Modeling the Risk of Radiation Pneumonitis in Esophageal Squamous Cell Carcinoma Treated with Definitive Chemoradiotherapy

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Research

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Abstract

Purpose: To develop and validate a nomogram for the prediction of symptomatic radiation pneumonitis (RP) in patients with esophageal squamous cell carcinoma (ESCC) who received definitive concurrent chemoradiotherapy.

Methods: Clinical factors, dose-volume histogram parameters, and pulmonary function parameters were collected from 402 ESCC patients between 2010 and 2017, including 321 patients in the primary cohort and 81 in the validation cohort. The end-point was the occurrence of symptomatic RP (grade ≥2) within the first 12 months after radiotherapy. Univariate and multivariate logistic regression analyses were applied to evaluate the predictive value of each factor for RP. A prediction model was generated in the primary cohort, which was internally validated to assess its performance.

Results: In the primary cohort, 31 patients (9.7%) experienced symptomatic RP. Based on logistic regression model, patients with larger planning target volumes (PTVs) or higher lung V_{20} had a higher predictive risk of RP, whereas the overall risk was substantially higher for three-dimensional conformal radiotherapy (3DCRT) than intensity-modulated radiotherapy. On multivariate analysis, independent predictive factors for RP were smoking history (P=0.018), radiotherapy modality (P<0.001), PTV (P=0.014), and lung V_{20} (P=0.002), which were incorporated into the nomogram. The areas under the receiver operating characteristic curve of the nomogram in the primary and validation cohorts were 0.772 and 0.900, respectively, which were superior to each predictor alone.

Conclusions: Non-smoking status, 3DCRT, lung V_{20} (>27.5%), and PTV (≥713.0 cc) were significantly associated with a higher risk of RP. A nomogram was built with satisfactory prediction ability.

Introduction

Esophageal cancer (EC) is one of the leading causes of cancer-related death worldwide, with an estimated 508,585 deaths yearly [1]. Definitive chemoradiotherapy (CRT) is the standard care in the management of unresectable EC [2, 3]. Radiation pneumonitis (RP) is one of the major complications after thoracic irradiation. Despite low mortality, RP can result in respiratory insufficiency, seriously affect patients' quality of life, influence the completion of radiotherapy and following treatment, and even reduce the curative effect, particularly for patients with symptomatic RP [4]. Although the survival benefit of concurrent CRT over radiotherapy alone is evident, the former has been demonstrated to be correlated with an increased risk of RP[5]. Therefore, decreasing the incidence of RP is of critical clinical significance for EC patients who received concurrent CRT.

An increasing number of studies have investigated predictors for RP [4–12]. Various risk factors, including clinical characteristics, dosimetric parameters, treatment-related variables, as well as serum biomarkers have been reported to be associated with the occurrence of RP [4–12]. However, the majority of these reports focused on patients with lung cancer, and data regarding EC patients undergoing definitive CRT is limited. Considering the differences in baseline pulmonary function and in the level of

radiation dose between lung cancer and EC patients, it is unreasonable to extrapolate risk factors for RP in lung cancer to EC. On the other hand, despite the significantly increasing use of intensity-modulated radiotherapy (IMRT) in recent years, its impact on RP remains unclear in EC.

Therefore, the purpose of study was to investigate the associations between clinical factors, dose-volume histogram (DVH) parameters, as well as pulmonary function parameters, and the risk of symptomatic RP in patients with esophageal squamous cell carcinoma (ESCC) who received definitive concurrent CRT. Then a nomogram model predicting RP was developed and validated to guide clinical decision-making.

Patients And Methods

Patients

All consecutive ESCC patients who underwent definitive CRT at our institution from January 2010 through October 2017 were retrospectively analyzed. Inclusion criteria were defined: pathologic confirmation of stage I-IVa ESCC according to the 8th TNM staging system of the American Joint Committee on Cancer [13], receipt of concurrent CRT with curative intent, DVH data retrievable from treatment planning system, radiographic images and symptom assessments available to evaluate the occurrence of RP, and the availability of pulmonary function tests prior to CRT. Patients with prior or concomitant malignancy, those with previous thoracic radiotherapy or surgery, and those with incomplete records were excluded. A total of 402 eligible ESCC patients were included, including 321 patients in the primary cohort and 81 patients in the validation cohort based on a randomization ratio of 4:1. This study was approved by the Institutional Review Boards of Sun Yat-sen University Cancer Center (No. B2019-010-01). Since this was a retrospective analysis of routine data, we requested, and were granted, a waiver of individual informed consent from the ethics committee. Patient records/information was anonymized and deidentified before analysis.

Data Collection

The following data were collected for each patient from the medical records: medical history, patient and tumor characteristics, treatment information, radiographic images, and symptom assessments. Pulmonary function parameters included forced expiratory volume in the first second and diffusing capacity for carbon monoxide. DVH parameters were extracted from the treatment planning system: planning target volume (PTV), total lung volume (TLV), mean lung dose (MLD), and the percentage of lung volume receiving more than x Gy (V_x), ranging from 5 to 30 Gy in increments of 5 Gy.

Treatment

A fraction of patients received 1 to 4 cycles of induction chemotherapy prior to CRT, and all patients received concurrent platinum- or taxane-based chemotherapy during radiotherapy, as determined by the multidisciplinary team. For radiotherapy, gross tumor volume (GTV) encompassed the primary tumor and involved lymph nodes. Clinical target volume (CTV) was defined as the GTV plus a 3-cm margin in proximal and distal direction and a radial margin of 0.5 to 1.0 cm. PTV was defined as CTV plus a 0.5–

0.8 cm margin to account for setup uncertainty. Patients were treated with three-dimensional conformal radiotherapy (3DCRT) or IMRT to deliver the prescribed dose of 50–70 Gy in 25–35 fractions. Dose constraints for normal tissues were defined as follows: the maximum dose of spinal cord < 45 Gy; lung V_5 < 65%, V_{20} < 30%, and MLD < 17 Gy; heart V_{30} < 40% and mean dose < 28 Gy.

