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## EDITED BY

Mingqiang Kang,  
Fujian Medical University Union  
Hospital, China

## REVIEWED BY

Yongfu Yu,  
Fudan University, China  
Ahmed Mahmoud Fouad,  
Suez Canal University, Egypt

## \*CORRESPONDENCE

Sheng-Guang Zhao  
zsg10935@rjh.com.cn  
Jia-Yi Chen  
chenjiayi0188@aliyun.com

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# No survival benefit could be obtained from adjuvant radiotherapy in esophageal cancer treated with neoadjuvant chemotherapy followed by surgery: A SEER-based analysis

Si-Yue Zheng, Wei-Xiang Qi, Sheng-Guang Zhao\* and Jia-Yi Chen\*

Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

**Background:** The aim of this study is to assess the clinical benefit of postoperative radiotherapy (PORT) in patients with esophageal cancer (EC) who treated with neoadjuvant chemotherapy (NAC) and surgery *via* a national population-based database.

**Methods:** Patients diagnosed with EC between 2004 and 2015 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Kaplan–Meier survival analysis was used to compare the overall survival (OS) and cause-specific survival (CSS) difference between PORT vs. no-radiotherapy (RT) groups before and after propensity score matching (PSM). After PSM for baseline characteristics, Cox proportional hazard regression was performed to investigate the factors associated with OS.

**Results:** A total of 321 patients were included in the analysis. Of them, 91 patients (28%) received PORT. In the unmatched population, the no-RT group had improved OS compared with PORT (44 vs. 25 months,  $p = 0.002$ ), and CSS was similar in patients undergoing NAC with or without PORT (42 vs. 71 months,  $p = 0.17$ ). After PSM for baseline characteristics, the OS benefit of the no-RT group over the PORT group remained significant with a median OS of 46 vs. 27 months ( $p = 0.02$ ), and CSS remained comparable between groups (83 vs. 81 months,  $p = 0.49$ ). In subgroup analyses, PORT did not improve the OS among patients with adenocarcinoma in the subgroups of cN0, cN1, and cN2–3 (all  $p > 0.05$ ). In Cox regression, aged  $\geq 71$  years old, cT3–4, cN2–3, and receiving PORT were independent predictors of worse OS, whereas cT4 and cN2–3 were independent predictors of worse CSS (all  $p < 0.05$ ).

**Conclusions:** The present study demonstrated that no survival benefit could be obtained from the additional use of PORT after NAC and surgery in patients with EC. Well-designed prospective trials are needed to confirm our findings.

#### KEYWORDS

esophageal cancer, postoperative radiotherapy, neoadjuvant chemotherapy, SEER, prognosis

## Introduction

In 2020, around 1 in every 18 cancer deaths is attributed to esophageal cancer (EC), which is now the seventh most common cancer and ranks sixth in mortality worldwide (1). Although esophagectomy is generally accepted as the mainstay treatment for decades, neoadjuvant and adjuvant therapies have been performed to improve the overall survival (OS) among these patients. The benefits of neoadjuvant chemotherapy (NAC) in EC have primarily been proven in the MAGIC trial, in which perioperative chemotherapy was superior to surgery alone for patients with gastroesophageal adenocarcinoma in terms of OS and progression-free survival (2). As demonstrated by the CROSS trial, neoadjuvant chemoradiotherapy (nCRT) could significantly prolong OS and disease-free survival (DFS) in patients with locally advanced EC compared with surgery alone (3). Subsequently, the NEOCRTEC 5010 trial also confirmed that treatment with nCRT plus surgery significantly improved long-term OS and DFS for patients with locally advanced esophageal squamous cell carcinoma (ESCC) (4).

However, the superiority of nCRT over NAC alone has not been evaluated in EC. Although few randomized controlled trials of small sample and meta-analyses have been performed to compare these two treatment modalities, controversy existed because of inconsistent conclusions and limited sample size (5–8). On the other hand, many patients with EC with poor performance status, older age, or comorbidities may be ineligible for nCRT due to expected high toxicity (9).

Meanwhile, the optimal postoperative therapeutic strategy remains undetermined. For those patients who undergo surgery without neoadjuvant therapy, several studies investigated the role of postoperative radiotherapy (PORT) in EC but reached conflicting conclusions (10–13). A prospective randomized study of 495 patients shows that PORT could improve the 5-year survival in patients with EC with positive lymph nodes and those with stage III disease (10). On the other hand, another prospective randomized study of 68 patients found no significant difference between the surgery alone group and the PORT group, and PORT significantly increased the incidence of esophagogastric fibrosis and affected the quality of life (11).

