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ORIGINAL ARTICLE

Neoadjuvant chemo(radio)therapy and anastomotic leakage risk in patients with esophageal squamous cell carcinoma

Quimio(radio)terapia neoadyuvante y riesgo de fuga anastomótica en pacientes con carcinoma de células escamosas esofágico

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Abstract

Objective: *To investigate the different impacts of neoadjuvant chemotherapy (NCT) and neoadjuvant chemoradiotherapy (NCRT) on anastomotic leakage after esophageal cancer resection.* **Methods:** *The data of three clinical studies (222 patients) launched were retrospectively collected, including 113 patients in the NCRT group and 109 patients in the NCT group. The NCT group received platinum-based doublet chemotherapy once every 3-4 weeks, whereas the NCRT group received platinum-based doublet chemotherapy weekly (taxane-containing regimen) or once every 3-4 weeks (5-Fu-containing regimen) concurrently with thoracic radiotherapy. After neoadjuvant therapy, all patients underwent Ivor-Lewis or McKeown esophagectomy. The study compared the pathologic complete remission (pCR) rate, 30-day post-operative mortality rate, incidence of anastomotic leakage, post-operative complications, and survival rates between the two groups.* **Results:** *The pCR rate, 30-day post-operative mortality rate, and the incidence of anastomotic leakage were 39.8% versus 5.5% ($p < 0.001$), 2.7% versus 0% ($p = 0.043$), and 28.3% versus 5.5% ($p < 0.001$) in the NCRT group and NCT group, respectively. Multivariate analysis showed that only NCRT significantly increased the incidence of anastomotic leakage (odds ratio 7.28, 95% confidence interval 2.44-21.78, $p < 0.001$).* **Conclusions:** *The results show that NCRT can improve the pathological response rate but will increase the incidence of anastomotic leakage. Radiation dose-volume parameters were not associated with anastomotic leakage risk.*

Keywords: *Malignant esophageal tumor. Neoadjuvant therapy. Anastomotic leak. Risk factors. Chemoradiation.*

Resumen

Objetivo: *Investigar el diferente impacto de la quimioterapia neoadyuvante (QTN) y la quimiorradioterapia neoadyuvante (QRTN) en la fuga anastomótica después de la resección de cáncer de esófago.* **Métodos:** *Se recopilaron retrospectivamente los datos de tres estudios clínicos (222 pacientes), incluyendo 113 pacientes en el grupo de QRTN y 109 pacientes en el grupo de QTN. El grupo de QTN recibió quimioterapia de doblete a base de platino una vez cada 3-4 semanas, mientras que el grupo de QRTN recibió quimioterapia de doblete a base de platino semanal (régimen que contiene taxano) o una vez cada 3-4 semanas (régimen que contiene 5-fluorouracilo) de forma concurrente con radioterapia torácica. Después del tratamiento neoadyuvante, todos los pacientes se sometieron a esofagectomía de Ivor-Lewis o McKeown. El estudio comparó las tasas de remisión completa patológica, mortalidad posoperatoria a 30 días, incidencia de fuga de anastomosis, complicaciones posoperatorias y tasas de supervivencia entre los dos grupos.* **Resultados:** *Las tasas de remisión completa patológica, mortalidad posoperatoria a 30 días e incidencia de fuga de anastomosis fueron del 39.8% frente al 5.5% ($p < 0.001$), del 2.7% frente al 0% ($p = 0.043$) y del 28.3% frente al 5.5% ($p < 0.001$) en el grupo de QRTN y en el grupo de QTN, respectivamente.*

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El análisis multivariado mostró que solo la QRTN aumentó significativamente la incidencia de fuga anastomótica (OR: 7.28; IC 95%: 2.44-21.78; p < 0.001). **Conclusiones:** *Los resultados muestran que la QRTN puede mejorar la tasa de respuesta patológica, pero aumentando la incidencia de fuga anastomótica. Los parámetros de dosis-volumen de radiación no estuvieron asociados con el riesgo de fuga anastomótica.*

Palabras clave: *Tumor maligno de esófago. Tratamiento neoadyuvante. Fuga de anastomosis. Factores de riesgo. Quimiorradioterapia.*

