A Novel Nomogram Containing Acute Radiation Esophagitis Predicting Radiation Pneumonitis in Thoracic Cancer Receiving Radiotherapy

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Abstract

Background

Radiation-induced pneumonitis (RP) is a non-negligible and sometimes life-threatening complication in patients with thoracic radiation. We initially aimed to ascertain the predict value of acute radiation-induced esophagitis (SARE, grade $\geq$ 2) to symptomatic RP (SRP, grade $\geq$ 2) among thoracic cancer patients receiving radiotherapy. Based on that, we also established a novel nomogram model to provide individualized risk assessment for SRP.

Methods

Patients with thoracic cancer who were treated with thoracic radiation from Jan 2018 to Jan 2019 in Shandong Cancer Hospital and Institute were enrolled prospectively. All patients were followed up during and after radiotherapy (RT) to observe the appearance of esophagitis and pneumonitis. Variables were analyzed by univariate and multivariate analysis using the logistic regression model, and a nomogram model was established to predict SRP by "R" version 3.6.0.

Results

A total of 123 patients were enrolled (64 esophageal cancer, 57 lung cancer and 2 mediastinal cancer) in this study prospectively. RP grades of 0, 1, 2, 3, 4 and 5 occurred in 29, 57, 31, 0, 3 and 3 patients, respectively. SRP appeared in 37 patients (30.1%). In univariate analysis, SARE was shown to be a significant predictive factor for SRP ($P < 0.001$), with the sensitivity 91.9% and the negative predictive value 93.5%. The incidence of SRP in different grades of ARE were as follows: Grade 0-1: 6.5%; Grade 2: 36.9%; Grade 3: 80.0%; Grade 4: 100%. Besides that, the dosimetric factors considering total lung mean dose, total lung V5, V20, ipsilateral lung mean dose, ipsilateral lung V5, and mean esophagus dose were correlated with SRP (all $P < 0.005$) by univariate analysis. The incidence of SRP was significantly higher in patients whose symptoms of RP appeared early. SARE (HR 34.408, $P = 0.001$), mean esophagus dose and ipsilateral mean lung dose were still significant in multivariate analysis, and they were included to build a predictive nomogram model for SRP.

Conclusions

SARE was an easy index that can reflect patients' radiosensitivity visually, which could be an applicable predictor for SRP in patients receiving thoracic radiation. And the nomogram could assist in accurate prediction to SRP in clinic.

Introduction

Radiotherapy (RT) plays a crucial role in the treatment of thoracic cancer, carrying nontrivial risks of radiation-induced lung toxicity (RILT) at the same time^[1]. The impact of lung toxicity can be associated with significant morbidity and limitation of quality of life. Radiation-induced pneumonitis (RP), the

commonest form of RILT, is a dose-limiting complication for thoracic cancer patients undergoing RT [2]. The lung has been known to be sensitive to the deleterious effects of ionizing radiation^{[1][3]}, and radiation-induced lung injury is usually irreversible. Acute radiation-induced pneumonitis often occurs within six months after finishing of RT^[1, 4], which can lead to pulmonary failure, and even become life-threatening [5, 6]. Notably, the establishment of early RP predictors is a significant work for clinicians.

The pathogenetic process leading to RP is an integrated response of the complex organization of lung tissue, which include edema, epithelial degeneration and subsequent regeneration, invasion of alveoli by bronchial epithelium, endothelial sloughing, disruption of microvasculature, and atelectasis^[2]. Radiation induced pulmonary damage can be varied and often long-lasting. Usually, it starts as an exudative inflammation, and as other chronic inflammations do, in scar formation, called lung fibrosis, which is the commonest end of radiation-induced lung damage^[3].

Previous studies have shown the importance of clinical characteristics, dosimetric parameters factors as well as laboratory indicators, such as pack-years, baseline pulmonary function, a history of lung resection, mean lung dose (MLD), total or ipsilateral lung volume receiving more than 2000 cGy (V20), total lung V10, total lung V13, ipsilateral lung V5, interleukin-8, recombinant human eotaxin-2, recombinant human eotaxin-22, recombinant human eotaxin-17 and so on^[6-13]. In addition, genetic variants of pulmonary surfactant-associated glycoprotein D, homeodomain interacting protein kinase 2 and interleukin-4 were also reported to be associated with risk of RP development^[14-16]. And the combination of chemotherapy has also been implicated in increasing chances of developing RP^[10, 17, 18].