Evaluation of RP and Follow-up

Patients were followed 1 month after CRT, then every 3 months during the first 2 years, every 6 months for the next 3 years, and then annually. Chest computed tomography was performed at each visit. The relevant clinical symptoms were recorded by the treating physician in medical records.

The end-point for this study was the occurrence of symptomatic RP (grade ≥ 2) within the first 12 months after radiotherapy, which was diagnosed by clinical symptoms, chest imaging, and evidence of medication and treatment in the medical records. RP was graded based on National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 (CTCAE v4.0).

Statistical Analysis and Modeling

Age, tumor length, radiation dose, and pulmonary function parameters were grouped by the median value as cut-offs. Univariate and multivariate logistic regression models were conducted to analyze possible predictors for RP. Variables with $P \leq 0.15$ in the univariate analysis were assessed in multivariate analysis (backward stepwise). Prior to multivariate analysis, Spearman rank correlation analyses were performed to check multicollinearity between factors.

Factors with significant predictive value in multivariate analysis were used to build the nomogram in the primary cohort. Then the nomogram was validated in the validation cohort. The performance of the nomogram was assessed by the area under the receiver operating characteristic (ROC) curve (AUC), calibration curve using 1000 bootstrap resamples, and decision curve analysis (DCA). Calibration curve was generated to compare the predicted with the observed probability of RP. DCA was employed to evaluate the clinical usefulness of the nomogram. Moreover, the optimal cut-offs of the continuous parameters in the nomogram was calculated using the ROC curves. Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL) and R software (version 3.4.3). A P value < 0.05 was considered to be statistically significant.

Results

Patient Characteristics

Patient and treatment characteristics of 402 ESCC patients who met the inclusion criteria are summarized in Table 1. For the primary cohort (n = 321), the median age was 59 years (range, 29–73 years) and the majority of the tumors were located in the upper/middle esophagus (86.0%). Of them, 218 patients (67.9%) were current or former smokers, and COPD accounted for only 5.6%. A total of 195 patients (60.7%) received induction chemotherapy prior to concurrent CRT. The majority of patients

(78.2%) were treated with IMRT, and the rest with 3DCRT, with the median radiation dose of 60.0 Gy (range, 36–70 Gy). A small fraction of patients (5.3%) received a dose of < 50.0 Gy owing to treatment-related toxicity. As for DVH parameters, the median PTV was 683.1 cc (range, 253.0–1566.0 cc) and median TLV was 3240.3 cc (range, 1697.3–7961.9.0 cc). MLD ranged from 4.9 to 21.5 Gy, with a median of 14.8 Gy. Median V_5, V_{10}, V_{15}, V_{20}, V_{25}, and V_{30} of lung were 70.1%, 49.5%, 36.2%, 27.3%, 20.6%, and 14.8%, respectively.

Table 1
Patient characteristics.

Characteristic	Total (n = 402), %	Primary cohort (n = 321), %	Validation cohort (n = 81), %	*P*-value
Clinical factors				
Age (years), Median (range)	59 (29–73)	59 (29–73)	60 (40–71)	0.087
Sex				0.004
Male	294 (73.1)	245 (76.3)	49 (60.5)	
Female	108 (26.9)	76 (23.7)	32 (39.5)	
Smoking history				0.670
Yes	270 (67.2)	218 (67.9)	53 (65.4)	
No	132 (32.8)	103 (32.1)	28 (34.6)	
COPD				0.845
Yes	23 (5.7)	18 (5.6)	5 (6.2)	
No	379 (94.3)	303 (94.4)	76 (93.8)	
ECOG performance status				0.893
0	268 (66.7)	215 (67.0)	53 (65.4)	
1–2	134 (33.3)	106 (33.0)	28 (34.6)	
Weight loss				0.790
< 10%	317 (78.9)	254 (79.1)	63 (77.8)	
≥ 10%	85 (21.1)	67 (20.9)	18 (22.2)	
Tumor location				0.045
Upper	159 (39.5)	127 (39.6)	32 (39.5)	
Middle	178 (44.3)	149 (46.4)	29 (35.8)	
Distal	65 (16.2)	45 (14.0)	20 (24.7)	
Primary tumor length				0.358

Abbreviations: COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; V_x: percentage of the total lung volume receiving more than x Gy; IQR, interquartile range; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; FEV1: forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide.

*: Single agent chemotherapy during radiotherapy (taxane or platinum).

Characteristic	Total (n = 402), %	Primary cohort (n = 321), %	Validation cohort (n = 81), %	*P*-value
< 6 cm	230 (57.2)	180 (56.1)	50 (61.7)	
≥ 6 cm	172 (42.8)	141 (43.9)	31 (38.3)	
Clinical TNM stage				0.851
I/II	42 (10.5)	34 (10.6)	8 (9.9)	
III/IVa	360 (89.6)	287 (89.4)	73 (90.1)	
Induction chemotherapy				0.655
Yes	242 (60.2)	195 (60.7)	47 (58.0)	
No	160 (39.8)	126 (39.3)	34 (42.0)	
Concurrent chemotherapy				/
Yes	402 (100.0)	321 (100.0)	81 (100.0)	
Chemotherapy regimen				0.009
Cisplatin/taxane	232 (57.7)	173 (53.9)	59 (72.8)	
Cisplatin/fluorouracil	78 (19.4)	68 (21.2)	10 (12.3)	
Other*	92 (22.9)	80 (24.9)	12 (14.8)	
Radiation dose (Gy)				0.617
≤ 60	299 (74.4)	237 (73.8)	62 (76.5)	
> 60	103 (25.6)	84 (26.2)	19 (23.5)	
Radiotherapy modality				0.137
3DCRT	92 (22.9)	70 (21.8)	24 (29.6)	
IMRT	310 (77.1)	251 (78.2)	57 (70.4)	
Dosimetric parameters				
V_5 (%), Median (IQR)	69.8 (60.6–80.9)	70.1 (60.8–81.3)	68.2 (57.3–75.5)	0.132
V_{10} (%), Median (IQR)	49.3 (42.3–56.1)	49.5 (42.4–57.2)	48.9 (41.4–53.7)	0.260

Abbreviations: COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; V_x: percentage of the total lung volume receiving more than x Gy; IQR, interquartile range; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; FEV1: forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide.