Introduction

Esophageal carcinoma has a poor prognosis after surgery alone, neoadjuvant chemoradiotherapy (NCRT) is currently considered the standard care for locally advanced esophageal carcinoma[1,2]. Neoadjuvant chemotherapy (NCT) is also a common practice in multimodality treatment due to the fear of excessive toxicity associated with NCRT, especially after the JCOG1109 NExT study[3] and the CMISG1701 trial[4]. Neoadjuvant therapy may increase the incidence of post-operative complications and even mortality[5]. Anastomotic leakage refers to the rupture of the anastomosis after esophageal cancer (EC) surgery, resulting in the leakage of gastric contents[6]. It is one of the most common complications after EC surgery and can lead to serious infection and even death. Radiation therapy in NCRT can damage tissue, affect wound healing, and increase the risk of anastomotic leakage. In addition, NCRT may lead to malnutrition, affect the patient's immune function, increase the risk of infection, and thereby increase the risk of anastomotic leakage[7]. Studies have shown that anastomotic leakage is closely related to both tumor recurrence and poor survival[8,9]. However, the impact of different neoadjuvant treatment patterns on anastomotic leakage is not well studied.

Radiotherapy can cause damage to microvessels and has a negative effect on irradiated tissue healing. Theoretically, the incidence of anastomotic leakage may be increased when radiotherapy is added to NCT, but rare data were reported from past studies. Most of the studies involve the comparison of anastomotic complications between NCRT and surgery alone, and the conclusions are inconsistent. Some studies have reported a higher incidence of anastomotic leakage in the NCRT group, whereas others have found no significant difference compared with surgery alone. This inconsistency may arise from variations in study design, patient populations, surgical techniques, and definitions of anastomotic leakage[10-12]. Unlike EC in Western countries, which has a high prevalence of esophagogastric junction adenocarcinoma, esophageal squamous cell carcinoma (ESCC) is the most common pathological type in East Asia, and most of the lesions are located in the upper middle portion of the chest. As a result, the radiation field is more closely related to the anastomotic region. In addition, the optimal radiation dose of NCRT has not yet been determined. In recent years, great progress has also been made in the technology of radiotherapy. Based on the above reasons, the risk factors for anastomotic leakage in multimodality treatment should be re-analyzed.

Therefore, clinical data from three prospective trials in neoadjuvant therapy were collected to evaluate whether adding radiotherapy to NCT would increase the incidence of anastomotic leakage, and the effect of radiation dose-volume parameters on rates of anastomotic leakage was also analyzed.

Methods

Clinical data

This study is a retrospective study. A total of 222 cases of clinical data from three prospective clinical studies (NCT01258192, NCT01463501, and NCT03381651) from February 2013 to December 2017 were selected. According to the choice of treatment, the NCT group formed the control group (n = 109), and the NRCT group formed the observation group (n = 113). The pre-treatment evaluation included chest and upper abdominal enhanced computed tomography (CT) scan and cervical B-ultrasound. Informed consent was waived due to the retrospective nature of the study.

Main inclusion criteria: (1) ECOG PS 0-1; (2) operable or potentially operable (cT2-4N0 or cN1) thoracic ESCC; (3) number of NCT cycles ≥ 2; (4) Ivor-Lewis esophagectomy or McKeown esophagectomy (open or laparoscopic) was mandatory; (5) intensity-modulated radiation therapy (IMRT) was mandatory. Exclusion

criteria: (1) salvage esophagectomy after chemoradiotherapy; (2) prophylactic cervical lymph node dissection; (3) jejunal or colon interposition for esophageal replacement; (4) exclude patients with chronic diseases such as malnutrition, diabetes, hypertension, coronary heart disease; (5) exclude patients who have received other anti-tumor treatments.

Data collection

The following data were collected: age, gender (male/female), smoking history (yes/no), drinking (yes/no), lesion location (upper/middle lower of the chest), lesion length, body mass index (BMI) before neoadjuvant treatment, types of neoadjuvant therapy (NCRT/NCT), time from the end of neoadjuvant therapy to surgery, pre-operative BMI, surgical approach (laparoscopic/open), intraoperative blood loss, anastomotic location (cervical/thoracic), residual esophageal length, degree of pathological remission (complete/incomplete), 30-day post-operative mortality rate, radiation prescribed dose, residual esophageal dose (maximum dose and average dose), and anastomotic region dose-volume parameters (V10, V20, V30, V40, V50, average dose, and maximum dose).