To date, the benefit of PORT in patients with EC undergoing NAC and surgery is not well established. Therefore, we sought to compare the survival benefit of patients with EC treated with and without PORT following NAC and surgery.

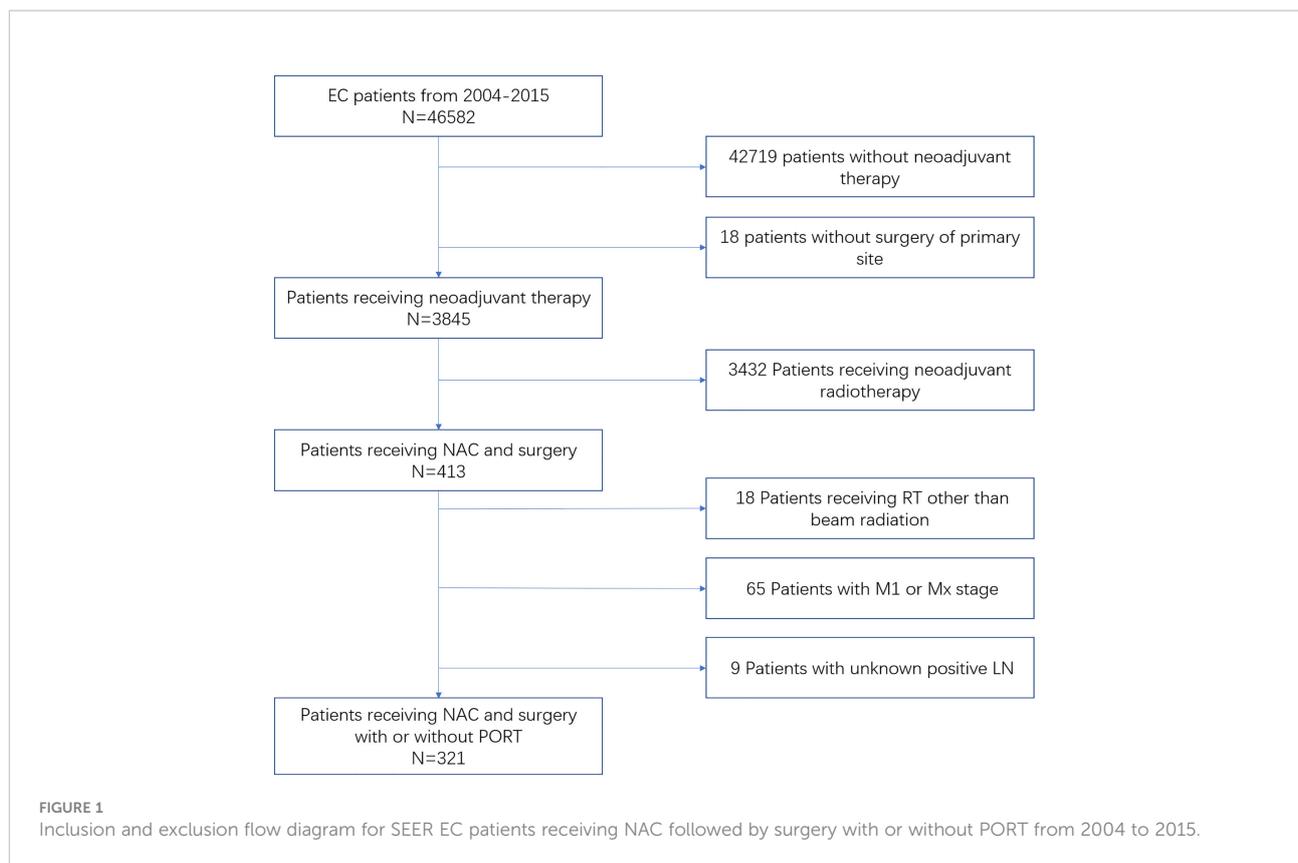
## Material and methods

### Patients

This population-based study was performed by using data from the Surveillance, Epidemiology, and End Results (SEER) database to identify patients with EC who underwent NAC and surgery diagnosed from 2004 to 2015. We obtained permission to access SEER Research Plus Data, Nov 2019 Sub (1975–2017) with reference number 11564-Nov2019. Cases eligible were required to have confirmed diagnosis with the recode as “only malignant in ICD-O-3” and the primary tumor site of the esophagus. Patients who received preoperative therapy without radiation prior to surgery were considered as having received NAC and included for analysis. For the sequence and type of radiation, only external beam radiation after surgery or no radiation was included for analysis. The following covariates were included: year of diagnosis, age, gender, race, chemotherapy, radiotherapy (RT) type and sequence, tumor histology, histological grade, clinical tumor (cT) stage, clinical nodal (cN) stage, clinical metastasis (cM) stage, and vital status, which includes the cause of death and the follow-up duration. cT, cN, and cM stages were categorized on the basis of the sixth edition of the American Joint Committee on Cancer/Union for International Cancer Control staging guidelines, and only cM0-stage patients were eligible. Patients with inadequate information were excluded from the final analysis. A flow diagram for patient inclusion and exclusion is shown in Figure 1.