*: Single agent chemotherapy during radiotherapy (taxane or platinum).

Characteristic	Total (n = 402), %	Primary cohort (n = 321), %	Validation cohort (n = 81), %	*P*-value
V_{15} (%), Median (IQR)	36.4 (31.3–40.9)	36.2 (31.5–41.2)	36.5 (30.5–39.9)	0.377
V_{20} (%), Median (IQR)	27.2 (22.3–30.2)	27.3 (22.8–30.5)	25.9 (20.8–29.6)	0.058
V_{25} (%), Median (IQR)	20.3 (16.0–23.0)	20.6 (16.3–22.9)	19.2 (13.7–23.1)	0.127
V_{30} (%), Median (IQR)	14.87 (11.0–17.7)	14.8 (11.5–17.7)	13.8 (8.6–18.3)	0.133
MLD (Gy), Median (IQR)	14.8 (12.6–16.6)	14.8 (12.9–16.7)	14.6 (12.0–16.1)	0.121
PTV (cc), Median (IQR)	663.4 (520.9–816.6)	683.1 (540.2–826.6)	576.7 (447.4–793.5)	0.004
TLV (cc), Median (IQR)	3207.9 (2698.1–3884.5)	3240.3 (2704.1–3897.0)	3177.0 (2689.7–3833.1)	0.394
Pulmonary function parameters				
FEV1 (L), Median (IQR)	2.7 (2.2–3.1)	2.7 (2.3–3.1)	2.6 (2.2–3.0)	0.492
FEV1 (%), Median (IQR)	93.5 (76.0–103.8)	93.6 (78.0–104.8)	93.2 (75.3–102.0)	0.473
DLCO (ml/mmHg/min), Median (IQR)	24.4 (20.7–27.5)	24.2 (20.8–27.7)	25.0 (20.7–27.1)	0.412

Abbreviations: COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; V_x: percentage of the total lung volume receiving more than x Gy; IQR, interquartile range; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; FEV1: forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide.

*: Single agent chemotherapy during radiotherapy (taxane or platinum).

The median follow-up time was 21.5 months (range, 3.5-108.8 months) for the primary cohort. During follow-up, 159 patients (49.5%) had grade 1 RP, 27 (8.4%) had grade 2 RP, 3 (0.9%) had grade 3 RP, 1 (0.3%) had grade 4 RP, and no patients had grade 5 RP. In total, 31 patients (9.7%) experienced symptomatic RP. The median interval from the completion of radiotherapy to the diagnosis of RP was 65 days (range, 20–137 days).

Univariate Analysis

The comparisons of clinical and dosimetric factors between patients with or without symptomatic RP are listed in Table 2 and Supplementary Fig. 1A. For clinical characteristics, univariate analysis showed that age, smoking history, performance status, primary tumor length, and radiotherapy modality were correlated with the development of RP. Among dosimetric parameters, PTV, Lung V_5 to V_{30}, and MLD were

significantly associated with the risk of RP ($P < 0.05$ for all). Nevertheless, no pulmonary function parameters were significant risk factors for RP.

Table 2
Univariate analysis for variables associated with symptomatic radiation pneumonitis in the primary cohort (n = 321).

Characteristic	With RP	Without RP	Univariate	
	(n = 31), %	(n = 290), %	Odds ratio (95% CI)	*P*-value
Clinical factors				
Age (years)				
< 59	9 (29.0)	147 (50.7)	Ref	
≥ 59	22 (71.0)	143 (49.3)	2.513 (1.119–5.643)	0.026
Sex				
Male	26 (83.9)	219 (75.5)	Ref	
Female	5 (16.1)	71 (24.5)	0.593 (0.220–1.602)	0.303
Smoking history				
Yes	17 (54.8)	201 (69.3)	Ref	
No	14 (45.2)	89 (30.7)	1.860 (0.878–3.938)	0.105
COPD				
Yes	2 (6.5)	16 (5.5)	Ref	
No	29 (93.5)	274 (94.5)	0.847 (0.185–3.867)	0.830
ECOG performance status				
0	16 (51.6)	199 (68.6)	Ref	
1–2	15 (48.4)	91 (31.4)	2.050 (0.972–4.326)	0.060
Weight loss				
< 10%	23 (74.2)	231 (79.7)	Ref	

Abbreviations: RP, radiation pneumonitis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; V_x: percentage of the total lung volume receiving more than x Gy; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; FEV1: forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide.

*: Single agent chemotherapy during radiotherapy (taxane or platinum).

Characteristic	With RP	Without RP	Univariate	
	(n = 31), %	(n = 290), %	Odds ratio (95% CI)	*P*-value
≥ 10%	8 (25.8)	59 (20.3)	1.362 (0.580–3.198)	0.478
Tumor location				
Upper	10 (32.3)	117 (40.3)	Ref	
Middle	17 (54.8)	132 (45.5)	1.320 (0.420–4.145)	0.634
Distal	4 (12.9)	41 (14.1)	0.876 (0.260–2.946)	0.831
Primary tumor length				
< 6 cm	13 (41.9)	167 (57.6)	Ref	
≥ 6 cm	18 (58.1)	123 (42.4)	1.880 (0.888–3.982)	0.099
Clinical TNM stage				
I/II	2 (6.5)	32 (11.0)	Ref	
III/IVa	29 (93.5)	258 (89.0)	1.798 (0.410–7.894)	0.437
Induction chemotherapy				
Yes	17 (54.8)	178 (61.4)	Ref	
No	14 (45.2)	112 (38.6)	1.309 (0.621–2.759)	0.479
Chemotherapy regimen				
Cisplatin/taxane	14 (45.2)	159 (54.8)	Ref	
Cisplatin/fluorouracil	6 (19.4)	62 (21.4)	0.552 (0.239–1.278)	0.165
Other*	11 (35.5)	69 (23.8)	0.607 (0.212–1.739)	0.352

Abbreviations: RP, radiation pneumonitis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; V_x: percentage of the total lung volume receiving more than x Gy; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; FEV1: forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide.