Treatment

Neoadjuvant therapy

The platinum-based doublet chemotherapy regimen was delivered once every 3-4 weeks in the NCT group, and few patients received a platinum-based triplet regimen[13,14]. In the NCRT group, platinum-containing doublet chemotherapy was given weekly (taxane-containing regimen) or once 3-4 weeks (5-Fu-containing regimen) concurrently with thoracic radiotherapy. IMRT was delivered in all patients, GTV included primary tumor and metastatic lymph node (> 5-10 mm in maximum diameter), which was contoured on the planning CT scans. The PTV was defined as GTV plus a 3-4 cm margin superior and inferior to the primary tumor and a 1-1.5 cm radial margin. For patients with lesions in the upper chest or lymph node metastasis in the superior mediastinum, prophylactic irradiation of para-recurrent laryngeal nerve lymph chain and lower neck lymph node was preferred, but the cervical esophagus and the bilateral lower neck should be protected from radiation as much as possible. The radiation dose was 40-50.4 Gy at 1.8-2 Gy per fraction.

Delineation of the residual esophagus and anastomotic region, and evaluation of dosimetry: a diagnostic CT scan which was performed within half a year after surgery with the same body position and layer thickness as planning CT scan was selected. Anastomosis was recognized in diagnostic CT slices through anastomosis staples and was uniformly expanded by 5 mm to create a so-called “anastomotic region,” which was then copied to the corresponding planning CT image. Delineation of the residual esophagus: the upper boundary was at the level of the cricothyroid membrane, and the lower boundary was at the level of the anastomotic region. To reduce the contour error, the delineation of the anastomotic region and residual esophagus were all completed by the first author. The evaluation of anastomotic region dose-volume parameters included V10, V20, V30, V40, V50, mean dose, and maximum dose. The evaluation of residual esophageal dose included the maximum dose and mean dose. The length of the residual esophagus was measured on the CT slice.

Surgery

Ivor-Lewis esophagectomy or McKeown esophagectomy was performed around 1.5 months after the completion of neoadjuvant therapy. Laparoscopic resection was also allowed. Jejunal or colon interposition for esophageal replacement was not allowed.

Definition of anastomotic leakage

Esophageal-gastric anastomotic leakage was diagnosed through clinical and/or adjuvant examination, including esophagography, digestive endoscopy, and diagnostic CT. The incidence of anastomotic leakage is usually highest within 5-7 days after surgery, but it also occurs in approximately 12% of patients 30 days after surgery. Therefore, we followed up with patients after surgery for EC for 60 days to monitor the occurrence of anastomotic leakage[15].

Definition of pathologic complete remission (pCR) rate

In patients with EC, the pCR rate usually refers to surgical resection after NCT or chemoradiotherapy, and pathological examination finds no residual tumor, including carcinoma *in situ* and invasive carcinoma.

PCR is one of the important indicators to evaluate the effect of neoadjuvant therapy for EC.

Statistical analysis

Detailed statistical analysis of the collected data was conducted using Statistical Package for Social Sciences 18.0 statistical software. Continuous numerical variables that conform to normal distribution are statistically described by mean standard deviation (x s), and a two-sample t-test is used for comparison between groups. Numerical variables that do not conform to the normal distribution are described by median (minimum–maximum), and Mann-Whitney U test is used for comparison between groups. Categorical data were statistically described using the number of cases (%), and X^2 tests were used for comparisons between groups. Univariable logistic regression model and multivariable Cox regression model analysis were used to evaluate risk factors associated with anastomotic leakage. $P < 0.05$ indicates that the difference is statistically significant.

Results

General information description

About 113 patients received NCRT, and 109 received NCT. The median age was 60 years (42-77 years old). There were 60 cases in stage IIA, 26 cases in stage IIB, 122 cases in stage III, and 14 cases in stage IVA. Among them, 38 (17.1%) patients had lesions in the upper thoracic region, 144 (64.9%) in the middle thoracic region, and 40 (18.0%) in the lower thoracic region. Compared with the NCT group, patients in the NCRT group had younger ages, longer time from the end of neoadjuvant therapy to surgery, shorter residual esophagus, less blood loss, and more laparoscopic surgery (Table 1). The dose of radiation was between 3,400 to 5,220 cGy (median radiation dose was 4,500 cGy). 89% of patients received taxane + platinum chemotherapy regimen, and other regimens included 5-Fu+platinum, NVB+ platinum.

