

# Long-term effects of radiation prior to surgery and chemotherapy on survival of esophageal cancer undergoing surgery

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## Abstract

Esophageal cancer (EC) is one of the most common cancers in the world, with continuously growing diagnoses and morbidity. Because it is still unclear how to choose the best treatment for EC patients, a multimodal treatment is necessary to improve the prospect of the malignancy, including a sequence of surgery, chemotherapy, and radiotherapy, whether alone or combination. Therefore, this paper aims to analyze the effect of the sequence of chemotherapy, radiotherapy, and surgery on the prognosis and survival rate of patients with EC.

The Surveillance, Epidemiology, and End Results (SEER) database was used to extract a dataset of patients who were diagnosed with EC from 1973 to 2015, with follow-up data for 6 years after diagnosis. The data were analyzed using correlation analysis, logistic regression Cox regression, and Kaplan–Meier analysis.

EC patients who had radiation prior to surgery and chemotherapy had a better prognosis than the cases without chemotherapy. Based on univariate logistic regression, the odds ratios of vital status recoded for “radiation prior to surgery combined with chemotherapy” is the lowest one among the 8 groups classified by radiation sequence with surgery and chemotherapy ( $P < .001$ ). Further, radiation prior to surgery and chemotherapy is an independent prognostic factor for better survival among EC patients.

In conclusion, in the treatment of EC, administering radiation prior to surgery and chemotherapy is better than no radiotherapy, perioperative radiotherapy, postoperative radiotherapy, and other combinations without chemotherapy.

**Abbreviations:** EC = esophageal cancer, HRs = hazard ratios, NCI = National Cancer Institute, ORs = odds ratios, OS = overall survival, PCR = polymerase chain reaction, SCC = squamous cell carcinoma, SEER = Surveillance, Epidemiology, and End Results, VEGF = vascular endothelial growth factor.

**Keywords:** chemotherapy, esophageal cancer, radiation prior to surgery, survival

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## 1. Introduction

Esophageal cancer (EC) is one of the most common cancers in the world, with continuously growing diagnoses and morbidity.<sup>[1]</sup> As EC features tumors with a high degree of malignancy, it has a poor prognosis. About 80% of cases occur in underdeveloped areas, with Eastern Asia, Eastern Africa, and Southern Africa having the highest incidence.<sup>[2]</sup> China, the largest country in Eastern Asia, has a high prevalence of EC per year. In 2012, there were about 286,700 new cases of EC in China, representing an incidence rate of 211.7 per million.<sup>[3]</sup> What's more, the morbidity of EC is 3 to 4 times higher in men than in women. Squamous cell carcinoma (SCC), a main subtype of esophageal cancer, will be discussed in this article, along with adenocarcinoma.<sup>[4]</sup> Previous studies have reported that cigarette smoking, alcohol consumption, and achalasia are the main risk factors for SCC.<sup>[5]</sup>

EC is a common malignant tumor that originates from esophageal mucosa epithelium.<sup>[6]</sup> The cancer cells gradually enlarge and invade the muscular layer, developing up and down along the esophagus, all around the lumen and in and out both directions, with varying degrees of esophageal obstruction.<sup>[7]</sup> Advanced cancer penetrates the esophageal wall and invades the mediastinum or pericardium. Esophageal cancer mainly spreads through lymphatic metastasis, while hematogenous metastasis occurs late.<sup>[8]</sup> According to the most recent data on the state of cancer worldwide,<sup>[9]</sup> the global number of new cases of esophageal cancer in 2012 was 456,000. It accounted for 3.2% of

all malignant tumor incidence, ranking 8th place in the incidence of malignant tumors. Specifically, there were 323,000 new cases of esophageal cancer in men and 133,000 new cases in women, ranking 7th and 13th place, respectively, in the incidence of malignant tumors. About 80% of new cases occur in developing countries, while China accounts for about 50% of all new cases of esophageal cancer worldwide.<sup>[10]</sup>