Although numbers of predictors had been reported to be related with RP, few of them can be truly applied clinically, and there is still a lack of consensus on the reliable and intuitionistic predictors for clinicians. More so, an accurate predictive model for RP with superior clinical utility was urgently needed. We observed a novel and interesting phenomenon that patients with symptomatic radiation-induced pneumonitis (grade $\geq$ 2, SRP) often suffered severe acute radiation-induced esophagitis (grade $\geq$ 2, SARE) during RT. This study aimed at exploring the predictive value of radiation-induced esophagitis for serious radiation-induced pneumonitis, also, trying to build and validate a visually nomogram model to predict SRP by using SARE as well as other significant clinical and dosimetric parameters factors in patients who underwent thoracic RT.

Materials And Methods

Patients Cohort

Between Jan 2018 and Jan 2019, thoracic malignancies patients such as lung cancer, esophageal carcinoma and some mediastinal malignant tumors were included in this study prospectively. All patients were treated with thoracic RT with or without sequential or concurrent chemotherapy. We included those whose esophagus and lung tissues were both exposed to radiation at the same time to explore the relation between the pneumonitis and esophagitis. Therefore, most of the patients included were central

bronchogenic carcinoma and esophagus cancer with mediastinal lymph node metastasis. The type of RT was determined by both the patient and the clinician. Most of them tolerated a total dose ≥ 5000 cGy. The inclusion criteria contained: (1) Receipt of thoracic radiotherapy; (2) Karnofsky Performance Status ≥ 70 ; (3) Age ≥ 18 ; (4) Ipsilateral lung volume receiving 500 cGy (V5) $\geq 20\%$ and maximum esophagus dose ≥ 4500 cGy (in order to select patients whose esophagus and lung tissues were both exposed to radiation). The exclusion criteria included: (1) Previous history of thoracic RT; (2) Receipt of stereotactic body RT; (3) Patients with a life expectancy of less than 6 months (because they might not benefit from local radiation and might not be assessable for late lung toxicity); (4) Patients that didn't come back to our hospital to take a chest computed tomography (CT) reexamination among the 6 months after RT; (5) Patients that failed to be contacted. No restrictions were placed on either the use of cytotoxic chemotherapy or the stage of disease. We seek for appropriate patients clinically, then observe and record the time, RTOG grade and duration of esophagitis symptoms during radiotherapy. All patients were followed up every month in the first 6 months after RT until the RP occurred.

Feature Definition and Endpoints

We analyzed 31 continuous and categorical variables in this study. The continuous features were age, smoking pack-years, total radiation dose, number of radiation fractions, radiation fraction size, some indicators of lung function (forced vital capacity FVC, forced expiratory volume in the first second FEV1, peak expiratory flow PEF, etc.), and some peripheral blood indicators before RT (erythrocyte count, white blood cell count, neutrophil count and lymphocyte count). We also collected the lowest hematology index during RT (white blood cell count, neutrophil count and lymphocyte count). We obtained some dosimetric parameters from dose–volume histogram (DVH) such as total lung V5, ipsilateral lung V20, mean esophagus dose, etc. For esophageal carcinoma or mediastinal tumor, ipsilateral lung refers to the side that received more radiation dose in RT. The time that pneumonitis symptoms appear after RT were included. The categorical features were gender, smoking status, SARE, esophagitis duration time after RT, etc. All data, including clinical parameters, blood samples as well as grading of RP/ARE were collected prospectively. ARE was graded in accordance with the Radiation Therapy Oncology Group (RTOG) acute radiation injury grading criteria. The primary endpoint of this study was grade ≥ 2 RP, defined in the Common Terminology Criteria for Adverse Events version 4.0 published by the National Cancer Institute. The choice of RT method is jointly formulated by clinicians, physicists and patients, and the lung function test was determined by the individual condition of every patient. RP was diagnosed by 2 radiation oncologists or pulmonologists based on clinical symptoms and any radiographic infiltration within the radiation field during the first 12 months after radiation.