*: Single agent chemotherapy during radiotherapy (taxane or platinum).

Characteristic	With RP	Without RP	Univariate	
	(n = 31), %	(n = 290), %	Odds ratio (95% CI)	*P*-value
Radiation dose (Gy)				
≤ 60	22 (71.0)	215 (74.1)	Ref	
> 60	9 (29.0)	75 (25.9)	1.173 (0.517–2.660)	0.703
Radiotherapy modality				
3DCRT	15 (48.4)	55 (19.0)	Ref	
IMRT	16 (51.6)	235 (81.0)	0.250 (0.116–0.535)	< 0.001
Dosimetric parameters				
V_5 (%), Median (IQR)	75.9 (71.6–89.2)	69.6 (59.9–80.9)	1.035 (1.009–1.062)	0.009
V_{10} (%), Median (IQR)	54.2 (48.5–67.3)	48.7 (41.5–56.0)	1.042 (1.013–1.072)	0.005
V_{15} (%), Median (IQR)	40.9 (37.2–49.0)	35.6 (30.9–40.9)	1.085 (1.039–1.134)	< 0.001
V_{20} (%), Median (IQR)	30.4 (28.3–33.1)	26.9 (22.3–29.9)	1.175 (1.080–1.278)	< 0.001
V_{25} (%), Median (IQR)	22.4 (20.7–23.9)	20.2 (16.0–22.7)	1.146 (1.049–1.252)	0.002
V_{30} (%), Median (IQR)	17.3 (13.3–19.8)	14.7 (11.2–17.4)	1.143 (1.045–1.250)	0.003
MLD (Gy), Median (IQR)	17.0 (15.2–18.2)	14.7 (12.6–16.5)	1.349 (1.158–1.572)	< 0.001
PTV (cc), Median (IQR)	772.0 (639.0–921.5)	665.6 (532.7–812.1)	1.002 (1.000–1.003)	0.019
TLV (cc)	3080.4 (2648.5–3938.1)	3265.4 (2711.0–3895.4)	0.693 (0.327–1.466)	0.717

Abbreviations: RP, radiation pneumonitis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; V_x: percentage of the total lung volume receiving more than x Gy; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; FEV1: forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide.

*: Single agent chemotherapy during radiotherapy (taxane or platinum).

Characteristic	With RP	Without RP	Univariate	
	(n = 31), %	(n = 290), %	Odds ratio (95% CI)	*P*-value
Pulmonary function parameters				
FEV1 (L), Median (IQR)	2.7 (2.3–3.1)	2.7 (1.9–3.2)	0.696 (0.336–1.440)	0.328
FEV1 (%), Median (IQR)	93.7 (78.2–104.8)	93.5 (78.0–103.7)	0.994 (0.951–1.040)	0.808
DLCO (ml/mmHg/min), Median (IQR)	24.2 (20.6–27.8)	24.2 (20.8–27.9)	1.001 (0.910–1.102)	0.977

Abbreviations: RP, radiation pneumonitis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; V_x: percentage of the total lung volume receiving more than x Gy; MLD, mean lung dose; PTV, planning target volume; TLV, total lung volume; FEV1: forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide.

*: Single agent chemotherapy during radiotherapy (taxane or platinum).

Multivariate Analysis

Considering the possible relationships between dosimetric parameters of lung, Spearman's correlation analysis was performed and indicated strong correlations between V_{10} and V_{15} ($\gamma = 0.901$, $P < 0.01$), as well as V_{25} and V_{30} ($\gamma = 0.906$, $P < 0.01$) (Supplementary Table 1). According to the odds ratios (OR), V_{15} instead of V_{10} and V_{25} instead of V_{30} were included in the multivariate analysis to avoid multicollinearity. On multivariate analysis, smoking history (OR: 2.842, $P = 0.018$), radiotherapy modality (OR: 5.294, $P < 0.001$), PTV (OR: 1.002, $P = 0.014$), and lung V_{20} (OR: 1.147, $P = 0.002$) were independent predictive factors for symptomatic RP (Table 3). Among these factors, smoking history was found to protect against RP.

Table 3
Multivariate and ROC analysis for variables associated with symptomatic radiation pneumonitis in the primary cohort.

Variable	Multivariate analysis		ROC curve	
	Odds ratio (95% CI)	*P*-value	AUC (95% CI)	*P*-value
Smoking history (no vs. yes)	2.842 (1.195–6.756)	0.018	0.572 (0.463–0.681)	0.008
Radiotherapy modality (3DCRT vs. IMRT)	5.294 (2.202–12.725)	< 0.001	0.647 (0.536–0.758)	0.096
PTV	1.002 (1.000–1.004)	0.014	0.724 (0.632–0.816)	0.484
Lung V_{20}	1.147 (1.053–1.250)	0.002	0.628 (0.529–0.727)	0.042
Nomogram	/	/	0.772 (0.673–0.871)	Ref.

Abbreviations: ROC, receiver operating characteristic; CI, confidence interval; AUC, area under the curve; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; V_{20}: percentage of the total lung volume receiving more than 20 Gy.

Figure 1 shows the predictive probabilities of symptomatic RP as a function of PTV or lung V_{20} for the two radiation modalities based on logistic regression model. Patients with larger PTVs or higher lung V_{20} had a higher predictive risk of RP, whereas the overall risk was substantially higher for 3DCRT than IMRT. For example, when PTV is 630.0 cc, the probability of developing symptomatic RP would be 5.0% in patients treated with IMRT versus 20.2% in those with 3DCRT.