### Statistical analysis

The chi-square test was used to compare the differences for categorical variables in clinicopathologic features between RT



and no-RT groups. A propensity score matching (PSM) analysis (1:2 ratio; method, nearest neighbor matching; caliper, 0.03) was performed to balance the observed characteristics between the two groups. OS and cause-specific survival (CSS) were estimated by the Kaplan–Meier method, and the log-rank test was applied to compare survival curves. Univariate and multivariate Cox regression models were performed to investigate risk factors for OS. The variables with  $p \leq 0.10$  in the univariate model were subsequently included in the multivariate analysis. All statistical analyses were performed in IBM SPSS version 23.0 and R statistical software version 4.0.3. Two-sided  $p < 0.05$  was considered as statistically significant.

## Results

### Patient characteristics

From 2004 to 2015, a total of 321 patients registered in the SEER database received NAC alone followed by esophagectomy; the mean age at diagnosis was  $62.41 \pm 8.99$  years. Of these, 230 patients (72%) did not receive adjuvant external beam radiation after surgery, whereas 91 patients (28%) received PORT.

The majority of the patients were of age from 61 to 70 years (43.9%), white (89.7%), and men (86.2%). The most frequent histological type was adenocarcinoma at 81.3% followed by ESCC at 18.7%. Notably, the patients who were treated with PORT tended to have a higher cN classification and a worse differentiated histological grade, whereas there was no statistically significant difference between the two groups in terms of age, sex, race, year of diagnosis, tumor histology, and cT classification. With PSM consisting of the number of positive lymph nodes and histological grade, 79 patients treated with PORT were successfully matched with 140 patients who did not receive postoperative radiation. The baseline clinicopathological characteristics for the study population before and after PSM are demonstrated in Table 1.

### Survival prior to PSM

The median follow-up time for the eligible patients was 74 months [interquartile range (IQR), 47–109 months] with the median OS being 37 months (IQR, 18–116 months). Figures 2A, B represent a Kaplan–Meier OS curve and a Kaplan–Meier CSS curve with the number of subjects at risk and 95% confidence

TABLE 1 Baseline characteristics of patients included in the analysis before and after PSM.

Characteristic	Before PSM			After PSM		
	Without PORT (n, %)	With PORT (n, %)	P-value	Without PORT (n, %)	With PORT (n, %)	P-value
<b>Total</b>	n = 230	n = 91		n = 140	n = 79	
<b>Year of diagnosis</b>			0.337			0.728
2004–2007	60 (26.1)	31 (34.1)		43 (30.7)	26 (32.9)	
2008–2011	101 (43.9)	34 (37.4)		59 (42.1)	29 (36.7)	
2012–2015	69 (30.0)	26 (28.6)		38 (27.1)	24 (30.4)	
<b>Gender</b>			0.211			0.07
Male	195 (84.8)	82 (90.1)		115 (82.1)	72 (91.1)	
Female	35 (15.2)	9 (9.9)		25 (17.9)	7 (8.9)	
<b>Age groups (years)</b>			0.838			0.911
≤50	19 (8.3)	10 (11.0)		12 (8.6)	8 (10.1)	
51–60	68 (29.6)	27 (29.7)		38 (27.1)	23 (29.1)	
61–70	101 (43.9)	40 (44.0)		64 (45.7)	36 (45.6)	
≥71	42 (18.3)	14 (15.4)		26 (18.6)	12 (15.2)	
<b>Race</b>			0.337			0.365
White	204 (88.7)	84 (92.3)		124 (88.6)	73 (92.4)	
Black and others	26 (11.3)	7 (7.7)		16 (11.4)	6 (7.6)	
<b>cT classification</b>			0.862			0.606
T1	34 (14.8)	12 (13.2)		18 (12.9)	12 (15.2)	
T2	37 (16.1)	15 (16.5)		22 (15.7)	15 (19.0)	
T3	141 (61.3)	59 (64.8)		89 (63.6)	49 (62.0)	
T4 and Tx	18 (7.8)	5 (5.5)		11 (7.9)	3 (3.8)	
<b>cN classification</b>			0.004			0.832
N0	134 (58.3)	36 (39.6)		66 (47.1)	35 (44.3)	
N1	54 (23.5)	24 (26.4)		46 (32.9)	24 (30.4)	
N2	26 (11.3)	23 (25.3)		23 (16.4)	16 (20.3)	
N3	16 (7.0)	8 (8.8)		5 (3.6)	4 (5.1)	
<b>Tumor histology</b>			0.448			0.896
Adenocarcinoma	195 (84.8)	74 (81.3)		116 (82.9)	66 (83.5)	
SCC	35 (15.2)	17 (18.7)		24 (17.1)	13 (16.5)	
<b>Histological grade</b>			0.041			0.865
Well	6 (2.6)	7 (7.7)		4 (2.9)	4 (5.1)	
Moderate	87 (37.8)	25 (27.5)		43 (30.7)	24 (30.4)	
Poor/Undifferentiated	113 (49.1)	53 (58.2)		83 (59.3)	46 (58.2)	
Unknown	24 (10.4)	6 (6.6)		10 (7.1)	5 (6.3)	

