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Analysis of Factors Related to Radiation Pneumonitis after Radiotherapy for Thoracic Segment Esophageal Cancer

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Abstract

Background: Multimodality therapy for esophageal cancer (EC) can cause a variety of treatment-related sequelae, especially pulmonary toxicities. The accurate prediction of radiation pneumonitis (RP) is essential to facilitate individualized radiation dosing that leads to maximized therapeutic gain. In this study, we performed a retrospective analysis to determine important factors that predict RP after radiotherapy (RT) for thoracic segment EC.

Methods: Data were retrospectively collected from two hundred and forty-seven patients with locally advanced EC who received RT or chemoradiotherapy (CRT). Clinical factors and dose-volume parameters were analyzed for their association with risk of RP. RP was graded according to Common Terminology Criteria for Adverse Events, version 3.0, with time to RP calculated from start of RT. All patient details have been de-identified.

Results: There were 118 cases of RP in 247 cases of EC patients who underwent RT or CRT. Among them, there were 54 cases of symptomatic pneumonitis (≥ 2 grade). The overall rate of symptomatic pneumonitis was 21.9%. In terms of RT techniques, there was no significant difference in the incidence of RP among three-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), and tomography (TOMO) ($P > 0.05$). V_5 - V_{40} and MLD were associated with all grades of RP ($P < 0.05$). Target volume, lung volume and their ratio were correlated with the incidence of RP ($P < 0.05$). Among clinical factors, the highest risk of RP (≥ 3 grade) was in patients > 400 of smoking index (SI: number of cigarettes smoked per day $\times$ years of smoking). Chronic obstructive pulmonary disease (COPD) is also related to the occurrence of RP (≥ 1 grade). In addition, V_5 and V_{40} were an independent risk factor for RP grade ≥ 1 (AUC 55.74%, 4.13%). MLD was an independent risk factor for RP grade ≥ 2 (AUC 11.91 Gy). V_5 was an independent risk factor for RP grade ≥ 3 (AUC 57.60%).

Conclusions: There was no significant difference in the incidence of RP regardless of radiation therapy technique (3D-CRT, IMRT, and TOMO) and treatment-related factors. SI and COPD are closely related to the occurrence of the corresponding grades of RP. Several lung dosimetric parameters (V_5 , V_{40} , MLD) may be the most effective predictive factor of RP. Due to the high correlation between the relative volume of lungs exposed to different dose thresholds. Therefore, we recommend evaluating the comprehensive parameters of DVH instead of individual dose volume limitations.

Keywords Esophageal cancer; Radiation therapy; Radiotherapy technology; Radiation pneumonia; Risk factor

Introduction

Esophageal cancer (EC) is the ninth most common cancer and the sixth leading cause of cancer deaths worldwide^[1]. Currently, radiotherapy (RT) is still the main treatment for locally advanced EC. It is an essential part of neoadjuvant chemoradiotherapy for operable locally advanced EC or radical chemoradiotherapy for inoperable EC^[2]. Radiation pneumonitis (RP) is one of the significant complications of thoracic RT, so it is one of the important considerations in radiation treatment planning^[3]. Although the clinical features are similar and the radiation dose is the same, the risk of RP in patients is different^[4]. However, dosimetric parameters and clinical features are still commonly used in RP prediction^[5]. Numerous studies^[6-8] have investigated predictive factors for RP and identified clinical factors that may influence risk, including performance status, pulmonary function before RT, tumor location, concurrent chemotherapy, total radiation dose, dose per fraction. In addition, many studies have shown that dosimetric factors from the lung dose–volume histogram (DVH), such as the mean lung dose (MLD)^[9-13] and the percent lung volume receiving more than a threshold radiation dose (V_{Dose})^[9-11,14-15], are important in predicting RP risk. The improvement of RT technology not only improves the local control rate of the tumor but also changes the lung dose distribution^[16-17]. At present, the mainstream RT technology for EC is image-guided precise therapy, including three dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), and tomography (TOMO). Under the same or similar dose and fractionation, it is necessary to explore the relationship between the difference of lung irradiated volume caused by different radiation techniques and different grades of RP. A previous report^[18] evaluated the risk of grade ≥ 3 RP in patients with inoperable NSCLC who received 3D-CRT or IMRT concurrently with platinum-based chemotherapy at The University of Texas M.D. Anderson Cancer Center (UTMDACC). None of the clinical factors investigated were found to be associated with the risk of RP. However, numerous dosimetric factors, including

MLD and V_5 – V_{65} , were significantly associated with the incidence of severe RP. Although there has been a lot of research on RP, it has not yet been systematized. This includes a lack of comprehensive consideration of factors related to RP occurrence, such as failure to consider lung function status, severity of smoking, and the proportion of high dose and low dose volumes of lung exposure to radiation caused by differences in RT techniques. In addition, previous studies have focused on RP for lung cancer, rather than EC. To address these doubts, we conducted a new study. In this study, retrospective analysis was used to summarize the clinical data of 247 EC patients who underwent precise RT to determine and predict the factors related to RP. To our knowledge, this is a significant study, to date, of RP risk among patients with EC receiving RT. Using this large cohort, we have identified a series of factors related to the risk of RP and provide a basis for optimized RT and treatment for EC patients.

