Longer interval between neoadjuvant chemoradiotherapy and surgery is associated with improved pathological response, but does not accurately estimate survival in patients with resectable esophageal cancer

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Abstract. Neoadjuvant chemoradiotherapy (nCRT) has been shown to reduce tumor burden and achieve tumor regression in patients with esophageal cancer (ESC). However, the most beneficial time interval between the administration of nCRT and surgery remains unclear. Therefore, the aim of the present study was to explore the association of the duration of time between nCRT and surgery with the prognosis of patients with ESC. Patients with ESC who received nCRT following surgical resection (n=161) were reviewed and divided into the prolonged time interval group (time interval ≥66 days) and the short time interval group (time interval <66 days), according to the median value. Subsequent analysis revealed that the prolonged time interval group achieved a higher pathological complete response (pCR) rate compared with the short time interval group (49.4 vs. 26.3%; P=0.003). Furthermore, multivariate logistic regression analysis showed that it was possible to independently estimate a higher pCR rate based on a prolonged time interval (odds ratio, 2.131; P=0.042). However, no association between a prolonged time interval and disease-free survival (DFS) was detected using Kaplan-Meier curves (P=0.252) or multivariate Cox regression (P=0.607) analyses. Similarly, no association was identified between a prolonged time interval and overall survival (OS; P=0.946) based on Kaplan-Meier curve analysis, and subsequent multivariate Cox regression analyses showed that the time interval also failed to independently estimate OS (P=0.581). Moreover, female sex (P=0.001) and a radiation dose ≥40 Gy (P=0.039) served as independent factors associated with a higher pCR rate, and the pCR rate was an independent predictor of favorable DFS (P=0.002) and OS (P=0.015) rates. In conclusion, the present study revealed that a prolonged time interval from nCRT to surgery was associated with a higher pCR rate, but it failed to estimate the survival profile of patients with ESC.

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Introduction

Esophageal cancer (ESC) is ranked sixth in terms of cancer-associated mortality rates globally and was responsible for ~544,000 deaths in 2020 (1). In terms of management options, surgery with curative intent remains the most viable treatment for patients diagnosed with early ESC (2,3). However, >50% of patients with ESC are diagnosed at a locally advanced stage when the tumor has become inoperable, leaving them with limited management options and a poor prognosis (4,5). Recently, due to the application of multimodality approaches, neoadjuvant therapy has assumed a critical role in ESC management (6-11). For example, neoadjuvant therapy has achieved a reduction in the tumor burden in patients with unresectable ESC, thereby providing them with the opportunity to undergo surgery (9). Furthermore, neoadjuvant therapy has been shown to improve the R0 resection rate, leaving tumor residues in fewer cases and thereby causing a reduction in the postoperative recurrence of ESC in patients following surgery (10,11).

Neoadjuvant chemoradiotherapy (nCRT) is a common type of neoadjuvant therapy, which has been shown to achieve a high pathological complete response (pCR) rate, as well as longer disease-free survival (DFS) and higher overall survival (OS) rates, in patients who received surgery and nCRT compared with those who underwent surgery alone (12,13).

It is generally recommended that nCRT is completed within a 6-8-week period prior to surgery for patients with ESC; however, the optimal time interval between nCRT and surgery remains controversial, and the time interval that is most beneficial to the patient requires further investigation (14,15). For example, several studies have illustrated that a prolonged time interval is associated with a higher pCR rate in patients with ESC, whereas other studies have found no association between the time interval and the pCR rate (15-17). Similarly, in terms of the survival profile, certain studies observed that a longer time interval was not associated with recurrence-free survival (RFS) or OS (15,17), whereas another study suggested that a prolonged time interval is indeed associated with a shorter OS in patients with ESC (18).

These inconsistent previous findings are the rationale for the exploration of the association of the time interval between nCRT and surgery with the treatment response and survival profile in patients with ESC in the present study. The aim of the study is to provide more evidence to support clinicians when making decisions regarding the optimal time interval between nCRT and surgery.

Materials and methods

Patients. The present study retrospectively reviewed a total of 161 patients with resectable ESC who were treated with nCRT followed by surgical resection at West China Hospital, Sichuan University (Chengdu, China) between July 2017 and June 2020. The screening of patients was performed, and patients were included in the present study if they met the following criteria: i) The patient was diagnosed with ESC based on gastroscopy and pathological examinations; ii) the patient was >18 years old; iii) the patient received nCRT followed by surgical resection in line with National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Esophageal and Esophagogastric Junction Cancers (19); iv) the patient had at least one measurable tumor, as evaluated by contrast-enhanced computed tomography (CT) scan according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (20); and v) clinical data and accessible follow-up data for study use were available for the patient. Patients who met the following criteria were excluded from the study: i) Previously received emergency surgery; ii) had salvage resection; and iii) were unresectable due to the involvement of the heart, great vessels, trachea or adjacent organs including the liver, pancreas, lung and spleen (19). The study was approved by the Institutional Review Board of West China Hospital, Sichuan University.

Data collection. The clinical characteristics of the patients were collected from the database of West China Hospital, Sichuan University. These characteristics included age, sex, tumor location, pathological type, tumor size, tumor-node-metastasis (TNM) stage according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM Staging System (21) and nCRT information. In addition, the time interval between nCRT and surgery were obtained, which was defined as the time interval from the end of the last dosage of nCRT to the day of surgery. In addition, follow-up data of the patients were collected, and the final date of follow-up was February 24, 2021. The median duration of follow-up was 15.8 months (range, 0.4-41.4 months).