Esophageal cancer is an aggressive disease with a poor prognosis. The standard treatment for early esophageal cancer is surgical resection.<sup>[11]</sup> However, most newly diagnosed esophageal cancer patients have locally advanced disease, and for these patients, surgical treatment alone is far from the best treatment strategy.<sup>[12]</sup> Recently, numerous studies have suggested that surgery combined with adjuvant therapy (such as chemotherapy and radiotherapy) is more beneficial for patients' prognosis than surgery alone.<sup>[13,14]</sup> However, there are still some questions about the therapeutic method, such as the sequence of surgery, radiotherapy, and chemotherapy.<sup>[15]</sup>

At present, surgical resection is considered the fundamental treatment in terms of locoregional control and long-term survival.<sup>[16]</sup> Many recent studies have shown that adjuvant treatments, such as chemotherapy and radiotherapy, followed by the surgery, is more conducive to patients' recovery versus surgery alone.<sup>[17-19]</sup>

Some supporting studies suggest that chemotherapy and radiotherapy could improve the control of local or general disease by downstaging the cancer and thereby increasing resectability, eradicating micrometastatic disease, decreasing cancer cell dissemination during intervention, and complementing another treatment modality without affecting postoperative mortality and morbidity.<sup>[20,21]</sup>

Radiotherapy plays a significant role in the comprehensive treatment of esophageal cancer. In patients requiring surgery, radiotherapy has been widely recognized as a treatment that improves outcomes.<sup>[22]</sup> However, the sequence of radiotherapy vis-a-vis surgery, including preoperative and perioperative radiotherapy, lacks definitive consensus.<sup>[23]</sup> Nevertheless, adjuvant radiotherapy significantly increased complications at the gastroplasty level.<sup>[24]</sup> Chemotherapy is another diffuse treatment, yet there is little comparative research to define an optimum chemotherapy regimen.<sup>[25]</sup>

As a result, it is still unclear how to choose the best treatment for EC patients, so a multimodal treatment is necessary to improve the prospect of the malignancy, including some sequence of surgery, chemotherapy, and radiotherapy, whether alone or in combination.<sup>[26]</sup> Therefore, the purpose of this study is to combine the information on the clinical practice of surgery, radiotherapy, and chemotherapy for patients with EC. It uses data from the United States National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program to analyze the effect of the sequence of chemotherapy, radiotherapy, and surgery on the prognosis and survival rate of patients with EC. We use the methods of correlation analysis, logistic regression, and Cox regression analysis to clarify the most effective treatment sequence.

## 2. Materials and methods

### 2.1. Ethics statement

Because the dataset of EC patients derives from the public sphere and the information of all individuals was authenticated when the data were uploaded into the website, it doesn't need to be

reviewed by the Research Ethics Committee, and the informed consent was waived.

### 2.2. Study patients and access to the public data

The NCI's SEER program is a source of epidemiologic information on the incidence and survival rates of cancer in the United States.<sup>[27]</sup> We used the SEER database, consisting of various information about therapy, prognosis, morbidity, and mortality of tumors, to extract a dataset of patients who were diagnosed with EC from 1973 to 2015, following up for 6 years after diagnosis.

### 2.3. Clinical study variables and outcome of the main analyses

Basic information on the EC patients was retrieved from the SEER database, including patient ID, radiation sequence with surgery, chemotherapy recode (yes or no), survival in months, and the vital status recode at last follow-up. The radiation sequence with surgery includes no radiation and/or cancer-directed surgery, radiation after surgery, radiation before and after surgery, and radiation prior to surgery. The main dependent variable of this study was the final survival status of patients with EC, defined as the number of months from the diagnosis of EC to death owing to EC. Individuals who were still alive at the end of the follow-up period, or who died from other causes, were excluded from the analysis.

### 2.4. Statistical analysis

The results are expressed as the number and percentage of cases. Associations between EC-specific survival and therapeutic methods were analyzed using the Pearson chi-squared test. For correlation analysis, the Spearman-rho test was used to compare the therapeutic methods. Then, the EC-specific survival was converted into natural logarithmic equivalent values for statistical analysis. We conducted a histogram and Shapiro-Wilk test to determine the residual distribution, and we found that the residuals had a well-modeled normal distribution.

