Pre- versus postoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma

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ABSTRACT

Objectives: Although preoperative chemoradiation followed by surgery has been recognized as an efficient strategy for esophageal cancer treatments, several studies demonstrate survival benefits of postoperative chemoradiation for those undergoing upfront resection. The optimal sequence of surgery and chemoradiation remains unclear.

Methods: Data of 1647 patients with clinical stage II/III esophageal squamous cell carcinoma (ESCC), including 1245 receiving preoperative chemoradiation followed by esophagectomy (pre-OP CRT group) and 402 receiving primary esophagectomy followed postoperative chemoradiation (post-OP CRT group), were obtained from a nationwide database. Propensity score matching identified 286 well-balanced pairs for outcome comparison.

Results: In matched patients, the 3-year overall survival (OS) rates/median survival were not significantly different between the 2 groups (44.0% 3-year OS/26.0 months; 95% confidence interval [CI], 18.9-89 38.0 months) in the pre-OP CRT group, versus 37.9% 3-year OS/23.5 months (95% CI, 18.5-29.9 months) in the post-OP CRT group, $P = .3152$). The 3-year disease-free survival rates (DFS)/median survival after surgery were 38.7% 3-year DFS/16.7 months (95% CI, 11.9-29.6 months) in the pre-OP CRT group, compared with 30.2% 3-year DFS/10.4 months (95% CI, 7.6-14.0 months) in the post-OP CRT group ($P = .0674$). In patients who had complete resection, the freedom from recurrence rate at 1 year after surgery was 74.8% and 67.6% in pre-OP CRT and post-OP CRT groups, respectively ($P = .2696$). In the multivariable analysis, treatment modality (pre- or post-OP CRT) was not a significant factor for OS ($P = .258$) or disease-free survival ($P = .521$).

Conclusions: Similar outcome can be achieved with postoperative chemoradiotherapy compared with preoperative chemoradiotherapy in patients with locally advanced ESCC. There is little difference between these 2 strategies. (J Thorac Cardiovasc Surg 2017;154:732-40)

No overall survival difference between pre- and postoperative chemoradiotherapy groups.

Central Message

No significant difference in overall survival and disease-free survival was observed between pre- and postoperative chemoradiotherapy groups in locally advanced esophageal cancer.

Perspective

Multimodality therapy is the mainstay of treatments for esophageal cancer, but the optimal sequence is unknown. In 286 well-balanced patients with esophageal squamous cell carcinoma, the overall and disease-free survival rates were not different between pre- and postoperative chemoradiotherapy groups. Our results support the notion that there is little difference between these 2 strategies.

See Editorial Commentary page 741.

See Editorial page 730.

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Esophageal cancer is the seventh most common cause of cancer-related death worldwide.¹ In 2012, an estimated 455,800 people were diagnosed with esophageal cancer and 400,200 people eventually died due to esophageal

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Abbreviations and Acronyms

ESCC	= esophageal squamous cell carcinoma
Post-OP CRT	= postoperative chemoradiation
Pre-OP CRT	= preoperative chemoradiation

cancer worldwide. Characterized by dismal prognosis and high frequency of both locoregional and distant disease recurrences, multimodality therapy consisting of chemotherapy, radiotherapy, and surgery has been the mainstay of treatments for esophageal cancer.²⁻⁵ The strategy of preoperative chemoradiation followed by surgery has been well recognized as an efficient approach.²⁻⁴ In the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, the median overall survival was 49.4 months in the preoperative chemoradiation followed by surgery group versus 24.0 months in the surgery alone group. A significant estimated 5-year overall survival benefit of 13% (47% vs 34%) was noted in favor of the preoperative chemoradiation followed by surgery arm.² On the other hand, several studies have shown survival benefits of postoperative chemoradiation for those who received esophagectomy as initial treatment.⁵⁻¹⁰ For example, our previous study demonstrated that the 3-year overall survival rate was 44.9% and 28.1% among patients with esophageal squamous cell carcinoma (ESCC) who underwent esophagectomy with postoperative chemoradiation and those who underwent surgery alone, respectively.⁵