Treatment procedures. All patients underwent nCRT followed by surgical resection and none of the patients received conversion surgery. The nCRT regimens included synchronous chemoradiotherapy and sequential chemoradiotherapy. The appropriate treatment regimen was selected for each patient according to the patient's disease condition. The chemotherapy protocols were platinum-based doublet chemotherapy regimens, including albumin-bound paclitaxel + carboplatin (AC), albumin-bound paclitaxel + nedaplatin (AN), albumin-bound paclitaxel + cisplatin (AP), fluorouracil + cisplatin (FP), taxol + carboplatin (TC), taxol + nedaplatin (TN) and taxol + cisplatin (TP). The radiotherapy schedules differed slightly according to the specific conditions of the patients. In all cases, a planned total radiation dosage of 40.0-50.4 Gy was administered in 20-28 fractions of 1.8 or 2.0 Gy on 5 days of each week; no radiation was administered at weekends. The timing of surgery was dependent upon the performance status and nutrient status of the patient as well as the availability of operating rooms. The accessibility of surgery in patients after nCRT was determined in line with NCCN guidelines (19).

Outcome assessment. A contrast-enhanced CT scan was performed to assess the clinical response of the patients at the end of the neoadjuvant treatment, according to the RECIST guidelines (20). The clinical response was classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). In addition, the pathological response was evaluated according to the tumor regression grade (TRG) system and classified as follows: TRG1, 0% residual tumor cells per tumor bed; TRG2, 1-50% residual tumor cells per tumor bed; and TRG3, >50% residual tumor cells per tumor bed (22). Patients who were classified as TRG1 were considered to have a pCR. In addition, DFS and OS were calculated based on the follow-up data; DFS was defined as the time interval between surgery and disease relapse or death, and OS was defined as the time interval between surgery and death. Patients who did not experience DFS or OS events at the time of the final analysis were censored at their last date of contact.

Statistical analysis. SPSS 22.0 (IBM Corp.) was used to perform the statistical analysis, and GraphPad Prism 6.1 (GraphPad Software, Inc.) was used to plot figures. The median time interval between nCRT and surgery was 66 days (range, 0-196 days), and the patients were divided into two groups based on the median value: <66 days (n=76; designated the short time interval group) and ≥66 days (n=85; designated the prolonged time interval group). Differences between groups were compared using unpaired Student's t-test, Wilcoxon rank sum test, χ^2 test or Fisher's exact test, as applicable. Factors associated with pCR and the objective response rate (ORR) were assessed using univariate and multivariate logistic regression analyses. DFS and OS were evaluated using Kaplan-Meier curves and compared using the log-rank test. The factors associated with DFS and OS were evaluated using univariate and multivariate Cox proportional hazards regression analyses.

Table I. Clinical characteristics.

Items	Patients (N=161)	Duration from nCRT to surgery		t/χ^2/Z-value	P-value
		<66 days (n=76)	≥66 days (n=85)		
Demographics					
Age (years), mean ± SD	61.0±7.9	61.5±8.4	60.6±7.4	0.707	0.481
Sex, n (%)				4.379	0.036
Male	131 (81.4)	67 (88.2)	64 (75.3)		
Female	30 (18.6)	9 (11.8)	21 (24.7)		
Disease characteristics					
Tumor location, n (%)				1.048	0.592
Upper	22 (13.7)	12 (15.8)	10 (11.8)		
Middle	108 (67.1)	48 (63.2)	60 (70.6)		
Lower	31 (19.3)	16 (21.1)	15 (17.6)		
Pathological type, n (%)				0.267	0.763[a]
SCC	152 (94.4)	71 (93.4)	81 (95.3)		
ADC	9 (5.6)	5 (6.6)	4 (4.7)		
Tumor size (cm), median (IQR)	5.0 (4.5-7.0)	5.0 (4.5-7.0)	5.0 (4.4-7.0)	-0.243	0.808
cT stage, n (%)				-0.800	0.424
cT2	16 (9.9)	9 (11.8)	7 (8.2)		
cT3	117 (72.7)	55 (72.4)	62 (72.9)		
cT4a	28 (17.4)	12 (15.8)	16 (18.8)		
cN stage, n (%)				-0.082	0.935
cN0	16 (9.9)	6 (7.9)	10 (11.8)		
cN1	83 (51.6)	41 (53.9)	42 (49.4)		
cN2	51 (31.7)	25 (32.9)	26 (30.6)		
cN3	11 (6.8)	4 (5.3)	7 (8.2)		
cM stage, n (%)				2.265	0.221[a]
cM0	159 (98.8)	74 (97.4)	85 (100.0)		
cM1	2 (1.2)	2 (2.6)	0 (0.0)		
cTNM stage, n (%)				-1.078	0.281
II	22 (13.7)	11 (14.5)	11 (12.9)		
III	100 (62.1)	50 (65.8)	50 (58.8)		
IV	39 (24.2)	15 (19.7)	24 (28.2)		
Treatment information					
nCRT sequence, n (%)				1.318	0.251
Synchronous nCRT	115 (71.4)	51 (67.1)	64 (75.3)		
Sequential nCRT	46 (28.6)	25 (32.9)	21 (24.7)		
Chemotherapy cycle, n (%)				0.064	0.801
<2 cycles	18 (11.2)	9 (11.8)	9 (10.6)		
≥2 cycles	143 (88.8)	67 (88.2)	76 (89.4)		
Chemotherapy regimens, n (%)				16.809	0.330
TP	96 (59.6)	39 (51.3)	57 (67.1)		
TN	14 (8.7)	6 (7.9)	8 (9.4)		
TC	13 (8.1)	9 (11.8)	4 (4.7)		
AN	10 (6.2)	5 (6.6)	5 (5.9)		
AC	7 (4.3)	3 (3.9)	4 (4.7)		
FP	4 (2.5)	4 (5.3)	0 (0.0)		
AP	3 (1.9)	1 (1.3)	2 (2.4)		
Others	14 (8.7)	9 (11.8)	5 (5.9)		
Radiation dose (Gy), median (IQR)	41.4 (40.0-45.0)	41.4 (40.0-45.0)	41.4 (40.0-45.5)	-0.650	0.516

