83
Grade 1	35	29.66
Grade 2	18	15.25
Grade 3	15	12.71
Grade 4	3	2.54
Mediastinal PTV/PGTV volume		
≤ 350	60	50.85
> 350	58	49.15
PTV/PGTV dose（Gy）		
≤ 57	42	35.59
> 57	76	64.41
Mean lung dose（Gy）		
≤ 12	42	35.59
> 12	76	64.41
Whole lung V5（%）		
≤ 55	57	48.31
> 55	61	51.69
Whole lung V10（%）		
≤ 48	58	49.15
> 48	60	50.85
Whole lung V20（%）		
≤ 25	59	50.00
> 25	59	50.00
Whole lung V30（%）		
≤ 12	58	49.15
> 12	60	50.85

2.2. Random forest model

The random forest can not only classify data according to data characteristics but also realize data regression. It is a widely used data mining algorithm. Besides, the random forest algorithm has the function of evaluating the importance of variables. The higher the score of the importance of variables, the better the ability of the variable to classify the outcome variables. Let the original sample size be n, and the variables of each influencing factor are $x_1, x_2, \ldots, x_m$. The out-of-bag data from each sampling can be used as test samples to evaluate the importance of each variable in the classification. The specific process is as follows. The self-help samples are used to form each tree classifier. At the same time, the corresponding o o b are classified, and the voting scores of each o b of K self-help samples are obtained, which are recorded as $rate_1, rate_2, \ldots, rate_k$. The order of variable x_i in K OOB samples is changed randomly to form a new OOB test sample, and then the new OOB is classified by the established random forest. The voting score of each instance is obtained according to the correct number of pieces. The result is expressed as a matrix

$$\begin{pmatrix} rate_{11} & \cdots & rate_{1k} \\ \vdots & \ddots & \vdots \\ rate_{p1} & \cdots & rate_{pk} \end{pmatrix} \tag{1}$$

Subtract $rate_1, rate_2, \ldots, rate_k$ from the i-th line vector corresponding to the above matrix, sum, and average, and then divide by the standard error to get the importance score of a variable x_i, that is

$$sore_i = (\sum_{j=1}^{k}(rate_j - rate_{ij})/k)/SE(1 《\mathrm{i} 《\mathrm{p}) \tag{2}$$

2.3. Radiation treatment and follow-up

Three radiotherapy methods was used, including conventional 3D conformal radiotherapy, intensity-modulated radiotherapy, or stereotactic body radiotherapy (SBRT). The X-ray voltage is 6 MV, with a total of 40–60 Gy, 2.0 Gy per day, five days a week for the conventional radiotherapy; with a total of 40–50 Gy, 8–10 Gy per day, three days a week for SBRT. The volume parameters for conventional radiotherapy were calculated by CT scan, including total tumor volume (GTV), internal target volume (ITV), and planned target volume (PTV). The volume parameters for SBRT were more complex. The GTV was difined by the maximum intensity projection in 4D-CT. The movement of GTV generated the ITV, and the 3–5 mm expansion generated the PTV. The planned CT scan and its respective planned dose were imported into MIM MaestroSoftware (version 6.5.9), and a composite plan was created [10,11]. Dose volume histogram (DVH) data were extracted from the software, including mean lung dose (MLD), lung V5, V10, V20, and V30. Measure the overlap between V5 and radiotherapy plans.

Chest radiography, complete blood counts, and CRP levels examination are recommended 1, 3 and 6 months after radiotherapy and every three months after that. When the new respiratory symptoms were found in special patients, the CT scanning would be excuted regularly. According to the symptoms and signs of hospitalized patients and auxiliary examination to understand the condition, the patients who have not completed the chemotherapy course or the progress of the disease in hospital treatment. For patients who did not receive regular re-examination after radiotherapy, telephone follow-up was conducted to understand the symptoms, diagnosis, and treatment of patients after treatment.

2.4. Evaluation of radiation pneumonia

The diagnosis of radiation pneumonia was evaluated using the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by the consensus of two radiation oncologists [12]. Radiation pneumonia is considered when consolidation or ground glass shadows appear on chest X-ray or CT images. These imaging findings are limited to the radiation field, and the boundary is relatively straightforward, and other possible causes of radiation changes in the lung are excluded.