A Wilcoxon signed-rank test was performed to compare EC-specific survival rates. Univariate and multivariate logistic regression analysis was used to calculate the odds ratios (ORs) of therapeutic methods for vital status recode of EC by its criteria. Furthermore, univariate and multivariate cox proportional hazards multivariable regression was used to calculate the hazard ratios (HRs) of therapeutic methods for vital status recode of EC. In order to certify the independent influence of certain therapeutic methods for the EC patients, the "a × b" interaction was applied in the univariate logistic regression analysis and Cox proportional hazards multivariable regression. The Kaplan-Meier method was used to illustrate the EC-specific survival further. All statistical analyses were conducted using SPSS software (version 21.0; IBM, SPSS Inc., Chicago, IL, USA). A *P* value of <.05 was considered statistically significant.

## 3. Results

### 3.1. Therapeutic methods and EC-specific survival

Participants' characteristics are shown in Table 1. One thousand six hundred ninety four (60.4%) of the 2805 participants with radiation prior to surgery didn't die of EC, the lowest mortality among the 4 groups classified by radiation sequence with surgery.

**Table 1**  
Therapeutic methods and the vital status recode.

Therapeutic methods			Died of esophagus cancer		P
			No	Yes	
A Radiation sequence with surgery	a No radiation and/or cancer-directed surgery	19232	5331 (27.7%)	13,901 (72.3%)	<.001*
	b Radiation after surgery	937	351 (37.5%)	586 (62.5%)	
	c Radiation before and after surgery	101	53 (52.5%)	48 (47.5%)	
	d Radiation prior to surgery	2805	1694 (60.4%)	1111 (39.6%)	
B Chemotherapy recode	No	9291	2365 (25.5%)	6926 (74.5%)	<.001*
	Yes	13784	5064 (36.7%)	8720 (63.3%)	
A and B	a without B	9128	2315 (25.4%)	6813 (74.6%)	<.001*
	a with B	10104	3016 (29.8%)	7088 (70.2%)	
	b without B	128	34 (26.6%)	94 (73.4%)	
	b with B	809	317 (39.2%)	492 (60.8%)	
	c without B	2	0 (0%)	2 (100.00%)	
	c with B	99	53 (53.5%)	46 (46.5%)	
	d without B	33	16 (48.5%)	17 (51.5%)	
	d with B	2772	1678 (60.5%)	1094 (39.5%)	

a=no radiation and/or cancer-directed surgery, A=radiation sequence with surgery, B=chemotherapy recode, b=radiation after surgery, c=radiation before and after surgery, d=radiation prior to surgery. Pearson chi-squared test was used.  
\* P<.05.

Eight thousand seven hundred twenty (63.3%) of the 13,784 participants with chemotherapy died of EC, and 6926 (74.5%) of the 9291 patients without chemotherapy died of EC. These results demonstrate that the EC patients with chemotherapy had a better prognosis than the cases without chemotherapy. One thousand six hundred seventy eight (60.5%) of the 2772 participants with radiation prior to surgery combined with chemotherapy didn't die of EC, exhibiting the highest survival rate in the 8 groups classified by radiation sequence with surgery and chemotherapy recodes (Table 1).

**3.2. The relationship between therapeutic methods and the vital status recode**

Table 1 shows the association between the different therapeutic methods and vital status recodes of EC patients. According to the Pearson chi-squared test, there are statistical significances between EC-specific survival and radiation sequence with surgery (P<.001), chemotherapy recode (P<.001), and radiation sequence with surgery and chemotherapy recode (P<.001) (Table 1).