Table I. Continued.

Items	Patients (N=161)	Duration from nCRT to surgery		t/χ^2/Z-value	P-value
		<66 days (n=76)	≥66 days (n=85)		
Interruption of radiotherapy, n (%)				0.087	0.768
No	87 (54.0)	42 (55.3)	45 (52.9)		
Yes	74 (46.0)	34 (44.7)	40 (47.1)		

[a]P-values calculated by Fisher's exact test. nCRT, neoadjuvant chemoradiotherapy; SD, standard deviation; SCC, squamous cell carcinoma; ADC, adenocarcinoma; cT, clinical tumor; cN, clinical node; cM, clinical metastasis; cTNM, clinical tumor-node-metastasis; TP, taxol + cisplatin; TN, taxol + nedaplatin; TC, taxol + carboplatin; AN, albumin-bound paclitaxel + nedaplatin; AC, albumin-bound paclitaxel + carboplatin; FP, fluorouracil + cisplatin; AP, albumin-bound paclitaxel + cisplatin; IQR, interquartile range.

P<0.05 was considered to indicate a statistically significant result.

Results

Clinical characteristics. The mean age of all recruited patients was 61.0±7.9 years (Table I). There were 131 (81.4%) males and 30 (18.6%) females. In terms of the clinical tumor (cT) stage, 16 (9.9%), 117 (72.7%) and 28 (17.4%) patients in the entire cohort were classified with cT2, cT3, and cT4a stage tumors, respectively. Patients with ESC in the cT4a stage, in which the tumors were growing into the pericardium, pleura or diaphragm, were resectable (19). There were 115 (71.4%) and 46 (28.6%) patients who received synchronous nCRT and sequential nCRT, respectively. Moreover, 18 (11.2%) patients received one cycle of chemotherapy, whereas the remaining 143 (88.8%) patients received two or more cycles of chemotherapy. The median radiation dosage was 41.4 Gy (interquartile range, 40.0-45.0 Gy). Statistical analyses revealed that the majority of the clinical features did not exhibit any differences when compared between the short and prolonged time interval groups (all P>0.05), with the exception that the proportion of females was higher in the prolonged time interval group compared with the short time interval group (P=0.036). The detailed clinical features of the patients are shown in Table I.

Surgery information. McKeown surgery and Ivor Lewis surgery are two main surgical approaches for patients with resectable ESC (23,24). In total, 145 (90.1%), 4 (2.5%) and 12 (7.5%) patients received McKeown surgery, Ivor Lewis surgery and other surgical approaches, respectively (Table SI). In detail, 76 (89.4%), 1 (1.2%) and 8 (9.4%) patients in the prolonged time interval group received the McKeown surgery, Ivor Lewis surgery and other surgical approaches, compared with 69 (90.8%), 3 (3.9%) and 4 (5.3%) in the short time interval group, respectively. In terms of lymphadenectomy, 145 (90.1%), 15 (9.3%) and 1 (0.6%) patient underwent two-field, three-field and other types, respectively. There were 77 (90.6%) and 8 (9.4%) patients in the prolonged time interval group who received two- and three-field lymphadenectomy, respectively, while 68 (89.5%), 7 (9.2%) and 1 (1.3) patient in the short time interval group received two-field, three-field and other types of lymphadenectomy, respectively. Moreover, the R0 resection rate was 93.8% for all total patients, with rates of 97.6 and 89.5% in the prolonged and short time interval groups, respectively. Regarding postoperative complications, 25 (15.5%), 10 (6.2%), 5 (3.1%), 3 (1.9%) and 6 (3.7%) resectable patients in the entire cohort experienced pulmonary infection, anastomotic leakage, anastomotic stenosis, incision infection and other complications after surgery. In detail, 14 (16.5%), 3 (3.5%), 3 (3.5%), 2 (2.4%) and 3 (3.5) patients in the prolonged time interval group and 11 (14.5%), 7 (9.2%), 2 (2.6%), 1 (1.3%), and 3 (3.9) patients in the short time interval group experienced pulmonary infection, anastomotic leakage, anastomotic stenosis, incision infection and other complications, respectively. No significant difference in surgical approaches, the degree of lymphadenectomy, R0 resection rate or postoperative complications was detected between the two groups (all P>0.05).