Statistics

Univariate and multivariate logistic regression analysis were performed to explore features associated with SRP. We also used the Gamma rank correlation coefficient to further confirm the relation between SARE and SRP. All statistical tests were two-tailed, with a *P* value less than 0.05 considered to be statistically significant. Receiver operating characteristic (ROC) curve analysis was used to confirm

optimal cut points for variables identified as influencing RP in this analysis. The variables were subjected to multivariate analysis only when a significant difference ($P<0.05$) was computed in the univariate analysis. Cumulative incidence of SRP was calculated from the end of RT to the date of SRP occurrence or to the date of last follow-up, patients lost to follow-up were censored. All statistical analyses were performed using the SPSS version 25.0. And the nomogram model was established by the package of rms in "R" version 3.6.0.

Results

Patients characteristics

From Jan 2018 to Jan 2019, a total of 123 thoracic tumor patients received thoracic RT were included prospectively in this study, which contained 57 (46.3%) lung cancer patients, 64 (52.0%) esophageal cancer patients and 2 (1.6%) mediastinal malignant fibrous adenoma patients. The median age was 64 (range 25~81) years old, and 94 (76.4%) patients were male. Most patients (103, 83.7%) received intensity-modulated radiation therapy (IMRT) in the study, 15 (12.2%) patients received 3D-conformal RT (3D-CRT), and 5 (4.1%) patients received tomotherapy (TOMO). The median dose of RT was 6000 cGy, range 4100 cGy to 6600 cGy. ARE appeared in this cohort were as follows: Grade 0~1 in 46 (37.4%) patients, Grade 2~5 in 77 (62.6%) patients. At the end of the follow up (July 6, 2019), 37 patients suffered SRP, 3 of them (8.1%) died of RT-related respiratory failure. And among those patients, 34 (91.9%) patients developed SARE. Details of the study and patient characteristics are shown in Table 1. And the incidence of SRP in different grades of ARE were explained in Figure 1.

Univariate analysis

In univariate logistic regression analysis, SARE were proved to be strongly correlated with SRP (HR 11.333, 95%CI 3.235-39.710, $P<0.001$). Furthermore, we explored the correlation between SARE with SRP by using the Gamma rank correlation coefficient (0.838, $P<0.001$). The sensitivity, specificity, positive predictive value and negative predictive value of SARE to predict SRP were 91.9%, 50.0%, 44.2% and 93.5%, respectively. The false negative rate was 8.1%. The dosimetric factors considered total lung MLD (TL-MLD, HR 11.333 $P<0.001$), ipsilateral lung MLD (IL-MLD, HR 3.956, $P=0.018$), total Lung V5 (TL-V5, HR 1.034, $P=0.035$), V20 (TL-V20, HR 1.063, $P=0.035$), ipsilateral lung V5 (IL-V5, HR 2.517, $P=0.034$), mean esophageal dose (MED, HR 1.000, $P=0.012$) correlated with SRP. Among these results, mean ipsilateral lung dose and ipsilateral lung V5 were nonsignificant when they expressed as continuous factors, then we used ROC analysis to determine the best cutoff points for mean ipsilateral lung dose (1186.78 cGy) and ipsilateral lung V5 (55.65%). The areas under the curve (AUC) were 0.583 and 0.589, respectively. And then, we found that when patients performed as mean ipsilateral lung dose ≥ 1186.78 cGy and ipsilateral lung V5 $\geq 55.65\%$, they might suffer a higher risk of RP. Besides that, the time that RP appeared after RT were also associated with the SRP (HR 0.986, $P=0.001$). No significant correlations were found for the peripheral blood information or lung function index. Table 2 summarizes these results. And the ROC curves illustrate the predictive value of SARE and other factors (Figure 2).

Multivariate analysis

All above significant factors were included in the multivariate logistic regression analysis to find the most meaningful early predictors for SRP. And the multivariable logistic prediction model included three clinical variables (mean esophagus dose, mean ipsilateral lung dose and SARE), as shown in Table 3. SARE was shown to be the best independent risk predictor for development of SRP (HR 34.470, 95%CI 3.638-77.230, $P<0.001$).

