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Original Article

Associated factors of radiation pneumonitis induced by precise radiotherapy in 186 elderly patients with esophageal cancer

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Abstract: Background: Radiation pneumonitis is one of the most severe complications of esophageal cancer. Purpose: To explore the factors correlated to radiation pneumonitis induced by precise radiotherapy for elderly patients with esophageal cancer. Methods: The retrospective analysis was used to collect clinical data from 186 elderly patients with esophageal cancer. The incidence of radiation pneumonitis was observed, followed by statistical analysis through ANVON or multiple regression analysis. Results: 27 in 186 cases of esophageal cancer suffered from radiation pneumonitis, with incidence of 14.52%. The single factor analysis showed that, Karnofsky performance status (KPS) score, chronic obstructive pulmonary disease, concurrent chemoradiotherapy, gross tumor volume (GTV) dose, lung V20, mean lung dose (MLD) and planning target volume (PTV) were associated with radiation pneumonitis. The logistic regression analysis indicated that, concurrent chemoradiotherapy, GTV dose, lung V20 and PTV were the independent factors of radiation pneumonitis. Conclusion: The concurrent chemoradiotherapy, GTV dose, lung V20, MLD and PTV are the major risk factors of radiation pneumonitis for elderly patients with esophageal cancer.

Keywords: Elderly, esophageal tumor, precise radiotherapy, radiation pneumonitis, factors

Introduction

Esophageal cancer is one of the commonest malignant tumors, of which the incidence is the fourth in all malignant tumors [1]. Concurrent chemoradiotherapy is the main treatment strategy for esophageal cancer patients who are in middle and late stage and cannot be performed with surgery [2, 3]. Radiation pneumonitis is one of the most severe complications of esophageal cancer or chest tumors [4, 5]. Elderly esophageal cancer patients are usually with other diseases, e.g., chronic obstructive pulmonary disease (COPD), and they have poor tolerance for radioactive lung injury and repairment ability, which easily results in radiation pneumonitis [6, 7]. Many studies [8-11] have reported that, the clinical factors are associated with radiation pneumonitis in elderly patients with esophageal cancer, but the results are not the same. Therefore, clarifying the factors correlated with radiation pneumonitis can help to find out the predictive indexes, and have important significance in clinical therapy for elderly patients with esophageal cancer. In this study, the retrospective analysis was used to summarize the clinical data from 186 elderly patients with esophageal cancer who were performed with precise radiotherapy and the relationship between clinical factors and radiation pneumonitis was observed. The objective is to find out and predict the factors related to radiation pneumonitis, and provide a basis for optimized radiotherapy and treatment for elderly patients with esophageal cancer.

Materials and methods

Clinical data

186 elderly patients with esophageal cancer (110 males and 76 females; aged from 65 to 92 years, mean age 71 years) who received precise radiotherapy in Department of Radiotherapy

of The First Affiliated Hospital of Bengbu Medical College (Bengbu, China) from January 2011 to September 2014 were enrolled in this study. All patients were confirmed with esophageal squamous cell carcinoma by pathological examination. Karnofsky performance status (KPS) scores showed that, 39 cases had less than 70 KPS scores and 147 cases had more than 70 KPS scores. There were 25 cases with lesion in cervical part and upper thoracic part, 110 cases with lesion in middle thoracic part and 51 cases with lesion in lower thoracic part. Furthermore, there were 35 cases combined with COPD and 151 cases without COPD, with 52 smokers and 134 non-smokers. 102 cases were performed with concurrent chemoradiotherapy and 84 cases were performed with radiotherapy. The predictive survival time in all patients was more than three months. This study was approved by the ethics committee of Bangbu Medical College. The informed consent was obtained from all patients.

Treatment method

186 patients were performed with precise radiotherapy (three-dimensional conformal radiotherapy), including 102 cases with concurrent chemoradiotherapy and 84 cases with radiotherapy.

The radiotherapy method was as follows: With simulation under CT, the three-dimensional reconstruction by therapy system was performed. According to CT images, the target areas were marked, including gross tumor volume (GTV), clinic target volume (CTV) and planning target volume (PTV). CTV was outside expansion of GTV by 0.5-0.8 cm, and the boundary was expanded 2-3 cm from up to down. The PTV was formed by isotropic expansion of CTV by 0.5 cm. The radiotherapy was conducted by two associate chief physicians. All patients were rechecked by barium meal every week to understand the tumor condition and perforation phenomenon.