Treatment response. In terms of the clinical response, 0 (0.0%), 111 (68.9%), 50 (31.1%) and 0 (0.0%) patients achieved CR, PR, SD and PD, respectively (Table II). In detail, a PR and SD were achieved by 63 (74.1%) and 22 (25.9%) patients in the prolonged time interval group and by 48 (63.2%) and 28 (36.8%) patients in the short time interval group, respectively; no patients in either group had PD. No difference in clinical response, ORR or DCR was detected between these two groups (all P>0.05).

Regarding the pathological response, there were 62 (38.5%), 78 (48.4%), 9 (5.6%) and 12 (7.5%) patients with TRG1, TRG2, TRG3 and no assessment data, respectively. In detail, TRG1, TRG2 and TRG3 pathological responses were achieved by 42 (49.4%), 37 (43.5%) and 4 (4.7%) patients in the prolonged time interval group compared with 20 (26.3%), 41 (53.9%) and 5 (6.6%) patients in the short time interval group, respectively. In addition, 2 (2.4%) patients in the prolonged time interval group and 10 (13.2%) patients in the short time interval group had no assessment data. Moreover, 62 (38.5%) patients in the entire cohort achieved a pCR. Comparison of the two groups revealed that the pCR rate (49.4 vs. 26.3%; P=0.003) and the TRG grade (P=0.001) were higher in the prolonged time interval group compared with the short time interval group.

Table II. Treatment response.

Items	Patients (N=161)	Duration from nCRT to surgery		Z/χ^2-value	P-value
		<66 days (n=76)	≥66 days (n=85)		
Clinical response					
Overall response, n (%)				2.251	0.134
CR	0 (0.0)	0 (0.0)	0 (0.0)		
PR	111 (68.9)	48 (63.2)	63 (74.1)		
SD	50 (31.1)	28 (36.8)	22 (25.9)		
PD	0 (0.0)	0 (0.0)	0 (0.0)		
ORR, n (%)	111 (68.9)	48 (63.2)	63 (74.1)	2.251	0.134
DCR, n (%)	161 (100.0)	76 (100.0)	85 (100.0)	-	-
Pathological response					
TRG, n (%)				-3.406	0.001
TRG1	62 (38.5)	20 (26.3)	42 (49.4)		
TRG2	78 (48.4)	41 (53.9)	37 (43.5)		
TRG3	9 (5.6)	5 (6.6)	4 (4.7)		
Not assessed	12 (7.5)	10 (13.2)	2 (2.4)		
pCR, n (%)	62 (38.5)	20 (26.3)	42 (49.4)	9.039	0.003

nCRT, neoadjuvant chemoradiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; TRG, tumor regression grade; pCR, pathological complete response.

Table III. Logistic regression analysis for pCR.

Items	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	β-value	OR (95% CI)	P-value	β-value	OR (95% CI)	P-value
Duration from nCRT to surgery (≥66 vs. <66 days)	1.006	2.735 (1.407-5.315)	0.003	0.757	2.131 (1.028-4.418)	0.042
Age (≥60 vs. <60 years)	-0.474	0.622 (0.326-1.189)	0.151	-0.492	0.611 (0.291-1.283)	0.193
Sex (female vs. male)	1.444	4.238 (1.824-9.848)	0.001	1.763	5.830 (2.038-16.678)	0.001
Tumor location						
Upper	Reference			Reference		
Middle	-0.067	0.935 (0.407-2.151)	0.874	0.366	1.442 (0.507-4.104)	0.493
Lower	0.531	1.700 (0.676-4.276)	0.260	0.319	1.376 (0.479-3.952)	0.554
Pathological type (SCC vs. non-SCC)	0.825	2.283 (0.459-11.360)	0.313	0.911	2.487 (0.379-16.301)	0.342
Tumor size (≥5 vs. <5 cm)	-0.087	0.917 (0.453-1.854)	0.809	0.044	1.045 (0.467-2.337)	0.915
cTNM stage (III-IV vs. II)	-0.332	0.717 (0.290-1.776)	0.473	-0.058	0.944 (0.301-2.961)	0.921
nCRT sequence (sequential nCRT vs. synchronous nCRT)	-0.493	0.611 (0.295-1.266)	0.185	-0.243	0.784 (0.290-2.122)	0.632
Chemotherapy cycle (≥2 vs. <2 cycles)	0.871	2.388 (0.748-7.620)	0.141	1.002	2.724 (0.587-12.638)	0.201
Radiation dose (≥40 vs. <40 Gy)	2.130	8.414 (1.066-66.417)	0.043	2.326	10.235 (1.120-93.552)	0.039
Interruption of radiotherapy (yes vs. no)	0.053	1.055 (0.558-1.993)	0.870	0.076	1.079 (0.511-2.278)	0.843

pCR, pathological complete response; OR, odds ratio; CI, confidence interval; nCRT, neoadjuvant chemoradiotherapy; SCC, squamous cell carcinoma; cTNM, clinical tumor-node-metastasis.