Nomogram model for SRP

Then, a visually predictive nomogram shown in Figure 3 was formulated based on the results of multivariate logistic regression analysis. Figure 4 demonstrates the area under the curve (AUC=0.827, $P<0.001$) of the data, and the predictive ability was estimated by AUC of ROC graphs. The ROC curve provides a visual representation of the sensitivity and specificity of measured parameters relative to RP risk. Bootstraps with 1,000 resample were used for the validation of nomogram and calibration curve construction, and we can see a great match of the actual probability with the predicted probability in Figure 5.

Discussion

To the best of our knowledge, our study indicated SARE as a significant predictor of $\geq$ grade 2 RP for the first time. SARE shown to be an independent predictor for SRP. As we all know, both the radiation-induced pneumonitis and radiation-induced esophagitis were typical adverse events in individuals receiving radiation. And it could not be hard for an experienced radiation oncologist to estimate the severity of radiation-induced esophagitis by the patient's symptoms and physical signs during RT. We observed possible relation between these two kinds of inflammations from the clinical observation and then designed this real-world study to explore the predictive value of SARE to SRP. Before us, numbers of studies have explored numerous predictive factors for RP following local RT. Based on these results, we collected some of the clinical, laboratory and dosimetric parameters factors that we can obtain as much as possible. We established an original nomogram model of symptomatic RP. And this study concluded that SARE can function as an easy and earlier signal for SRP in future's clinical work.

The high incidence of SRP was estimated to be in the range of 15~40% among patients with thoracic RT by previous studies^[19], which was consistent with 30.8% in this study. The mortality associated with RP was estimated to be less than 2%^[20], and the risk of this study was 1.6%. Although the mortality of RP was not extremely high, it did influence tumor patients' quality of life and led to poor prognosis^[21, 22]. And some more severe infection may accrue because of the increase of the lung's susceptibility. There was a 64-year-old patient with esophageal cancer in this study who died of RP related pulmonary infection. After only 10 fractions of RT, this old man suffered intractable grade 4 SARE with diffuse esophagus mucosal erosion, ulceration, and hemorrhage (Figure 6A). And this discomfort continued for the subsequent treatment even after RT. Then the pneumonitis symptoms appeared about 4 days after RT.

And unfortunately, the man got infected of pneumocystis carinii during the following treatment for RP (Figure 6B~D). It's worth noting that RP can not only reduce lung tolerance but increase the chance of severe pulmonary infection, so early finding of RP is necessary. If we can realize the strong connection between SARE and SP, the radiation oncologists can modify the radiotherapy plan in time and avoid the subsequent tragedy.

In our study, we set both the esophagus and lung dose limits in the enrollment criteria to ensure that the lung and esophagus tissue of the patients do suffer a certain amount of radiation. In another word, these patients are likely to suffer from the two types of inflammation. Our results demonstrated that grade ≥ 2 radiation-induced esophagitis was significantly associated with SRP. This acute esophagus toxicity is the response to esophageal mucosa irradiation, patients often develop dysphagia and odynophagia, which may lead to appetite loss and weight loss^[23, 24]. ARE usually appears at 2 to 4 weeks of the treatment, some even early in the first two weeks. In addition to affecting quality of life, SARE can necessitate treatment break, which is associated with inferior survival results^[25, 26]. Usually, ARE acts as a kind of self-limited complication. There is no specific cure for it, but symptoms can regress 2 to 4 weeks after the completion of RT^[26]. Compared with previously reported laboratory or dosimetric predictors for RP, SARE has its unique advantages. Our results show the SARE is associated with two dosimetric indicators about esophagus, they are esophagus volume receiving more than 3000 cGy (V30) and maximum esophagus dose. The two indicators show a small connection with SARE (HR: 1.000 and 1.010) and they don't influence the SRP. It can reflect the sensitivity of individual's normal tissue to the radiation directly. For those patients with a radiation field that contains both the lungs and esophagus, if the patient develops SARE earlier, he/she should be vigilant of the possibility of RP. The patient should pay more attention to keep warm after RT to avoid catching cold and return to hospital in time for chest CT reexamination. If the patient suffers intolerable SARE during RT, the clinician should take timely chest CT to determine the patient's lung condition and change the patient's treatment plan if necessary.