2.5. Statistical analysis

The SAS 9.4 statistical software was used to analyze the data. The univariate analysis was done with χ^2 tests. Variables with a $P < 0.05$ on univariate analysis were then entered in a stepwise method in a binary logistic regression analysis to develop a multivariate model of independent factors predicting radiation pneumonia. Furthermore, the receiver operator characteristic (ROC) curves were constructed, and cut-off values were determined using the Youden index. A probability (P) value of < 0.05 was considered significant for all analyses.

3. Results

3.1. Treatment outcome

A total of 118 subjects were included in this study, including 85 males (72.03%). There were 51 cases (43.22%) with age less than or equal to 75 years old, 67 patients (56.78%) were over 75 years old. Other feature composition ratios are shown in Table 1.

A total of 71 patients (60.17%) in this study had radiation pneumonia, and 47 patients (39.83%) did not have radiation pneumonia. Among them, there were 35 cases (29.66%) of grade 1 radioactive pneumonia, 18 cases (15.25%) of grade 2 radioactive pneumonia, 15 cases (12.71%) of grade 3 radioactive pneumonia, and 4 cases (2.54%) of radioactive pneumonia. Typical cases were showed in Figures 1–3.

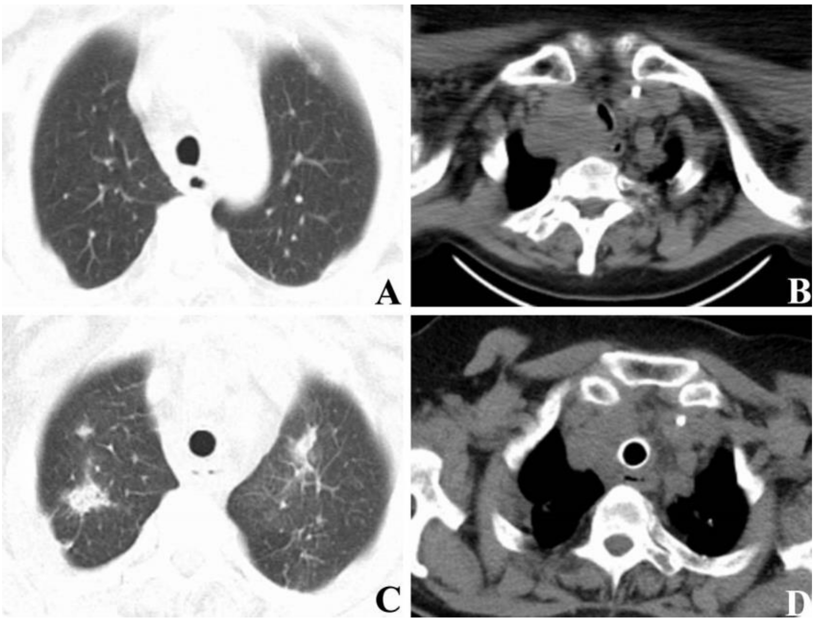

Figure 1. Radiation pneumonia in a 74-year-old female patient with cervical esophageal cancer. A: Lung window before radiotherapy. B: Mediastinal window before radiotherapy. C: Lung window after radiotherapy, shows grade I radiation pneumonia. D. Mediastinal window after radiotherapy.

