BMC Cancer

RESEARCH Open Access

The addition of pembrolizumab to neoadjuvant chemoradiotherapy did not increase the risk of developing postoperative anastomotic leakage for ESCC: an analysis from a prospective cohort

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Abstract

Background To compare the difference of postoperative anastomotic leakage (AL) rate between neoadjuvant chemoradiotherapy (NCRT) with pembrolizumab and NCRT group, and investigate the risk factors of developing AL for locally advanced esophageal squamous cell cancer (ESCC).

Materials and methods The GF was contoured on the pretreatment planning computed tomography and dosimetric parameters were retrospectively calculated. Univariate and multivariate logistic regression analysis was performed to determine the independent risk predictors for the entire cohort. A nomogram risk prediction model for postoperative AL was established.

Results A total of 160 ESCC patients were included for analysis. Of them, 112 were treated with NCRT with pembrolizumab and 44 patients with NCRT. Seventeen (10.6%) patients experienced postoperative AL with a rate of 10.7% (12/112) in NCRT with pembrolizumab and 11.4% (5/44) in NCRT group. For the entire cohort, mean, D50, Dmax, V5, V10 and V20 GF dose were statistically higher in those with AL (all $p < 0.05$). Multivariate logistic regression analysis indicated that tumor length ($p = 0.012$), volume of GF ($p = 0.003$) and mean dose of GF ($p = 0.007$) were independently predictors for postoperative AL. Using receiver operating characteristics analysis, the mean dose limit on the GF was defined as 14 Gy.

Conclusion Based on our prospective database, no significant difference of developing AL were observed between NCRT with pembrolizumab and NCRT group. We established an individualized nomograms based on mean GF dose combined with clinical indicators to predict AL in the early postoperative period.

Keywords Esophageal squamous cell carcinoma, Neoadjuvant chemoradiotherapy, Pembrolizumab, Anastomotic leakage, Gastric fundus, Nomogram

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Introduction

According to the global cancer statistics 2020, esophageal cancer (EC) ranked the seventh in cancer incidence and sixth in mortality worldwide [1]. China was a high-incidence area for EC in the world, with newly diagnosed cases accounting for half of world's new cases [2]. And 90% of those patients presented with esophageal squamous cell carcinoma (ESCC). ESCC was an aggressive disease, with a 5-year survival of 20% after surgery alone [3]. Since the publication of CROSS trial [4] and NEOCRTEC5010 trial [5], neoadjuvant chemoradiotherapy(NCRT) followed by surgery become the standardized treatment option for locally advanced EC. However, although NCRT combined with surgery significantly improved the survival outcomes of EC patients, concerns had raised regarding potentially increased risk of postoperative complications and mortality [6]. Anastomotic leakage (AL) was one of the major severe complication after esophagectomy, which significantly associated with a reduced quality of life and an decreased survival [7].

Currently, esophagectomy could be performed by using a variety of surgical techniques, with the predominant preference of using gastric tube as the conduit for reconstruction. The anastomosis could be performed in the thorax or cervically through a neck incision. Prior to the present study, several studies had been performed to investigate the impact of dosimetry of the gastric conduit on the risk of AL, but the results are controversial. Two studies found that the RT dose on the gastric fundus was significantly associated with increased risk of AL, and recommended to minimize the radiation dose to the gastric fundus when planning NCRT [8, 9]. Another research with large sample size found that anastomosis placed within the preoperative radiation field, but not the RT dose on the gastric fundus, was an independent risk predictor for AL [10], while other four small size studies did not found a correlation between the RT dose on the gastric fundus and risk of AL [11–14]. Therefore, the relationship between RT dose of GF and risk of developing AL after surgery remained undetermined.

Recently, immune checkpoint inhibitors (ICIs) had been investigated in different stages of clinical trials [15, 16]. PD-1/PD-L1 inhibitors, such as pembrolizumab and nivolumab, had become the standard of care for the treatment of metastatic esophageal cancer [17–20]. Additionally, more trials had been performed to investigate the efficacy and toxicities of ICIs as neoadjuvant treatment for ESCC [21, 22]. Our previous study had showed that the combination of pembrolizumab with NCRT in ESCC patients achieved a pCR of 55.6% in ESCC patients [23]. However, to our best knowledge, whether the addition of pembrolizumab would increase the risk of developing AL for ESCC patients remained unknown. In addition, no related research had been performed to investigate the risk factors associated with AL among Chinese ESCC patient population, which was significantly different from those western patients. As a result, we performed the present study to compared to the difference of AL rate between NCRT with pembrolizumab and NCRT group, and to investigate the relation between GF radiation dose and risk of AL among a prospective cohort, and develop a novel nomogram prediction model based on clinical and dosimetric data to predict individualized risk of AL.