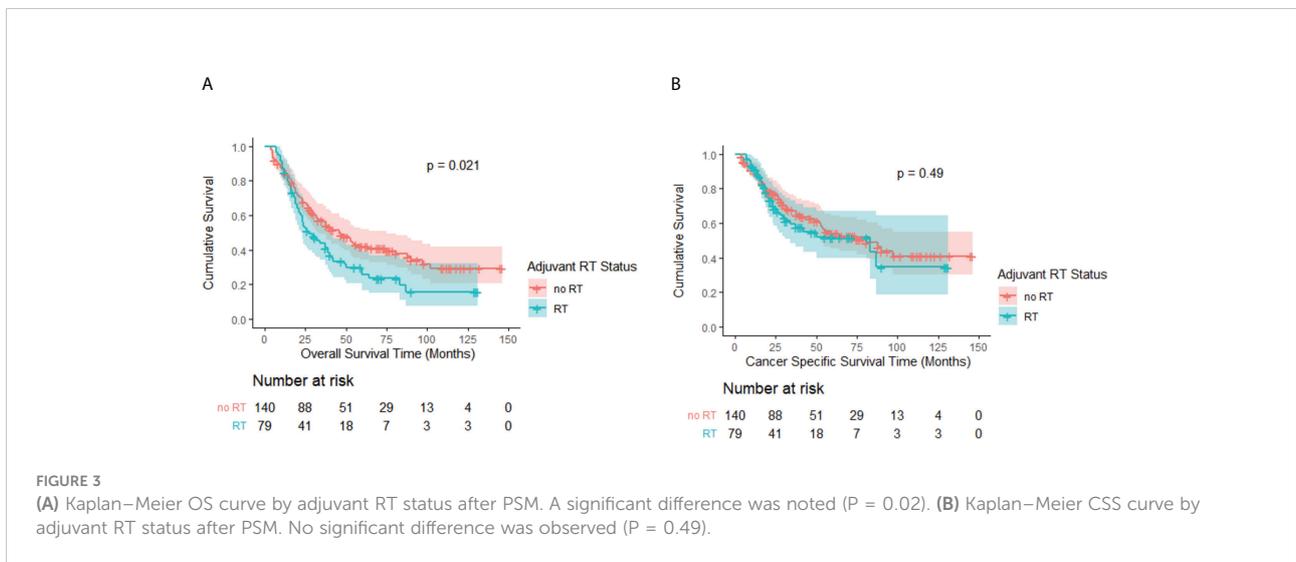
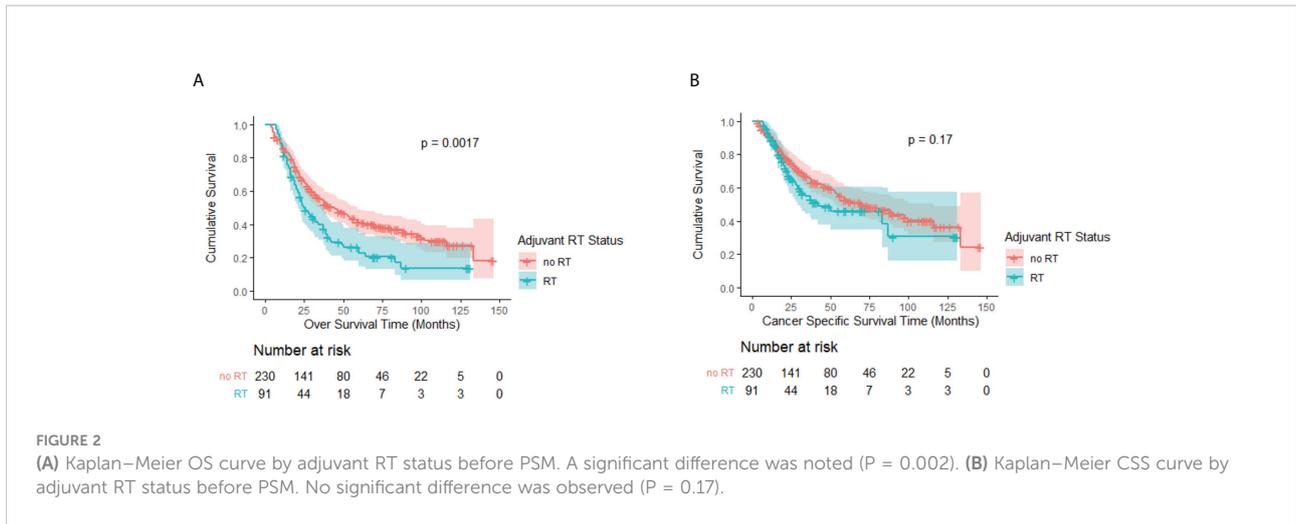
PSM, propensity score matching; PORT, postoperative radiotherapy; T, tumor; N, nodal; SCC, squamous cell carcinoma.

