Original Article

Is postoperative adjuvant radiotherapy necessary for patients with esophageal cancer after neoadjuvant chemoradiotherapy?

An analysis based on the SEER database

Qiuying An, *MD,* ***Yuhao Su,*** *MD,* ***Yajing Wang,*** *MD,* ***Chanjun Zhen,*** *MD,* ***Wenwen Bai,*** *MD,* ***Liyuan Fu,*** *MD,* ***Yibing Liu,*** *MD, PhD,* ***Ping Zhang,*** *MD, PhD,* ***Zhiguo Zhou,*** *MD, PhD.*

ABSTRACT

الأهداف: تقييم نتائج العلاج الإشعاعي المساعد لدى المرضى المصابين بسرطان المريء الذين خضعوا لعملية استئصال المريء بعد العلاج الإشعاعي الكيميائي المساعد.

المنهجية: حصلنا على بيانات مرضى التهاب الدماغ القهقري الذين تلقوا العلاج المساعد بعد العلاج باستخدام المركز الوطني لبحوث السرطان بين عامي 2004م و 2019م من قاعدة بيانات SEER. تم تقسيم المرضى إلى مجموعات العلاج الإشعاعي المساعد مع أو بدون العلاج الكيميائي (RT±CT) والعلاج الكيميائي المساعد (CT). واستخدمت عملية مطابقة درجة الميل.

النتائج: تم توظيف 157 مريضًا إجماليًا في كل مجموعة علاج بعد PSM. لم تكن هناك اختلافات يُعتد بها في البقاء العام (OS) أو البقاء النوعي للسرطان (CSS) بين مجموعات RT±CT و CT (وسيط نظام التشغيل: 28 شهرًا مقابل 51 شهرا، p=0.063 ؛ متوسط فترة الضمان الاجتماعي الشامل: 31 شهرا مقابل 52 شهرا، p=0.16). ضمن مجموعة الاشعة المقطعية، المرضى الذين يعانون من مرحلة الورم من النوع الثاني أو النوع الثاني، ونسبة العقد الليمفاوية الإيجابية (LNR ≤0.1)، وحجم الورم 50≤ مم (p<0.05) كان لديهم ارتفاع في معدل الإصابة بالتعرض المقطعي مقارنة بمجموعات RT±CT. بين المرضى الذين يعانون من cT3–4 أورام في مجموعة تخفيض المرحلة N، كان نظام التشغيل و CSS أكبر بكثير لأولئك الذين خضعوا ل RT±CT مقابل مجموعة CT (نظام التشغيل لمدة 5 سنوات: 56.6% مقابل 19.4%، p=0.042 ؛ 5 سنوات CSS: 67.9% مقابل 19.4%، p=0.023). تحليل كوكس متعدد المتغيرات حدد درجة أنسجة الورم كعامل تنبؤ مستقل من OS و CSS.

الخلاصة: العلاج الإشعاعي القائم على العلاج المساعد لا يحسن بشكل كبير من توقعات سير المرض لمرضى EC بعد NCRT، على الرغم من أنه قد يوفر فائدة البقاء على قيد الحياة للمرضى الذين يعانون من cT3–4 أورام في المرحلة N.

Objectives: To evaluate the outcomes of adjuvant radiotherapy in patients with esophageal cancer (EC) who underwent esophagectomy following neoadjuvant chemoradiotherapy (NCRT).

Methods: The data of EC patients who received adjuvant therapy after NCRT between 2004 to 2019 was retrieved from the SEER database. The patients were split into the adjuvant radiotherapy with or without chemotherapy (RT±CT) and the adjuvant chemotherapy (CT) groups. The process of propensity score matching (PSM) was employed.

Results: Following PSM, 157 patients in total were recruited in each treatment group. There were no significant variations in either overall survival (OS) or cancer-specific survival (CSS) between the RT±CT and CT groups (median OS: 28 months versus. 51 months, p=0.063; median CSS: 31 months versus. 52 months, p=0.16). Within the CT group, patients with ypI/II or cI/II tumor stage, positive lymph node ratio (LNR) ≤0.1, and tumor size ≥50 mm (p<0.05) had higher OS compared to the RT±CT groups. Among patients with cT3-4 tumors in N-stage downstaging group, the OS and CSS were significantly greater for those underwent RT±CT as opposed to the CT group (5-year OS:56.6% versus 19.4%, p=0.042; 5-year CSS:67.9% versus. 19.4%, p=0.023). Multivariate Cox regression analysis identified the tumor histology grade as an independent prognostic factor of OS and CSS.

Conclusion: Radiotherapy-based adjuvant therapy does not significantly improve the prognosis of EC patients after NCRT, although it may provide a survival benefit for patients with cT3-4 tumors in N-stage downstaging.

Keywords: esophageal cancer, neoadjuvant chemoradiotherapy, esophagectomy, adjuvant therapy, SEER

Saudi Med J 2024; Vol. 45 (9): 900-910
doi: 10.15537/smj.2024.45.9.20240045

From the Department of Radiation Oncology (An, Su, Wang, Zhen, Bai, Fu, Zhang, Zhou) and from the Department of Medical Oncology (Liu), The Fourth Hospital of Hebei Medical University, Hebei Province, China.

Received 3rd February 2024. Accepted 11th July 2024.

Address correspondence and reprint request to: Dr. Zhiguo Zhou, Department of Radiation Oncology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China.
E-mail: chenk777@126.com
ORCID ID: https://orcid.org/0000-0002-5373-8098

Previous research demonstrated that patients with resectable esophageal cancer (EC) can experience considerably higher survival rates while receiving neoadjuvant chemoradiotherapy (NCRT) in addition to esophagectomy.[1] Therefore, NCRT is recommended as the standard treatment modality for patients with resectable EC in the NCCN guidelines (version 2.2023).[2] Nevertheless, the survival chances after surgical resection following NCRT are still dismal, with distant metastases and local recurrence being the primary causes of failure.[3-5] Hence, there is an urgent need for a more effective postoperative management model to enhance the long-term survival prognosis of patients. While some research indicates that postoperative adjuvant therapy boosts survival rates for EC patients undergoing NCRT, there is inefficient comparison of postoperative adjuvant treatment modes.[6-8] The role of postoperative adjuvant radiotherapy in the management paradigm remains unclear. Hence, this research aims to assess the outcomes of postoperative adjuvant radiotherapy in EC patients after NCRT using SEER database.

Methods. The clinical information of individuals diagnosed with EC between 2004 and 2019 were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. The permission to access the SEER Research Plus database was obtained on Nov 2021 Sub (2000–2019). This study was conducted in The Fourth Hospital of Hebei Medical University, Hebei, China. Previous studies related to this project can be searched through PubMed and Web of science.