Post-operative results between NCRT group and NCT group

The pathological complete remission rate (pCR) in the NCRT group and NCT group was 39.8% and 5.5%, respectively ($p < 0.001$), and the 30-day post-operative morality was 2.7% and 0%, respectively, the log-rank test showed that there was a significant difference in survival between the two groups ($p = 0.019$). One patient in the NCRT group died from major bleeding caused by anastomotic leakage (Table 2).

About 38 patients had a post-operative anastomotic leakage, 27 of which were diagnosed by clinical plus adjuvant examination, nine were diagnosed according to clinical examination, and two were confirmed by adjuvant examination. The median time of leakage occurrence after surgery was 13 days (4 days-57 days). The incidence of anastomotic leakage in the NCRT group and NCT group was 28.3% and 5.5%, respectively, with a statistically significant difference ($p < 0.001$) (Table 2).

Univariate and multivariate analysis of clinicopathologic factors associated with anastomotic leakage incidence in whole group

Univariate analysis showed that NCRT ($p < 0.001$), cervical anastomosis ($p = 0.002$), laparoscopic surgery ($p = 0.017$), longer time from the end of neoadjuvant therapy to surgery ($p = 0.010$), and shorter residual esophageal length ($p = 0.001$) were significantly associated with the risk of anastomotic leakage. The multivariate analysis showed that NCRT was an independent risk factor for anastomotic leakage (odds ratio 7.28, 95% confidence interval 2.44-21.78, $p < 0.001$). However, this study only included patients in the NCT and NCRT groups, and the impact of other factors on anastomotic leakage requires further study (Table 3).

Univariate and multivariate analysis of risk factors associated with anastomotic leakage in NCRT group

Further analysis of the dosimetry parameters related to anastomotic leakage in the NCRT group found no significant association between anastomotic leakage incidence and the radiation prescribed dose, anastomotic region dose-volume parameters (V10, V20, V30, V40, V50, mean dose, and maximum dose), and residual esophageal dose (mean dose and maximum dose) based on univariate and multivariate analysis (Table 4).

Table 1. Baseline characteristics between NCRT group and NCT group

Characteristics	NCRT (n = 113)	NCT (n = 109)	u/X^2	p
Gender, n (%)			0.005	0.944
Male	106 (93.8)	102 (93.6)		
Female	7 (6.2)	7 (6.4)		
Smoking, n (%)			0.059	0.808
Yes	84 (74.3)	84 (77.1)		
No	29 (25.7)	25 (22.9)		
Drinking, n (%)			0.073	0.797
Yes	89 (78.8)	85 (78.0)		
No	24 (21.2)	23 (21.1)		
Lesion location, n (%)			0.055	0.815
Upper chest	20 (17.7)	18 (16.5)		
Middle-lower chest	93 (82.3)	91 (83.5)		
cTNM stage, n (%)			1.348	0.717
IIA	27 (23.9)	33 (30.3)		
IIB	13 (11.5)	13 (11.9)		
III	66 (58.4)	56 (51.4)		
IVA	7 (6.2)	7 (6.4)		
Surgery approach, n (%)			51.061	0.000
Open	45 (39.8)	94 (86.2)		
Laparoscopic	68 (60.2)	15 (13.8)		
Anastomotic location, n(%)			110.47	0.000
Cervical	113 (100)	37 (33.9)		
Intrathoracic	0 (0)	72 (66.1)		
Median age (years)	59 (42-77)	61 (43-73)	8.371	0.009
Lesion length (cm), mean ± SE	6.05 ± 0.18	5.94 ± 0.23	0.427	0.191
BMI before neoadjuvant therapies (kg/m^2), mean ± SE	21.82 ± 0.27	22.23 ± 0.27	0.401	0.204
Median time from the end of neoadjuvant therapy to surgery (days)	35 (15-80)	29 (11-55)	11.745	0.000
Pre-operative BMI (kg/m^2), mean ± SE	21.38 ± 0.29	22.00 ± 0.23	2.355	0.060
Intraoperative blood loss (mL), mean ± SE	219.42 ± 13.61	240.54 ± 17.03	3.597	0.034
Residual esophageal length (cm), mean ± SE	3.76 ± 0.09	6.25 ± 0.23	9.471	0.000
TNM stage			0.821	0.365
II	43	48		
III	70	61		
T staging of tumor			0.427	0.514
T2	18	21		
T3	95	88		

cTNM: clinical tumor node metastasis; TNM: tumor node metastasis; BMI: body mass index; SE: standard error.