interval (CI) comparing patients who either received or did not receive PORT. The results of the log-rank test are also shown in Figures 2A, B. A significant OS benefit was noted between the no-RT and RT groups ( $P = 0.002$ ). The median OS rates for patients who received and did not receive PORT were 25 months (95% CI, 18.7–31.3 months) and 44 months (95% CI, 32.6–55.4 months), respectively. The log-rank test did not indicate a significant CSS difference between the two groups ( $P = 0.17$ ). However, the patients not receiving PORT still had a longer median CSS of 71 months (95% CI, 46.7–95.3 months), followed by the patients receiving RT only with a CSS of 42 months (95% CI, 7.6–76.4 months).

## Survival after PSM

In the matched cohort, the OS advantage of the no-RT group over the RT group persisted with a median OS of 46 months (95% CI, 33.3–58.7 months) and 27 months (95% CI, 16.9–37.1 months), respectively ( $p = 0.02$ ; Figure 3A). CSS remained comparable between the groups ( $p = 0.49$ ; Figure 3B). The no-RT group still had more favorable median CSS of 83 months (95% CI, 49.2–112.8 months) versus 81 months (95% CI, 22.2–143.8 months) for the RT group.

Moreover, Kaplan–Meier analysis stratified by the cN stage among patients with adenocarcinoma revealed no statistical



significance between the RT and no-RT groups. The median OS rates of the two groups were all not reached in the cN0 and cN1 subgroups, whereas the 3-year OS rates of the RT group were higher than those of the no-RT group but showed no significance (cN0: 69.7% vs. 58.9%,  $p = 0.42$ , Figure 4A; cN1: 61.9% vs. 47.4%,  $p = 0.22$ , Figure 4B). There is also no survival benefit of PORT in the cN2–3 subgroup (median OS: 22 months vs. 19 months,  $p = 0.56$ , Figure 4C).