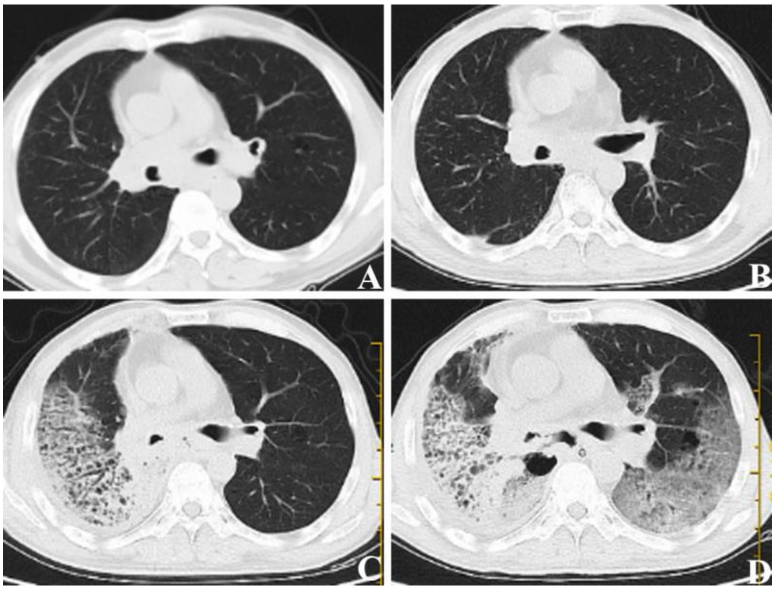

Figure 2. Radiation pneumonia in a 56-year-old male patient with middle thoracic esophageal cancer. A: Lung window before radiotherapy. B: Lung window after radiotherapy shows mild radiation pneumonia. C: Lung window after radiotherapy shows aggravation of radiation pneumonia. D. Lung window after radiotherapy shows severe radiation pneumonia.

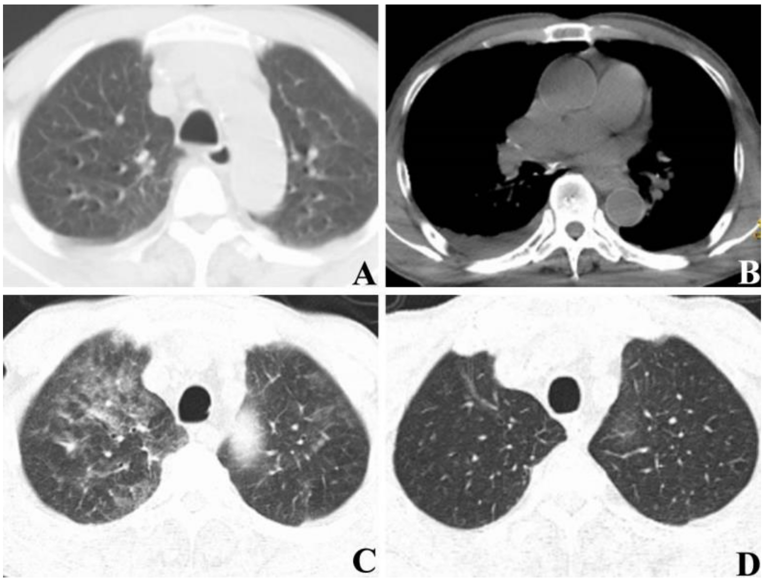

Figure 4. Radiation pneumonia in a 57-year-old female patient with cervical esophageal cancer. A: Lung window before radiotherapy. B: Mediastinal window before radiotherapy. C: Lung window after radiotherapy, shows moderate radiation pneumonia. D. Recovery of radiation pneumonia.

3.2. Results of univariate analysis of radiation pneumonia

Single-factor analysis was performed by grouping different factors into χ^2 tests to determine whether radiation pneumonia occurred. As shown in Table 2, in the univariate analysis, age, PTV length, KPS score, emphysema, presence or absence of chemotherapy, and mediastinal PTV/PGTV volume in the two groups showed statistical significance in the proportion of radiation pneumonia ($P > 0.05$). Among them, patients aged 75 years old with > have a relatively high incidence of radiation pneumonia compared with patients aged less than or equal to 75 years old. Secondly, PTV length < 12, KPS score < 90, emphysema, no chemotherapy, and mediastinal PTV/PGTV volume > 350 were the main factors for the increased proportion of patients with radiation pneumonia, respectively.

Table 2. Single factor analysis of radiation pneumonia after radiotherapy for esophageal cancer.