Materials and methods

Patients

The study was designed as a prospective cohort from four prospective trials (NCT NCT04435197, NCT04435197, NCT04513418, NCT03990532) [24–26], and all included patients were treated with NCRT with or without pembrolizumab followed by esophagectomy and reconstructed the conduit with a narrow gastric tube intrathoracic or cervical anastomosis at Ruijin Hospital, Shanghai Jiao Tong university school of medicine, between Jan 2019 and July 2023. Data regarding surgical procedures, neoadjuvant therapy, and potential confounding clinical and demographic data (sex, age, body mass index, medical history, smoking status, alcohol use, location of tumor, radiotherapy modality, location of anastomosis, clinical TNM stage) were manually extracted.

Treatment protocol

During this study period, patients treated with standard-care NCRT of 41.4 Gy in 23 fractions, on five fractions per week with concurrent 5-fluorouracil (5-FU)/S-1 and cisplatin or weekly carboplatin (area under the curve of 2 mg/mL per min) and paclitaxel/nab-paclitaxel (50 mg/m2 of body surface area). According to trial protocol, patients enrolled in PALACE trial would receive additional two cycles of pembrolizumab on days 1 and 22 of the neoadjuvant therapy at a dose of 200 mg, which had been reported in our previous studies [23, 27]. All planning was to be carried out with a computed tomography (CT)-based three-dimensional planning system with inhomogeneity correction. Patients were positioned for treatment according to marks in the skin and radiological landmarks in the vertebral column. The gross tumor volume (GTV), including the primary tumor (GTVp) and the positive regional lymph nodes (GTVn), was determined by all available information including the contrast enhanced CT, barium swallow, endoscopic examination, and ^{18}F-fluorodeoxyglucose positron emission tomography if available. GTV contained both. The clinical target volume included the GTVp with a cranial and caudal margin of 3 cm and 0.5 cm radial margin, as well as GTVn with 0.5 cm margin adjusted for anatomical

structures. The planning target volume was defined as the CTV with a 0.5 cm margin in all directions. Radiation planning was performed on the Eclipse Treatment Planning System 16.1 (Varian Medical Systems, Palo Alto, CA), patients were treated with intensity-modulated radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMRT) utilizing 6-MV photons. After 4–6 weeks with completion of NCRT, all patients treated with esophagectomy. For tumor located in the proximal third of esophagus or patient presented with cervical lymph node involvement, McKeown esophagectomy with three-field lymph node dissection and cervical esophagogastric anastomosis was performed. The Ivor Lewis esophagectomy with two-field lymph node dissection and intrathoracic anastomosis was performed for middle and distal third located ESCC patients. According to the consensus of Esophagectomy Complications Consensus Group (ECCG), anastomotic leakage was defined as a disruption of the esophagogastric anastomosis, which was identified by clinical observations, radiographic examination, esophago-gastroscopy [28].

Gastric fundus contouring

The GF was retrospectively delineated on the pretreatment planning CT according to the recommendations by Vande Walle C. et al [8], which had been adopted by several previous studies [9, 14]. Firstly, the superior most part of stomach within the diaphragmatic dome was countered in the transverse plane of 3 mm thickness. Then, four consecutive sections in caudal direction were countered at these levels. The resulting three dimensions structure was defined as gastric fundus. The volumes and the dose-volume histograms were created using the Eclipse Treatment Planning System 16.1 to calculate the following GF dose-volume parameters: (1) mean dose (Dmean), median dose (D50), minimal and maximal dose; (2) percentage of volume receiving a certain minimal dose, ranging from 5 Gy (V5) to 30 Gy(V30).