Materials and Methods

Patients

This is a retrospective single institutional study. The study was conducted in accordance with the ethical standards of Declaration of Helsinki and was approved by the institutional research ethics board of Shandong Cancer Hospital and Institute (SDTH EC201703014). A waiver of patient consent was granted because the research involved no more than minimal risk to the participants and the waiver will not adversely affect the rights and welfare of the participants. The study identified 247 thoracic segment EC patients who were diagnosed by endoscopic pathology from June 2019 to June 2022. The inclusion criteria were as follows: (1) no previous history of thoracic RT, (2) Karnofsky performance score (KPS) ≥ 70 , (3) all the patients receive radical RT, (4) availability of dosimetric parameters and clinical features, and (5) complete follow-up data and continuous follow-up time $\geq$ ten months. The exclusion criteria were as follows: (1) history of surgical resection of EC; (2) general pulmonary infection unrelated to RT; (3) treatment break of more than seven days during RT; and (4) incomplete radiotherapy follow-up data. There were 195 ma

les (78.9%) and 52 females (21.1%) with an average age of 64 years (range 41-87 years). Pathological features: 237 cases (96.0%) of squamous cell carcinoma, 6 cases (2.4%) of adenocarcinoma, and 4 cases (1.6%) of small cell carcinoma. Clinical stage (II: 34 cases, 13.8%; III: 130 cases, 52.6%, IV: 83 cases, 33.6%). Patients underwent 3DCRT (n = 21; 8.5%), IMRT (n=161; 65.2%), and TOMO (n = 65; 26.3%).

Basic requirements of RT

The target design is based on simulated localization in contrast-enhanced CT for diagnostic examination results, such as endoscopic ultrasonography and positron emission tomography (PET). The target area includes gross tumor volume (GTV), CT imaging visible esophageal tumour and positive lymph nodes. The clinical target volume (CTV) is the upper and lower outward expansion of the esophageal tumor and related lymphatic drainage area. The planned target volume (PTV) has an outward expansion of the CTV of 6-8 mm. In addition, there is no standard for target delineation for the volume range of CTV/PTV, since we consider the patient's physical condition (KPS, age), N stage (how many lymph nodes metastases), and other factors. We have given two different irradiation methods, namely, elective node irradiation (ENI) and involved-field irradiation (IFI), resulting in different CTV/PTV sizes.

IMRT adopts a fixed field static intensity modulation technique, and 5-7 fields of coplanar irradiation fields are uniformly divided according to the specific situation of the case. The required target parameters are then set, and the dose distribution is obtained by inverse calculation of the treatment planning system. The dose distribution was then graded (stratified), and each field was decomposed into a series of subfields. IMRT does not include simplified intensity-modulated radiotherapy (sIMRT) or volumetric intensity-modulated arc therapy (VMAT). TOMO adopts the spiral TOMO intensity modulation technique, and each spiral contains 51 beams. 3DCRT and IMRT plans were generated in the Eclipse system (Varian Medical Systems, Palo Alto, CA, Version 13.5.35), and TOMO plans were generated in the TomoTherapy® Planning Station (Accuray, Sunnyvale, CA, Hi-Art, Version 5.1.3). 3DCRT and IMRT were administered by a Varian Linac Accelerator with 6-MV X-ray and 95% PTV and radiation doses of 50-66 Gy

(median dose of 60 Gy) and 1.8-2.0 Gy/fraction, five times a week were prescribed. Normal tissue constraints were prioritized in the following order for treatment planning purposes: maximum spinal cord dose of 45 Gy, relative volume of total lung treated with ≥ 5 Gy (V_5) $\leq 60\%$, relative volume of total lung treated with ≥ 20 Gy (V_{20}) $\leq 28\%$, mean lung dose (MLD) ≤ 20 Gy, relative volume of the heart treated with ≥ 30 Gy (V_{30}) $\leq 40\%$, and relative volume of the heart treated with ≥ 40 Gy (V_{40}) $\leq 30\%$.