**3.3. Correlation between therapeutic methods and EC-specific survival**

To ensure that “radiation sequence with surgery,” “chemotherapy recode,” and “radiation sequence with surgery and chemotherapy recode” had an impact on EC-specific survival, we performed a further analysis of vital status recode and different therapeutic methods. Spearman's correlation coefficient was used in the correlation analysis, and “radiation sequence with surgery” (ρ=-0.217, P<.001), “chemotherapy recode” (ρ=-0.118, P<.001), and “radiation sequence with surgery & chemotherapy recode” (ρ=-0.186, P<.001), were significantly correlated with EC-specific survival (Table 2).

**3.4. Proportional hazards analysis of related therapeutic methods for vital status recode based on univariate logistic regression**

Table 3 shows univariate ORs and 95% confidence intervals (95% CI) for subjects with EC. The ORs for vital status recode

were 1.381 (95% CI, 0.928–2.056) in the group with “radiation before and after surgery” compared with “radiation prior to surgery.” These figures increased to 2.546 (95% CI, 2.186–2.965) and 3.976 (95% CI, 3.663–4.316) respectively in the groups with “radiation after surgery” and “no radiation and/or cancer-directed surgery” (P<.001). The ORs of vital status recode were 1.701 (95% CI, 1.605–1.802) in the group with chemotherapy compared with individuals without chemotherapy (P<.001). The adjusted ORs of vital status recode for “radiation prior to surgery combined with chemotherapy” are the lowest among the 8 groups classified by radiation sequence with surgery and chemotherapy recode (P<.001) (Table 3). Based on the multivariate logistic proportional regression analysis, participants with “radiation sequence with surgery” had a significantly greater benefit than “chemotherapy recode.” The OR of “radiation sequence with surgery” is 0.654 (95% CI, 0.636–0.673; P<.001), while the OR of “chemotherapy recode” is 0.791 (95% CI, 0.743–0.842; P<.001) (Table 4).

**3.5. Radiation prior to surgery and chemotherapy for patients with EC was correlated with better EC-specific survival**

Univariate Cox proportional hazard analyses for EC-specific survival are summarized in Table 5. Kaplan–Meier overall survival (OS) curves are shown in Fig. 1. “Radiation prior to

**Table 2**  
The correlation of the therapeutic methods between the vital status recode.

Therapeutic methods	Vital status recode	
	Correlation coefficient	P-value
A Radiation sequence with surgery	-0.217	<.001*
B Chemotherapy recode	-0.118	<.001*
A and B	-0.186	<.001*

A=radiation sequence with surgery, B=chemotherapy recode. Spearman-rho test was used.  
\* P<.05

**Table 3****Therapeutic methods and their effect on vital status recode based on univariate logistic regression analysis.**

Therapeutic methods			Vital status recode		
			OR	95% CI	P
A Radiation sequence with surgery	a Radiation prior to surgery	2805	1		<.001*
	b No radiation and/or cancer-directed surgery	19,232	3.976	3.663–4.316	
	c Radiation after surgery	937	2.546	2.186–2.965	
	d Radiation before and after surgery	101	1.381	0.928–2.056	
B Chemotherapy recode	Yes	13784	1		<.001*
	No	9291	1.701	1.605–1.802	
A and B	d with B	2772	1		<.001*
	a without B	9128	4.514	4.127–4.937	
	a with B	10104	3.605	3.303–3.933	
	b without B	128	4.241	2.844–6.323	
	b with B	809	2.381	2.028–2.795	
	c without B	2	-	-	
	c with B	99	1.331	0.890–1.990	
	d without B	33	1.630	0.820–3.239	

95% CI=95% confidence interval, a=no radiation and/or cancer-directed surgery, A=radiation sequence with surgery, B=chemotherapy recode, b=radiation after surgery, c=radiation before and after surgery, d=radiation prior to surgery, OR=odds ratio.

\*  $P < .05$ .

**Table 4****Therapeutic methods and their effect on vital status recode based on multivariate logistic regression analysis.**

Therapeutic methods	Vital status recode		
	OR	95% CI	P
Radiation sequence with surgery	0.654	0.636–0.673	<.001*
Chemotherapy recode	0.791	0.743–0.842	<.001*

95% CI=95% confidence interval, OR=odds ratio.