Few studies to date have specifically focused on the prognostic impact of the sequence of surgery and chemoradiation in esophageal cancer, with conflicting results.^{11,12} Hong et al¹¹ studied the Surveillance, Epidemiology, and End Results (SEER) database and demonstrated that preoperative chemoradiation has superior survival over postoperative chemoradiation for locally advanced esophageal cancer. On the other hand, the prospective trial by Lv et al¹² demonstrated that preoperative and postoperative chemoradiation provided similar survival benefit for patients with locally advanced ESCC. As the optimal timing and sequence of surgery and chemoradiation for esophageal cancer remains controversial, this study was conducted to analyze treatment outcomes between patients with ESCC who underwent preoperative chemoradiation followed by surgery and those who had postoperative chemoradiation following primary esophagectomy.

METHODS

This study's design was reviewed by the institutional review board of the Taipei-Veterans General Hospital, and the requirement for informed consent was waived, due to the retrospective design (VGHIRB No. 2015-06-001BC). Patient data were obtained from Taiwan Cancer Registry database, which is a national population-based database that was implemented in 1979 and is currently administered by the Health Pro-

motion Administration, Ministry of Health and Welfare, Executive Yuan, Taiwan.¹³ Hospitals with more than a 50-bed capacity that provide outpatient and hospitalized cancer care are recruited to participate and report all newly diagnosed malignant neoplasms to the registry. The registry currently includes 80 hospitals that account for >90% of all cancer cases in Taiwan. Confidentiality was ensured by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Executive Yuan, Taiwan. The HWDC encrypts individual identifiers to protect privacy before releasing information to investigators for research purposes.

The inclusion criteria for this study were patients with newly diagnosed clinical stage I, II, and III ESCC between 2008 and 2013, based on their International Classification of Diseases for Oncology (ICD-O-3) site codes (C15.0–C15.5, C15.8, and C15.9) and morphology codes (8052, 8070–8074, 8076, 8077, 8083, and 8084); and had undergone preoperative chemoradiation followed by surgical resection (pre-OP CRT group) or surgical resection followed by postoperative chemoradiation (post-OP CRT group) as the initial treatment modality. During the study period, the registry contained data of 11,607 patients with newly diagnosed ESCC. Among them, 1566 and 610 patients with clinical stage I, II, and III ESCC received preoperative and postoperative chemoradiation, respectively, as initial treatments. The exclusion criteria included clinical stage I tumors (n = 284), incomplete clinicopathological information (n = 63), and loss of follow-up, either in recurrence or survival status (n = 182). After exclusion, the remaining 1647 patients with clinical stage II and III ESCC, including 1245 patients in the pre-OP CRT group and 402 patients in the post-OP CRT group, were considered eligible for this study. In the pre-OP CRT group, the median interval between the start of radiotherapy and surgery was 85 (25%Q1: 72; 75%Q3: 105) days; whereas the median interval between surgery and the start of radiotherapy was 42 (25%Q1: 34; 75%Q3: 54) days in the post-OP CRT group.

Disease recurrence was classified as locoregional failure or distant metastasis. Locoregional failure was defined as recurrence at the anastomotic site, or within the area of the previous resection, and nodal clearance in the cervical, mediastinum, or upper abdomen regions. Distant metastasis included distant lymph node dissemination, hematogenous metastasis to solid organs, or recurrence in the pleura or peritoneal cavities.