Table 2. Post-operative results between NCRT group and NCT group

Characteristics	NCRT (n = 113)	NCT (n = 109)	X^2	p
R0, n (%)	106 (93.8)	105 (96.3)	0.751	0.386
pCR, n (%)	45 (39.8)	6 (5.5)	36.927	0.000
pT0, n (%)	61 (54.0)	7 (6.4)	59.063	0.000
pN0, n (%)	66 (58.4)	47 (43.1)	5.189	0.022
Anastomotic leakage, n (%)	32 (28.3)	6 (5.5)	20.354	0.000
30-day post-operative mortality rate, n (%)	3 (2.7)	0 (0)	-	-

NCT: neoadjuvant chemotherapy; NCRT: neoadjuvant chemoradiotherapy; R0: macroscopic complete resection; pCR: pathologic complete remission; pT0: pathologic T0; pN0: pathologic n0.

Discussion

This study compared the impact of NCT and NCRT on anastomotic leakage after EC resection. The results showed that compared with NCT, NCRT significantly increased the rate of pCR but also increased the incidence of anastomotic leakage. Multivariate analysis confirmed that NCRT was an independent risk factor for anastomotic leakage. Further dosimetry analysis showed no significant association between anastomotic leakage risk and radiation dose to the residual esophagus and anastomotic region.

Our findings are similar to those of previous studies[2,9,15-23]. For example, the CROSS study reported

Table 3. Univariate and multivariate analysis of clinicopathologic factors associated with anastomotic leakage incidence in whole group

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Gender, male/female	0.29	0.04-2.28	0.241			
Smoking, yes/no	1.56	0.64-3.76	0.325			
Drinking, yes/no	1.08	0.46-2.53	0.866			
Tumor location, proximal third/middle-lower third	2.23	1.00-5.00	0.050			
Type of neoadjuvant therapy, NCRT/NCT	7.51	3.01-18.75	< 0.001	7.28	2.44-21.78	< 0.001
Surgery approach, open/laparoscopic	0.43	0.21-0.86	0.017	0.47	0.33-1.17	0.144
Anastomosis location, cervical/thoracic	25.07	3.37-186.54	0.002	10.381	0.84-65.41	0.082
Age (years)	0.98	0.94-1.04	0.532			
Lesion length (cm)	1.15	0.99 ± 1.33	0.068			
BMI before neoadjuvant therapies (kg/m^2)	0.94	0.83-1.06	0.301			
Time from the end of neoadjuvant therapy to surgery (days)	1.04	1.01-1.07	0.010	1.28	0.87-1.36	0.085
Pre-operative BMI (kg/m^2)	0.98	0.87-1.11	0.767			
Intraoperative blood loss (mL)	1.00	1.00-1.00	0.288			
Residual esophageal length (cm)	0.71	0.58-0.87	0.001	0.62	0.64-1.22	0.064

OR: odds ratio; CI: confidence interval; BMI: body mass index.

an anastomotic leakage rate of 22% in the NCRT group[2]. A retrospective study of 686 ESCC patients in Japan showed that the incidences of anastomotic leakage were 27.9% in the NCRT group (376 patients with a radiation dose of 30-42 Gy) and 16.5% in the surgery group (310 patients)[9]. The incidence of anastomotic leakage in the NCT group was similar to that reported in the surgery-alone groups in other studies[17-19], suggesting that NCT does not significantly increase the incidence of anastomotic leakage.

The current results suggest that factors other than NCRT and tumor size may contribute to anastomotic leakage. Although the dose parameters V20, V30, and V40 have been shown to be associated with anastomotic leakage, the underlying mechanisms are unclear. Patient-specific factors such as comorbidities or nutritional status may play a role. The surgical technique itself, such as the type of anastomosis or the use of drains, may also have an impact.