The inclusion criteria were i) The pathological diagnosis indicated primary esophageal cancer; ii) received preoperative chemoradiotherapy; iii) received esophagectomy; iv) received adjuvant therapy. The exclusion criteria were i) staging at M1/MX stage and TX/NX stage (AJCC 8th); ii) Unknown preoperative and postoperative treatments.

The screening process is shown in Figure 1. The adjuvant chemotherapy (CT) group and the adjuvant radiotherapy with or without chemotherapy (RT±CT) group comprised the included patients. The study used established data and did not involve interaction with patients. Approval has been granted by our Institutional Review Board, and this research strictly adhered to the principles outlined in the Helsinki Declaration.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Statistical analysis. The Chi-square test was employed to compare the baseline characteristics between the RT±CT and CT groups. Propensity score matching (1:1) was performed for age, tumor histology, histological grade, tumor location, T stage (yp/c), number of lymph nodes (LNs) removed, and count of pathologically positive LNs (ypN) using the Stata software (version 16.0). The Kaplan-Meier method was employed to estimate overall survival (OS) and cancer-specific survival (CSS), and the log-rank test was performed to compare survival curves. Forest plots showed the results of subgroup analysis. Ultimately, variables associated with OS and CSS after PSM were identified using univariate and multivariate Cox regression models. The multivariate analysis included variables that showed a *p*-value of 0.2 or less in the univariate model. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA). The forest plots and survival curves were plotted using the "survminer" and "forestplot" packages of R statistical software (version 4.2.2). A 2-sided *p*-value <0.05 was deemed statistically significant.

Results. An entire group of 489 patients were included for this analysis. After PSM, 314 patients were analyzed and classified into the RT±CM group (n=157) and the CT group (n=157). The clinicopathological features of the 2 groups did not differ significantly, according to the results of the Chi-square test. Table 1 displays the study population's baseline characteristics. Survival analysis before PSM.

Before PSM, the group as a whole had median OS (mOS) and CSS durations of 34 months (95% Cl, 30-43 m) and 38 months (95% Cl, 31-49 m) before PSM. In addition, the 3-year OS and CSS rates were 48.6% and 50.4%, and the 5-year OS and CSS rates were 35.5% and 37.9%. The mOS duration was 42 months (95% Cl, 32-54m) in the CT group and 28 months (95% Cl, 23-35m) in the RT±CT group, and the difference was not significant (*p*=0.096). Likewise, the median CSS (mCSS) durations in the CT and RT±CT groups were also similar (*p*=0.22, Figure 2A) at 44 months (95% Cl, 34-54m) and 31 months (95% Cl, 25-41m). The 3-year OS (54% vs. 38.9%, *p*=0.096) and CSS (55% versus. 41.9%, *p*=0.22) rates were greater in the CT group, whereas the 5-year or long-term survival rates were similar in both groups (5-year OS:36.9% versus32.3%, *p*=0.096; 5-year CSS:37.9% versus 38%, *p*=0.22).

Survival analysis after PSM. After PSM, the CT and RT±CT groups had mOS durations of 51 months (95% Cl, 31-58 m) and 28 months (95% Cl, 23-35 m) (*p*=0.063), and the mCSS durations were 31 months

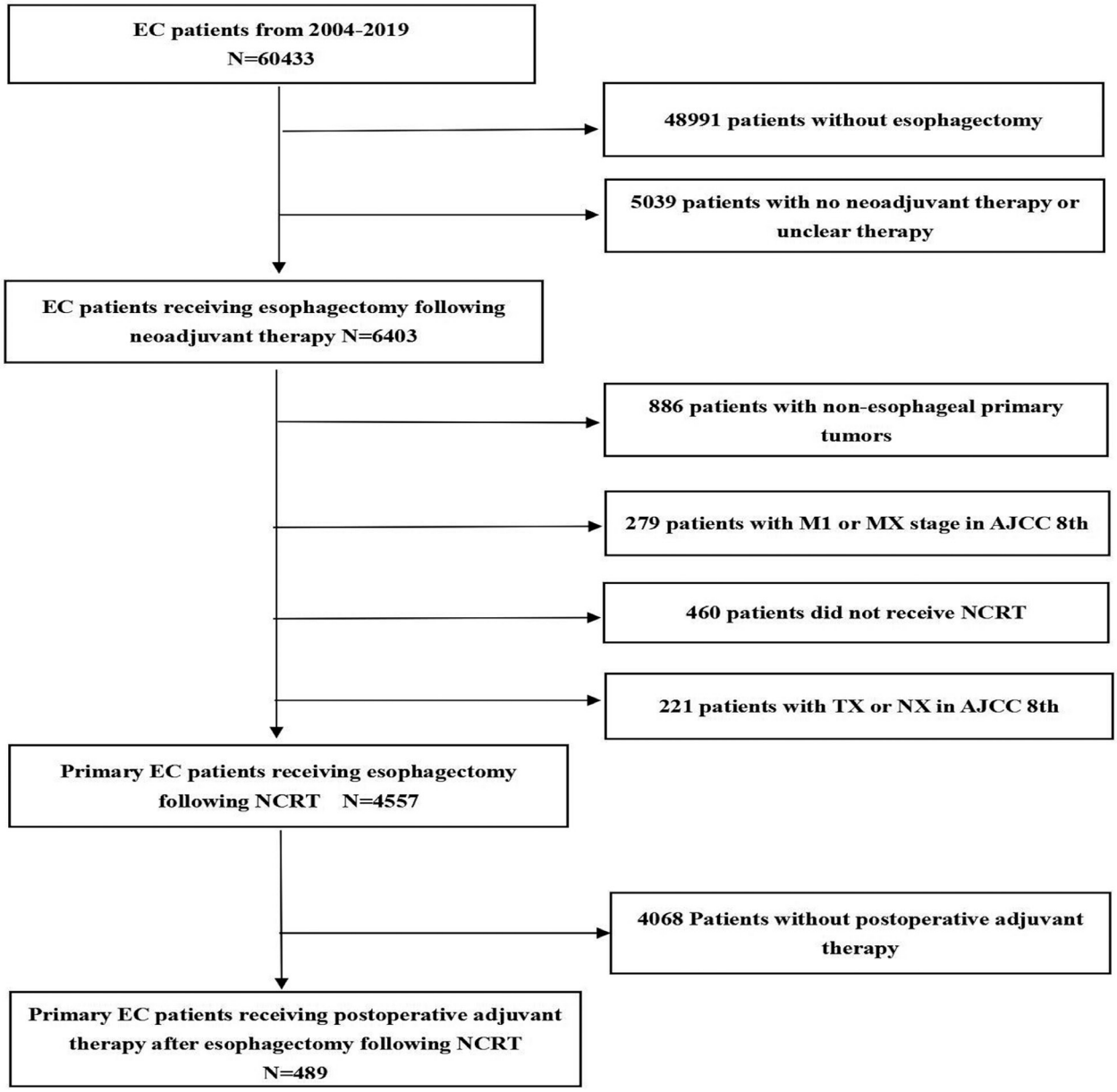

Figure 1 - Inclusion and exclusion flow diagram for SEER EC patients who received adjuvant therapy after esophagectomy following NCRT between 2004 to 2019. EC: sophageal cancer, NCRT: neoadjuvant chemoradiotherapy