Categorical and continuous variables were compared with the χ^2 test and Student *t* test, respectively. Propensity score matching was performed to decrease confounding effects due to nonrandomized assignment.¹⁴ First, a propensity score for each patient was calculated by logistic regression by using the variables of age, sex, clinical stage, tumor location, differentiation grade, and tumor length. Then a 1:1 matched study group was created with use of a greedy matching algorithm. The missing data were incorporated as a missing value variable without any type of imputation. After matching, 286 well-balanced pairs of patients were identified for outcome comparison. Cox proportional hazards regression model was used for univariable and multivariable survival analyses. Survival curves were plotted using the Kaplan-Meier method and compared with the log-rank test. The overall survival was calculated as the period between the date of initial treatment and the date of death. The disease-free survival was calculated as the interval between the date of surgery and the earliest date of event, which included death, recurrence, and positive surgical margin, because patients with non-R0 resection were considered without a disease-free period. We also calculated the recurrence-free interval (freedom from recurrence), which is the period between the date of complete resection and the date of disease recurrence (but not death). Patients who survived to the end of the follow-up period (December 31, 2014) were censored. All statistical calculations were performed with Statistical Analysis System (version 9.3; SAS Institute, Inc, Cary, NC) and Statistical Product and Service Solutions (version 20; SPSS Inc, Chicago, IL). A *P* < .05 was considered statistically significant.

TABLE 1. Patient demographics before and after propensity score matching

	Before matching				<i>P</i>	<i>SDif*</i>	After matching				<i>P</i>	<i>SDif*</i>
	Pre-OP CRT		Post-OP CRT				Pre-OP CRT		Post-OP CRT			
	<i>n</i>	%	<i>n</i>	%			<i>n</i>	%	<i>n</i>	%		
Total	1245	100	402	100			286	100	286	100		
Age, years, mean ± SD	54.0 ± 8.6		54.5 ± 9.2		.351	0.053	54.4 ± 8.4		54.6 ± 9.2		.798	0.021
Sex					.795						.404	
Male	1184	95.1	381	94.8		0.015	276	96.50	272	95.10		0.070
Female	61	4.9	21	5.2		0.015	10	3.50	14	4.90		0.070
cStage					<.001						.055	
II	214	17.2	203	50.5			92	32.17	114	39.86		
III	1031	82.8	199	49.5			194	67.83	172	60.14		
cT stage					<.001						1.000	
1/2	149	12.0	136	33.8		0.539	68	23.78	68	23.78		0.000
3/4	1096	87.3	266	66.2		0.539	218	76.22	218	76.22		0.000
cN stage					<.001						.846	
0	155	12.4	148	36.8		0.590	69	24.13	71	24.83		0.016
+	1090	87.6	254	63.2		0.590	217	75.87	215	75.17		0.016
p (or yp) T stage												
T0	411	33.0	0	0			91	31.82	0	0		
T1	167	13.4	33	8.2			50	17.5	21	7.34		
T2	248	19.9	59	14.7			52	18.18	38	13.29		
T3	369	29.6	282	70.2			86	30.07	205	71.68		
T4	50	4.0	28	7.0			7	2.45	22	7.69		
p (or yp) N stage												
N0	868	69.7	92	22.9			195	68.18	66	23.08		
N1	260	20.9	166	41.3			66	23.08	120	41.96		
N2	75	6.0	112	27.9			16	5.59	78	27.27		
N3	26	2.1	17	4.2			6	2.10	12	4.20		
Unknown†	16	1.3	15	3.7			3	1.05	10	3.50		
Tumor length, cm, mean ± SD	5.9 ± 2.6		4.6 ± 2.0		<.001		5.2 ± 2.7		4.9 ± 2.0		.196	
≤ 4.6‡	277	22.3	233	58.0		0.782	139	48.6	145	50.7		0.042
<4.6	637	51.2	158	39.3		0.240	147	51.4	141	49.3		0.042
Unknown	331	26.6	11	2.7			0	0	0	0		
Location					<.001						.928	
Upper	294	23.6	132	32.8		0.151	98	34.27	94	32.87		0.035
Middle	483	38.8	126	31.3		0.157	83	29.02	89	31.12		0.046
Lower	167	13.4	35	8.7		0.206	30	10.49	27	9.44		0.030
Unknown	301	24.2	109	27.1		0.067	75	26.22	76	26.57		0.008
Differentiation					<.001						.846	
Good	27	2.2	12	3.0		0.052	8	2.80	9	3.15		0.021
Moderate	571	45.9	238	59.2		0.270	175	61.19	184	64.34		0.065
Poor	252	20.2	144	35.8		0.352	99	34.62	89	31.12		0.074
Unknown	395	31.7	8	2.0		0.865	4	1.40	4	1.40		0.000
Margin status					<.001						<.001	
Negative (R0)	1118	89.8	311	77.4			257	89.86	219	76.57		
Positive (R1/2)	127	10.2	91	22.6			29	10.14	67	23.43		