\*  $P < .05$ .

surgery,” “chemotherapy,” and “radiation prior to surgery combined with chemotherapy” were predictive of a better OS (Fig. 1). In addition, univariate Cox proportional hazard analysis revealed that “radiation prior to surgery,” “chemotherapy,” and “radiation prior to surgery combined with chemotherapy” were significantly associated with a better OS ( $P < .001$ ) (Table 5).

**Table 5****Therapeutic methods and their effect on vital status recode based on univariate Cox regression analysis.**

Therapeutic method			Vital status recode		
			HR	95% CI	P
A Radiation sequence with surgery	a Radiation prior to surgery	2805	1		<.001*
	b No radiation and/or cancer-directed surgery	19,232	2.993	2.815–3.182	
	c Radiation after surgery	937	1.893	1.713–2.092	
	d Radiation before and after surgery	101	1.290	0.966–1.723	
B Chemotherapy recode	Yes	13,784	1		<.001*
	No	9291	1.783	1.727–1.841	
A and B	d with B	2772	1		<.001*
	a without B	9128	3.736	3.504–3.983	
	a with B	10,104	2.535	2.379–2.703	
	b without B	128	2.754	2.231–3.400	
	b with B	809	1.796	1.615–1.998	
	c without B	2	3.080	0.769–12.33	
	c with B	99	1.263	0.941–1.697	
	d without B	33	1.564	0.969–2.526	

95% CI=95% confidence interval, a=no radiation and/or cancer-directed surgery, A=radiation sequence with surgery, B=chemotherapy recode, b=radiation after surgery, c=radiation before and after surgery, d=radiation prior to surgery, HR=hazard ratio.

\*  $P < .05$ .

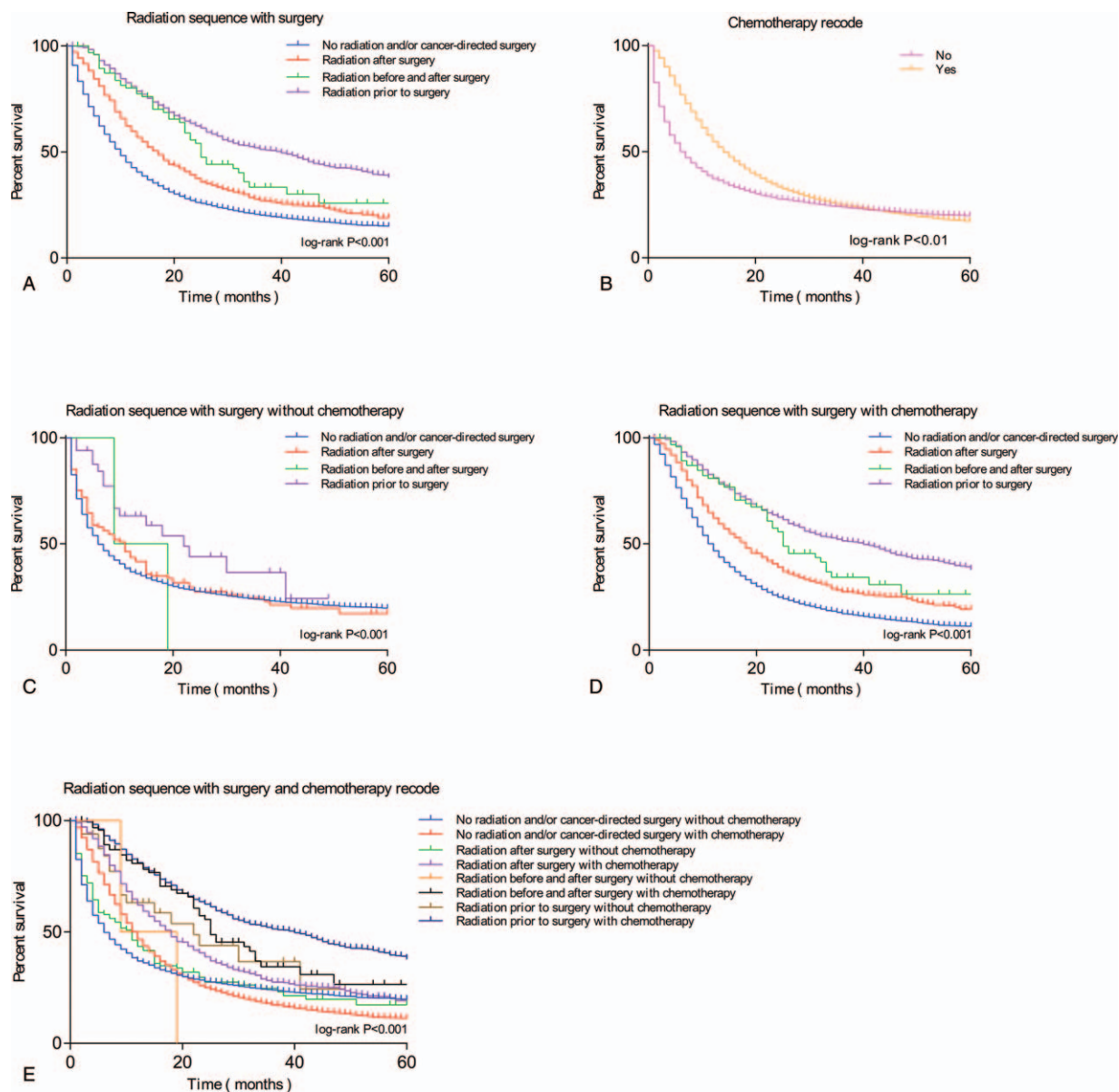
### 3.6. Radiation prior to surgery and chemotherapy in patients with EC is an independent prognostic factor for better survival