(95% Cl, 25-41 m) and 52 months (95% Cl, 32-77 m) (p=0.16, Figure 2B). In contrast to the RT±CT group, the 3-year OS (56% versus 38.9%, p=0.063) and CSS (56.4% versus 41.9%, p=0.16) rates of the CT group were higher. In contrast, the 5-year OS (39.7% versus 32.3%, p=0.063) and CSS (40.7% versus 38%, p=0.16) rates were similar for both groups.

We next evaluated the survival of the 2 treatment groups across the different clinical subgroups, including overall TNM stage, ypN stage, T stage (yp/c), number of nodes excised, tumor size, and positive lymph node ratio (LNR). The OS of the CT group was considerably superior than that of the RT± CT group among patients with ypI/II stage tumors (mOS: 54 m versus 24 m, p=0.008), cI/II stage tumors (mOS: 124 m versus 27 m, p=0.033), tumor size ≥50 mm (mOS: 54 m versus 30 m, p=0.023) and LNR ≤0.1 (mOS: 56 m versus 33 m, p=0.035). Furthermore, the CSS was also significantly higher for the CT group among the individuals with stage ypI/II tumors (mCSS: 54 m versus 24 m,

Table 1 - Baseline characteristics of patients included in the analysis before and after propensity score matching (PSM).

Characteristic	Before PSM			After PSM		
	RT±CT (n,%)	CT (n,%)	*P*-value	RT±CT (n,%)	CT (n,%)	*P*-value
Total	**n=157**	**n=332**		**n=157**	**n=157**	
Age						
<65	87 (55.4)	221 (66.6)	0.017	87 (55.4)	87 (55.4)	1.0
≥65	70 (44.6)	111 (33.4)		70 (44.6)	70 (44.6)	
Gender						
Male	133 (84.7)	299 (90.1)	0.085	133 (84.7)	141 (89.8)	0.176
Female	24 (15.3)	33 (9.9)		24 (15.3)	16 (10.2)	
Race						
White	142 (90.4)	313 (94.3)	0.12	142 (90.4)	146 (93.0)	0.413
Black and others	15 (9.6)	19 (5.7)		15 (9.6)	11 (7.0)	
Tumor histology						
AC	124 (79.0)	294 (88.6)	0.005	124 (79.0)	125 (79.6)	0.889
SCC and others	33 (21.0)	38 (11.4)		33 (21.0)	32 (20.4)	
Histological grade						
Well	5 (3.2)	18 (5.4)	0.179	5 (3.2)	8 (5.1)	0.400
Moderate	59 (37.6)	115 (34.6)		59 (37.6)	47 (34.6)	
Poor/undifferentiated	70 (44.6)	168 (50.6)		70 (44.6)	81 (52.9)	
Unknown	23 (14.6)	31 (9.3)		23 (14.6)	21 (7.4)	
Tumor location						
middle	16 (10.2)	12(4.8)	0.081	16 (10.2)	11 (7.0)	0.569
lower	130 (82.8)	292(88.0)		130 (82.8)	133 (84.7)	
others	11 (7.0)	24(7.2)		11 (7.0)	13 (8.3)	
AJCC 8th Tumor, Node, Metastasis stage*						
yp I/II	24 (15.3)	27 (8.1)	0.064	24 (15.3)	25 (15.9)	0.811
yp III	19 (12.1)	35 (10.5)		19 (12.1)	21 (13.4)	
yp IVA	4 (2.5)	17 (5.1)		4 (2.5)	10 (6.4)	
cI/II	25 (15.9)	35 (10.5)		25 (15.9)	27 (17.2)	
cIII	56 (35.7)	124 (37.3)		56 (35.7)	48 (30.6)	
cIVA	4 (2.5)	16 (4.8)		4 (2.5)	5 (3.2)	
I/II (unknown)	7 (4.5)	15 (4.5)		7 (4.5)	8(5.1)	
III (unknown)	16 (10.2)	54 (16.3)		16 (10.2)	11 (7.0)	
IVA (unknown)	2 (1.3)	9 (2.7)		2 (1.3)	2 (1.3)	
AJCC 8th T stage*						
ypT1-2	16 (10.2)	12 (3.6)	0.003	16 (10.2)	11 (7.0)	0.351
ypT3-4	31(19.7)	67 (20.2)		31 (19.7)	45 (28.7)	
cT1-2	24 (15.3)	29 (8.7)		24 (15.3)	16 (10.2)	
cT3-4	61 (38.9)	146 (44.0)		61 (38.9)	64 (40.8)	
T1-2 (unknown)	10 (6.4)	19 (5.7)		10 (6.4)	9 (5.7)	
T3-4 (unknown)	15 (9.6)	59 (17.8)		15 (9.6)	12 (7.6)	
AJCC 8th ypN stage			0.011			0.721
ypN0	68 (43.3)	109 (32.8)		68 (43.3)	66 (42.0)	
ypN1	38 (24.2)	106 (31.9)		38 (24.2)	42 (26.8)	
ypN2	20 (12.7)	60 (18.1)		20 (12.7)	22 (14.0)	
ypN3	9 (5.7)	31 (9.3)		9 (5.7)	12 (7.6)	
Unknown	22 (14.0)	26 (7.8)		22 (14.0)	15 (9.6)	
Number of nodes removed						
<15	74 (47.1)	149 (44.9)	0.071	74 (47.1)	68 (43.3)	0.241
≥15	69 (43.9)	169 (50.9)		69 (43.9)	81 (51.6)	
Unknown	14 (8.9)	14 (4.2)		14 (8.9)	8 (5.1)	
LNR (positive lymph node ratio)						
≤0.1	89 (56.7)	173 (52.1)	0.008	89 (56.7)	90 (57.3)	0.358
>0.1	43 (27.4)	130 (39.2)		43 (27.4)	50 (31.8)	
Unknown	25 (15.9)	29 (8.7)		25 (15.9)	17 (10.8)	
Tumor size						
<50mm	76 (48.4)	137 (41.4)	0.271	76 (48.4)	67 (42.7)	0.419
≥50mm	49 (31.2)	126 (38.0)		49 (31.2)	60 (38.2)	
Unknown	32 (20.4)	69 (20.8)		32 (20.4)	30 (19.1)	