Chemotherapy regimens

Most patients separately received induction, concurrent, or sequential chemotherapy based on an individualized treatment strategy. The chemotherapy regimens included cisplatin with fluorouracil (PF regimen) and cisplatin with paclitaxel (TP regimen). In all patients, 42 patients (17.0%) did not receive chemotherapy, 97 patients (39.3%) received induction chemotherapy, 21 patients (8.5%) received induction and concurrent chemoradiotherapy, 62 patients (25.1%) received concurrent chemoradiotherapy, and 25 patients (10.1%) received consolidation chemotherapy after RT. The median number of chemotherapy cycles was 4 (range, 2~6 cycles). The doses and adjustments of chemotherapy regimens followed the guidelines of the National Comprehensive Cancer Network (NCCN) for EC.

Staging criteria and segments

(1) EC staging criteria: The American Joint Commission on Cancer (AJCC) TNM Staging System (8th Edition); (2) segments: The distance between the upper incisor and the epicenter of the tumor is used to indicate the specific position. Upper thoracic esophagus: from the thoracic entrance to the lower edge of the azygos vein arch, endoscopic examination 20-25 cm away from the incisor. Middle thoracic esophagus: from the lower edge of the azygos vein arch to the level of the inferior pulmonary vein, endoscopic examination is 25-30 cm away from the incisor. Lower thoracic esophagus: from the level of the lower pulmonary vein down to the gastroesophageal junction, endoscopy 30-35 cm away from the incisor.

Observation index

The observation index includes sex, age, tumor stage, SI, COPD, chemotherapy regimen, and dosimetric parameters. The dose parameters included total radiation dose, lung volume, target

volume, MLD, and the relative volume of the total lung treated with $\geq 5\sim 40$ Gy ($V_5\sim V_{40}$).

Follow-up and Evaluation of RP

The follow-up items included chest CT, physical examination and the clinical symptoms. Patients were evaluated weekly during RT, followed up at one month after completion of the initial treatment and then were followed up every 2-3 months, at least until half a year after the end of RT. The diagnosis and classification of RP were confirmed by two senior radiologists (professional years ≥ 5 years) and one radiologist. In addition, while some patients may have varying degrees of RP at different points in time, the RP grade we provide is when patients have the most severe RP during follow-up. The RP was graded by the Common Terminology Criteria for Adverse Events, version 4.0.3 (CTCAE 4.0.3). The diagnostic criteria for RP were as follows: Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated; Grade 2: Symptomatic; medical intervention indicated; limiting instrumental activities of daily living (ADL); Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: Life-threatening respiratory compromise; urgent intervention indicated; and Grade 5: Death.

Statistical Analysis

All data were analysed using the statistical package for the Social Science program (SPSS for Windows, version 17.0, IBM, Armonk, NY, USA). The quantitative data were compared by ANOVA, and the count data were compared by χ^2 tests or Fisher's exact probability test. Univariate analysis was conducted for all the influencing factors involved in this study. Multivariate analysis was performed for those with $P < 0.05$ after univariate analysis. The results of the multivariate analysis were all independent risk factors. Logistic regression analysis was used to analyse independent risk factors. The optimal cut-off values of parameters were calculated using receiver operating characteristic (ROC) curves. A value of two-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics and incidence of RP in different grades

The characteristics of the 247 patients included in this study are listed in Table 1. The follow-up time of all patients was more than six months; the median follow-up time was 10 months. Among them, 64 cases were grade 1 RP (25.9%), 37 cases were grade 2 RP (14.9%), 12 cases were grade 3 RP (4.9%), 5 cases were grade 4 RP (0.2%), and no cases were grade 5 RP (0.0%). Fifty-four patients with RP grade ≥ 2 were treated with oxygen therapy or $\pm$ antibiotics or glucocorticoid (dexamethasone or methylprednisolone). Among them, 50 patients were improved or cured, and two patients were complicated with pulmonary insufficiency and severe pulmonary fibrosis, requiring long-term oxygen therapy. Three patients (one case with grade 2 and two cases grade ≥ 3) died of respiratory failure due to severe infection and respiratory distress syndrome. There was no significant correlation in the risk of RP (grade ≥ 1 , ≥ 2 , ≥ 3) between patient factors (sex, age, tumor stage, tumor location, diabetes, hypertension) and treatment factors (chemotherapy or lack thereof, chemotherapy mode or regimens, delivered RT dose, induction chemotherapy cycle). More importantly, there was no significant difference in the incidence of RP between 3DCRT, IMRT and TOMO (RP grade ≥ 1 (47.6% vs 50.3% vs 41.5%), grade ≥ 2 (33.3% vs 22.4% vs 16.9%), and grade ≥ 3 (9.5% vs 7.5% vs 4.6%)). Although there was no significant difference in the incidence of RP $\geq$ grade 1 and $\geq$ grade 2 between nonsmokers and smokers, the incidence of RP $\geq$ grade 3 in smokers with SI > 400 was significantly higher ($P = 0.001$). In addition, COPD was significantly correlated with RP $\geq$ grade 1 ($P = 0.003$), as shown in Table 1. Multivariate analysis showed that SI > 400 was an independent risk factor for RP $\geq$ grade 3 (Wald= 5.964, $P < 0.05$), and COPD was an independent risk factor for RP $\geq$ grade 1 (Wald= 6.110, $P < 0.05$), as shown in Table 3.