Factors associated with pCR rate. A prolonged time interval between nCRT and surgery was found to be associated with an improved pCR rate [odds ratio (OR): 2.735, 95% confidence interval (95%CI): 1.407-5.315, P=0.003] based on univariate Cox regression analyses, and independently associated with a higher pCR rate based on a multivariate Cox regression model (OR: 2.131, 95%CI: 1.028-4.418, P=0.042; Table III). Sex (female vs. male; OR: 5.830, 95% CI: 2.038-16.678, P=0.001)

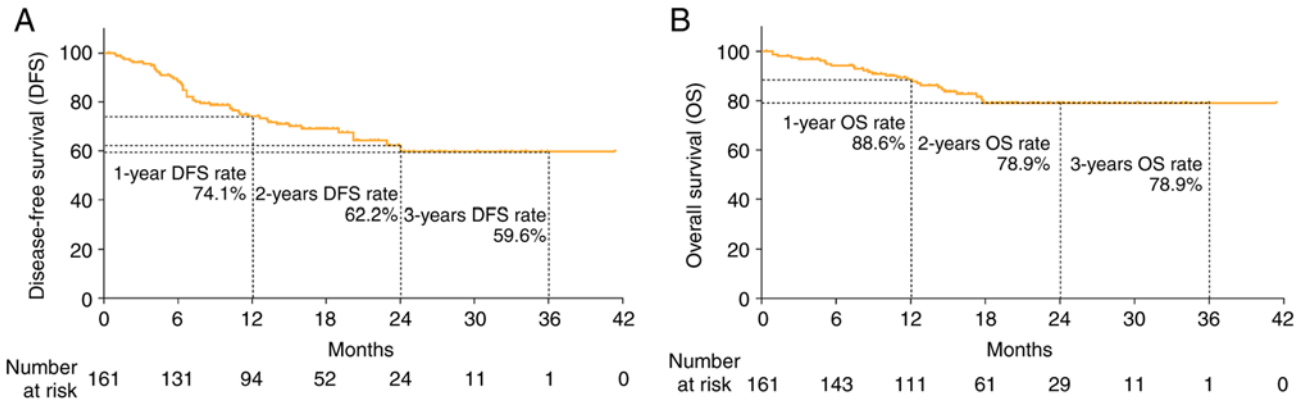

Figure 1. Survival profiles in patients with esophageal cancer who underwent neoadjuvant chemoradiotherapy and surgery. (A) Disease-free survival and (B) overall survival profiles.