Nomogram Development and Validation

Based on the multivariate analysis, a nomogram model was built to predict the risk of symptomatic RP, including smoking history, radiotherapy modality, PTV, and lung V_{20} (Fig. 2). The AUC of predictive model was 0.772 (95% CI: 0.673–0.871), which was superior to each predictor alone (smoking history: 0.572, 95% CI: 0.463–0.681; radiotherapy modality: 0.647, 95% CI: 0.536–0.758; PTV: 0.724, 95% CI: 0.632–0.816; and lung V_{20}: 0.628, 95% CI: 0.529–0.727) (Fig. 3A). The optimal cut-offs for PTV and lung V_{20} were 713.0 cc and 27.5%, respectively. Additionally, the calibration curve showed favorable agreement between the prediction by nomogram and the actual observation (Fig. 3B). Also, the DCA exhibited satisfactory positive net benefits of the model among the majority of threshold probabilities, indicating excellent clinical utility (Fig. 3C).

In the validation cohort (n = 81), 10 patients (12.3%) experienced grade ≥ 2 RP. The comparisons of lung dosimetric factors between patients with or without symptomatic RP are listed in Supplementary Fig. 1B.

Application of the nomogram model in the validation cohort yielded an excellent AUC of 0.900 (95% CI: 0.779–1.000) (Supplementary Table 2 and Supplementary Fig. 2).

Discussion

Symptomatic RP is a common side effect of radiotherapy for EC with incidence of 5.7–35.0% [5–11], which is confirmed by our study. In this cohort of ESCC patients undergoing definitive CRT, smoking history, radiotherapy modality, PTV, and lung V_{20} were significant predictive factors for symptomatic RP. More importantly, a nomogram has been built and validated, indicating satisfactory prediction ability. Thus, this prediction model could help clinicians select high-risk patients who may benefit from modified treatment approaches to reduce the risk of RP prior to the initiation of treatment.

In recent years, radiation techniques have evolved from 3DCRT to IMRT and proton therapy in EC. Numerous dosimetric studies have well demonstrated the superiority of IMRT over 3DCRT in improving target coverage and sparing adjacent organs, but whether the dosimetric benefits could translate into clinical benefit, especially reducing the incidence of radiation-related toxicities, remains inconclusive due to the lack of prospective evidence [14]. In a large-scale retrospective study reported by He et al, IMRT significantly reduced the incidence and postponed the onset of pleural effusion in EC patients, compared to 3DCRT [15]. However, Haefner et al found no evident difference in acute toxicities between IMRT and 3DCRT, possibly due to the small sample size of the cohort and the higher radiation dose in the IMRT group [16]. In our study, after adjusting for smoking history, PTV, and Lung V_{20}, IMRT was associated with a substantially lower risk of RP than 3DCRT. This is in consistence with the secondary analysis of results from RTOG 0617, which prospectively demonstrated that IMRT group had significantly less severe RP than 3DCRT group in locally advanced non-small cell lung cancer (3.5% vs. 7.9%, $P = 0.039$) [17]. In addition, IMRT could also reduce the incidence of postoperative pulmonary and cardiac complication in EC patients who received neoadjuvant CRT and surgery, as reported by Lin et al [18]. Furthermore, IMRT was associated with more favorable survival outcomes than 3DCRT in EC [14]. Collectively, despite the paucity of prospective evidence, the current findings strongly suggest the routine use of IMRT in EC.

As a novel radiation technique with superior physical properties, proton therapy has the potential to improve normal tissue sparing as compared to 3DCRT or IMRT [14]. Several studies have investigated the clinical advantages of proton therapy compared to photon therapy. For EC patients who underwent neoadjuvant CRT, proton therapy was superior to IMRT in reducing incidence of pulmonary complications [18]. Recently, Lin et al reported that the proton arm experienced numerically fewer cardiopulmonary toxicities compared with IMRT arm in a phase IIB randomized trial for EC [19]. The ongoing larger cooperative group studies will clarify the clinical benefit of proton therapy in EC, such as NRG-GI006.

There has been a general consensus that DVH parameters are important predictors for RP. However, there is still no recommendation of dose-volume constraints for EC. Wang et al reported that the volume of the lung spared from doses of ≥ 5 Gy was the only independent dosimetric factor associated with pulmonary complications [20]. Cho et al indicated that MLD was the parameter most related to pulmonary

complications in EC [21]. Likewise, a recent study demonstrated the strong correlation between MLD and severe RP in 416 EC patients undergoing CRT [22]. Consistent with studies reported by Asakura et al and Shaikh et al [9, 23], all DVH parameters (lung V_5-V_{30} and MLD) were significantly associated with RP in univariate analysis in our cohort. Of them, V_{20} was the only independent predictor in multivariate analysis, with the optimal threshold value of V_{20} (27.5%). The failure of the other dosimetric parameters to be retained significance in the multivariate model could be explained by their potential correlation with V_{20}. Thus, other dosimetric parameters should also be taken into consideration when performing treatment planning for EC.

In addition to lung dosimetric parameters, we observed that patients with greater PTVs had a remarkably higher incidence of RP. In line with our results, Cui et al also reported the strong correlation between PTV and the occurrence of RP in elderly EC [24]. Considering PTV is a variable that could be modified, smaller radiation volumes might reduce the risk of RP. A meta-analysis reported that neither local control rates nor survival outcomes differed significantly between elective nodal irradiation and involved-field irradiation in ESCC, whereas incidences of severe RP and radiation esophagitis were significantly lower in the latter group [25]. Therefore, involved-field irradiation should be considered in clinical practice, especially for elderly patients. Among clinical factors, smoking history was found to be a protective factor for RP in our study, which is consistent with previous studies [26, 27]. The possible explanations are smoking-associated hypoxia and a decreased inflammatory reaction induced by irradiation among smokers [28, 29], but the underlying mechanism for the smoking effect on RP remains unclear.

Compared with each separate predictor, integrating predictive factors to develop a statistical model will further improve predictive accuracy. So far, only one study reported by Wang et al had built a combined model to predict severe RP in EC [22]. However, this study included a fraction of patients without concurrent chemotherapy during radiotherapy, which might affect the incidence of RP. Moreover, this study incorporated not only pretreatment factors but also the changes of inflammatory indexes during radiotherapy into the nomogram [22]. Despite excellent discriminatory power of the model, it is of less value to guide decision-making before the initiation of treatment.