Table 1 Clinical characteristics and treatment model of RP patients of different grades

Characteristics	n	≥ 1 grade [n, (%)]	χ^2 value	P- value	≥ 2 grade [n, (%)]	χ^2 value	P- value	≥ 3 grade [n, (%)]	χ^2 value	P- value
Sex										

Male	195	91(46.7)	0.455	0.534	37(19.0)	4.522	0.039	12(6.2)	0.764	0.382
Female	52	27(51.9)			17(32.7)			5(9.6)		
Age (years)										
<60	78	41(52.6)	1.049	0.339	19(24.4)	0.416	0.513	10(12.8)	6.272	0.027
≥60	169	77(45.6)			35(20.7)			7 (4.1)		
Smoking index										
0	137	68(49.6)	2.676	0.262	29(21.1)	5.976	0.050	6(4.4)	13.295	0.001
100 ~ 400	39	14(35.9)			4(10.3)			0(0)		
>400	71	36(50.7)			21(29.6)			11(15.5)		
Tumor stage										
II	34	14(41.1)	1.175	0.556	9(26.5)	1.184	0.553	1(2.9)	2.665	0.264
III	130	61(46.9)			25(19.2)			12(9.2)		
IV	83	43(51.8)			20(24.1)			4(4.8)		
Tumor location										
Upper	44	20(45.5)	0.709	0.702	9(20.5)	4.787	0.091	3(6.8)	1.051	0.591
Middle	152	71(46.7)			39(25.7)			12(7.9)		
Lower	51	27(52.9)			6(11.7)			2(3.9)		
COPD										
No	212	93(43.9)	9.146	0.003	42(19.8)	3.684	0.075	14(6.6)	0.181	0.671
Yes	35	25(71.4)			12(34.3)			3(8.6)		
Diabetes										
No	217	103(47.5)	0.068	0.847	47(21.7)	0.043	0.816	15(6.9)	0.002	0.960
Yes	30	15(50.0)			7(23.3)			2(6.6)		
Hypertension										
No	202	99(49.0)	0.680	0.510	45(22.3)	0.112	0.843	14(6.9)	0.004	0.950
Yes	45	19(42.2)			9(20.0)			3(6.6)		
RTT										
3DCRT	21	10(47.6)	1.434	0.488	7(33.3)	2.469	0.291	2(9.5)	0.871	0.647
IMRT	161	81(50.3)			36(22.3)			12(7.5)		
TOMO	65	27(41.5)			11(16.9)			3(4.6)		
Delivered dose (Gy)										
<60	74	30(40.5)	2.215	0.165	14(18.9)	0.536	0.506	2(2.7)	2.880	0.105
≥60	173	88(50.9)			40(23.1)			15(8.7)		
Chemotherapy mode										
No	42	20(47.6)	3.672	0.452	12(28.6)	4.928	0.295	2(4.7)	4.793	0.309
Induce	97	51(52.6)			25(25.8)			7(7.2)		
Concurrent	62	30(48.4)			11(17.7)			6(9.7)		
Induce +Concurrent	21	9(42.9)			3(14.3)			2(9.5)		
Adjuvant	25	8(32.0)			3(12.0)			0(0.0)		
Chemotherapy regimen										
No	42	20(47.6)	2.054	0.358	12(28.6)	3.388	0.184	2(4.8)	4.437	0.109
TP	132	68(51.5)			31(23.5)			13(9.8)		
PF	73	30(41.1)			11(15.1)			2(2.7)		
ICC(NO.)										