Characteristic	radioactive pneumonia （n = 71）	Non-radioactive pneumonia （n = 47）	χ^2	P value
Sex				
Male	49 (69.01)	36 (76.60)	0.807	0.369
Female	22 (30.99)	11 (23.40)		
Age				
≤ 75	25 (35.21)	26 (55.32)	4.659	0.031
> 75	46 (64.79)	21 (44.68)		
Tumor Location				
Upper lobe	16 (22.54)	13 (27.66)	0.554	0.758
Middle lobe	30 (42.25)	20 (42.55)		
lower lobe	25 (35.21)	14 (29.79)		
PTV				
≥ 12 cm^3	46 (67.65)	20 (44.44)	6.001	0.014
< 12 cm^3	22 (32.35)	25 (55.56)		
KPS score				
> 90	15 (21.13)	21 (44.68)	7.400	0.007
< 90	56 (78.87)	26 (55.32)		
Current smoker				
Yes	36 (50.70)	19 (40.43)	1.201	0.273
NO	35 (49.30)	28 (59.57)		
Diabetes mellitus				
Yes	12 (16.90)	7 (14.89)	0.084	0.771
NO	59 (83.10)	40 (85.11)		
High blood pressure				
Yes	29 (40.85)	17 (36.17)	0.260	0.610
NO	42 (59.15)	30 (63.83)		
Pulmonary emphysema				
Yes	32 (45.07)	7 (14.89)	11.638	0.001
NO	39 (54.93)	40 (85.11)		
Chemotherapy				

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Characteristic	radioactive pneumonia （n = 71）	Non-radioactive pneumonia （n = 47）	χ^2	P value
Yes	22 (31.43)	25 (53.19)	5.541	0.019
NO	48 (68.57)	22 (46.81)		
Mediastinal PTV/PGTV volume				
≤ 350	30 (42.25)	30 (63.83)	5.268	0.022
> 350	41 (57.75)	17 (36.17)		
PTV/PGTV dose（Gy）				
≤ 57	29 (40.85)	13 (27.66)	2.145	0.143
> 57	42 (59.12)	34 (72.34)		
Mean lung dose（Gy）				
≤ 12	22 (30.99)	20 (42.55)	1.651	0.199
> 12	49 (69.01)	27 (57.45)		
Whole lung V5（%）				
≤ 55	30 (42.25)	27 (57.45)	2.614	0.106
> 55	41 (57.75)	20 (42.55)		
Whole lung V10（%）				
≤ 48	34 (47.89)	24 (51.06)	0.114	0.735
> 48	37 (52.11)	23 (48.94)		
Whole lung V20（%）				
≤ 25	31 (43.66)	28 (59.57)	2.864	0.091
> 25	40 (56.34)	19 (40.43)		
Whole lung V30（%）				
≤ 12	31 (43.66)	27 (57.45)	2.150	0.143
> 12	40 (56.34)	20 (42.55)		

3.3. Multivariate analysis of radiological pneumonia

According to the above results, multi-factor analysis for binary classification variables by radioactive pneumonia of the Logistic regression analysis. The model eventually includes gender, age, classification, emphysema, KPS score, PTV length-related clinical factors, and dosimetry parameters PTV/PGTV dose, V5, V10 V20, and V30. The regression coefficient was obtained by the maximum likelihood method, and the corresponding OR value was calculated. The specific results were shown in Table 3.

Table 3. Multivariate analysis of factors influencing radiation pneumonia after radiotherapy for esophageal cancer.

Variable	Coefficient	standard error	wald statistics	P value	OR	95% CI	
Constant term	1.346	0.764	3.100	0.078			
Sex	-0.785	0.563	1.942	0.164	0.456	0.151	1.376

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Variable	Coefficient	standard error	wald statistics	P value	OR	95% CI	
age	-0.773	0.497	2.416	0.120	0.462	0.174	1.224
KPS score	-1.381	0.542	6.496	0.011*	0.251	0.087	0.727
Pulmonary emphysema	2.014	0.608	10.959	0.001*	7.491	2.274	24.677
PTV/PGTV volume	0.389	0.534	0.530	0.467	1.475	0.518	4.196
PTV/PGTV dose	-1.585	0.592	7.163	0.007*	0.205	0.064	0.654
MLD	-0.443	0.942	0.221	0.638	0.642	0.101	4.067
V5	1.072	0.655	2.682	0.102	2.921	0.810	10.536
V10	-1.033	0.808	1.632	0.201	0.356	0.073	1.736
V20	1.299	0.708	3.363	0.067	3.665	0.915	14.686
V30	0.802	0.595	1.817	0.178	2.23	0.695	7.154

The results of model fitting showed statistically significant differences between dependent variables in the presence or absence of emphysema, KPS score, and PTV/PGTV dose factors under the control of other factors, suggesting that the above factors were independent predictors of the occurrence of radioactive pneumonia.