Pre-OP CRT, Preoperative chemoradiotherapy; Post-OP CRT, postoperative chemoradiotherapy; *SDif*, standardized differences; *SD*, standard deviation. **SDif* values of factors used for propensity score matching are provided. An *SDif* of <0.10 likely denotes a negligible imbalance between case patients and their matched controls. †Definite positive lymph node number was not recorded. ‡Median tumor length in the matched cohort.

RESULTS

The clinical and pathological characteristics of the patients before and after propensity score matching are summarized in Table 1. The distribution of propensity scores is displayed in Figure 1. Patients who received preoperative chemoradiation had more advanced tumors in terms of

clinical stage III, cT3/4, cN(+), and larger tumor size. With regard to the surgical results, 411 (33.3%) patients in the pre-OP CRT group had no detectable primary tumor and 356 (28.6%) patients achieved complete pathological response (ypT0N0). In the post-OP CRT group, most patients (*n* = 249, 61.9%) were seen to have pathological

FIGURE 1. Mirrored histogram displaying distribution of propensity scores among matched and unmatched patients. *Pre-OP CRT*, Preoperative chemoradiotherapy; *Post-OP CRT*, postoperative chemoradiotherapy.

stage III tumors. In the pre-OP CRT and post-OP-CRT groups, respectively, 10.2% and 22.6% of patients had positive margins before matching ($P < .001$), whereas 10.1% and 23.4%, respectively, after matching ($P < .001$), which reflected that positive margin (non-R0 resection) was a common indication for postoperative chemoradiation. Surgical mortality was noted in 27 (2.2%, 27/1245) and 0 patients in the pre-OP CRT and post-OP CRT groups, respectively.

In the survival analysis, the median follow-up time was 31.7 months (95% confidence interval [CI], 12.4-71.9 months) for the surviving patients. In matched patients, the 1-year, 3-year overall survival rates and median survival were 79.3%, 44.0%, and 26.0 months (95% CI, 18.9-38.0 months) in the pre-OP CRT group, versus 72.9%, 37.9%, and 23.5 months (95% CI, 18.5-29.9 months) in the post-OP CRT group ($P = .3152$, Figure 2). The 1-year, 3-year disease-free survival rates and median survival after surgery were 55.7%, 38.7%, and 16.7 months (95% CI, 11.9-29.6 months) in the pre-OP CRT group,

compared with 45.1%, 30.2%, and 10.4 months (95% CI, 7.6-14.0 months) in the post-OP CRT group ($P = .0674$, Figure 3). In patients who had complete resection, the freedom from recurrence rate at 1 year after surgery was 74.8% and 67.6% in the pre-OP CRT and post-OP CRT groups, respectively ($P = .2696$, Figure 4). There were also no significant differences between the 2 groups in the freedom from locoregional failure (89.7% vs 85.2%, $P = .1924$) and freedom from distant metastasis (81.3% vs 77.7%, $P = .2108$) at 1 year (Survival curves including all patients was in Figure E1).