0 ~ 3	203	93(45.8)	1.755	0.244	40(19.7)	3.106	0.106	14(6.9)	0.000	0.985
≥3	44	25(56.8)			14(31.8)			3(6.8)		

3DCRT=three-dimensional conformal radiotherapy; IMRT=intensity-modulated radiotherapy; TOMO=helical tomotherapy; RTT= radiotherapy

Correlation between dose-volume parameters and the incidence of RP in different grades

In the whole group, the mean (standard deviation) doses of V_5 were 54.78 ± 12.58 (%), V_{10} was 36.98 ± 9.91 (%), V_{15} was 28.04 ± 7.29 (%), V_{20} was 20.44 ± 5.62 (%), V_{30} was 10.75 ± 4.58 (%), V_{40} was 4.77 ± 3.03 (%), and the mean MLD dose was 11.21 ± 3.06 (Gy). The mean lung volume was 3447.7 ± 917.8 (cm^3), GTV was 144.42 ± 116.38 (cm^3), and PTV was 400.93 ± 216.26 (cm^3). Both

$V_5 \sim V_{40}$ and MLD were associated with the occurrence of RP $\geq$ grade 1, $\geq$ grade 2, and $\geq$ grade 3 ($P < 0.05$). Moreover, GTV, PTV, GTV/total lung volume, and PTV/total lung volume were all associated with RP $\geq$ grade 1 and $\geq$ grade 2 ($P < 0.05$), while total lung volume (cm^3) was not related to the occurrence of RP at any level ($P > 0.05$), as shown in Table 2. Multivariate analysis showed that V_5 and V_{40} were independent risk factors for RP $\geq$ grade 1 ($P < 0.05$); MLD and V_5 were independent risk factors for RP $\geq$ grade 2 and $\geq$ grade 3 ($P < 0.05$), respectively, as shown in Table 3.

Table 2 Irradiation dose -volume parameters of patients with different grades of RP ($\bar{X} \pm S$)

Parameter	All (n=247)	≥ 1 grade RP		P-value	≥ 2 grade RP		P-value	≥ 3 grade RP		P-value
		No (n=129)	Yes (n=118)		No (n=193)	Yes (n=54)		No (n=230)	Yes (n=17)	
V_5	54.78 ± 12.58	50.39 ± 10.97	59.57 ± 12.51	0.000	52.40 ± 12.03	63.25 ± 10.79	0.000	54.05 ± 12.43	64.62 ± 10.49	0.001
V_{10}	36.98 ± 9.91	33.87 ± 8.68	40.38 ± 10.08	0.000	35.27 ± 9.36	43.12 ± 9.45	0.000	36.43 ± 9.85	44.42 ± 7.59	0.001
V_{15}	28.04 ± 7.29	25.68 ± 6.64	30.62 ± 7.11	0.000	26.77 ± 6.97	32.59 ± 6.60	0.000	27.68 ± 7.31	32.91 ± 4.97	0.004
V_{20}	20.44 ± 5.62	18.54 ± 5.13	22.52 ± 5.41	0.000	19.36 ± 5.32	24.30 ± 4.98	0.000	20.19 ± 5.61	23.79 ± 4.74	0.011
V_{30}	10.75 ± 4.58	9.43 ± 4.18	12.20 ± 4.58	0.000	9.89 ± 4.32	13.82 ± 4.18	0.000	10.53 ± 4.54	13.69 ± 4.32	0.007
V_{40}	4.77 ± 3.03	3.79 ± 2.26	5.85 ± 3.39	0.000	4.13 ± 2.50	7.07 ± 3.61	0.000	4.57 ± 2.88	7.52 ± 3.67	0.001
MLD(Gy)	11.21 ± 3.06	10.18 ± 2.59	12.33 ± 3.15	0.000	10.54 ± 2.79	13.59 ± 2.80	0.000	11.05 ± 3.03	13.38 ± 2.65	0.002
TLV(cm^3)	3447.7 ± 917.82	3512.4 ± 916.16	3377.0 ± 918.20	0.248	3486.0 ± 871.51	3310.8 ± 1064.91	0.263	3472.9 ± 923.05	3107.4 ± 790.60	0.113
GTV(cm^3)	144.42 ± 116.38	123.89 ± 85.71	166.85 ± 139.53	0.041	132.97 ± 100.86	185.34 ± 154.37	0.029	140.19 ± 107.29	201.63 ± 199.38	0.421
PTV(cm^3)	400.93 ± 216.26	357.09 ± 190.55	448.86 ± 232.75	0.001	375.50 ± 196.29	491.81 ± 258.31	0.002	393.20 ± 203.51	505.55 ± 337.34	0.275
GTV/TLV	0.05 ± 0.05	0.04 ± 0.03	0.06 ± 0.07	0.020	0.04 ± 0.05	0.06 ± 0.06	0.012	0.05 ± 0.05	0.07 ± 0.08	0.159
PTV/TLV	0.13 ± 0.09	0.11 ± 0.08	0.04 ± 0.10	0.001	0.12 ± 0.08	0.17 ± 0.11	0.001	0.13 ± 0.08	0.17 ± 0.13	0.175

MLD = mean lung dose, V_5 , V_{10} , V_{15} , V_{20} , V_{30} , V_{40} = relative volume of total lung treated with $\geq 5, 10, 15, 20, 30$, and 40 Gy ;

TLV = Total lung volume, PTV = plan target volume, GTV = gross target volume.