Numerous dosimetric indicators of the lung have been widely verified in previous studies for RP, such as total or ipsilateral lung V5, V10, V13, V20^[6-14]. Furthermore, the dosimetric indicators about esophagus, which may have not been previously well established as predictors, were also considered in this study. And we also set enrollment limits on IL- V5 and MED to reduce the bias of individual dose difference among the lung and esophagus, in order to avoid their affection on RP. We collected the esophagus mean and esophagus V30, and esophagus mean made sense both in the univariate analysis and multivariate analysis. We admitted it as a significant predictor of SRP, but that didn't mean it was the cause of RP. It served as an indirect indicator that could reflect the distribution and volume of pulmonary disease surrounding the esophagus, which eventually would be reflected in the pulmonary dosimetric outcomes. And previous study had already found that esophagus dosimetric indices were positively correlated with lung dosimetric indices^[7].

There are several possible reasons that may explain the predictive value of SARE to SRP. First of all, SARE can reflect the high esophageal radiation dose^[26, 27], which may further implicates the increase of

radiation dose in the surrounding lung tissue. Secondly, the esophagus and lung are both radiosensitive organs, and the early occurrence of SARE may further indicate the high radiosensitivity of the body tissue. More than this, Previous studies have confirmed multiple inflammatory cytokines were closely related to SARE as well as SRP^[10, 26, 28, 29], so it may be a signal of activation of the systemic inflammatory system. And we look forward to more basic experiments to better explain this relationship.

Although we obtained a considerable result from 123 patients, it is far away to get a convincing conclusion. The main limitations of the study are the relatively low number of patients and some indexes tested. More so, we validated the nomogram internally by Bootstraps with 1,000 resample instead of an external database. In addition, some more fundamental research toward the common nature of these two inflammations is needed to finally prove it.

Conclusion

This study shows the predictive value of SARE to SRP, especially for central bronchogenic carcinoma patients and esophageal cancer patients with a huge irradiation volume. Additionally, further clinical studies leveraging these relation are warranted. Our nomogram model will provide an opportunity to guide clinicians for personalized radiation dose prescription in clinical practice and improve long-term survival by decreasing the risk of severe radiation-induced pneumonitis.

Abbreviations

radiotherapy (RT)

radiation-induced lung toxicity (RILT)

radiation-induced pneumonitis (RP)

mean lung dose (MLD)

volume receiving more than 2000 cGy (V20)

symptomatic radiation-induced pneumonitis (SRP)

severe acute radiation-induced esophagitis (SARE)

forced vital capacity (FVC)

forced expiratory volume in the first second (FEV1)

peak expiratory flow (PEF)

dose–volume histogram (DVH)

Radiation Therapy Oncology Group (RTOG)

receiver operating characteristic (ROC)

intensity-modulated radiation therapy (IMRT)

tomotherapy (TOMO)

3D-conformal RT (3D-CRT)

ipsilateral lung(IL)

total lung(TL)

mean esophageal dose (MED)

areas under the curve (AUC)

computed tomography (CT)

Declarations

Ethical Approval and Consent to participate: This study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute, and written informed consents were obtained from all included individuals.

Consent for publication: Manuscript is approved by all authors for publication.

Availability of data and materials: The datasets used 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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The funders had role in the study design, data collection, article review and editing.

Authors' contributions:

- Writing - original draft: WJT
- Writing - review and editing: JMY, NFL and PX

- Conceptualization: PX, XLL, HNY
- Data collection: WJT, XYY, BZ, TTZ, JLC
- Project administration: XDS, JMY, PX

All authors have read and approved the manuscript.