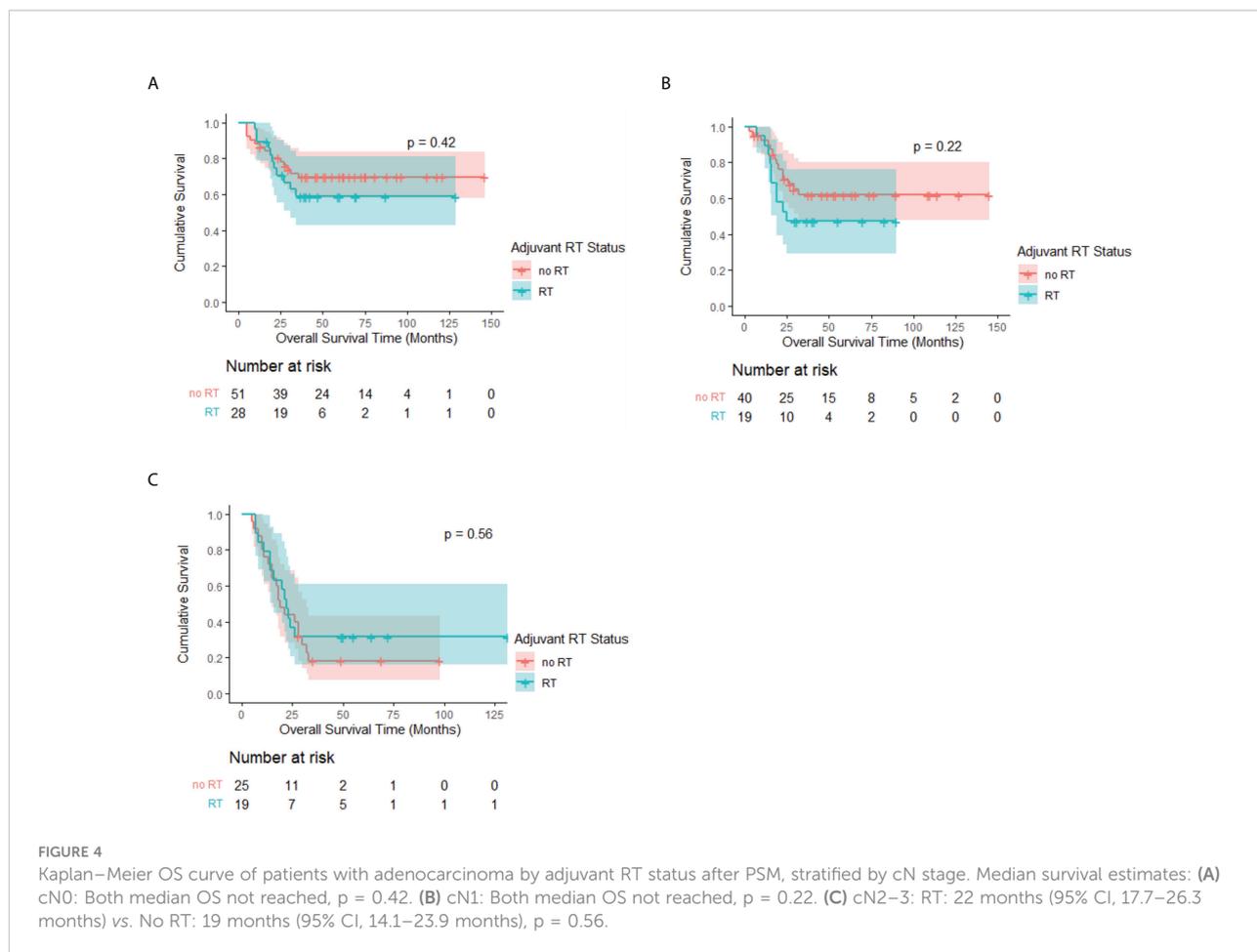
The prognostic factors associated with OS in univariate and multivariate analyses for the matched cohort are shown in Table 2. Univariate analysis showed that the factors associated with worse OS included age  $\geq 71$  years old, cT3–4, cN2–3, and receiving PORT, which remained independent factors significantly decreasing OS in multivariate analysis.

The prognostic factors associated with CSS in univariate and multivariate analyses for the matched cohort are shown in

Table 3. On univariate analysis, the factors associated with worse CSS included male sex, cT3–4, cN2–3, and adenocarcinoma. On multivariate analysis, cT4 and cN2–3 were still independently associated with a decreased CSS.

## Discussion

According to the National Comprehensive Cancer Network guideline (version 3.2021) recommendation, all patients with EC who have not received nCRT or NAC with R1 or R2 resection should receive PORT. For R0 cases, PORT is only recommended for T3–T4a or N1–3 patients with adenocarcinoma without nCRT or NAC (14). However, the efficacy of adding PORT in patients with EC after NAC alone remains unclear. To the best of our knowledge, this is the first



retrospective study to investigate the role of PORT for patients with EC after NAC and surgery.