Table 3 Multivariate analysis results of risk factors for patients with different grades of RP

Grade	Risk factors	<i>B</i>	Standard error	<i>Wald</i>	<i>P</i> -value	<i>EXP(B)</i>	<i>EXP(B)</i> -95% <i>CI</i>	
							lower limit	upper limit
RP $\geq$ 1	COPD	1.102	0.446	6.110	0.013	1.332	1.017	5.739
	V ₅	0.054	0.029	3.427	0.041	1.055	1.004	1.095
	V ₄₀	0.319	0.155	4.250	0.039	1.375	1.016	1.862
RP $\geq$ 2	MLD(Gy)	0.253	0.150	2.832	0.012	1.289	1.059	1.730
RP $\geq$ 3	Smoking index > 400	1.443	0.591	5.964	0.015	4.233	1.330	13.479
	V ₅	1.541	0.628	6.013	0.014	1.241	1.063	1.734

COPD= chronic obstructive lung disease,MLD = mean lung dose

Predictive risk assessment models

The receiver operating characteristic curves (ROCs) of V₅, V₄₀ and the MLD were drawn to clarify the relationship between the dosimetric parameters and the risk of RP in the multivariate results, as shown in Figure 1. The thresholds of V₅ and V₄₀ (RP $\geq$ grade 1) were 55.74% and 4.13%, respectively. The AUCs of V₅ and V₄₀ (RP $\geq$

grade 1) were 0.714 (95% CI, 0.649–0.778, *P*< 0.001) and 0.688 (95% CI, 0.622–0.754, *P*< 0.001), respectively (Figure 1A). The threshold of MLD (RP $\geq$ grade 2) was 11.91Gy. The AUC of MLD (RP $\geq$ grade 2) was 0.773 (95% CI, 0.703–0.844, *P*<0.001) (Figure 1B). The threshold of V₅ (RP $\geq$ grade 3) was 57.60%. The AUC of V₅ (RP $\geq$ grade 3) was 0.749 (95% CI, 0.648–0.850, *P*< 0.001) (Figure 1C).

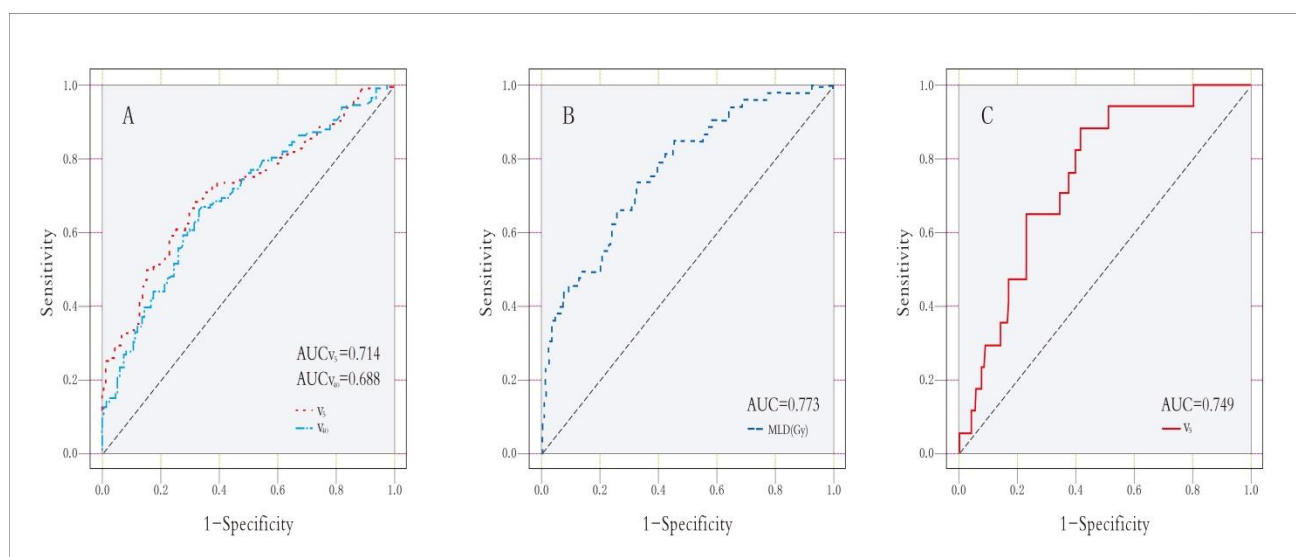


Figure 1 ROC curve for predicting the corresponding grade RP (Figure 1). A) RP $\geq$ grade 1 (Figure. B) RP $\geq$ grade 2 (Figure. C) RP $\geq$ grade 3