The chemotherapy method was as follows: 5-fluorouracil (10 ml: 0.25 mg; Tianjin Jinyao Amino Acid Co., Ltd., Tianjin, China) combined with cis-platinum (6 ml: 30 mg; Jiangsu Hansoh Pharmaceutical Company, Lianyungang, China) was used for chemotherapy regimen. From the first day of radiotherapy, 500 mg/m^2 of 5-fluorouracil was intravenously dripped for 5 days, and 20 mg/m^2 cis-platinum was intravenously dripped for 4 days. Every four weeks were set as one radiotherapy period. Furthermore, concurrent chemotherapy was conducted for two periods during radiotherapy. The routine blood examination was rechecked every week, and the liver and renal functions were rechecked every two weeks. If necessary, steroids, antibiotics, leucocytes increasing agents and antiemetic were administrated for support therapy. For patients with radiation pneumonitis, large doses of steroids, oxygen uptake, antibiotics and Chinese drugs were administrated. One case died of radiation pneumonitis and other patients were alleviated after positive therapy.

Evaluation standard of curative effect

Esophagogram and chest CT results after radiotherapy were classified into complete remission (CR), partial remission (PR), no change (NC) and progressive disease (PD). The clinical benefit rate was the ratio of (CR+PR+NC) and total patients numbers.

Evaluation standard of radiation pneumonitis

The chest x-ray or CT showed diffuse high-density shadow. The radiation pneumonitis was graded according to CTCAE V4.0 version system. In this study, the radiation pneumonitis was with 2nd grade, and should be performed positive clinical therapy.

Follow-up and statistical analysis

All patients had entire follow-up data, and the deadline was March 2015. The follow-up time for all patients was more than six months. The median follow-up time was 18 months (ranged from 6 months to 36 months). SPSS 17.0 software was used to perform chi-square test. Meanwhile, ANVON and Logistic regression analysis were conducted.

Results

Recent effect and survival time

Recent effects were evaluated 3 months after radiotherapy. There were 41 cases in CR (22.04%), 110 cases in PR (59.14%), 23 cases in NC (12.37%) and 12 cases in PD (6.45%). The clinical benefit rate was 93.55%.

Occurrence of radiation pneumonitis

There were 27 cases who suffered from radiation pneumonitis, and the incidence was

Table 1. Relationship between factors and radiation pneumonitis by single factor analysis

Factor	Total number	Number of pneumonitis case	χ^2	P
Sex			0.69	0.41
Male	110	14 (12.73)		
Female	76	13 (17.11)		
KPS			4.92	0.03
< 70	39	10 (25.64)		
≥ 70	147	17 (11.56)		
Lesion region			1.18	0.55
Cervical and upper thoracic	25	2 (8.0)		
Middle thoracic	110	18 (16.36)		
Lower thoracic	51	7 (13.73)		
COPD			6.86	0.01
Yes	35	12 (34.29)		
No	151	15 (9.93)		
Concurrent chemoradiotherapy			6.71	0.01
Yes	102	1 (20.59)		
No	84	6 (7.14)		
Lung V20			7.11	0.01
25%	78	5 (6.41)		
≥ 25%	108	22 (20.37)		
Lung V5			0.07	0.80
< 65%	80	11 (13.75)		
≥ 65%	106	16 (15.09)		
MLD (Gy)			6.29	0.01
< 13	128	13 (10.16)		
≥ 13	58	14 (24.14)		
GTV dose (Gy)			15.50	0.00
< 60	112	7 (6.25)		
≥ 60	74	20 (27.03)		
PTV (cm^3)			4.30	0.04
< 450	103	10 (9.71)		
≥ 450	83	17 (20.48)		
Smoking history			0.08	0.78
Yes	52	8 (15.38)		
No	134	19 (14.18)		

KPS, Karnofsky performance score; COPD, chronic obstructive pulmonary disease; MLD, mean lung dose; GTV, gross tumor volume; PTV, planning target volume.

14.52%. The occurrence time was 0.5-6 months after radiotherapy (median time: 3 months).

Single factor analysis results for occurrence of radiation pneumonitis

KPS, COPD, concurrent chemoradiotherapy, GTV dose, lung V20, MLD and PTV were correlated to radiation pneumonitis ($P < 0.05$). However, sex, smoking history and lesion region had no correlation with radiation pneumonitis ($P > 0.05$) (**Table 1**).

Logistic regression analysis results for occurrence of radiation pneumonitis

Seven factors, including KPS scores, COPD, concurrent chemoradiotherapy, GTV dose, lung V20, MLD and PTV, were performed with Binary Logistic regression analysis. Results showed that, concurrent chemoradiotherapy, GTV dose, lung V20 and PTV were the independent risk factors for occurrence of radiation pneumonitis (**Table 2**).

Discussion

Radiation pneumonitis is one of the commonest complications in esophageal cancer or chest tumors [4-6]. Elderly patients combined with COPD have poor tolerance to radioactive lung injury and repairment capacity, which not only limits radiotherapy dose, but affects tumor local controlling rate and life quality of patients.