*The staging provided in the database was further subdivided into yp and c stages based on the "CS Lymph Nodes Eval (2004-2015)" field extracted from the SEER data. 2018-2019 was not marked with a staging type and was defined as unknown. AC: Adenocarcinoma, SCC: Squamous cell carcinoma, AJCC: American Joint Committee on Cancer, RT±CT: radiotherapy with or without chemotherapy

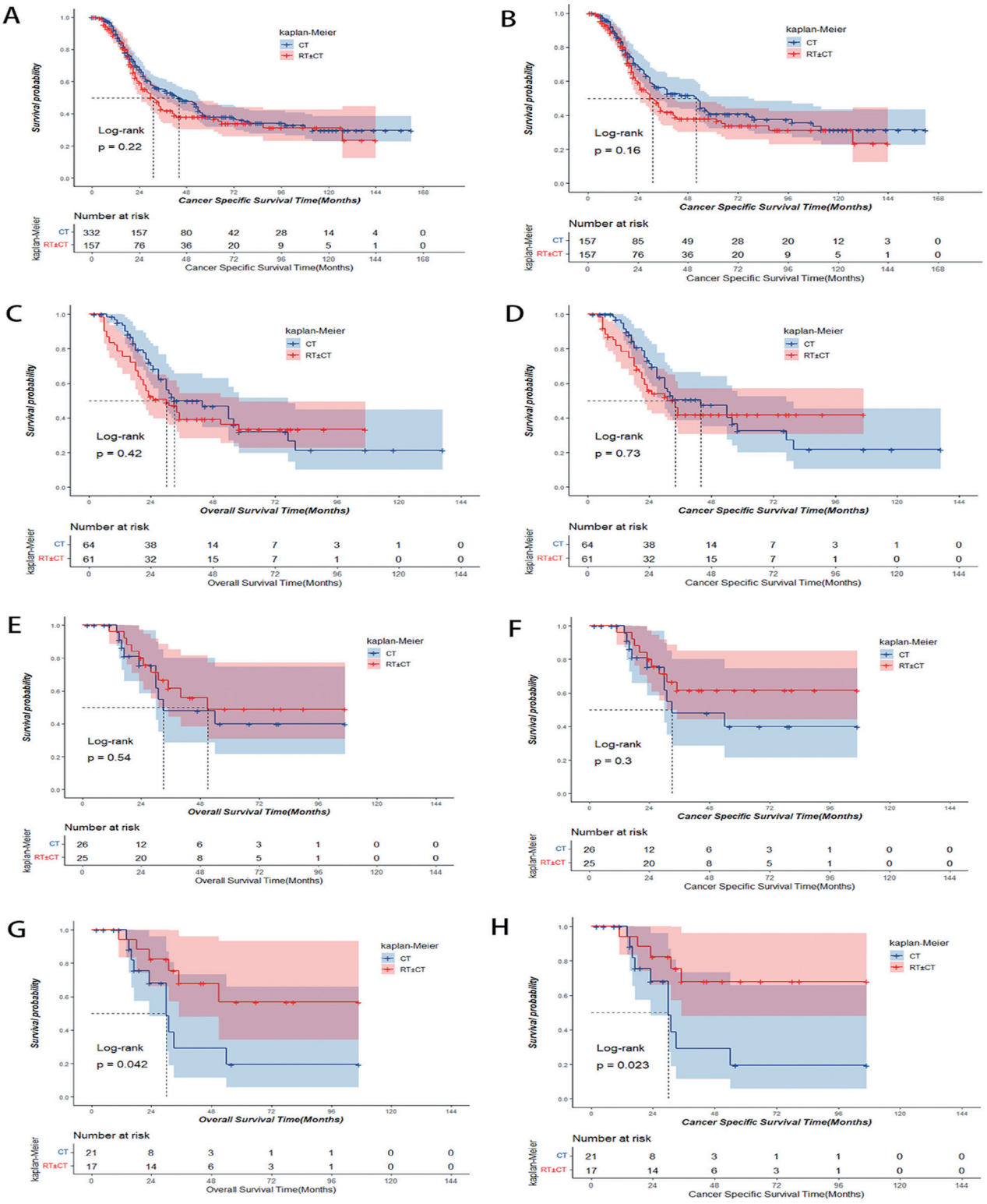

Figure 2 - Kaplan-Meier curves of overall survival (OS) and cancer-specific survival (CSS) for patients who underwent CT and RT±CT. **A)** Curve showed the CSS for the entire cohort before PSM. **B)** Curve showed the CSS for the entire cohort after PSM. **C & D)** Survival curves showed the OS and CSS for the patients with cT3-4 stage. **E** & **F)** Survival curves showed the OS and CSS for patients with N-stage downstaging group (ypN stage is lower than the cN stage). G and H survival curves showed the OS and CSS for patients with cT3-4 tumors in N-stage downstaging.

p=0.005). The outcome hazard ratios for CSS are shown in Figure 3.

Moreover, Kaplan–Meier analysis stratified by the ypT stage, ypN stage, and the number of LNs removed revealed a significant variance in the OS among the two groups only in the ypN0-1 subgroup (mOS: 56 m versus 31 m, p=0.021), indicating that patients receiving CT had an obvious survival advantage. In contrast, RT±CT did not confer any survival benefit to patients with ypT3-4 stage tumors (mOS: 41 m versus 23 m, p=0.13; mCSS: 51 m versus 24 m, p=0.2) and removal of fewer than 15 lymph nodes (mOS: 38 m versus 25 m, p=0.081; mCSS: 38 m versus 25 m, p=0.19).

Based on the initial N stage (cN) and the ypN stage, we further divided the patients into the N-stage non-downstaging group (ypN stage consistent with cN stage) and the N-stage downstaging group (ypN stage lower than the cN stage). In the downstaging group, the RT±CT group had marginally higher survival compared to the CT group (p=0.54, Figure 2E). Moreover, the RT±CT group had somewhat improved 3-year OS (p=0.54, Figure 2E) and CSS (p=0.3, Figure 2F) rates. Furthermore, patients in the RT±CT group who were initially staged as cT3-4 showed a slight improvement in 5-year or long-term OS (p=0.423, Figure 2C) and CSS (p=0.734, Figure 2D). The OS (p=0.0442, Figure 2G) and CSS (p=0.023, Figure 2H) rates were significantly better for cT3-4 stage patients in the RT±CT group with N-stage downstaging, whereas no survival benefit was observed in the absence of N-stage downstaging (5-year OS: 28.5% versus 38.4%, p=0.063; 5-year CSS: 31.2% versus 38.4%, p=0.12).