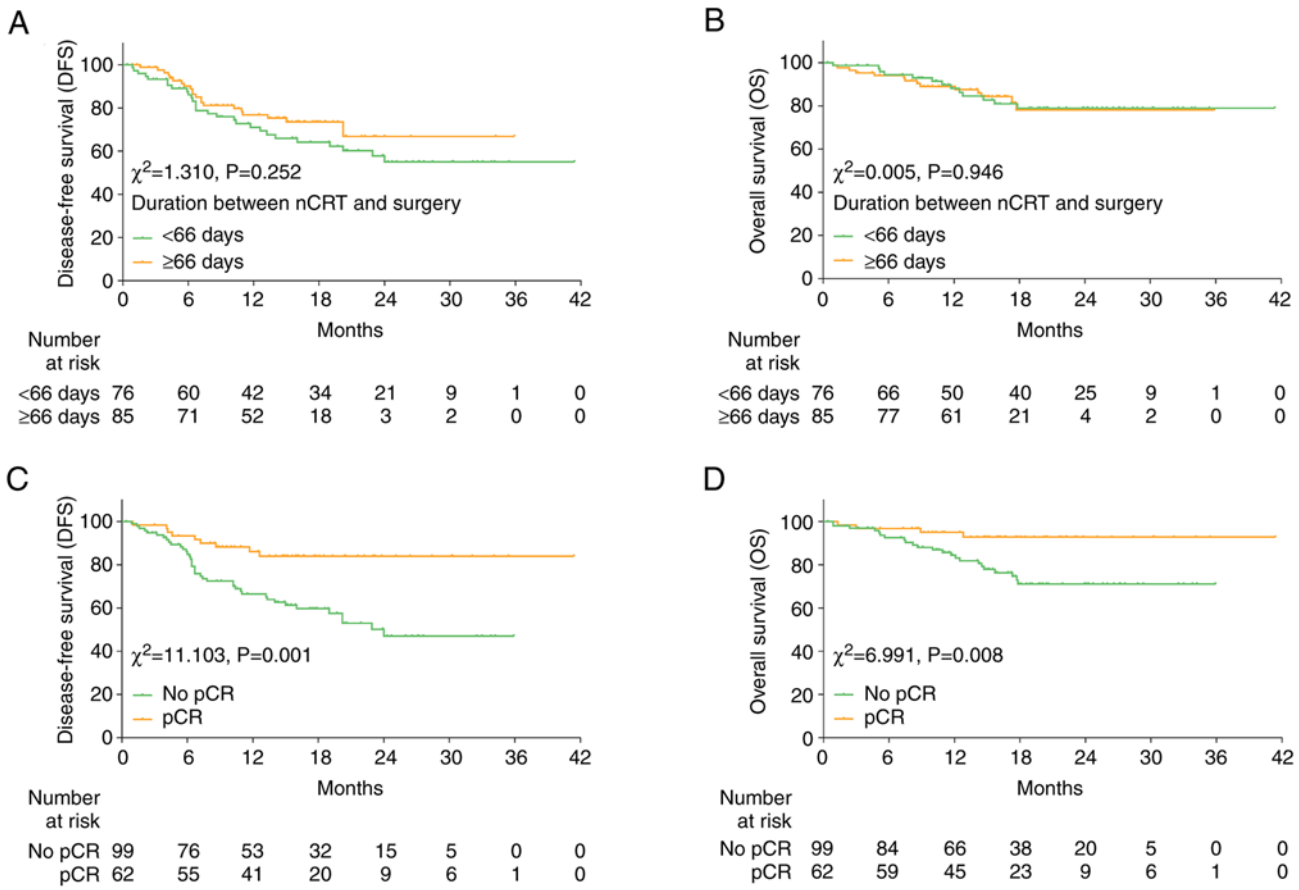

Figure 2. Comparison of survival profiles between different groups of patients with esophageal cancer. Comparison of (A) DFS and (B) OS rates between patients whose time interval from nCRT to surgery was <66 days and those whose time interval from nCRT to surgery was ≥66 days. Comparison of the (C) DFS and (D) OS rates between patients who reached pCR and those who did not reach pCR. DFS, disease-free survival; OS, overall survival; nCRT, neoadjuvant chemoradiotherapy; pCR, pathological complete response.

and radiation dose (≥40 vs. <40 Gy; OR: 10.235, 95% CI: 1.120-3.552, P=0.039) were also independently associated with an elevated pCR. The factors were also assessed for association with the ORR as displayed in Table SII, but none of the included factors could independently predict ORR (all P>0.05; Table SII).

Survival profile. The median duration of follow-up was 15.8 months (range, 0.4-41.4 months). At the last date of follow-up, the DFS and OS rates had not attained the median value. Fig. 1A shows the DFS rate within 1 year (74.1%), 2 years (62.2%) and 3 years (59.6%) of treatment and Fig. 1B shows the OS rate within 1 year (88.6%), 2 years (78.9%) and 3 years (78.9%) of treatment.

During the follow-up period, 27 (16.8%) total deaths were recorded among which 14 (16.5%) cases occurred in the prolonged time interval group and 13 (17.1%) cases occurred in the short time interval group; no difference in death rate was

Table IV. Cox proportional hazards regression analysis for disease-free survival.

	Univariate Cox regression analysis			Multivariate Cox regression analysis		
Items	β-value	HR (95% CI)	P-value	β-value	HR (95% CI)	P-value
Duration from nCRT to surgery (≥66 vs. <66 days)	-0.334	0.716 (0.403-1.272)	0.255	-0.157	0.855 (0.471-1.552)	0.607
Age (≥60 vs. <60 years)	-0.162	0.850 (0.483-1.498)	0.574	-0.307	0.735 (0.411-1.316)	0.301
Sex (female vs. male)	-0.280	0.756 (0.339-1.683)	0.493	0.007	1.007 (0.410-2.474)	0.987
Tumor location						
Upper	Reference			Reference		
Middle	-0.233	0.792 (0.366-1.716)	0.555	-0.346	0.707 (0.270-1.855)	0.481
Lower	0.304	1.355 (0.625-2.936)	0.442	0.428	1.533 (0.656-3.587)	0.324
Pathological type (SCC vs. non-SCC)	-0.214	0.807 (0.250-2.601)	0.720	-0.252	0.778 (0.179-3.370)	0.737
Tumor size (≥5 vs. <5 cm)	0.153	1.165 (0.607-2.236)	0.647	0.186	1.205 (0.610-2.379)	0.592
cTNM stage (III-IV vs. II)	0.658	1.931 (0.694-5.375)	0.208	0.533	1.704 (0.576-5.042)	0.336
nCRT sequence (sequential nCRT vs. synchronous nCRT)	0.106	1.112 (0.606-2.042)	0.732	0.053	1.054 (0.494-2.248)	0.891
Chemotherapy cycle (≥2 vs. <2 cycles)	-0.058	0.944 (0.401-2.218)	0.894	0.162	1.176 (0.415-3.330)	0.760
Radiation dose (≥40 vs. <40 Gy)	0.153	1.165 (0.417-3.254)	0.770	0.455	1.576 (0.543-4.578)	0.403
Interruption of radiotherapy (yes vs. no)	-0.158	0.854 (0.486-1.501)	0.584	-0.112	0.894 (0.492-1.623)	0.712
pCR (yes vs. no)	-1.163	0.313 (0.152-0.645)	0.002	-1.222	0.295 (0.135-0.641)	0.002

HR, hazard ratio; CI, confidence interval; nCRT, neoadjuvant chemoradiotherapy; SCC, squamous cell carcinoma; cTNM, clinical tumor-node-metastasis; pCR, pathological complete response.

Table V. Cox proportional hazards regression analysis for overall survival.