Statistical analysis

Continuous variables were summarized by median and range, and categorical variables were expressed by frequency and proportion. Fisher's test, Student's t test, and Mann-Whitney U test were used to compare the distribution of clinicopathological and dosimetric features between the groups. Univariable and multivariate logistic regression models were used to investigate the risk factors for developing AL. If the radiation dose parameters were to be found significantly related to AL, multivariable logistic regression would be used to assess the risk factors associated with AL. For the dosimetric parameters that were significantly related to anastomotic leakage, receiver operating characteristics (ROC) analysis was performed to identify ideal cutoff values in which equal weight was given to sensitivity and specificity. High correlations between some parameters were expected (e.g., V5 to V30 values and mean dose), resulting in the statistical problem of (multi)collinearity. As a result, only the mean dose was preselected for multivariate logistic analysis. All statistical tests were performed using SPSS 25.0 (IBM corporation, NewYork, NY, USA) and R version 3.6.1 software (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org), and p value <0.05 was considered as significant.

Results

During the study period, a total of 183 ESCC patients treated with NCRT followed by esophagectomy were included for analysis. Of these patients, 18 were excluded for analysis because these patients were treated with NCRT alone and refused to esophagectomy, 5 patients were excluded due to disease progression after treating with NCRT. The baseline characteristics have been listed in Table 1. For the entire cohort, the majority of included patients were male, accounting for 83.1%. the median age was 66 years and median tumor length was 4 cm. 76.9% of included patients were stage IIIB and 13.1% patients were stage IVA. 53.1% of whom had lower third esophagus and 2.5% of whom had gastroesophageal junction (GEJ) cancer. 84/160 (52.5%) of the patients received volumetric modulated arc radiation, while 76/160 (47.5%) received IMRT.

Of the 160 included patients, 116 patients treated with NCRT+pembrolizumab and 44 patients treated with NCRT. The baseline characteristics between NCRT+pembrolizumab and NCRT were comparable excepting for cT stage (Table 1). A total of seventeen (10.6%) ESCC patients experienced postoperative AL, with a rate of 10.7% (12/112) in NCRT combined with pembrolizumab and 11.4% (5/44) in NCRT group, no significant differences could be observed between the two groups. The median NCRT duration was 32 days (ranges: 22–71). The common postoperative complications were pneumonia (11 patients, 6.9%) and arrhythmia (20 patients, 12.5%). With regard to treatment-related mortality, four patients (2.5%) died during the early postoperative period: 3 died of from complications after anastomotic leakage, and 1 died of pulmonary infection and septic shock. All post-operative complications were recorded and presented in supplemental Table 1.

Among the entire cohort, mean, Maximum and D50 dose to the gastric fundus was significantly higher for those with an anastomotic leak when compared to those without an anastomotic leak (15.76 Gy vs. 7.99 Gy, $p=0.006$; 29.94 Gy vs. 17.86 Gy, $p=0.013$; 15.45 Gy vs. 7.56 Gy $p=0.047$, Table 2), respectively. Additionally, V5, V10 and V20 of GF in anastomotic leak group was higher than those without an anastomotic leak (all $p<0.05$,

Table 1 Baseline characteristics of included patients

Characteristics	Entire cohort	NCRT + pembrolizumab (*n* = 116)	NCRT (*n* = 44)	*P* value
Age, median	66 years	65 years	67.5 years	0.37
≤ 65y, n	79	60	19	0.69
> 65y, n	81	56	25	
cT				
cT2	18	9	9	0.025
cT3	135	100	35	
cT4	7	7	0	
cN				
cN0	7	5	2	0.81
cN1	61	47	14	
cN2	75	50	25	
cN3	17	14	3	
Stage				
II	7	5	2	0.89
IIIA	9	9	0	
IIIB	123	84	39	
IVA	21	18	3	
BMI	21.97 (16.43–30.89)	22.38(17.13–30.39)	21.18(16.43–26.53)	0.086
Volume of Gastric fundus	15.47 (4.8-41.4cm^3)	15.8(4.8-41.4cm^3)	13.35(7.4-36.8cm^3)	0.19
Sex				
Male	133	98	35	0.61
Female	27	18	9	
Tumor length	4 cm	4 cm	4.5 cm	0.26
Smoking status				
Yes	103	76	27	0.76
No	57	40	17	
Drinking history				
Yes	98	73	25	0.60
No	62	43	19	
Co-morbidity				
Yes	67	51	16	0.49
No	93	65	28	
Tumor location				
Upper third	21	18	3	0.46
Middle third	50	38	12	
Lower third	85	58	27	
GEJ	4	2	2	
Location of anastomosis				
Cervical anastomosis	92	70	22	0.32
Intrathoracic anastomosis	68	46	22	
RT modality				
IMRT	76	62	30	0.13
VMRT	84	54	14	