It should be noted that our work also has several limitations. Firstly, selection bias existed due to the retrospective nature of this study. Secondly, the sample size of the validation set is relatively small, and an independent external validation is needed. Thirdly, although all patients included were treated with concurrent CRT, treatment modalities such as the utility of induction chemotherapy and chemotherapy regimens were not identical in this study. However, these factors were not correlated with the risk of RP in univariate analysis. Finally, serum biomarkers as well as radiomics-based features were not incorporated into the study, which might further promote predictive ability of the model.

Conclusions

Non-smoking status, 3DCRT, lung V_{20} (> 27.5%), and PTV (≥ 713.0 cc) were significantly associated with a higher risk of symptomatic RP in ESCC patients treated with definitive CRT. Then a nomogram was built

and validated, exhibiting satisfactory prediction ability. Further studies are warranted to verify the efficacy of the predicting model and to explore potential strategies for minimizing the risk of RP in high-risk patients.

Abbreviations

AUC: Area Under the Curve; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; CRT: Definitive Chemoradiotherapy; CTCAE: National Cancer Institute Common Toxicity Criteria for Adverse Events; CTV: Clinical Target Volume; DCA: Decision Curve Analysis; DLCO: Diffusing Capacity for Carbon Monoxide; DVH: Dose-Volume Histogram; EC: Esophageal Cancer; ECOG: Eastern Cooperative Oncology Group; ESCC: Esophageal Squamous Cell Carcinoma; FEV1: Forced Expiratory Volume in the First Second; GTV: Gross Tumor Volume; IMRT: Intensity-Modulated Radiotherapy; MLD: Mean Lung Dose; PTV: Planning Target Volume; ROC: Receiver Operating Characteristic; RP: Radiation Pneumonitis; TLV: Total Lung Volume; Vx: Percentage of the Total Lung Volume Receiving more than x Gy; 3DCRT: Three-Dimensional Conformal Radiotherapy.

Declarations

Ethics approval and consent to participate

The study was approved by our institution.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study were included in this published article.

Competing interests

The authors declare that there is no conflict of interest.

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Author contributions

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Acquisition of data: KQL, CX, SLL, JHZ, YDY, LZ, MX.

Analysis and interpretation of data: KQL, CX, SLL, JHZ, YDY, LZ, MX.

Writing, review, and/or revision of the manuscript: KQL, CX, SLL, JHZ, YDY, LZ, MX.

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References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623-7.
3. Conroy T, Galais M-P, Raoul J-L, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. The Lancet Oncology. 2014;15(3):305-314.
4. Hanania AN, Mainwaring W, Ghebre YT, et al. Radiation-Induced Lung Injury: Assessment and Management. Chest. 2019;156(1):150-162.

5. McCurdy M, McAleer MF, Wei W, et al. Induction and concurrent taxanes enhance both the pulmonary metabolic radiation response and the radiation pneumonitis response in patients with esophagus cancer. Int J Radiat Oncol Biol Phys. 2010;76(3):816-23.
6. Zhao L, Ji W, Ou G, et al. Risk factors for radiation-induced lung toxicity in patients with non-small cell lung cancer who received postoperative radiation therapy. Lung Cancer. 2012;77(2):326-30.
7. Zhang L, Yang M, Bi N, et al. ATM polymorphisms are associated with risk of radiation-induced pneumonitis. Int J Radiat Oncol Biol Phys. 2010;77(5):1360-8.
8. Lu SL, Hsu FM, Tsai CL, et al. Serum Transforming Growth Factor-beta1 Change After Neoadjuvant Chemoradiation Therapy Is Associated With Postoperative Pulmonary Complications in Esophageal Cancer Patients Undergoing Combined Modality Therapy. Int J Radiat Oncol Biol Phys. 2015;93(5):1023-31.
9. Asakura H, Hashimoto T, Zenda S, et al. Analysis of dose-volume histogram parameters for radiation pneumonitis after definitive concurrent chemoradiotherapy for esophageal cancer. Radiother Oncol. 2010;95(2):240-4.
10. Wang S, Liao Z, Wei X, et al. Association between systemic chemotherapy before chemoradiation and increased risk of treatment-related pneumonitis in esophageal cancer patients treated with definitive chemoradiotherapy. J Thorac Oncol. 2008;3(3):277-82.
11. Nomura M, Kodaira T, Furutani K, et al. Predictive factors for radiation pneumonitis in oesophageal cancer patients treated with chemoradiotherapy without prophylactic nodal irradiation. Br J Radiol. 2012;85(1014):813-8.
12. Ueyama T, Arimura T, Takumi K, et al. Risk factors for radiation pneumonitis after stereotactic radiation therapy for lung tumours: clinical usefulness of the planning target volume to total lung volume ratio. Br J Radiol. 2018;91(1086):20170453.
13. Rice TW, Ishwaran H, Blackstone EH, et al. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29(8):913-919.
14. Xi M, Lin SH. Recent advances in intensity modulated radiotherapy and proton therapy for esophageal cancer. Expert Rev Anticancer Ther. 2017;17(7):635-646.
15. He L, Chapple A, Liao Z, et al. Bayesian regression analyses of radiation modality effects on pericardial and pleural effusion and survival in esophageal cancer. Radiother Oncol 2016;121(1):70-74.
16. Haefner MF, Lang K, Verma V, et al. Intensity-modulated versus 3-dimensional conformal radiotherapy in the definitive treatment of esophageal cancer: comparison of outcomes and acute toxicity. Radiat Oncol. 2017;12(1):131.
17. Chun SG, Hu C, Choy H, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol. 2017;35(1):56-62.