Discussion

RP is an inflammation of normal lung tissue caused by RT^[19]. If RP occurs, it will seriously affect the quality of life and survival prognosis. Therefore, it is imperative for EC patients undergoing RT to identify lung toxicity at the earliest possible time. This study was part of our previous investigations of the incidence of RP among EC patients^[20-21]. Unlike our previous studies, this study focuses more

on clinical factors and dose-volume parameters. Among these factors, the lung dose-volume parameter is still an essential indicator. Univariate analysis showed that V₅-V₄₀, MLD, GTV, PTV, GTV/total lung volume, and PTV/total lung volume were associated with the occurrence of RP at all levels. Multivariate results showed that V₅ was an independent risk factor for RP $\geq$ grade 1 and $\geq$ grade 3, and MLD was an independent risk factor for RP $\geq$ grade 2. However, the traditional prediction parameters

ter V_{20} does not reflect the actual prediction efficiency. The reason is that 1/4 of the enrolled patients adopted TOMO technology to effectively reduce the lung volume in the high-dose area; in addition, we may have strict restrictions on V_{20} when making the actual physical plan.

Our research is basically consistent with relevant research findings in recent years. Studies^[22-23] have suggested that low-dose parameters such as V_5 and V_{10} are the most critical factors related to RP. Jin et al.^[24] considered that the low-dose parameter V_{13} can also be used as a predictor of RP, and $V_{13} < 40\%$ can reduce the incidence of RP. Moreover, MLD is also one of the parameters concerned in thoracic RT. Several studies^[25-26] have shown that MLD is an essential predictor of $RP \geq$ grade 2. The incidence of RP has an obvious correlation with GTV dose and PTV^[27]. Vogelius et al.^[28] reported that both GTV and PTV dose were critical factors affecting the occurrence of RP. It can be seen that the occurrence of RP is not the result of a single dose-volume parameters. We noted high correlations among relative volumes of lung exposed to various dose thresholds. Therefore, we recommend evaluating the comprehensive parameters of DVH, rather than individual dose-volume constraints.

In previous studies, most patients underwent Non image-guided radiotherapy(non-iGRT), while the mainstream RT technology has been IGRT (e.g., 3DCRT, IMRT, TOMO) in recent years. The improvement of RT technology has brought about changes in lung-dose volume parameters, but the relationship between this change and RP is still uncertain. MD Anderson Tumor Center analysis^[29] showed that IMRT could significantly reduce V_{20} , but V_5 was increased simultaneously. Although V_{20} decreased, the probability of RP did not change. TOMO technology has been widely used in the RT of thoracic tumors. Some studies^[30-31] suggest that TOMO is safe in the treatment of lung cancer. EC studies^[32-33] compared lung dose parameters by selecting a few patients and designing several different physical plans; however, there is no real-world report on the occurrence of RP in EC after different irradiation techniques. We analysed the incidence of RP in 247 patients with EC undergoing RT. The incidence of $RP \geq$ grade 2 was 22.4% in IMRT and 16.9% in TOMO. More importantly, we found that the incidence of $RP \geq$ grade 1, $\geq$ grade 2, and $\geq$ grade 3 was not related to

radiation technology. Therefore, precise RT does not decrease the incidence of RP, which was in line with a previous study^[34-35]. However, we realize that our study is a single institution retrospective analysis and the findings need to be validated using other comparable dataset(s) from other institution(s).

As mentioned above, although lung dose parameters are associated with RP in patients with EC, the results reported in the literature are not uniform. Therefore, the occurrence of RP is not only related to lung dose volume parameters. We should comprehensively evaluate the clinical characteristics and treatment factors of patients. Studies^[36] have confirmed that RP is related to many factors, such as smoking status, chronic lung disease, and chemotherapy. Laucis^[37] deemed that smoking did not increase radiation-related lung toxicity. Moreover, a meta-analysis^[38] found that patients with a history of smoking or current smoking have a reduced risk of RP. We introduced the smoking index to study the relationship between patients with different smoking levels and RP. The results showed that there was no significant correlation between nonsmokers and the incidence of $RP \geq$ grade 1 and $RP \geq$ grade 2 in patients with different degrees of smoking. The results should in no way be taken to encourage patient smoking; rather, further investigations on underlying causes for the smoking effect should be undertaken. $RP \geq$ grade 3 was significantly increased in patients with a smoking index > 400 . The reason may be related to the complications of COPD caused by severe smoking, and smokers frequently have a history of COPD, making them less likely to notice and report symptoms of RP than non-smokers and former smokers. Zhang et al.^[39] found that for smokers with severe chronic lung disease, smoking has become an adverse factor of RP. The severity of smoking is an important influencing factor of severe RP. However, when the effects of tobacco are ignored, the results may be different from the perspective of COPD or essential pulmonary function. A previous report^[40] based on stereotactic body radiotherapy (SBRT) showed that the risk of RP in COPD and non-COPD patients was similar. Wang J et al.^[41] analyzed 260 patients with stage I-III non-small cell lung cancer who received conventional RT and found that there was no increase in the incidence of grade ≥ 2 RP in patients with poor basic lung function due to COPD. Furthermore, in their study, patients with symptoma