Abbreviations GEJ: Gastroesophageal junction; IMRT: Intensity-modulated radiotherapy; VMRT: Volumetric Modulated Arc Therapy; BMI: Body mass index

Table 2 Univariable Logistic Regression Analysis of gastric Fundus dose characteristics between patients with Versus without Anastomotic complications

Characteristics	OR (95%CI)	*P* value
Mean dose, Gy	1.05(1.01–1.10)	0.009
Minimum dose, Gy	1.06(0.97–1.15)	0.19
D50, Gy	1.05(1.01–1.09)	0.011
Maximum dose, Gy	1.03(1.01–1.06)	0.019
V5, %	1.01(1.00-1.03)	0.023
V10,%	1.02(1.00-1.03)	0.039
V15,%	1.02(1.00-1.03)	0.039
V20,%	1.02(1.00-1.03)	0.017
V25,%	1.02(1.00-1.04)	0.015
V30,%	1.02(1.00-1.04)	0.017

Table 2). On univariate logistic regression analysis, there was significant association between the dose-volume parameters of GF including mean dose, D50, Maximum dose, V5, V10, V15, V20, V25 and V30 and the risk of developing anastomotic leak (all $p<0.05$, Supplemental Table 1). The typical cases of dose distributions in relation to the gastric fundus in ESCC patients with and without anastomotic leakage were presented in Fig. 1. These findings suggest that effects should be made to limit the dose to the gastric fundus when planning NCRT for ESCC.

For clinical-pathological variables, only tumor length ($p=0.004$) and volume of gastric fundus ($p=0.033$) were significantly associated with risk of developing AL on univariate analysis (Table 3). Multivariate logistic regression analysis indicated that tumor length($p=0.012$), volume of gastric fundus ($p=0.003$) and mean dose of gastric fundus($p=0.007$) were independent risk factors for developing AL in early postoperative period (Table 4). Using ROC analysis, the mean dose to the gastric fundus above which the risk of early anastomotic leakage significantly increased was identified as 14.27 Gy, and the area under the curve was 0.689 (supplemental Table 2). Finally, three independent variables including tumor length, volume of gastric fundus and mean dose of gastric fundus, were selected for the construction of a nomogram of AL rate (Fig. 2). The C-index of the nomogram was 0.824(Fig. 3), and the calibration plot indicated that there was a good concordance between the predicted and observed AL probabilities (Fig. 4).

Discussion

Currently, NCRT followed by esophagectomy with lymphadenectomy remained the standardized choice for the treatment of esophageal cancer. However, esophagectomy was a technically complex procedure which was associated with major complications, occurring over 17% of the patients [29]. Anastomotic leakage after esophagectomy, including cervical anastomotic leakage and

Table 3 Univariable Logistic Regression Analysis of clinical characteristics between patients with Versus without Anastomotic complications

Characteristics	OR (95%CI)	*P* value
Age		
≤ 65y	1	
> 65y	2.57 (0.86–7.68)	0.09
Stage		
II/IIIA	1	
IIIB/IVA	2.02 (0.25–16.23)	0.51
Sex (female vs. male)		
Female	1	
Male	1.59 (0.34–7.39)	0.55
BMI	0.96(0.79–1.14)	0.62
Location		
Upper third	1	
Middle third	0.40 (0.05–3.08)	0.38
Lower third/ GEJ	1.60(0.33–7.72)	0.56
Tumor length	1.32(1.09–1.60)	0.004
Volumes of GF, ml	1.07(1.01–1.15)	0.033
Smoking status		
No	1	
Yes	1.37(0.46–4.11)	0.57
Drinking status		
No	1	
Yes	1.59(0.53–4.76)	0.41
Co-morbidity		
No		
Yes	1.27(0.46–3.47)	0.66
Location of anastomosis		
Cervical anastomosis	1	
Intrathoracic anastomosis	1.40(0.49-4.00)	0.52
NCRT regimen		
NCRT alone	1	
NCRT + pembrolizumab	1.15(0.38–3.48)	0.80
Radiation modality		
IMRT	1	
VMRT	2.37(0.80–7.06)	0.12