Univariate and multivariate analyses. Univariate analysis revealed that histological tumor grade, total TNM stage, T stage (yp/c), ypN stage, and LNR were all significantly correlated with OS and CSS (p<0.05). Additionally, the tumor histology grade was found to be an independent predictive predictor for both OS and CSS using multivariate Cox regression analysis. Poor/undifferentiated tumors and ypN3 stage were independent predictors of worse CSS (Figure 4).

Discussion. As recommended by the NCCN guidelines (version 2.2023), there is no definitive agreement on the utilization of a radiotherapy-based adjuvant approach following NCRT or NAC for EC patients, regardless of margin status. Recently, multiple studies have indicated that postoperative adjuvant chemoradiotherapy can enhance the survival of some EC patients after NCRT.[6-8] However, the role of postoperative radiotherapy in them was not further explored in these studies. Therefore, we compared the OS and CSS of EC patients who received RT±CT or CT as postoperative adjuvant therapy after NCRT using data retrieved from the SEER database. Our findings indicate that RT±CT did not confer any significant survival benefit to the patients compared to CT (p>0.05). This may be attributed to the adverse effects of re-radiation, such as radiation-induced esophagitis or pneumonia, or the hematological complications, which can affect patient survival. In contrast, chemotherapy has a relatively good safety and tolerability profile.[9-13] Furthermore, the radiation dose is also a significant factor in the translation of the local effects of radiotherapy to long-term survival.

Previous researches have demonstrated that postoperative adjuvant chemoradiotherapy can effectively improve the survival rate of EC patients whose tumors are at theypT3-4 stage or persistent positive lymph nodes (ypN+) after NCRT. However, the control arm in these studies consisted of patients who did not receive postoperative adjuvant therapy.[7,8] Therefore, we also analyzed the ypN+ or ypT3-4 subgroups in our study, and found that there was no survival benefit of RT±CT versus CT in the ypN+ patients, especially those staged as ypN1. This is similar to previous reports that showed a survival benefit of adjuvant chemotherapy but not of adjuvant radiotherapy in patients with ypN+ following NCRT.[14,15] We hypothesize that the insignificant improvement in patient survival after adjuvant radiotherapy following NCRT may be the result of increased re-radiation-induced toxicity. However, there are few studies have focused on reducing the toxicity of re-irradiation after NCRT, and only some have mentioned the issue of radiation dose. In one study, conventional fractionated irradiation with 20–30Gy selected on the basis of the dose and risk-tolerant organs of NCRT resulted in better tolerance.[7] Nevertheless, another study showed that ≥45Gy conventional fractionated irradiation did not improve patient survival, although the toxicity was not recorded.[14] Therefore, the dose of re-irradiation warrants further consideration. Unfortunately, since the SEER database does not contain information regarding the radiation dose and toxicity, we were not able to validate the impact of the radiation dose on patient survival. Furthermore, the OS and CSS were worse in the RT±CT group compared to the CT group for patients with ypT3-4 tumors. We hypothesize that some patients in this group did not respond well to chemoradiotherapy and did not have a significant reduction in the T stage following NCRT, which likely resulted in low sensitivity to re-irradiation, and eventually shorter survival duration. Interestingly,

Subgroup	CT	RT±CT	HR （95%CI)	P-Vaule
All Patients	**157**	**157**	**0.805（0.591-1.096）**	**0.168**
Age				
＜65	87	87	0.825（0.547-1.244）	0.358
≥65	70	70	0.816（0.510-1.306）	0.397
Gender				
Male	141	133	0.823（0.592-1.144）	0.245
Female	16	24	0.610（0.231-1.608）	0.317
Race				
White	146	142	0.859（0.624-1.183）	0.352
Black and others	11	15	0.248（0.063-0.972）	0.045
Tumor histology				
AC	125	124	0.846（0.599-1.194）	0.341
SCC and others	32	33	0.606（0.296-1.241）	0.171
Histological grade				
Well	8	5	0.651（0.142-2.997）	0.582
Moderate	47	59	0.849（0.459-1.569）	0.601
Poor/Undifferentiated	81	70	0.830（0.552-1.248）	0.371
Tumor location				
Middle	11	16	0.542（0.137-2.141）	0.382
Lower	133	130	0.807（0.579-1.125）	0.206
Others	13	11	0.849（0.272-2.651）	0.778
TNM stage*				
yp I/II	25	24	0.400（0.205-0.781）	0.007
yp III	21	19	1.129（0.540-2.358）	0.747
yp IVA	10	4	0.724（0.173-3.037）	0.659
C I/II	27	25	0.519（0.216-1.249）	0.143
C III	48	56	1.026（0.587-1.795）	0.928
C IVA	5	4	0.507（0.110-2.351）	0.386
T stage*				
ypT1-2	11	16	0.862（0.374-1.991）	0.729
ypT3-4	45	31	0.704（0.407-1.218）	0.209
cT1-2	16	24	0.250（0.055-1.150）	0.075
cT3-4	64	61	0.921（0.568-1.492）	0.737
ypN stage*				
ypN0	66	68	0.739（0.443-1.233）	0.247
ypN+	77	76	0.794（0.522-1.208）	0.282
Number of nodes removed*				
＜15	68	74	0.748（0.479-1.168）	0.202
≥15	81	69	0.780（0.490-1.242）	0.295
LNR*				
≤0.1	90	89	0.696（0.453-1.070）	0.099
＞0.1	50	43	0.799（0.471-1.354）	0.404
Tumor size*				
＜50mm	67	76	0.889（0.553-1.430）	0.629
≥50mm	60	49	0.638（0.372-1.095）	0.103

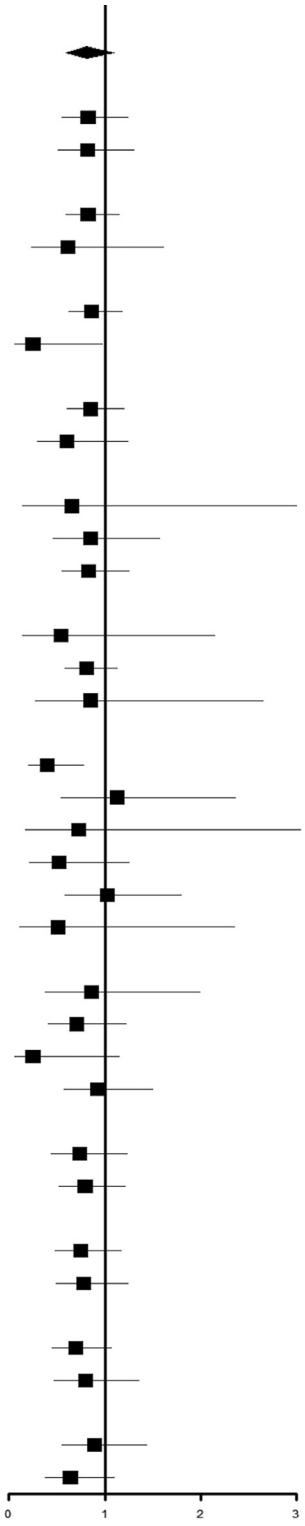

Figure 3 - Forest plot for esophageal cancer patients in the subgroup analysis (CT vs RT±CT). Hazard ratio (HR) with 95% confidence interval (Cl) for death in terms of the cancer-specific survival (CSS) of patients with esophageal cancer who underwent CT or RT±CT. P-values of the Cox proportional hazards regression are reported. The left side of the invalid line indicates that CT is better and the right side of the invalid line indicates that RT±CT is better.