	Univariable Cox regression analysis			Multivariable Cox regression analysis		
Items	β-value	HR (95% CI)	P-value	β-value	HR (95% CI)	P-value
Duration from nCRT to surgery (≥66 vs. <66 days)	0.026	1.027 (0.481-2.192)	0.946	0.226	1.254 (0.562-2.795)	0.581
Age (≥60 vs. <60 years)	-0.071	0.931 (0.432-2.007)	0.856	-0.564	0.569 (0.217-1.489)	0.251
Sex (female vs. male)	0.079	1.082 (0.409-2.862)	0.873	0.454	1.575 (0.497-4.993)	0.440
Tumor location						
Upper	Reference			Reference		
Middle	-0.118	0.889 (0.330-2.395)	0.816	-0.697	0.498 (0.110-2.265)	0.367
Lower	0.257	1.293 (0.436-3.832)	0.643	0.368	1.445 (0.450-4.644)	0.536
Pathological type (SCC vs. non-SCC)	-0.758	0.469 (0.141-1.557)	0.216	-1.384	0.251 (0.038-1.643)	0.149
Tumor size (≥5 vs. <5 cm)	0.451	1.569 (0.594-4.147)	0.364	0.525	1.690 (0.626-4.561)	0.300
cTNM stage (III-IV vs. II)	0.231	1.260 (0.379-4.187)	0.706	-0.174	0.840 (0.227-3.116)	0.795
nCRT sequence (sequential nCRT vs. synchronous nCRT)	0.078	1.081 (0.473-2.470)	0.853	-0.087	0.916 (0.291-2.890)	0.882
Chemotherapy cycle (≥2 vs. <2 cycles)	-0.536	0.585 (0.222-1.545)	0.279	-0.582	0.559 (0.145-2.153)	0.398
Radiation dose (≥40 vs. <40 Gy)	0.900	2.460 (0.333-18.145)	0.377	1.156	3.179 (0.409-24.714)	0.269
Interruption of radiotherapy (yes vs. no)	0.023	1.023 (0.481-2.178)	0.953	0.064	1.066 (0.468-2.426)	0.879
pCR (yes vs. no)	-1.332	0.264 (0.091-0.763)	0.014	-1.478	0.228 (0.070-0.748)	0.015

HR, hazard ratio; CI, confidence interval; nCRT, neoadjuvant chemoradiotherapy; SCC, squamous cell carcinoma; cTNM, clinical tumor-node-metastasis; pCR, pathological complete response.

detected between these two groups (P=0.914; Table SIII). The cause of death was cancer, pulmonary infection and esophageal-tracheal fistulate in 25 (92.6%), 1 (3.7%) and 1 (3.7%) patients, respectively, and no significant difference in the cause of death was detected between the prolonged and short time interval groups (P=0.367).

Kaplan-Meier analyses revealed that DFS (P=0.252) and OS (P=0.946) did not differ between the prolonged and short time interval duration groups (Fig. 2A and B). However, DFS (P=0.001; Fig. 2C) and OS (P=0.008; Fig. 2D) were both found to be significantly longer in patients who achieved pCR compared with patients who did not achieve pCR. Further subgroup analyses stratified patients based on TRG and the results demonstrated that neither DFS nor OS differed between the prolonged and short time interval group in patients with TRG1 (both P>0.05; Fig. S1A and B); in patients with TRG2 (both P>0.05; Fig. S1C and D) or in patients with TRG3 (both P>0.05; Fig. S1E and F).

Factors associated with DFS and OS. Univariate and multivariate Cox regression analyses revealed that the time interval between the completion of nCRT and surgery failed to enable DFS (Table IV) or OS (Table V) to be estimated (all P>0.05). Furthermore, only pCR achievement [yes vs. no; hazard ratio (HR): 0.295, 95%CI: 0.135-0.641, P=0.002] served as an independent factor for prolonged DFS. In addition, pCR (yes vs. no; HR: 0.228, 95%CI: 0.070-0.748, P=0.015) was independently associated with longer OS. TRG grade was not included in the regression analyses because it is a well-known confounding factor associated with other tumor features, including cT stage and lymphovascular invasion (25-27); therefore, TRG grade served as a compounding factor in the regression model.

Discussion

The effect of the time interval between nCRT and surgery on the pCR rate of patients with ESC is unclear. For example, a time interval of >13 weeks was found to be associated with an increased likelihood of a prolonged pCR rate in patients with ESC or gastroesophageal junction cancer (GEJC) in one study (16). Interestingly, another study divided the time interval between nCRT and surgery into five different quantiles, specifically 15-37, 38-45, 46-53, 54-64 and 65-90 days, and discovered that the time interval was positively correlated with the pCR rate of patients with ESC (17). However, a different study observed no association of a prolonged time interval of 7-8 weeks with improved pCR rates in patients with ESC and GEJC (15). Comparing these studies reveals that the findings were inconsistent, and the time intervals being investigated were also quite different. To identify the optimal time interval, the median value of the time interval between nCRT and surgery was found to be 66 days in the present study. Subsequently, a series of analyses were conducted to compare the response profiles of patients with ESC with time intervals of ≥66 and <66 days. Based on these analyses, it was observed that a prolonged time interval was associated with a higher pCR rate in patients with ESC; furthermore, the time interval was independently associated with an elevated pCR rate in patients with ESC. These findings are in line with those of previous studies (15,17). We hypothesize that there may be a delay, or lag phase, after the receipt of nCRT before the patients with ESC benefit fully from the antitumor effects of the radiotherapy, and therefore an extended period is necessary, which accounts for a longer time interval being associated with improved pCR rates in patients with ESC.