Table 4 Multivariable logistic regression analysis of characteristics between patients with Versus without Anastomotic complications

Characteristics	OR (95%CI)	*P* value
Tumor length	1.27(1.05–1.53)	0.012
Volumes of Gastric Fundus, ml	1.12(1.04–1.22)	0.003
Mean dose of gastric fundus, Gy	1.07(1.02–1.12)	0.007

intrathoracic anastomotic leakage, was one of the major severe complication, which was reported in the literature to occur in between 3% and 36% of patients after esophagectomy [3, 30]. Recently, multiple studies had been performed to investigate the efficacy of combination ICIs with neoadjuvant treatment for ESCC patients. However, concerns had raised regarding potentially increased risk of postoperative anastomotic leakage (AL) for the combination of NACT and ICIs. To our best knowledge, this was the first study to investigate the risk of developing postoperative AL among ESCC patients treated NCRT with or without ICIs. In the present study, a total of seventeen (10.6%) ESCC patients experienced postoperative AL in our patient cohort. The incidence of developing AL in NCRT combined with pembrolizumab was comparable to those in NCRT group (10.7% vs. 11.4%, $p=0.98$). AL was associated with prolonged hospital stay, increased costs and postoperative 90-day mortality [31, 32]. In our cohort, 3/17 (17.6%) patients with AL experienced 90-day mortality after trimodality therapy. As a result, AL after esophagectomy was a severe complication with a high mortality rate, but the combination of pembrolizumab with NCRT did not increase the risk of developing AL for ESCC patients. Moreover, it was very important to identify potentially risk factors to reduce the occurrence of AL in early postoperative period.

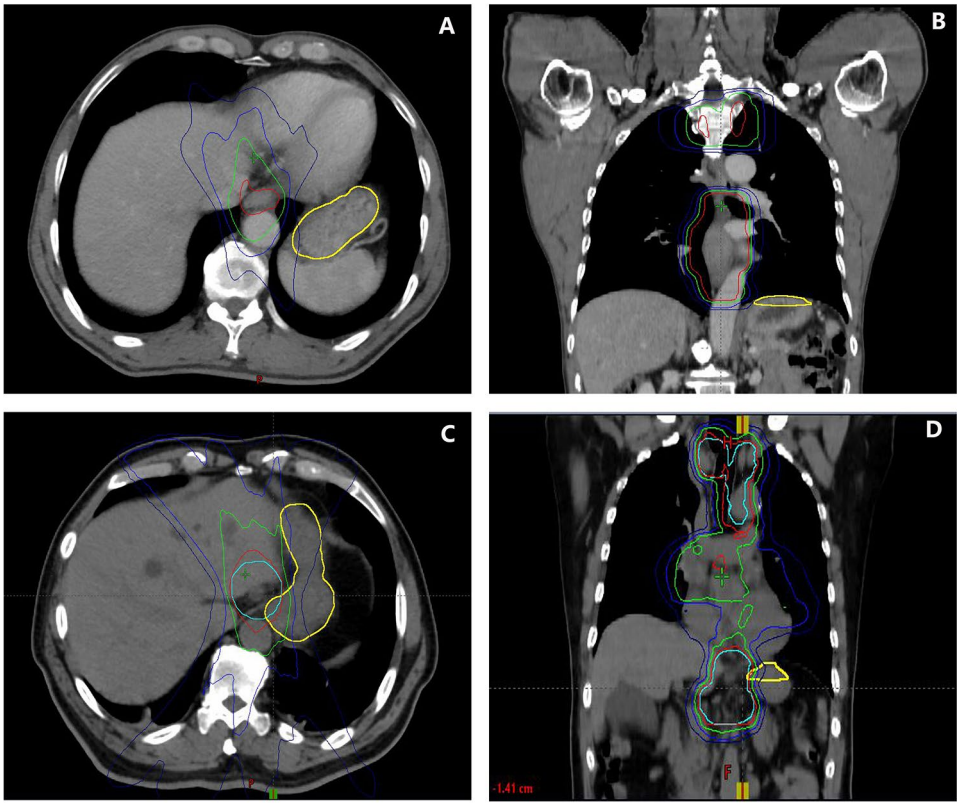

Fig. 1 Axial and coronal section of planning CT scan showing the contoured gastric fundus with dose distributions: **A** and **B**: a patient who did not experience postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 3.3 Gy; **C** and **D**: a patient who experienced postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 25.9 Gy. The red, green, light blue and purple lines were 40, 30,20 and 10 Gy isodose, the yellow line was the gastric fundus