In the Cox regression model based on propensity score-matched patients, only T3/4 stage was an independent prognostic factor for overall survival (Table 2), whereas treatment modality (pre-OP CRT or post-OP CRT) was not ($P = .258$). In the subgroup analysis, the significant prognostic factors included ypT3/4 (hazard ratio [HR] 1.84; 95% CI, 1.33-2.55, $P = .0002$), and ypN+ (HR 2.07; 95% CI, 1.50-2.87, $P < .001$) in the pre-OP CRT group. In the post-OP CRT

FIGURE 2. A, Overall survival, with 95% confidence interval, of patients in pre-OP CRT (blue line) and post-OP CRT (red line) groups, respectively. B, Overall survival, with 95% confidence interval, of patients in pre-OP CRT with ypT0N0 (green line) and pre-OP CRT without ypT0N0 (red line), and post-OP CRT (blue line) groups, respectively. *Pre-OP CRT*, Preoperative chemoradiotherapy; *Post-OP CRT*, postoperative chemoradiotherapy.

group, the independent prognostic factors included cT3/4 stage (HR 2.06; 95% CI, 1.36-3.10, $P = .006$), pT3/4 stage (HR 1.82; 95% CI, 1.19-2.79, $P = .006$), pN+ (HR 1.56; 95% CI, 1.06-2.28, $P = .023$), and tumor length >4.6 cm (HR 1.39; 95% CI, 1.03-1.87, $P = .031$). In patients who had complete resection, the only independent prognostic factor for disease-free survival was clinical T stage (cT3/4 vs cT1/2, HR 1.45; 95% CI, 1.06-2.00, $P = .021$). No difference was observed between pre- and postoperative chemoradiotherapy groups ($P = .521$, Table 3). (Cox regression analysis in all patients were in Tables E1 and E2.)

DISCUSSION

The dismal prognosis of locally advanced esophageal cancer has motivated multiple strategies in an effort to

enhance patient outcome. In this nationwide population-based study, there was no significant difference in overall survival between pre-OP CRT and post-OP CRT groups. Although the pre-OP CRT group seemed to have better disease-free survival than post-OP CRT group on the Kaplan-Meier plot, this small and nonsignificant difference in survival might be attributable to the proportion of positive margin, which itself was an indication for postoperative chemoradiation and definitively would be higher in the post-OP CRT group.

Preoperative chemoradiation is now widely used because it is believed to be able to eradicate systemic micrometastasis, downstage the tumor, and facilitate the subsequent radical resection, which in turn improves patient survival. The success of the pivotal CROSS trial has established

FIGURE 3. Disease-free survival, with 95% confidence interval, of patients in pre-OP CRT (blue line) and post-OP CRT (red line) groups, respectively. *Pre-OP CRT*, Preoperative chemoradiotherapy; *Post-OP CRT*, postoperative chemoradiotherapy.

the role of preoperative chemoradiation followed by esophagectomy for treating locally advanced esophageal cancer.³ In the long-term follow-up report, the median overall survivals were 48.6 months (95% CI, 32.1-65.1 months) after preoperative chemoradiotherapy plus surgery and 24.0 months (95% CI, 14.2-33.7 months) after surgery alone ($P = .003$). Compared with patients who underwent surgery alone, patients who underwent preoperative chemoradiotherapy plus surgery experienced significantly less locoregional recurrence (22% vs 38%) and distant recurrence (39% vs 48%).⁴

On the other hand, the advantage of postoperative treatments includes the indication for chemoradiation is based on accurate pathological staging, rather than inaccurate

clinical staging; thus, the risk of overtreatment would be minimized. Our previous single institute experience has demonstrated that postoperative chemoradiotherapy with a radiation field encompassing the tumor bed as delineated on imaging studies would have better overall survival than surgery alone (3-year overall survival rates: 79.0% vs 57.0%, $P = .016$).⁶ The subsequent nationwide population-based study also showed that esophagectomy with postoperative chemoradiation is significantly more effective than surgery alone for increasing overall survival among patients with ESCC.⁵ The median survival and 3-year survival rates were 27.2 months (95% CI, 17.6-40.3 months) and 44.9% among patients who underwent esophagectomy with postoperative chemoradiation,

FIGURE 4. Recurrence-free interval, with 95% confidence interval, of patients in pre-OP CRT (blue line) and post-OP CRT (red line) groups, respectively, at 1 year after surgery. *Pre-OP CRT*, Preoperative chemoradiotherapy; *Post-OP CRT*, postoperative chemoradiotherapy.