tic RP had higher basal of forced exhalation in the first second (FEV1%) (71.7% vs. 65.9%, $p = 0.07$) than those without it. In our study, EC patients with COPD did not increase the incidence of symptomatic RP. On the contrary, these patients were more likely to develop asymptomatic RP. Fortunately, grade 1 RP is an asymptomatic radiological change according to CTCAE criteria, clinical treatment is not required even when it occurs. Therefore, we should pay more attention to the relationship between COPD and symptomatic RP ($\geq$ grade 2).

Chemoradiotherapy is the dominant mode of nonsurgical treatment for EC. Thus, the effect of chemotherapy on RP in patients with EC is also a concern. Our study did not identify any effects of chemotherapy on risk of RP, although this subject is highly controversial. In lung cancer, we can see that the research results of the effect of chemotherapy on RP are not consistent. Kishida *et al.*^[42] reported that RT combined with paclitaxel drugs increased the incidence of RP in lung cancer patients, but Shaikh *et al.*^[43] concluded that concurrent paclitaxel chemotherapy during RT did not affect RP. In breast cancer patients, for example, oxaliplatin and paclitaxel have been found to enhance the effects of radiation in inducing lung injury^[44]. Study of patients with EC treated with concurrent radiotherapy and chemotherapy, induction chemotherapy was associated with an increased rate of pneumonitis^[45]. Possibly, the conflicting results can be explained by the doses of radiation and/or chemotherapy used. In addition, the adverse effects of chemotherapy might be more evident than the effects of radiation. In our study, 205 patients (82.9%) received chemotherapy, including induction chemotherapy, concurrent chemotherapy, and consolidation chemotherapy. However, no correlation was found between RP and chemotherapy. Considering that our study is not a large sample, this result is not enough to confirm that chemotherapy does not induce or aggravate RP. In addition, different chemotherapeutic agents are likely to affect the risk of RP differently.

As a retrospective study, this study still has some limitations. The sample size of the included group was relatively small, while the RP influencing factors involved were relatively large, which may cause deviation in the results. It can be considered that the sample selection method in this study is a continuous observational study. The samples are all from cases within the same research center and

a fixed span of time. This sample selection method cannot include all patients who meet the inclusion criteria, as some patients cannot obtain data from our research center's workstations for subsequent diagnosis and treatment. For example, patients who return to local hospitals for treatment. Therefore, this study cannot reflect the incidence of RP in EC in the region, as it can only analyze the risk factors of RP. The follow-up observation time was relatively short, and there was no correlation analysis for the patients who may have radiation-induced pulmonary fibrosis beyond the follow-up period. The construction of the MV models is not optimal. For example, different clinical factors are eligible to be entered in different models. The model was not constructed using the same set of possible entry variables, and in the case of collinearity, no variables were pre-specified. It is useful to find the cut-off value of the factors that have significant influence on RP by ROC curve, but the AUCs of the three factors in this study are less than 0.8, so the prediction efficiency is insufficient. This seems to be an insurmountable problem in current clinical work. Fortunately, in my in-depth research^[20], the RP prediction model was established by using CT radiomics analysis technology combined with clinical characteristics and dosimetric parameters, which made up for the insufficiency of lower AUCs prediction in the current study. Although interstitial lung disease (ILD) is a related factor of RP, our study did not address it due to the difficulty of sample collection. The main reason was that before radiologists developed radiation therapy plans for patients, ILD was already considered a high-risk factor for RP and excluded. The choice of RT technology was not randomization but considered the size of the tumor target area or patient economy and other factors, which may affect the experimental results.

Conclusions

We comprehensively discussed the influencing factors of RP in patients with thoracic EC who received RT. Different lung dose-volume parameters have an essential influence on the occurrence of RP. In the implementation of EC radiation therapy, we should pay attention to dosimetry parameters such as lung V_5 and MLD, regardless of which radiotherapy technique is used. Due to the high correlation between the relative volume of lungs exposed

to different dose thresholds. Therefore, we recommend evaluating the comprehensive parameters of DVH instead of individual dose volume limitations. In addition, we cannot ignore the significant role of the index of smoking and essential pulmonary function.

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