Prior to the present study, several studies had been published to investigate the relation between radiation dose to gastric fundus and the incidence of AL in patients undergoing NCRT followed by construction of an intrathoracic/cervical anastomosis, but the results were controversial. Therefore, whether the dose constraints on gastric fundus could reduce the risk of anastomotic leakage in the treatment of ESCC remains undetermined. The present study was a large prospective cohort data to comprehensively assess the impact of clinical-pathological and dosimetric parameters on risk of AL occurrence in Chinese ESCC patients. In the present study, we found that mean, D50, Dmax, V5, V10 and V20 of GF dose were statistically higher in those with AL (all $p<0.05$), while Dmin, V15, V20, V25, V30 doses did not significantly differ between those with and those AL (all $p>0.05$). Multivariate logistic regression analysis indicated that mean dose of GF was an independently predictor for postoperative AL. In consistent with Juloori er al's study, the authors also found that there was an association of the mean dose to the stomach and substructures to the incidence of all grade leaks [10]. Using receiver operating characteristics analysis, the area under the curve was 0.689, and the Mean limit on the GF was defined as 14 Gy. According to the results of present study, limiting the mean dose to 14 Gy could decrease the risk of anastomotic leakage to 15% in this setting.

In the present study, volume of GF was another independent factor for the development of anastomotic leakage, and volume of GF in patients with anastomotic leakage was significantly larger than those without AL($p<0.05$). However, in Goense et al's work, volume of GF was not a risk factor for developing AL [9]. One possible explanation for this finding was that all ESCC patients in our cohort would drink oral contrast agent before scanning a contrast-enhanced simulation computerized tomography scan. The volume of GF in our study was 16.82±6.82 ml, which was significantly larger than Goense et al's work (11.8 ml). Therefore, more healthy tissue of GF in AL group would be irradiated. In our study, 13/17(76%) AL occurred in lower third/GEJ and there was a tendency to increased risk of developing AL in the lower third/GEJ (RR1.60, 95%:0.33–7.72). However, the 95% confidence interval of RR is wide, thus it suggested insufficient sample size in the present study, and further large studies focus on investigating the risk of developing AL in esophageal cancer were still needed. Additionally, tumor length was another risk factor for

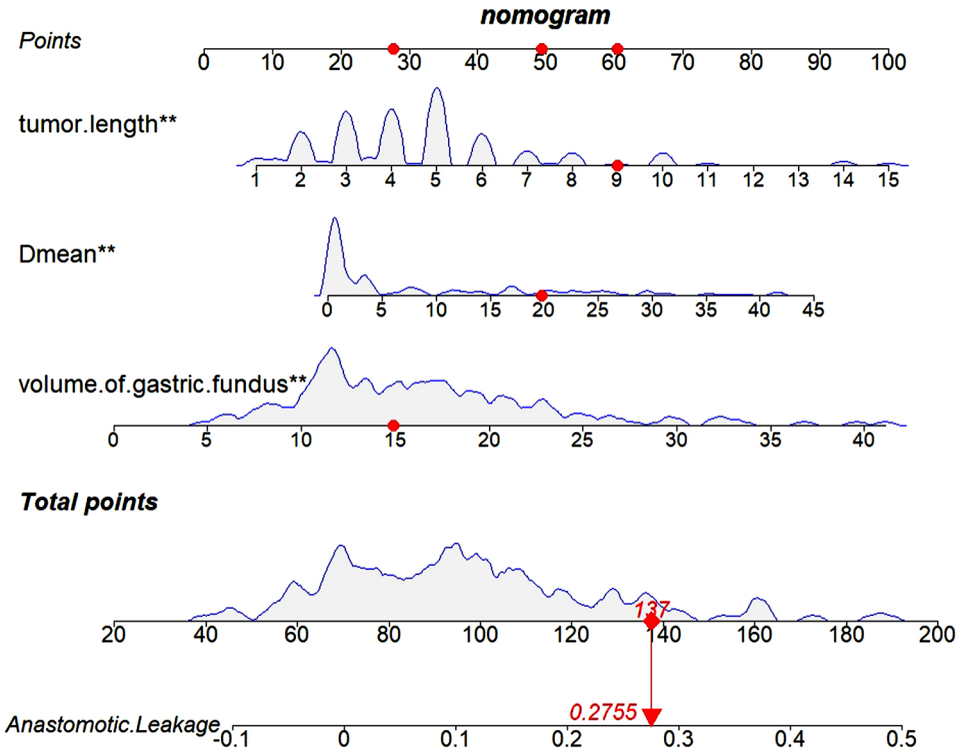

Fig. 2 Nomogram for predicting postoperative anastomotic leakage after trimodality therapy for esophageal squamous cell carcinoma