We revealed that omitting PORT after NAC and surgery showed a significantly better OS than the PORT group before and after PSM, whereas there were no significant differences in CSS between the two groups. In subgroup analysis according to recurrence risk factors, we also found that no survival benefit could be obtained in those with cT3 stage or positive nodes, which was quite different from previous studies focusing on the effectiveness of PORT in patients with EC without defining the use of NAC (15, 16). This may be attributed to the treatment toxicities caused by PORT, which have already been affected by the chemotherapy and surgery. Wang et al. revealed that 18% of the patients with EC experienced grade 3 or higher cardiac events after RT, which was associated with worse OS ( $p = 0.041$ ) (17). Pinder-Arabpour et al. demonstrated that ventilation heterogeneities occurred in 30% of the patients with EC undergoing RT (18). Although currently we did not find any research comparing the side effects between NAC + surgery with and without PORT, Zhang et al. reported that NAC caused fewer cardiopulmonary events than nCRT (19). The patients analyzed in our study were diagnosed in the years from 2004 to 2015, and

most of them received conventional radiation therapy by using two parallel beams with opposed orientations. Therefore, relatively large volumes of normal tissues adjacent to the treatment field (including the mediastinum, chest wall, and adjacent lung) are irradiated. Further investigations with advanced technology such as intensity-modulated radiation therapy and proton therapy are in progress to confirm the safety of the treatment strategy (NCT01512589).

In our study, adenocarcinoma accounts for 83.8% of all 321 patients, which reflects the high prevalence of adenocarcinoma in Western countries just as most clinical trials conducted in Europe and Northern America (2, 3, 20). Conversely, considering that SCC was the most common histological subtype among Chinese patients with EC, the conclusion might not be directly applied to East Asia people (21). As the 10-year outcome of the CROSS trial demonstrated, nCRT tended to be more beneficial in the SCC group than in the adenocarcinoma group with a 10-year OS in the nCRT-surgery group of 46% and 36%, respectively (22). The conclusion was confirmed by the NEOCRTEC5010 trial, in which the median OS for Chinese patients with ESCC receiving nCRT plus surgery was 100.1 months and the 3-year OS was 69.1%, which is

TABLE 2 Univariate and multivariate analysis of OS for the matched cohort after PSM.

Characteristic	Univariate			Multivariate		
	P-value	OR	95% CI	P-value	OR	95% CI
<b>Year of diagnosis</b>	0.599					
2004–2007	1					
2009–2011	0.731	0.936	0.641–1.367			
2012–2015	0.314	0.783	0.487–1.260			
<b>Gender</b>						
Male	1					
Female	0.135	0.671	0.397–1.132			
<b>Age groups (years)</b>	0.024			0.002		
≤50	1			1		
51–60	0.976	1.01	0.521–1.956	0.511	1.262	0.630–2.526
61–70	0.381	1.318	0.711–2.444	0.068	1.817	0.957–3.451
≥71	0.032	2.098	1.068–4.123	0.002	3.052	1.496–6.228
<b>Race</b>						
White	1					
Black and others	0.293	0.708	0.372–1.348			
<b>cT classification</b>	0.004			0.003		
T1	1			1		
T2	0.45	1.306	0.654–2.609	0.399	1.358	0.667–2.763
T3	0.01	2.153	1.205–3.847	0.013	2.132	1.177–3.862
T4	0.002	4.236	1.684–10.652	0.001	4.91	1.888–12.768
Tx	0.852	0.868	0.196–3.846	0.745	0.777	0.170–3.546
<b>cN classification</b>	< 0.001			< 0.001		
N0	1			1		
N1	0.158	1.332	0.895–1.984	0.159	1.337	0.892–2.002
N2	0.001	2.106	1.349–3.288	0.001	2.177	1.359–3.486
N3	< 0.001	4.597	2.237–9.449	<0.001	4.079	1.965–8.467
<b>Tumor histology</b>						
Adenocarcinoma	1					
SCC	0.934	1.019	0.651–1.596			
<b>Histological grade</b>	0.567					
Well	1					
Moderate	0.251	1.985	0.616–6.393			
Poor/Undifferentiated	0.285	1.876	0.592–5.944			
Unknown	0.169	2.453	0.684–8.800			
<b>PORT</b>						
Yes	1			1		
No	0.024	0.674	0.479–0.948	0.012	0.638	0.448–0.907

T, tumor; N, nodal; SCC, squamous cell carcinoma; PORT, postoperative radiotherapy.

obviously better than that reported in previous trials containing more patients with adenocarcinoma (4, 20). On the other hand, NAC is suggested as the standard treatment for locally advanced ESCC in Japan according to the result of the JCOG9907 trial, in which the 5-year OS of the NAC group was 55% (23, 24). In our study, the 3- and 5-year OS rates of patients with SCC in the PORT group after PSM were 25.6% and 17.1%, respectively, and those in the no-RT group were 56.1% and 44.9%, respectively. Comparing our results with those of the clinical trials mentioned

above, the OS of both groups in our study showed a reduction by at least 10% compared with the prognosis in the NEOCRTEC5010 and JCOG9907 trials. Taken together, the present study demonstrated that the addition of PORT to NAC combined with surgery in patients with ESCC may also be associated with a higher mortality and adjuvant RT is also not recommended in patients with ESCC treated with NAC.