The relationship between radiation dose and anastomotic leakage is more complicated. Despite the high pre-operative radiation dose given (50.4 Gy/28 F), the CALGB9781 study reported a low leakage incidence of 8%[22], which was similar to that in the NEOCRTEC5010 study (8.6%)[16], but lower than that in the CROSS study (22%)[2]. A lower irradiation dose was prescribed in both NEOCRTEC 5010 (40Gy) and CROSS study (41.4Gy). Our study also found a non-significant relationship between radiation dose and leakage. When the influence of radiation dose on leakage was investigated, the relationship between radiation fields and the location of anastomosis should also be considered. A retrospective study from MD Anderson revealed that the incidence of anastomotic leakage was 11% in NCRT (radiation dose: 50.4Gy/28F), and the incidence of leakage was increased significantly (39% vs. 2.6%) when the anastomosis was placed within the pre-operative radiation field[24]. Another study from France showed that although the anastomosis was within the radiation field, the leakage incidence did not rise significantly when thoracic anastomosis was performed[17]. Since a wide range of irradiation doses was delivered in NCRT and the spatial relationship between the radiation field and the anastomosis location was sometimes difficult to define accurately, it is more reasonable to explore the relationship between radiation dose of the anastomotic region and leakage incidence. Our results indicated

Table 4. Univariate analysis of risk factors associated with anastomotic leakage in NCRT group

Characteristics	Univariate analysis		
	OR	95% CI	p
Gender, male/female	2.56	0.30-22.13	0.393
Smoking, yes/no	1.19	0.45-3.17	0.727
Drinking, yes/no	1.44	0.54-3.84	0.461
Tumor location, proximal third/ middle-lower third	1.84	0.67-5.03	0.234
Surgery approach, open/laparoscopic	1.13	0.50-2.57	0.773
Age (years)	1.02	1.00-1.09	0.427
Lesion length (cm)	1.15	0.94-1.42	0.181
BMI before neoadjuvant therapies (kg/m^2)	0.99	0.86-1.13	0.846
Time from the end of neoadjuvant therapy to surgery (days)	1.02	0.98-1.05	0.349
Pre-operative BMI (kg/m^2)	1.04	0.91-1.18	0.610
Intraoperative blood loss (mL)	1.00	1.00-1.01	0.038
Residual esophageal length (cm)	1.12	0.73-1.74	0.601
Anastomotic region			
V10	1.00	0.99-1.01	0.893
V20	1.00	0.99-1.01	0.891
V30	1.00	0.99-1.01	0.592
V40	1.00	0.99-1.01	0.432
V50	0.99	0.99-1.01	0.298
Average dose	1.00	1.00-1.00	0.565
Maximum dose	1.00	1.00-1.00	0.586
Residual esophagus			
Average dose	1.00	1.00-1.00	0.586
Maximum dose	1.00	1.00-1.00	0.537
Radiation dose	1.00	1.00-1.00	0.968

NCRT: neoadjuvant chemoradiotherapy; OR: odds ratio; CI: confidence interval; BMI: body mass index.

that there was no significant relationship between the dose-volume parameters of the anastomotic region and leakage incidence. In MD Anderson's study, the anastomotic region should have been exposed to a dose of ≥ 50Gy in those patients whose anastomosis was completely placed within the irradiation field. In our study, we tried to protect the lower neck or cervical esophagus from being irradiated when a higher dose was prescribed, and neck anastomosis was performed in all patients receiving NCRT. Thus, the average dose in the anastomosis was only 37Gy, and V40, V45, and V50 were 64%, 41%, and 22%, respectively, suggesting that good communication between the surgeon and radiotherapist is indispensable in irradiation field design.

Our study had some limitations, as all retrospective studies did. Although the anastomotic region was delineated by the same investigator, there still might be some deviations in identifying the location of the anastomosis and delineating it on the corresponding planning CT slices, especially for patients with manual anastomosis. Moreover, mixed factors were thought to work together in the development of leakage, posing some potential confounding factors that could not be included in this retrospective analysis. Furthermore, the relatively few studies included in our analysis may limit the generalizability of our findings. Future studies of a larger sample size and a more diverse patient population are needed to further validate our results.

Conclusion

Our results confirmed that NCRT could improve the pathologic response rate but also increase the incidence of anastomotic leakage simultaneously. However, neither the prescribed radiation dose nor the doses to the anastomotic site and residual esophageal tissue were significantly associated with anastomotic leakage risk.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of Humans and Animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, Informed Consent, and Ethical Approval. The authors have followed their institution's confidentiality protocols and obtained informed consent from patients. The authors have obtained approval from the Ethics Committee for the analysis of routinely

obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the Use of Artificial Intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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