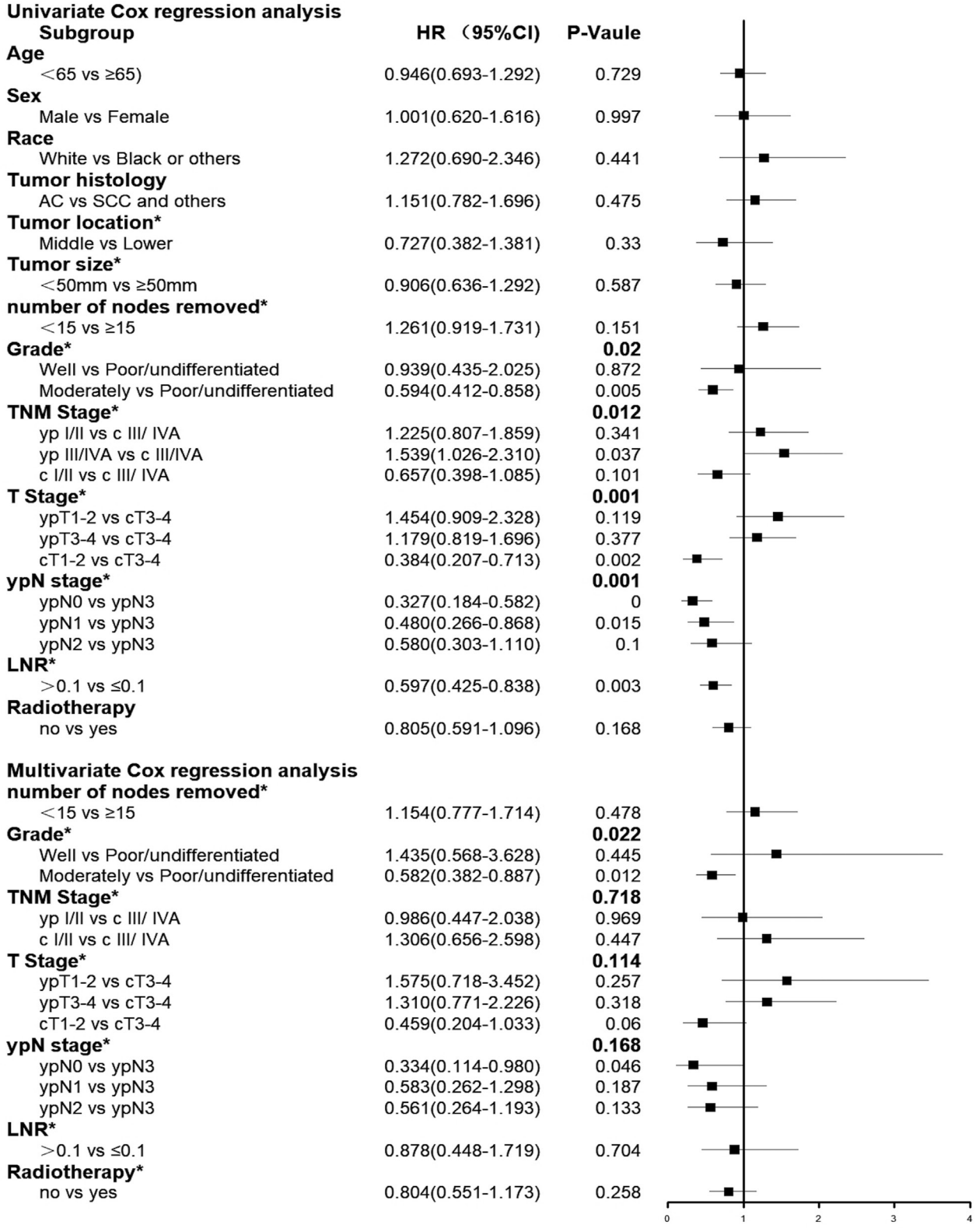

Figure 4 - Univariate and multivariate Cox regression analysis of factors affecting Cancer-specific survival (CSS). (*unknown subgroups were not included in the analysis)

RT±CT improved the survival of patients with N-stage downstaging (**Figure 2**), indicating that these patients had superior response to chemoradiotherapy, and the therapeutic advantages of re-irradiation likely outweighed its toxic side effects. Therefore, the response of patients to NCRT may affect the result of postoperative adjuvant radiotherapy.

Some studies have shown that even though patients with the initial cT3-4 stage can achieve complete pathological remission (pCR) following NCRT, over 30% of the patients still experience recurrence after surgery, and the initial cT3-4 stage is still an independent risk factor for tumor recurrence.[16] However, fewer studies have demonstrated that EC patients at the cT3-4 stage require postoperative adjuvant therapy following NCRT. We observed a trend towards 5-year and longer survival rates of patients with cT3-4 stage in the RT±CT group, although there was no statistically significant distinction among the RT±CT and CT groups (**Figure 2**). Moreover, patients at the cT3-4 with N-stage downstaging had a significantly higher survival rate in the RT±CT group. In the absence of N-stage downstaging, however, patients receiving RT±CT did not have a survival advantage. This indicated that patients who achieve N-stage downstaging may benefit from postoperative radiotherapy. We were unable to ascertain whether T-stage downstaging was achieved after NCRT in this subgroup due to database restrictions. Nevertheless, we hypothesize that re-irradiation may improve survival in patients with T/N stage downstaging.