Multivariate Cox proportional hazard analyses of factors associated with OS are shown in Table 6. Radiation sequence with surgery (HR=0.733; 95% CI, 0.718–0.748,  $P < .001$ ) and chemotherapy recode (HR=0.677; 95% CI, 0.655–0.700,  $P < .001$ ) were significant independent prognostic factors for OS (Table 6).

## 4. Discussion

After investigating this question, the present study found that surgery followed with radiation prior to surgery and chemotherapy is the best therapeutic strategy among the 8 sequential options. For radiation prior to surgery, many studies have shown that radiotherapy can improve local disease control, especially in





**Figure 1.** Overall survival (OS) curves of patients with esophageal cancer. (A) Association of OS with radiation sequence with surgery. (B) Association of OS with chemotherapy recode. (C) Association of OS with radiation sequence with surgery among the EC patients without chemotherapy. (D) Association of OS with radiation sequence with surgery among the EC patients with chemotherapy. (E) Association of OS with radiation sequence with surgery and chemotherapy recode. P values were determined by comparing survival distributions using the log-rank test.

subgroups of patients who underwent palliative resection.<sup>[28,29]</sup> Gignoux et al<sup>[30]</sup> observed that the postoperative local recurrence rate in patients receiving radiation prior to surgery was significantly lower than the incidence of surgery alone (46%

vs 67%). Nygaard et al<sup>[31]</sup> reported an improvement in 3-year overall survival (OS) (21% vs 9%) in patients treated with radiation prior to surgery combined with surgery, compared with those treated with surgery alone. Our results are consistent with these findings.

However, some studies<sup>[32]</sup> suggest that there is no significant difference in efficacy between radiation prior to surgery and simple surgery. The Esophageal Cancer Society once cited a quantitative meta-analysis from 5 RCTS that got negative results. This meta-analysis assessed whether radiation prior to surgery could improve the incidence of esophageal cancer in 1147 patients. Analysis based on age, sex, and tumor location determined whether there were different therapeutic effects among the patients. In conclusion, there is insufficient evidence that radiation prior to surgery improves survival in patients with

**Table 6**  
Therapeutic methods and their effect on vital status recode based on multivariate Cox regression analysis.

Therapeutic methods	Vital status recode		
	HR	95% CI	P
Radiation sequence with surgery	0.733	0.718–0.748	<.001*
Chemotherapy recode	0.677	0.655–0.700	<.001*

95% CI = 95% confidence interval, HR = hazard ratio.  
\* P < .05.

potentially resectable esophageal cancer. Even if the radiation prior to surgery regimen does improve patient survival, the results may be modest. Therefore, more randomized controlled clinical trials are needed to comprehensively weigh and evaluate the advantages and disadvantages of radiation prior to surgery in the treatment of esophageal cancer patients.