18. Lin SH, Merrell KW, Shen J, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. Radiother Oncol. 2017;123(3):376-381.
19. Lin SH, Hobbs BP, Verma V, et al. Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. J Clin Oncol. 2020;38(14):1569-1579.
20. Wang SL, Liao Z, Vaporciyan AA, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys. 2006;64(3):692-9.
21. Cho WK, Oh D, Kim HK, et al. Dosimetric predictors for postoperative pulmonary complications in esophageal cancer following neoadjuvant chemoradiotherapy and surgery. Radiother Oncol. 2019;133:87-92.
22. Wang L, Liang S, Li C, et al. A Novel Nomogram and Risk Classification System Predicting Radiation Pneumonitis in Patients With Esophageal Cancer Receiving Radiation Therapy. Int J Radiat Oncol Biol Phys. 2019;105(5):1074-1085.
23. Shaikh T, Churilla TM, Monpara P, et al. Risk of radiation pneumonitis in patients receiving taxane-based trimodality therapy for locally advanced esophageal cancer. Pract Radiat Oncol. 2016;6(6):388-394.
24. Cui Z, Tian Y, He B, et al. Associated factors of radiation pneumonitis induced by precise radiotherapy in 186 elderly patients with esophageal cancer. Int J Clin Exp Med. 2015;8(9):16646-51.
25. Cheng YJ, Jing SW, Zhu LL, et al. Comparison of elective nodal irradiation and involved-field irradiation in esophageal squamous cell carcinoma: a meta-analysis. J Radiat Res. 2018;59(5):604-615.
26. Jin H, Tucker SL, Liu HH, et al. Dose-volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. Radiother Oncol. 2009;91(3):427-32.
27. Vogelius IR, Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. Acta Oncol. 2012;51(8):975-83.
28. Bjermer L, Franzen L, Littbrand B, et al. Effects of smoking and irradiated volume on inflammatory response in the lung of irradiated breast cancer patients evaluated with bronchoalveolar lavage. Cancer Res. 1990;50(7):2027-30.
29. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers–a different disease. Nat Rev Cancer. 2007;7(10):778-90.

Figures

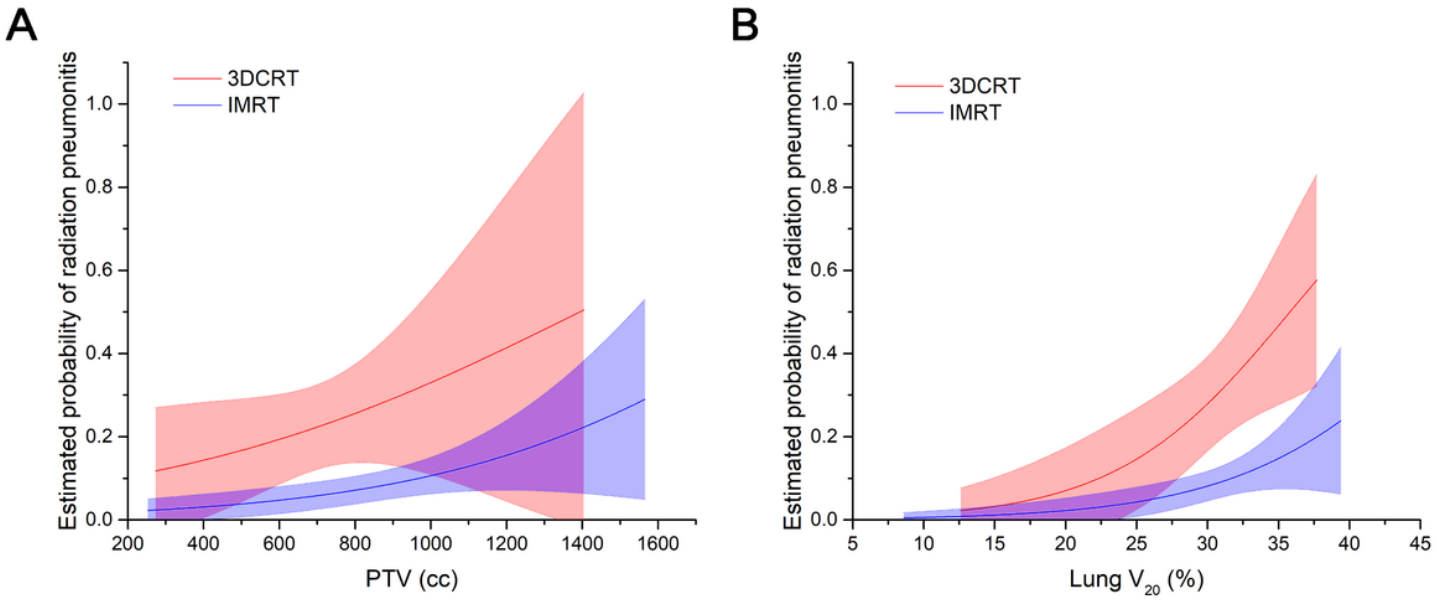

Figure 1

Model to represent the estimated risk of symptomatic radiation pneumonitis as a function of planning target volume (A) and lung V20 (B) for the two radiation modalities based on logistic regression model in the primary cohort. Red line represents three-dimensional conformal radiotherapy (3DCRT) and blue line represents intensity-modulated radiotherapy (IMRT). Shaded regions represent 95% point-wise confidence intervals.