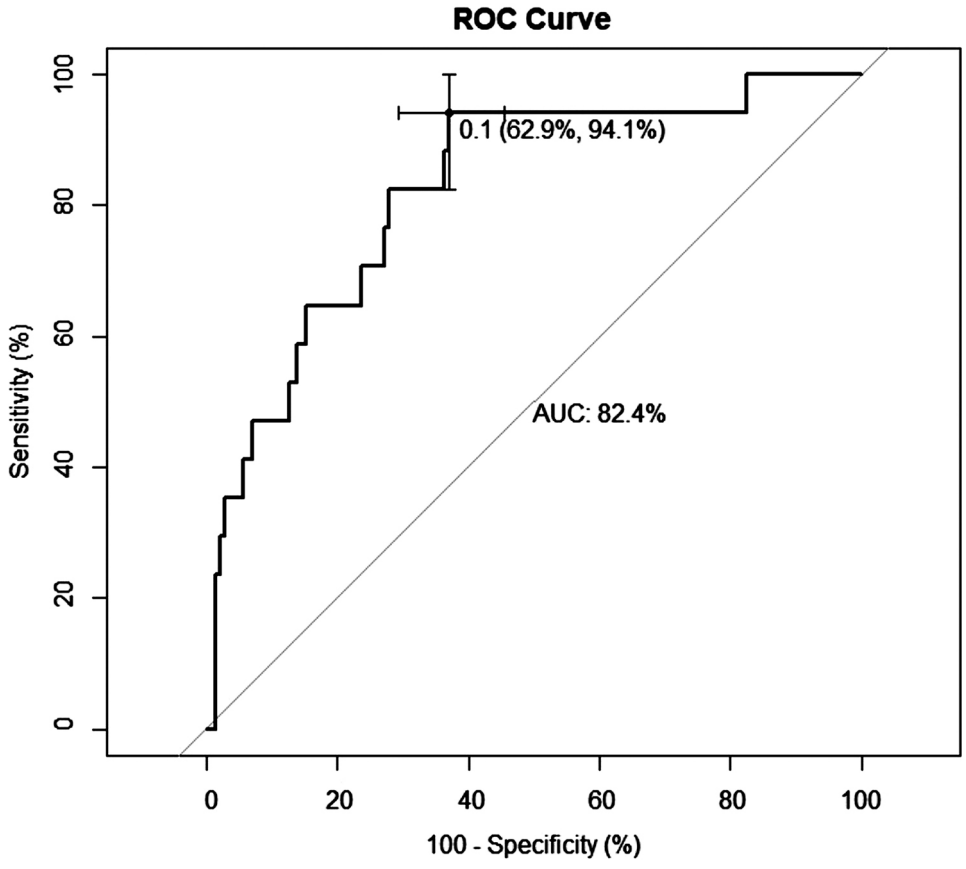

Fig. 3 Receiver operating characteristic curves for risk model to predict the anastomotic leakage after trimodality therapy