The subgroup analysis showed that patients with stage cI/II and ypI/II tumors did not benefit from postoperative adjuvant radiation in terms of OS ($p<0.05$). Specifically, most of these patients had early-stage cancer without lymph node metastases (T2-3N0M0), and were therefore at a lower risk of recurrence.[17] Re-radiotherapy may cause more detrimental side effects, and may be less beneficial to patient survival. Second, according to the findings of the CROSS trial, patients who underwent NCRT and esophagectomy had a higher likelihood of developing distant metastases rather than localized isolated recurrence, suggesting that local radiotherapy may offer limited advantages.[4,18] For patients in stage cI/II, there remains controversy regarding the necessity to intensify postoperative adjuvant therapy. Given the data from this study, it appears that these patients often present with unfavorable factors that can impact postoperative survival, including cT3 stage, tumor length exceeding 50 mm, and low pathological differentiation grade. We hypothesize that these factors could be significant drivers for considering adjuvant therapy in patients at stage cI/II. Furthermore, despite tumor length being a crucial prognostic factor for EC patients with cT1-2 stage, and the fact that longer tumor lengths correlate with a heightened risk of recurrence and distant metastasis.[19-21] Unfortunately, RT±CT did not enhance OS or CSS in these patients. Hence, the selection of adjuvant therapy needs to be considered in combination with the risk of postoperative recurrence and treatment tolerance.

The number of positive lymph nodes after NCRT significantly affects patient prognosis.[22] However, it is unclear how many lymph nodes should be removed from the patients after NCRT.[23-25] Following the recommendations of a review, we conducted a subgroup analysis with removal of at least 15 LNs as the cut-off.[26] However, adjuvant radiotherapy did not confer a survival benefit in either subgroup. This may be related to the increase in adverse effects after re-radiation. At the same time, neither the univariate nor multivariate analyses showed a correlation between the number of LNs and the prognosis ($p>0.05$). According to a study that evaluated the outcomes of LN dissection for rectal cancer following NCRT, this may be connected to tumor regression grade after NCRT, and may decrease the number of lymph nodes that need to be removed if the regression grade is favorable.[27] However, another study showed that lymph node removal should be performed for EC patients regardless of the response to NCRT.[28,29] Further randomized clinical trials are required to address this issue. Some studies have shown that the LNR is more helpful in predicting OS of patients with esophageal cancer following NCRT, and high LNR (>0.1) is a risk factor for recurrence.[30,31] This is consistent with the findings of the univariate analysis in this study. According to the subgroup analysis, we found that postoperative adjuvant radiotherapy failed to enhance the OS in patients with LNR ≤0.1, which is not surprising given the minimal risk of recurrence in these patients.

Study limitations. It is noteworthy that the predominant histological type (79.3%) in our cohort was esophageal adenocarcinoma (EAC). However, patients with adenocarcinoma, have a lower probability of local recurrence and a higher rate of hematogenous metastasis when compared to those with squamous cell carcinoma (ESCC).[32] Thus, systemic therapy may be more successful than local radiation in EAC patients. Furthermore, our findings may not pertain to patients with tumors in the upper or middle third part of the esophagus since the predominant tumor location in our cohort was the lower third of the esophagus (83.7%). More rigorous clinical trials are needed to resolve this

issue. As this study included some cases with close or positive surgical margin status, it may not be entirely suitable for patients with R0 resection and needs to be considered with caution by investigators. Additionally, as the study was retrospective, selection bias was inevitable even with the use of PSM to reduce confounding bias. Second, information about radiotherapy target areas, doses, equipment, and chemotherapy regimens is not included in the SEER database. Finally, prognostic factors such as the interval between NCRT and surgery, the condition of the postoperative margins, and the degree of pathological regression following NCRT were also not evaluated. All of these concerns may affect the reliability of our results.

Implications of findings for future research. This article explores the relevance of postoperative adjuvant therapy following NCRT in EC patients. Our findings indicate a potential benefit of postoperative adjuvant radiotherapy, particularly for patients getting cT3-4 tumors in N-stage downstaging. This suggests that individuals presenting adverse prognostic factors and experiencing N-stage downstaging after neoadjuvant therapy might derive greater advantage from postoperative adjuvant therapy. However, the decision to opt for postoperative adjuvant radiotherapy must be tailored to each patient, considering factors like radiotherapy dose, the scope of the radiotherapy target area, and the chemotherapy regimen. These aspects merit further examination and deliberation. We expect the insights gained from this study to provide a significant reference for determining surgical adjuvant treatments following neoadjuvant immunotherapy.

In conclusion, radiotherapy-based adjuvant therapy does not significantly improve the prognosis of EC patients after NCRT, although it may provide a survival benefit for patients with cT3-4 tumors in N-stage downstaging.

Acknowledgment. *The authors gratefully acknowledge TopEdit (www.topeditsci.com) for the English language editing of this manuscript.*

References

1. Wang H, Tang H, Fang Y, Tan L, Yin J, Shen Y et al. Morbidity and mortality of patients who underwent minimally invasive esophagectomy after neoadjuvant chemoradiotherapy vs neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma: A randomized clinical trial. *JAMA Surg* 2021; 156: 444-451.
2. Ajani JA, D'Amico TA, Bentrem DJ, Cooke D, Corvera C, Das P et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2023, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2023; 21: 393-422.
3. Liu S, Wen J, Yang H, Li Q, Chen Y, Zhu C et al. Recurrence patterns after neoadjuvant chemoradiotherapy compared with surgery alone in oesophageal squamous cell carcinoma: results from the multicenter phase III trial NEOCRTEC5010. *Eur J Cancer* 2020; 138: 113-121.
4. Eyck BM, van Lanschot JJB, Hulshof MCCM, van der Wilk BJ, Shapiro J, van Hagen P et al. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: The randomized controlled CROSS trial. *J Clin Oncol* 2021; 39: 1995-2004.
5. Liu G, Hu B, Chen T, Zhang X, Tang Y, Chen Q et al. Recurrence timing and patterns incorporating lymph node status after neoadjuvant chemoradiotherapy plus esophagectomy for esophageal squamous cell carcinoma. *Front Oncol* 2024; 14: 1310073.
6. Lee Y, Samarasinghe Y, Lee MH, Thiru L, Shargall Y, Finley C et al. Role of adjuvant therapy in esophageal cancer patients after neoadjuvant therapy and esophagectomy: A systematic review and meta-analysis. *Ann Surg* 2022; 275: 91-98.
7. Yap WK, Shih MC, Chang YC, Lin CH, Huang SM, Tsai TY et al. Adjuvant chemoradiotherapy associated with improved overall survival in resected esophageal squamous cell carcinoma after neoadjuvant chemoradiotherapy in intensity-modulated radiotherapy era. *Biomedicines* 2022; 10: 2989.
8. Raja S, Rice TW, Lu M, Semple ME, Blackstone EH, Murthy SC et al. Adjuvant therapy after neoadjuvant therapy for esophageal cancer: Who needs it? *Ann Surg* 2023; 278: e240-e249.
9. Zhao K, Si Y, Sun L, Meng X, Yu J. Efficacy and toxicity of re-irradiation for esophageal cancer patients with locoregional recurrence: a retrospective analysis. *Radiat Oncol* 2020; 15: 243.
10. Lan K, Chen J. Efficacy and safety of re-irradiation for locoregional esophageal squamous cell carcinoma recurrence after radiotherapy: a systematic review and meta-analysis. *Radiat Oncol* 2022; 17: 61.
11. Gabrys D, Kulik R, Namysł-Kaletka A. Re-irradiation for intra-thoracic tumours and extra-thoracic breast cancer: dose accumulation, evaluation of efficacy and toxicity based on a literature review. *Br J Radiol* 2022; 95: 20201292.
12. Lin JW, Li C, Yeh HL, Chuang CY, Chen CC. Adjuvant chemotherapy for pathological node-positive disease in squamous cell carcinoma of the esophagus after neoadjuvant chemoradiotherapy plus surgery. *J Pers Med* 2022; 12: 1252.
13. Park SY, Kim HK, Jeon YJ, Lee J, Cho JH, Choi YS et al. The role of adjuvant chemotherapy after neoadjuvant chemoradiotherapy followed by surgery in patients with esophageal squamous cell carcinoma. *Cancer Res Treat* 2023; 55: 1231-1239.
14. Li X, Luan S, Yang Y, Zhou J, Shang Q, Fang P et al. Trimodal therapy in esophageal squamous cell carcinoma: Role of adjuvant therapy following neoadjuvant chemoradiation and surgery. *Cancers (Basel)* 2022; 14: 3721.
15. Drake J, Tauer K, Portnoy D, Weksler B. Adjuvant chemotherapy is associated with improved survival in patients with nodal metastases after neoadjuvant therapy and esophagectomy. *J Thorac Dis* 2019; 11: 2546-2554.
16. La Mendola R, Bencivenga M, Torroni L, Alberti L, Sacco M, Casella F et al. Pretreatment primary tumor stage is a risk factor for recurrence in patients with esophageal squamous cell carcinoma who achieve pathological complete response after neoadjuvant chemoradiotherapy. *Ann Surg Oncol* 2021; 28: 3034-3043.