TABLE 2. Cox regression analysis in matched groups for overall survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, y				
≤55	1		1	
>55	1.02 (0.82-1.27)	.863	1.00 (0.80-1.25)	.992
Sex				
Male	1		1	
Female	0.71 (0.38-1.32)	.276	0.79 (0.42-1.49)	.467
cT stage				
T1/2	1		1	
T3/4	1.53 (1.16-2.03)	.003	1.47 (1.10-1.96)	.010
cN stage				
N0	1		1	
N+	1.01 (0.78-1.30)	.957	1.02 (0.78-1.33)	.885
Location				
Lower third	1		1	
Middle third	1.09 (0.83-1.44)	.548	1.08 (0.82-1.43)	.592
Upper third	1.15 (0.77-1.72)	.490	1.07 (0.71-1.63)	.739
Differentiation				
Good	1		1	
Moderate	0.63 (0.36-1.10)	.101	0.66 (0.37-1.16)	.149
Poor	0.86 (0.49-1.53)	.606	0.89 (0.50-1.59)	.687
Tumor length, cm				
≤4.6	1		1	
>4.6	1.11 (0.90-1.39)	.329	1.07 (0.86-1.34)	.540
Treatment modality				
Pre-OP CRT	1		1	
Post-OP CRT	1.12 (0.90-1.39)	.316	1.14 (0.91-1.41)	.258

HR, Hazard ratio; CI, confidence interval; Pre-OP CRT, preoperative chemoradiotherapy; Post-OP CRT, postoperative chemoradiotherapy.

compared with 18.2 months (95% CI, 14.3-24.5 months) and 28.1% among patients who underwent surgery alone ($P = .0055$). In the literature, several studies also suggested postoperative chemoradiation may be beneficial in patients with esophageal cancer with certain characteristics, such as positive nodal involvement and extracapsular invasion.⁷⁻¹⁰ The toxicity associated with chemoradiation is always a concern for patients after esophagectomy. Before the advent of minimally invasive esophagectomy, patients who undergo esophagectomy are typically debilitated and unable to withstand any postoperative treatments. With the advancement of endoscopic surgical approach, the early restoration of physical function may render patients better able to tolerate adjuvant therapy.¹⁵ According to our previous report and the phase II study by the Cleveland Clinic group, postoperative 5-fluorouracil and cisplatin-based chemoradiation has acceptable toxicity for patients with esophageal cancer after primary surgical resection.^{6,16} Taken together with other reports, the results from current study indeed provide a basis to reappraise the role of postoperative chemoradiation in ESCC.

To determine the optimal timing and sequence of surgery and chemoradiation for esophageal cancer, Hong et al¹¹

TABLE 3. Cox regression analysis for disease-free survival in matched patients who had curative resection

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, y				
≤55	1		1	
>55	1.08 (0.85-1.39)	.522	1.04 (0.81-1.33)	.763
Sex				
Male	1		1	
Female	0.53 (0.24-1.19)	.125	0.55 (0.24-1.24)	.149
cT stage				
T1/2	1		1	
T3/4	1.52 (1.13-2.06)	.007	1.45 (1.06-2.00)	.021
cN stage				
N0	1		1	
N+	0.91 (0.68-1.21)	.498	0.89 (0.66-1.20)	.428
Location				
Lower third	1		1	
Middle third	0.93 (0.68-1.27)	.662	0.89 (0.65-1.23)	.484
Upper third	1.09 (0.67-1.77)	.726	0.96 (0.59-1.58)	.882
Differentiation				
Good	1		1	
Moderate	0.65 (0.33-1.28)	.211	0.69 (0.35-1.35)	.279
Poor	0.92 (0.46-1.83)	.814	0.97 (0.49-1.95)	.940
Tumor length, cm				
≤4.6	1		1	
>4.6	1.06 (0.83-1.35)	.656	0.98 (0.76-1.26)	.885
Treatment modality				
Pre-OP CRT	1		1	
Post-OP CRT	1.06 (0.82-1.35)	.673	1.09 (0.85-1.39)	.521