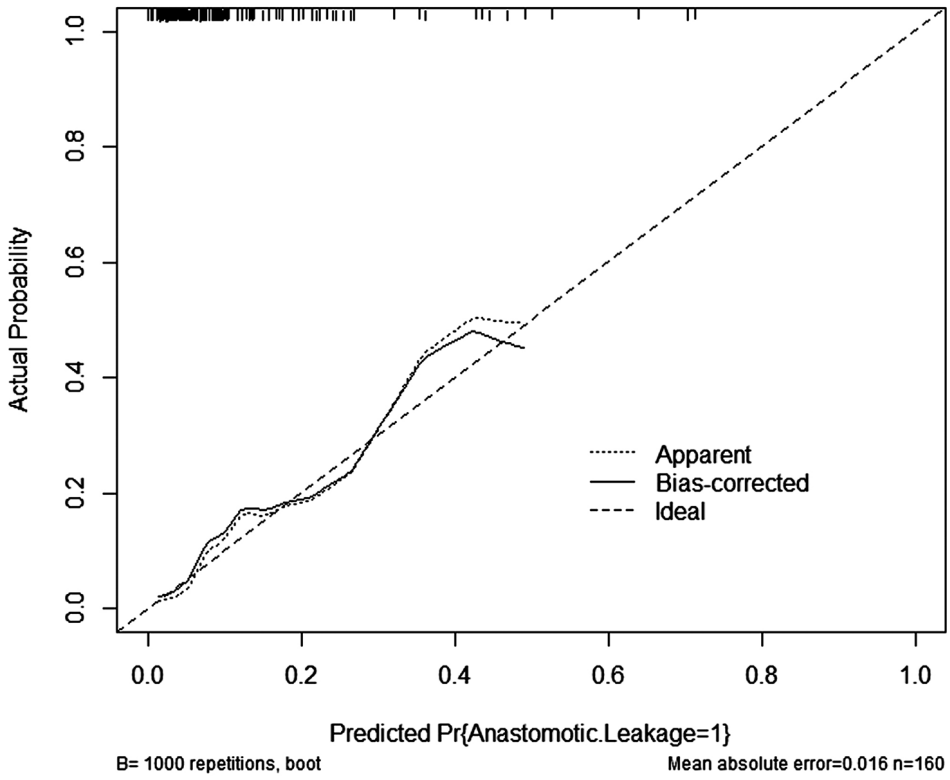

Fig. 4 Calibration curves for the nomogram to estimate anastomotic leakage after trimodality therapy

AL in the present study. For patients with longer tumor length, more healthy esophagus tissue would be removed and those patients would be at high risk of leakage due to excessive tension on the anastomosis. Finally, we established a nomogram to predict the risk of AL among ESCC patients treated trimodality therapy based on these three risk factors.

The present study had the largest sample size focusing on Chinese ESCC patients treated with current trimodality therapy and is the first-study to investigate the risk of developing AL for ESCC patients treated with combined of ICIs and NCRT. However, our study had several limitations. First of all, both of cervical and intrathoracic anastomosis were included for analysis, which might a source of heterogeneity on the association between radiation dose and anastomotic leakage. Secondly, we were unable to assess the impact of breathing-induced organ motion on the irradiation dose to the gastric fundus. Thirdly, the patients were obtained from a single medical institute, further studies with large samples were still needed to externally validate our findings.

Conclusion

Based on the prospective cohort data, the addition of pembrolizumab did not significantly increase the risk of developing AL. In addition, we identified tumor length, volume of GF and mean dose of GF were three independently predictors for postoperative AL. Based on these three factors, we established a nomogram to predict the risk of AL among ESCC patients treated with NCRT followed by esophagectomy with lymphadenectomy. When planning RT treatment, effect should be made to limit the Dmean of gastric fundus to 14 Gy. Further studies were still needed to confirm our findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12774-w.

Supplementary Material 1

Acknowledgements
None.

Author contributions
Principal investigator: J.C. and S.Z. Drafting of the protocol manuscript: W.X.Q.Conceptualization: J.C. and W.X.Q.; Project administration: S.L. and H.L. data analysis, acquisition, and interpretation: W.X.Q., J.C.; manuscript preparation: W.X.Q., S.L., H.L., J.C. and S.Z. Final approval of manuscript: all authors.

Funding
This study was supported in part by the Shanghai Sailing Program (No. 21YF1427700), the National Science Foundation of China (No. 82102819), Beijing Science and Technology Innovation Medical Development Foundation (grant number KC2021-JX-0170-9), Clinical Research Special Project of Shanghai Municipal Health Commission Health Industry (202340226), Shanghai Science and Technology Innovation Action Plan Medical Innovation

Research Project (23Y11904700) and Shanghai Key Laboratory of Proton-therapy (23dz2261000). The funding agency plays no role in the design or execution of the study.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Ruijin hospital, Shanghai Jiao Tong University School of Medicine. Informed consent to participate was obtained from all of the participants in the study.

Competing interests
The authors declare no competing interests.

Received: 18 March 2024 / Accepted: 6 August 2024
Published online: 20 August 2024

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