3.4. ROC curve analysis results

ROC curve directly expresses the sensitivity and specificity of the two fundamental indicators in the diagnostic test through the area under the curve. The more the ROC curve moves to the left and upward, the greater the area under the curve and the greater its clinical diagnostic value. Therefore, for further ROC curve analysis, the predicted value of occurrence probability of radioactive pneumonia was taken as the detection variable. Grouping was taken as the state variable, and the value of the fixed state variable was 1 to establish the ROC curve. The results showed that the area under the ROC curve for predicting radiation pneumonia was 0.825 (95% CI: 0.748–0.904). The difference was statistically significant (P = 0.028), indicating that the prediction model of radioactive pneumonia had a certain diagnostic value. The ROC curve was shown in Figure 4.

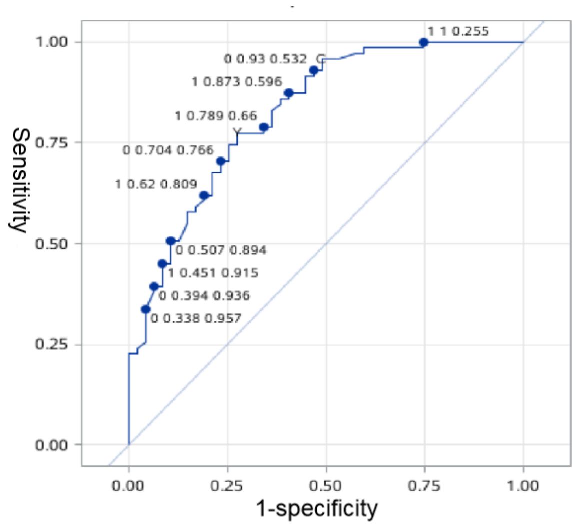

Figure 4. ROC curve of factors independently influencing the occurrence of radioactive pneumonia.

Table 4. ROC optimal cut-point.

Criterion	Symbol	Cut-point	Sensitivity	Specificity	Value
Correct	C	0.351	0.958	0.511	0.780
Youden	Y	0.554	0.775	0.723	0.498

As shown in the analysis above, the optimal entry point is the Y marker (the standard Youden index for the optimal cut-off point selection). The prediction sensitivity and specificity of the ROC curve are 0.775 and 0.723, respectively (Table 4).

4. Discussion

Compared with western countries, Chinese people have many differences in genetics, living environment, eating habits, and other aspects, making esophageal cancer incidence significantly higher in China. For patients with esophageal cancer in China, the tumor is usually located in the middle and upper part of the esophagus, with squamous cell carcinoma accounting for the majority, which has Chinese characteristics. Based on this, this study was conducted on esophageal cancer patients in China. To ensure the purity of the data and eliminate the possible adverse effects caused by the complex data set, this study unified the data from the same institution to confirm the validity of the data to ensure the significance of the relevant results.

Radioactive pneumonia refers to the lung tissue caused by accepting specific doses of ionizing radiation in a series of acute inflammatory reactions. The majority of patients after stop radiation exposure can be gradually restored. Still, a few patients will be progressively developed into radioactive pulmonary fibrosis, and severe cases can lead to respiratory failure. There must be a specific volume of lung tissue received a dose of radiation occurs radiation pneumonia [13]. Therefore, the occurrence of radiation pneumonia may be related to the amount received per unit volume of lung tissue. The occurrence of radioactive pneumonia is a severe complication of tumor radiotherapy. If the patient suffers from radioactive pneumonia caused by radiotherapy during hospitalization, hospitalization will be prolonged, and the hospitalization cost will be increased. In severe cases, it may endanger life. Therefore, it has been a research hotspot to find the factors that can accurately predict radiation pneumonia. Although more studies have been conducted in recent years, there are still few research data focusing on the impact of a single factor on acute radioactive pneumonia and few comprehensive studies [14]. In our study, 118 esophageal cancer patients who received radiation therapy were analyzed, and the results showed that the incidence of radiation pneumonia was 60.17%%. The present study examined the clinical and dosimetric factors as predictors of radiation pneumonia and evaluated the usefulness using receiver operating characteristic (ROC) analyses. The findings revealed that with or without pulmonary emphysema, mediastinal PTV/PGTV volume and KPS score were associated with the risk of radiation pneumonia.