HR, Hazard ratio; CI, confidence interval; Pre-OP CRT, preoperative chemoradiotherapy; Post-OP CRT, postoperative chemoradiotherapy.

compared the outcome of pre- and postoperative chemoradiotherapy in nonmetastatic T3+ or N+ esophageal cancer by using the SEER-Medicare database. The multivariable analysis controlling for age, marital status, and histology showed that preoperative chemoradiotherapy had better overall survival versus postoperative chemoradiotherapy (HR 1.63; $P = .03$). On the other hand, the prospective study by Lv et al¹² showed conflicting results. The 5-year overall survival rates were 43.5% and 42.3% in pre- and postoperative chemoradiotherapy groups, respectively, in patients with clinical stage II and III ESCC. The 5-year progression-free survival rates were 37.5% and 37.2% in pre- and postoperative chemoradiotherapy groups, respectively, which indicated no significant survival differences between the pre- and postoperative chemoradiotherapy groups. Similar concepts also have been observed in esophageal adenocarcinoma. Zahoor et al¹⁷ compared survival for patients with stage II or higher esophageal adenocarcinoma treated with primary esophagectomy followed by postoperative therapy or preoperative therapy protocol. In propensity-matched pairs, the HR for death and recurrence patterns were similar between the 2 groups, which

suggested that the strategy of primary esophagectomy followed by postoperative chemotherapy does not negatively influence survival compared with the preoperative therapy protocol.

The rate of complete pathologic response in the preoperative chemoradiotherapy group was 28.6%, which is compatible with other values reported in the literature.^{18,19} But in the CROSS trial, the rate was significantly higher in squamous cell carcinoma (49%) than in adenocarcinoma (23%), leading to an impression that squamous cell carcinoma is more responsive to chemoradiation. In fact, a recent systematic review also suggested preoperative chemoradiotherapy with paclitaxel plus platinum regimen to be a better treatment than platinum plus 5-fluorouracil regimen for locoregional ESCC.²⁰ Moreover, the role of surgery in patients with squamous cell carcinoma who achieve complete clinical response after chemoradiation is still under debate. If more systematic planned resections were performed (eg, in a prospective randomized trial), the pathologic complete response rate would be higher; in contrast, if a more nonoperative approach with intensive surveillance (eg, symptom relief after preoperative chemoradiation) were chosen, the rate would be lower.

Although this current study attempted to find balanced groups of patients with a propensity score–matching method, there might still be hidden unmeasurable factors that influenced treatment options and survival. For example, surgeons may perform primary esophagectomy for patients with clinically N1, but with limited lymph node involvement, whereas they will suggest preoperative chemoradiation for those with bulky clinical N1 lymph nodes. In patients receiving preoperative chemoradiation, surgeons might refuse surgery for patients with comorbidities or poor clinical response, selecting only patients assumed to have better outcome for surgical resection. Similarly, in patients after primary esophagectomy, postoperative chemoradiation was performed only for those considered to have ominous prognostic factors based on pathologic examination. The impact of these and other possible sources of bias could not be precisely evaluated. In addition, we did not include patients who failed to survive preoperative chemoradiotherapy or those who failed to survive primary surgery and could not complete treatments, which violates the intention-to-treat principle. Furthermore, because the Taiwan Cancer Registry database is a prospectively maintained database, it has limitations that are inherent to all retrospective studies, such as lacking detailed information on staging workup, chemoradiation regimens, radiation fields, surgical techniques, surgical complications, and follow-up protocol. Furthermore, in patients who received preoperative chemoradiation and esophagectomy in different hospitals, some pretreatment factors (eg, tumor length, location, and differentiation) could not be precisely recorded. However, as positron emission tomography/computed tomography (PET/CT) is reimbursed