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Tables

Table 1. Patient characteristics (N=123)

Variables	Cohort, No. (%)
Median age	64.22 (range 25~81)
Gender	
Male	94(76.40)
Female	29(23.60)
Smoking status	
No smoking	52(42.30)
Current	31(25.20)
Former	40(32.50)
Tumor type	
Lung cancer	57(46.30)
Esophageal cancer	64(52.00)
Mediastinal malignant fibrous adenoma	2 (1.60)
RT modality	
IMRT	103(83.74)
3D-CRT	15(12.20)
TOMO	5 (4.06)
Total prescribed dose (cGy)	
≥ 6000	64(52.03)
5000~6000	24(19.51)
≤ 5000	35(28.46)
ARE	
Grade 0-1	46(37.40)
Grade 2-5	77(62.60)
RP	
Grade 0-1	86(69.90)
Grade 2-5	37(30.10)

Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT: 3D-conformal radiotherapy; TOMO: tomotherapy; ARE: acute radiation-induced esophagitis; RP: radiation-induced pneumonitis.

Table 2. Univariate Logistic Regression Analysis Results

Variables	HR	P-value	95% CI	AUC
SARE	11.333	0.000	3.235-39.710	0.736
TL-MLD	1.001	0.024	1.000-1.002	0.615
TL-V5	1.034	0.035	1.002-1.067	0.586
TL-V20	1.063	0.035	1.004-1.124	0.590
IL-MLD (>1186.78 cGy)	3.956	0.018	1.270-12.317	0.610
IL-V5 (>55.65%)	2.517	0.034	1.073-5.905	0.595
MED	1.000	0.012	1.000-1.001	0.641
Time	0.986	0.001	0.978-0.994	0.156

Abbreviations: HR, hazard ratio; CI, confidence interval; SARE: severe acute radiation-induced esophagitis; MLD: mean lung dose; TL: total lung; IL: ipsilateral lung; MED: mean esophagus dose; Time: the time that pneumonia symptoms appear.; AUC: areas under the curve.

Table 3. Multivariate Logistic Regression Analysis Results

Variables	HR	P-value	95% CI
SARE	34.470	0.000	3.638-77.230
MED	1.000	0.044	1.000-1.001
IL-MLD (>1186.78 cGy)	4.716	0.048	1.013-12.495

Abbreviations: HR, hazard ratio; CI, confidence interval; SARE: severe acute radiation-induced esophagitis; MLD: mean lung dose; IL: ipsilateral lung; MED: mean esophagus dose;

Figures

Figure 1

Incidence of SRP in different grades of ARE population. Abbreviations: ARE: acute radiation-induced esophagitis; SRP: severe radiation-induced pneumonitis.

Figure 1

Incidence of SRP in different grades of ARE population. Abbreviations: ARE: acute radiation-induced esophagitis; SRP: severe radiation-induced pneumonitis.

Figure 2

Receiver operating characteristic (ROC) curves illustrating the relative predict power of these factors. And SARE seems to be a better predictor for symptomatic radiation-induced pneumonitis (SRP) with areas under the curve (AUC) values of 0.778, $P < 0.001$. Besides that, MED, $AUC = 0.614$ $P = 0.019$; IL-MLD: $AUC = 0.610$ $P = 0.067$; TIME, $AUC = 0.844$ $P < 0.001$. Abbreviations: SARE: severe acute radiation-induced esophagitis; TLMLD: total mean lung dose; ILMLD: ipsilateral mean lung dose; MED: mean esophagus dose; Time: the time that pneumonia symptoms appear.

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Nomogram for the prediction of SRP, based on multivariable model. Instructions: To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the axes to determine the likelihood of SRP. Abbreviations: ARE: acute radiation-induced esophagitis; MED: mean esophagus dose; ILMLD: mean ipsilateral lung dose; SRP: severe radiation-induced pneumonia.

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ROC curve of the nomogram model for SRP: the area under the curve is 0.827 (95% CI: 0.746-0.908, $P < 0.001$).

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Figure 5

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Figure 6

This 64-year-old esophageal cancer patient suffered grade 4 severe acute radiation-induced esophagitis (SARE) after only 10 fractions of radiotherapy. And he developed symptomatic radiation-induced pneumonitis (SRP) only 4 days after radiotherapy (RT) and then got infected of pneumocystis carinii during RT treatment. A: Endoscopy reveals diffuse mucosal erosion, sloughing, ulceration, and hemorrhage, and the endoscopic secretion culture revealed the fungal infection. B: Computed tomography (CT) image before radiotherapy; C: CT image that 6 days after radiotherapy; D: CT image that got infected of pneumocystis carinii during RP treatment.

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