Aside from the pCR rate, the effect of the time interval between nCRT and surgery on the survival profile of patients with ESC is also of great interest. However, the findings from previous studies in this regard are also inconsistent. For example, one study reported that neither RFS nor OS differed among patients with esophageal squamous cell carcinoma cancer according to whether they experienced shorter or longer time intervals between nCRT and surgery (28). Furthermore, patients with ESC or GEJC with a prolonged time interval of ≥50 days achieved a similar OS to those patients with time interval of <50 days (15). By contrast, another study suggested that a time interval >100 days was associated with reduced OS in patients with esophageal adenocarcinoma (18). In the present study, it was observed that in patients with ESC there was no association between the time interval from nCRT to surgery and the survival profile, whereas DFS and OS were prolonged in patients with ESC who reached pCR compared with those who did not. These findings are also in line with previous studies (15,28). The possible explanations for these observations are as follows: i) The follow-up period was relatively short in the present study, since neither DFS nor OS reached the median follow-up date, and few cases of disease relapse or mortality occurred in patients with ESC, which led to low statistical power and no significant differences in DFS or OS for patients with ESC between the prolonged or short time interval groups; and ii) numerous factors are capable of affecting the survival of patients with ESC, including the heterogeneous properties of ESC, postoperative surveillance and management, and consequently, the time interval may have little effect on ESC survival (29-31).

The present study also identified that sex (female vs. male) and radiation dose (≥40 vs. <40 Gy) were independently associated with improved pCR rates in patients with ESC. These findings regarding sex and radiation dose may be explained as follows: i) Women are subjected to lower levels of androgenic hormones such as testosterone, dihydrotestosterone and androstenedione, compared with men, which may afford them some protection from carcinogenesis mediated via downstream androgen receptor signaling, thereby leading to improved pCR rates in female patients with ESC (32); and ii) high radiation doses may exert stronger antitumor effects compared with low radiation doses by directly causing genetic damage in cancer cells and indirectly promoting the immune response in the local tumor microenvironment, thereby leading to improved pCR rates in patients with ESC (33). Moreover, achieving a pCR served as an independent factor for longer DFS and OS in patients with ESC, since this indicated that no residual tumor cells remained in the patient following the surgical removal of the tumor, which would be favorable to the survival of the patient.

Although it is recommended that the surgery is performed 6-8 weeks after the completion of nCRT in patients with resectable ESC, the time interval between nCRT and surgery

differs in the existing literature. Several studies observed a prolonged time interval of >8 weeks between nCRT and surgery for patients with resectable ESC, the reasons for which may be older age, more morbidities, advanced cancer stage or overloaded surgical schedules (16,17,34). In the present study, the median time interval between nCRT and surgery was 66 days in patients with resectable ESC, which is longer than recommended. One possible reason for this is that patients with resectable ESC may require an extended period of time to recover from nCRT due to poor performance status, nutrient status or chronic comorbidities, which is in line with previous studies (16,17).

The present study applied contrast-enhanced CT rather than positron emission tomography (PET)/CT for the assessment of the treatment response in patients with resectable ESC. The reasons for this were as follows: i) Contrast-enhanced CT for the initial workup exhibited more sensitivity and a well-differentiated cT stage compared with PET/CT for patients with T1-T3 tumors (35); ii) PET/CT was unnecessary for patients with the absence of distant metastasis; and iii) the cost of PET/CT is not covered by health insurance in China, so patients are required to pay for this expensive examination fees themselves. Moreover, PET/CT usually requires multiple assessments during the whole perioperative period, which may be a considerable financial burden on patients.

The present study only enrolled patients with resectable ESC; therefore, preoperative chemoradiotherapy was applied in a neoadjuvant setting. Patients with unresectable ESC may be offered curative surgery following treatment with definitive chemotherapy or chemoradiotherapy preoperatively, which is known as conversion surgery. However, none of the patients included in the current study received conversion surgery. The reason for this was that conversion surgery is only available for a small proportion of patients, and most patients with unresectable ESC experienced rapid progression and distant metastasis. Therefore, the current study did not include any patients with conversion surgery, but this could be addressed in future studies.

The present study has certain limitations. First, the follow-up period was relatively short since most patients were not local residents and some of them transferred to local hospitals after discharge, which increased the difficulty of regular follow-up for these patients. Therefore, further studies with a longer follow-up period are required to address this issue. Moreover, further studies could explore the relationship between time interval and the change in the standardized uptake value obtained using PET/CT in resectable ESC patients. Also, a larger sample size is necessary to enable more subgroup analyses to be conducted, with the aim of identifying the optimal time interval for patients with ESC with different causes of death.

In conclusion, the present study shows that a prolonged time interval between nCRT and surgery is associated with a higher pCR rate, although it is not possible to estimate the DFS or OS in patients with ESC from the time interval. Based on these findings, the optimal time interval for balancing the benefit of pathological response with prognosis remains uncertain. This may serve as an interesting topic for clinicians and prompt them to perform more research into this topic.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YML designed and supervised the study. JQL and XXZ conceived the study. XJZ, YX and ZYD participated in the experiments and data collection. YH, YY and LQC performed the data analysis, and wrote the manuscript. JW and YL contributed to the analysis of the results and revised the manuscript. YML and JQL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of West China Hospital, Sichuan University (Chengdu, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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