by the Taiwan National Health Insurance system, almost all patients with a diagnosis of esophageal cancer receive PET/CT for free as a staging workup. Moreover, the only regimen reimbursed by Taiwan National Insurance System is cisplatin/5-fluorouracil–based chemotherapy, which is frequently used preoperatively or postoperatively. In addition, the high incidence of upper/middle-third tumors in Taiwan has made McKweon esophagectomy, which means esophagogastric anastomosis at neck, a routine procedure.²¹ The Ivor-Lewis and transhiatal esophagectomy, which are frequently used for adenocarcinoma of lower-third esophagus or esophagogastric junction, are rarely performed for ESCC. This study is also limited by the absence of documentation of the patient's comorbidities, which are often used in propensity matching in retrospective studies, especially when they play a pivotal role in deciding to use additional treatments or not. However, all patients in the current study underwent trimodality treatments, only the sequence was different, which means that all included patients were considered to be able to complete these treatments. In Taiwan, there is increasing adoption of preoperative chemoradiotherapy protocol, but still some prefer upfront surgery. Therefore, the treatment protocol decision mostly depends on the surgeon's or institution's preferences. Because patients' comorbidities were not a factor in deciding which treatment protocol they received, we did not include them during the propensity matching.

In conclusion, given the limitations of the database and our study design, we could not show any difference in overall survival or disease-free survival between preoperative and postoperative chemoradiotherapy groups in clinical stage II and III ESCC. Although preoperative chemoradiation followed by surgery is the more frequently chosen approach for locally advanced esophageal cancer, our results suggested that there is not a substantial difference between the preoperative and postoperative chemoradiotherapy strategies.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: adjuvant, chemoradiotherapy, esophageal cancer, neoadjuvant

FIGURE E1. Survival curves including all patients (blue: pre-OP CRT group; red: post-OP CRT group, $P = .264$).

TABLE E1. Cox regression analysis in all patients for overall survival

	Multivariable analysis	
	HR (95% CI)	P
Age, y		
≤55	1	
>55	1.12 (0.97-1.29)	.114
Sex		
Male	1	
Female	0.87 (0.62-1.22)	.425
cT stage		
T1/2	1	
T3/4	1.20 (0.97-1.48)	.088
cN stage		
N0	1	
N+	1.09 (0.90-1.32)	.379
Location		
Lower third	1	
Middle third	1.10 (0.91-1.33)	.316
Upper third	1.44 (1.12-1.84)	.004
Differentiation		
Good	1	
Moderate	0.71 (0.48-1.07)	.104
Poor	0.94 (0.62-1.43)	.777
Tumor length, cm		
≤4.6	1	
>4.6	1.09 (0.92-1.28)	.315
Treatment modality		
Pre-OP CRT	1	
Post-OP CRT	1.16 (0.97-1.39)	.110

HR, Hazard ratio; CI, confidence interval; Pre-OP CRT, preoperative chemoradiotherapy; Post-OP CRT, postoperative chemoradiotherapy.

TABLE E2. Cox regression analysis for disease-free survival in all patients who had curative resection

	Multivariable analysis	
	HR (95% CI)	P
Age, y		
≤55	1	
>55	1.17 (0.99-1.37)	.063
Sex		
Male	1	
Female	0.91 (0.63-1.31)	.605
cT stage		
T1/2	1	
T3/4	1.12 (0.89-1.41)	.333
cN stage		
N0	1	
N+	1.02 (0.82-1.27)	.844
Location		
Lower third	1	
Middle third	0.94 (0.76-1.15)	.520
Upper third	1.30 (0.98-1.72)	.066
Differentiation		
Good	1	
Moderate	0.58 (0.37-0.90)	.016
Poor	0.78 (0.49-1.23)	.280
Tumor length, cm		
≤4.6	1	
>4.6	1.12 (0.94-1.34)	.215
Treatment modality		
Pre-OP CRT	1	
Post-OP CRT	1.11 (0.90-1.37)	.336

HR, Hazard ratio; CI, confidence interval; *Pre-OP CRT*, preoperative chemoradiotherapy; *Post-OP CRT*, postoperative chemoradiotherapy.