Studies [12, 13] have different opinions on the incidence of radiation pneumonitis caused by tumor radiotherapy. The incidence of radiation pneumonitis is ranged from 8% to 30%, which happened in 6 weeks to 6 months after radiotherapy, and the 2nd to 3rd month after radiotherapy is peak of occurrence. The median occurrence time was 50 days after radiotherapy. These statistics are mostly about radiation pneumonitis with clinical grade more than stage 2. The present study found that, the incidence of radiation pneumonitis was 14.52% and the median occurrence time was 3 months after radiotherapy, which was in line with previ-

Table 2. Influence factors of radiation pneumonitis by logistic regression analysis

Factor	B	SE	Wald	P
KPS score	0.032	0.023	1.966	0.161
COPD	0.632	0.958	0.435	0.509
Concurrent chemoradiotherapy	-1.978	0.834	5.634	0.018
GTV dose	-0.155	0.051	9.308	0.002
V20	-0.422	0.104	16.418	0.000
MLD	0.109	0.138	0.629	0.428
PTV	-0.56	0.017	10.877	0.001

KSP, Karnofsky performance status; COPD, chronic obstructive pulmonary disease; GTV, gross tumor volume; MLD, mean lung dose; PTV, planning target volume.

ous studies. In above previous studies, mostly patients were conducted with common radiotherapy. In recent years, precise radiotherapy increasingly becomes major radiotherapy method. Therefore, studying radiation pneumonitis related to precise radiotherapy has important significance. Our results showed that, the precise radiotherapy can improve the local controlling rate and survival rate, but has not obviously declined the incidence of radiation pneumonitis, which was in line with the previous study [14].

The mechanism of radiation pneumonitis is related to the type II alveolar cell injury and vascular endothelial cell injury [15, 16]. Elderly patients usually suffered from many basic diseases such as COPD, and the KPS scoring is very low, which affects the tolerance to lung injury and repairment capacity. In this study, there were 25.64% patients with radiation pneumonitis, whose KPS scores were less than 70. Only 4.92% patients had KPS scores more than 70. Concurrent chemoradiotherapy can further aggravate type II alveolar cell injury and vascular endothelial cell injury, thus increasing the incidence of radiation pneumonitis. Therefore, elderly patients with esophageal cancer treated with concurrent chemoradiotherapy are more susceptible radiation pneumonitis than common radiotherapy [17, 18]. The ratio of radiation pneumonitis in this study was 20.59% in concurrent chemoradiotherapy group and 7.14% in pure radiotherapy group. However, other study [7] proved that, the concurrent chemoradiotherapy could not increase the incidence of radiation pneumonitis. The difference may be related to the age of patients, type of chemotherapeutics and sample of cases, which needs to be further verified.

The incidence of radiation pneumonitis has obvious correlation with GTV dose and PTV [19, 20]. Vogelius et al [21] reported that, both GTV dose and PTV were the important factors to affect the occurrence of radiation pneumonitis. When tumor radiation dose was more than 70 Gy, the radiotherapy could not improve the survival rate but increase the incidence of radiation pneumonitis and adverse reaction, thus affecting the life quality. In the present study, the incidence of radiation pneumonitis was 6.25% for patients with less than 60 Gy radiation dose, but 27.03% for patients with more than 60 Gy radiation dose, and this result was in line with the previous studies [12, 13]. Therefore, under the premise of not reducing the local control rate, reduction of GTV dose and PTV can decline the possibility of radiation pneumonitis for elderly esophageal cancer patients. Dose-volume histogram (DVH) is used to accurately reflect the relationship between volume and dose, and some parameters of DVH can rationally predict the adverse reactions of radiation pneumonitis. V5 and V20 are common parameters to evaluate radiation pneumonitis [22, 23]. However, Kharofa et al [24] have observed 256 consecutive patients treated with definitive radiation and find that, V5 and V20 are the predictors of radiation pneumonitis. Asakura et al [25] reported that, lung V20 not V5 had a statistical significance with the occurrence of radiation pneumonitis. The present study indicated that, the incidence of radiation pneumonitis was 6.41% when lung V20 was less than 25%. When V20 was more than 25%, the incidence of RP was 20.37%. Most importantly, there was no correlation between V5 and radiation pneumonitis. These results indicate that, controlling lung V20 value has an important significance in reducing the occurrence of radiation pneumonitis for elderly patients with esophageal cancer.

In conclusion, the concurrent chemoradiotherapy, GTV dose, lung V20 and PTV are the independent factors of radiation pneumonitis induced by precise radiotherapy for elderly patients with esophageal cancer. In clinic, these high risk factors should be sufficiently assessed according to the patient conditions combined with DVH, and the basic diseases should be treated positively. This can improve

the radiotherapy effect and reduce the incidence of radiation pneumonitis for elderly patients with esophageal cancer.

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Disclosure of conflict of interest

None.

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