17. Leng X, He W, Yang H, Chen Y, Zhu C, Fang W et al. Prognostic Impact of Postoperative Lymph Node Metastases After Neoadjuvant Chemoradiotherapy for Locally Advanced Squamous Cell Carcinoma of Esophagus: From the Results of NEOCRTEC5010, a Randomized Multicenter Study. ***Ann Surg*** 2021; 274: e1022-e1029.
18. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z et al. Long-term efficacy of neoadjuvant chemoradiotherapy plus surgery for the treatment of locally advanced esophageal squamous cell carcinoma: The NEOCRTEC5010 randomized clinical trial. ***JAMA Surg*** 2021; 156: 721-729.
19. Wu Z, Yu B. Tumor size as a critical prognostic factor in T1-2 stage esophageal cancer. ***Gastroenterol Res Pract*** 2020; 2020: 2796943.
20. Koterazawa Y, Oshikiri T, Goto H, Kato T, Sawada R, Harada H et al. Impact of tumor size on survival outcome in esophageal squamous cell carcinoma after esophagectomy following neoadjuvant chemotherapy. ***Ann Surg Oncol*** 2024; 31: 2482-2489.
21. Zhang Y, Zhang Y, Peng L, Zhang L. Research progress on the predicting factors and coping strategies for postoperative recurrence of esophageal cancer. ***Cells*** 2022; 12:114.
22. Kandilis A, Iniguez CB, Khalil H, Mazzola E, Jaklitsch MT, Swanson SJ et al. Residual lymph node disease and mortality following neoadjuvant chemoradiation and curative esophagectomy for distal esophageal adenocarcinoma. ***JTCVS Open*** 2021; 5: 135-147.
23. Tian D, Li HX, Yang YS, Yan HJ, Jiang KY, Zheng YB et al. The minimum number of examined lymph nodes for accurate nodal staging and optimal survival of stage T1-2 esophageal squamous cell carcinoma: A retrospective multicenter cohort with SEER database validation. ***Int J Surg*** 2022; 104: 106764.
24. Zheng YZ, Li XQ, Wang JY, Yang H, Wen J, Zhai WY et al. Impact of examined lymph node count for oesophageal squamous cell carcinoma in patients who underwent left transthoracic oesophagectomy. ***Eur J Surg Oncol*** 2020; 46: 1956-1962.
25. Zheng YZ, Li XQ, Wang JY, Yang H, Wen J, Zhai WY et al. Impact of examined lymph node count for esophageal squamous cell carcinoma in patients who underwent right transthoracic esophagectomy. ***Ann Surg Oncol*** 2021; 28: 3025-3033.
26. Yeung JC, Bains MS, Barbetta A, Nobel T, DeMeester SR, Louie BE et al. How many nodes need to be removed to make esophagectomy an adequate cancer operation, and does the number change when a patient has chemoradiotherapy before surgery? ***Ann Surg Oncol*** 2020; 27: 1227-1232.
27. Liu X, Yang X, Wu Q, Zhang T, Jiang D, Wang Z. Can patients with good tumor regression grading after neoadjuvant chemoradiotherapy be exempted from lateral lymph node dissection? ***Discov Oncol*** 2022; 13: 144.
28. Sihag S, Nobel T, Hsu M, Tan KS, Carr R, Janjigian YY et al. A more extensive lymphadenectomy enhances survival after neoadjuvant chemoradiotherapy in locally advanced esophageal adenocarcinoma. ***Ann Surg*** 2022; 276: 312-317.
29. Hagens ERC, Künzli HT, van Rijswijk AS, Meijer SL, Mijnals RCD, Weusten BLAM et al. Distribution of lymph node metastases in esophageal adenocarcinoma after neoadjuvant chemoradiation therapy: A prospective study. ***Surg Endosc*** 2020; 34: 4347-4357.
30. Zhang Y, Cao Y, Zhang J, Huang M, Roy P, Huang B et al. Lymph node ratio improves prediction of overall survival in esophageal cancer patients receiving neoadjuvant chemoradiotherapy: A national cancer database analysis. ***Ann Surg*** 2022; 277: e1239-e1246
31. Sun Z, Xu X, Zhao X, Ma X, Ye Q. Impact of postoperative lymph node status on the prognosis of esophageal squamous cell carcinoma after esophagectomy following neoadjuvant chemoradiotherapy: a retrospective study. ***J Gastrointest Oncol*** 2021; 12: 2685-2695.
32. Xi M, Yang Y, Zhang L, Yang H, Merrell KW, Hallemeier CL et al. Multi-institutional analysis of recurrence and survival after neoadjuvant chemoradiotherapy of esophageal cancer: Impact of histology on recurrence patterns and outcomes. ***Ann Surg*** 2019; 269: 663-670.