It is also worth mentioning that immunotherapy has shown positive impacts on patients with advanced EC from back line to

TABLE 3 Univariate and multivariate analysis of CSS for the matched cohort after PSM.

Characteristic	Univariate			Multivariate		
	P-value	OR	95% CI	P-value	OR	95% CI
<b>Year of diagnosis</b>	0.903					
2004–2007	1					
2009–2011	0.838	0.952	0.592–1.530			
2012–2015	0.651	0.875	0.490–1.562			
<b>Gender</b>						
Male	1			1		
Female	0.056	0.491	0.237–1.018	0.148	0.574	0.270–1.219
<b>Age groups (years)</b>	0.554					
≤50	1					
51–60	0.617	1.223	0.556–2.694			
61–70	0.657	1.188	0.555–2.546			
≥71	0.215	1.715	0.732–4.021			
<b>Race</b>						
White	1					
Black and others	0.177	0.537	0.218–1.325			
<b>cT classification</b>	0.001			0.002		
T1	1			1		
T2	0.650	0.807	0.320–2.034	0.454	0.697	0.270–1.797
T3	0.034	2.127	1.058–4.276	0.083	1.880	0.921–3.838
T4	0.002	5.201	1.843–14.676	0.009	4.107	1.420–11.875
Tx	0.647	0.617	0.078–4.874	0.423	0.424	0.052–3.455
<b>cN classification</b>	0.001			0.004		
N0	1			1		
N1	0.176	1.407	0.857–2.310	0.269	1.330	0.802–2.206
N2	0.003	2.285	1.318–3.962	0.010	2.116	1.195–3.748
N3	< 0.001	4.859	2.003–11.789	0.002	4.134	1.688–10.127
<b>Tumor histology</b>						
Adenocarcinoma	1			1		
SCC	0.031	0.428	0.198–0.926	0.129	0.538	0.242–1.198
<b>Histological grade</b>	0.410					
Well	1					
Moderate	0.380	1.902	0.453–7.989			
Poor/Undifferentiated	0.406	1.821	0.443–7.487			
Unknown	0.156	3.037	0.655–14.071			
<b>PORT</b>						
Yes	1					
No	0.494	1.164	0.754–1.797			

T, tumor; N, nodal; SCC, squamous cell carcinoma; PORT, postoperative radiotherapy.

first line, according to the result of several clinical trials such as KEYNOTE-590 and ESCORT-1st, but little is confirmed about its role in neoadjuvant therapy regimen (25, 26). Some single-armed trials focused on preoperative immuno-chemo-radiotherapy. For example, the PERFECT trial combined Atezolizumab with nCRT, and the pathologic complete response (PCR) rate was 25% (27). PALACE-1 used Pembrolizumab and got a higher PCR rate of 55.6% (28). Meanwhile, some other trials combined chemotherapy alone

with immunotherapy. Yang et al. evaluated the efficacy and safety of camrelizumab plus nab-paclitaxel and S1 capsule followed by surgery, and the PCR rate was 33.3% (29). Xing et al. designed a phase II randomized trial, in which both groups received chemotherapy on day 1, then the experimental group received toripalimab on day 3, while the control group received it on day 1. The PCR rates were 36% and 7%, respectively (30). However, none of those neoadjuvant chemoimmunotherapy studies allowed PORT, which may be due to the safety

concern. The studies mentioned above are all with a small sample size, and the value of PORT for patients with EC under the brand new neoadjuvant therapeutic regimen including immunotherapy and chemotherapy needs to be redefined in the future.

However, we acknowledge several important limitations in our study. First, selection bias could not be avoided because of the retrospective nature of our study, although PSM was performed. Second, in the SEER database, it lacks detailed information regarding chemotherapy regimen, radiation dose, surgical margin, and certain risk factors such as smoking and alcohol exposure, which can affect the reliability of our findings.

In summary, our results detect no survival benefit with the use of PORT after NAC and surgery in patients with EC. Furthermore, multivariate analysis indicates that PORT, age  $\geq 71$  years old, cT3–4, and cN2–3 are independent predictors of worse OS. Further study is needed to identify an optimal treatment strategy in patients with EC after NAC and surgery.

## Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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## Author contributions

S-YZ and W-XQ contributed to the design of the research, to the analysis of the data, and to the writing of the manuscript. S-GZ and J-YC were in charge of overall direction. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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