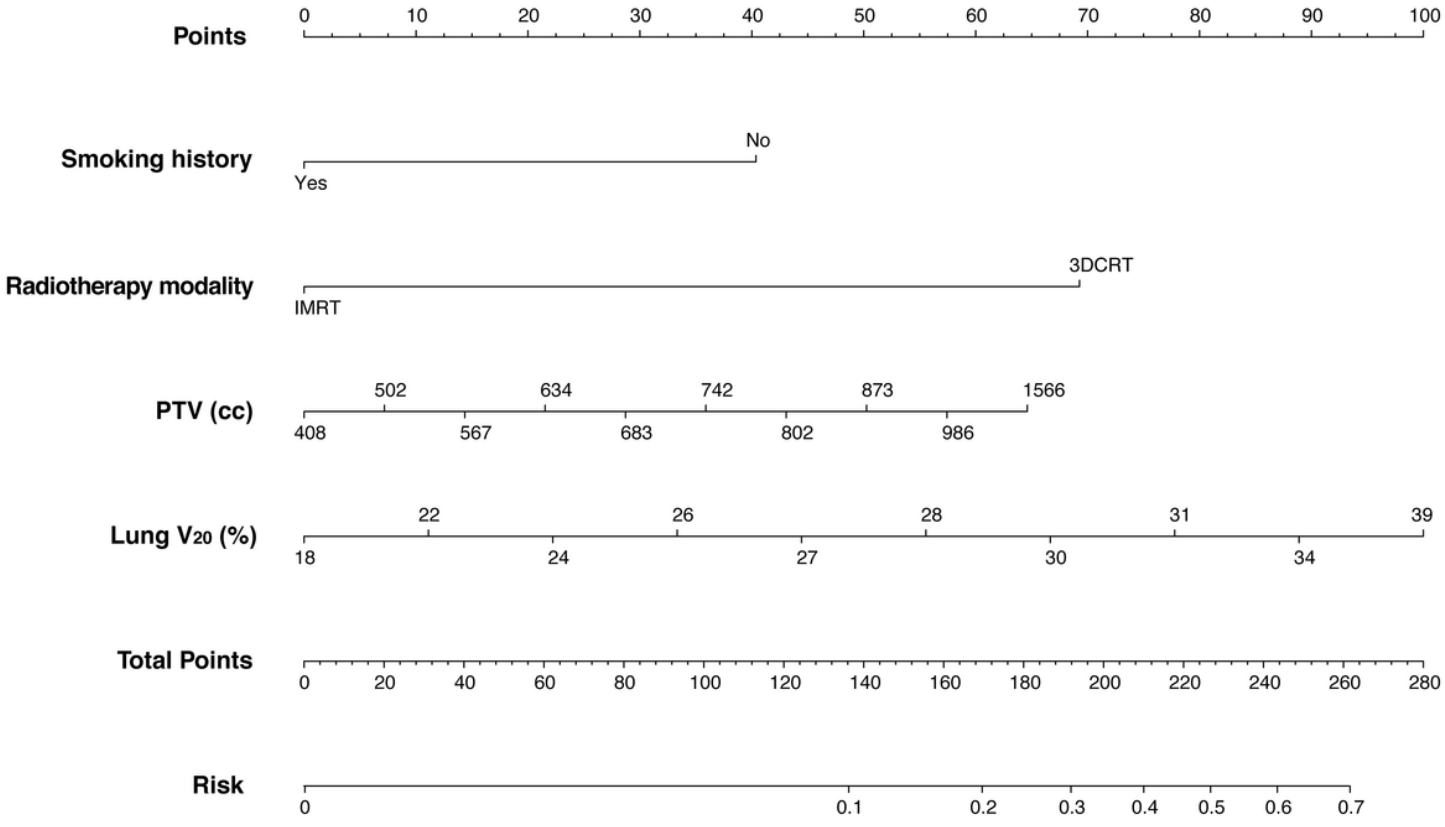

Figure 2

Nomogram predicting the risk of symptomatic radiation pneumonitis in patients with esophageal squamous cell carcinoma who received definitive chemoradiotherapy. For each individual patient, four lines are drawn upward to determine the points received from the four variables in the nomogram. The sum of these points is located on the “Total Points” axis, then a line is drawn downward to predict the risk.

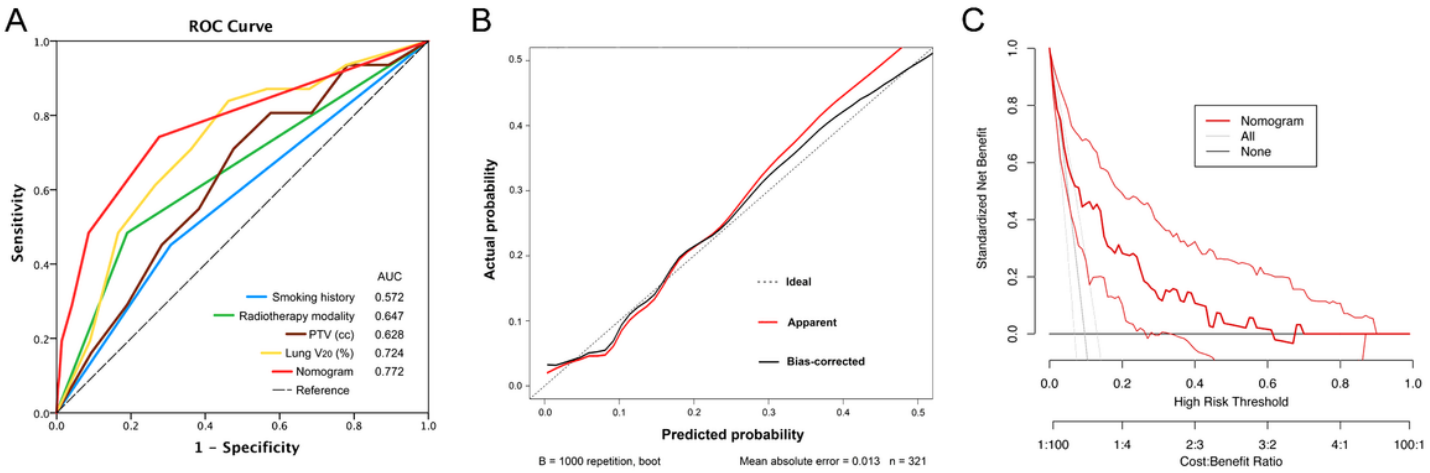

Figure 3

(A) ROC curves of smoking history, radiotherapy modality, PTV, lung V20, and the nomogram in the primary cohort. (B) Calibration curve of the nomogram predicting the risk of symptomatic radiation pneumonitis in the primary cohort. The x-axis and y-axis indicate the predicted and actual probabilities of radiation pneumonitis, respectively. (C) Decision curves of the nomogram predicting the risk of radiation pneumonitis in the primary cohort. The x-axis and y-axis show the threshold probabilities and the net benefit, respectively.

Supplementary Files

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