Radiation pneumonia is one of the potentially restrictive side effects of chest radiotherapy, limiting the radical dose of radiotherapy or combined chemotherapy. Several health-related factors have been implicated in increasing the chances of developing radiation pneumonia [15–17]. The meta-analysis published by Vogelius et al. [18] synthesized the data from 31 independent studies and found the advanced age and pulmonary comorbidities were significantly associated with the risk of developing radiation pneumonia. Similarly, other studies demonstrated that the older the patient is, the higher the incidence of radiation pneumonia is. Old age is an independent risk factor for the occurrence of radiation pneumonia, which may be related to the reduced resistance and poor tolerance of elderly patients [19,20]. Another study also reported that the incidence of radiation pneumonia in women is significantly higher than that in men, which is not consistent with the results of this study [21]. They suggested that the occurrence of radiation pneumonia is related to hypersensitivity, and the mechanism is similar to that of autoimmune diseases, which are more common in women. The main reasons for the difference are the choice of sample size and different regions. Smoking may be associated with a better response to inhaled steroids [22], whether a protective factor for radiation pneumonia is uncertain. At the same time, this study also found no correlation between smoking and the occurrence of radioactive pneumonia. Some studies also reported that the tolerance of smoking patients to lung injury increased, so it was not easy to develop radioactive pneumonia [18]. Our study also found that smoking history showed a significant protective effect (P = 0.273). Several possible explanations have been proposed: reduced inflammatory response, smoking-induced hypoxia, and decreased resistance to oxidative stress, and repair of DNA damage in smokeless patients [23]. Besides, smokers are more likely to have lung symptoms at baseline, so they are less likely to identify and report symptoms.

In this report, the patient suffered from pulmonary dysfunction due to a large area, central recurrence, and almost right atelectasis. One month after radiotherapy, he suffered from grade III radiation pneumonia with cough, shortness of breath, and low-grade fever. To prevent the occurrence of radiation pneumonia, radiation doses should be reduced as far as possible. The literature has reported the correlation between radiation dosimetry parameters and radiation pneumonia [24]. Most studies have confirmed that V20 and mean lung dose (MLD) are the most commonly correlated parameters. However, several other variables also show predictability, including acceptance of ⩾ 5 Gy (V5), ⩾ 13 Gy (V13), ⩾ 25 Gy (V25) and ⩾ 30 Gy (V30) [26]. These parameters are often very collinear (that is, adding a parameter, such as V20, will increase other parameters). The difference of predicted values between different dosimetric variables is often tiny. As a general rule, the risk for radiation pneumonia sharply increases with a mean lung dose > 20 Gy, V20 > 30%, and V30 > 20%. For our patient, mean lung dose、radiotherapy dose V5, V10, V20, and V30 is not a factor in radiation pneumonia.

At the last of our study, we used ROC curve analysis to the predicted value of occurrence probability of radioactive pneumonia. The results showed that the area under the ROC curve for predicting radiation pneumonia was 0.8245 (95% CI: 0.748–0.901), and the difference was statistically significant (P = 0.028). The prediction sensitivity and specificity of the ROC curve are 0.775 and 0.723, respectively. This study showed that the AUC value of the prediction model established was 0.8245, indicating that radioactive pneumonia had a particular diagnostic value.

5. Conclusions

To sum up, the occurrence of radiation pneumonia is affected by many factors, and the age and lung function of patients should be fully considered when making a radiotherapy plan. The results showed that mediastinal PTV/PGTV volume and KPS score were associated with the risk of radiation pneumonia. The corresponding treatment plan should be formulated to reduce the occurrence of radiation pneumonia and ensure the effective treatment of esophageal cancer.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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