Chemotherapy is also one of the most common adjuvant therapies for cancer.<sup>[33]</sup> Chemotherapy is used in the treatment of esophageal cancer, which can help to inhibit the residual cancer cells and reduce the recurrence rate after surgery. In addition, chemotherapy is also commonly used in the treatment of advanced esophageal cancer, as it can directly kill cancer cells, shrink the tumor, and control the development of cancer.<sup>[34]</sup> Large randomized controlled studies<sup>[21,35]</sup> showed that adjuvant chemotherapy could achieve a better survival benefit for patients with advanced esophageal cancer, but considering the inclusion criteria of patients in these studies, there are still questions about the centralized use of adjuvant chemotherapy for all patients with esophageal cancer. In addition, the best example of adjuvant chemotherapy is the CROSS regimen, which includes chemotherapy drugs with relatively low toxicity (paclitaxel and carboplatin) and radiotherapy dose (41.4 Gy)<sup>[35,36]</sup> with a higher treatment completion rate (91%). A research<sup>[37]</sup> demonstrated that chemotherapy might be the preferred neoadjuvant modality to expedite resection, reduce postoperative complications and operative mortality, and increase the survival in EC patients. This may be an option to maximize the prognostic benefits of adjuvant chemotherapy.

In addition, according to the results, in terms of surgery, radiation prior to surgery combined with chemotherapy plays a certain role in the prognosis of patients with esophageal cancer. For radiation prior to surgery, chemotherapy adds the following advantages<sup>[28,38]</sup>: control of micrometastasis of cancer cells and reduced systemic failure, an additive effect on radiation by acting on different tumor cell groups, and assisting in the radiotherapy of local diseases (space cooperation). The combination of radiation prior to surgery and chemotherapy can play a synergistic role. Previous studies have also shown that radiotherapy combined with chemotherapy can improve the efficacy of various treatments for esophageal cancer.<sup>[39,40]</sup> One study manifested that the EC patients undergoing radiation prior to surgery combined with chemotherapy have the better overall survival compared with individuals with radiation prior to surgery alone.<sup>[41]</sup> Stahl et al<sup>[42]</sup> also found the overall survival superiority for radiation prior to surgery combined with chemotherapy compared with preoperative chemotherapy in EC patients. Furthermore, Swisher's study<sup>[43]</sup> showed that in the EC patients, preoperative chemoradiation therapy was related with the improved disease-free ( $P=.015$ ) and overall survival rates ( $P=.046$ ) and increased pathologic complete response ( $P<.001$ ) when compared with the preoperative chemotherapy. However, in the Burmeister<sup>[44]</sup> research, although there is no difference about overall survival between preoperative chemoradiation therapy and preoperative chemotherapy, preoperative chemoradiation therapy could improve the general appearance for bulky, locally advanced resectable EC. Although radiation prior to surgery combined with chemotherapy could lead to an obviously better complete pathologic response rate than the chemotherapy alone, that didn't result in a long-term survival superiority.<sup>[37]</sup> Therefore, our study provides more evidence that radiation prior to surgery combined with chemotherapy is superior to other treatment regimens for esophageal cancer.

How to predict the curative effect of preoperative chemoradiotherapy is an important topic in clinical treatment of esophageal cancer, among which tumor molecular markers are particularly important. The main role of tumor markers included early diagnosis of tumors, prognosis of disease without any intervention, and prediction of tumor response to treatment. The paragraph would review the advances in molecular prediction of sensitivity to preoperative chemoradiotherapy for EC. Brucher et al<sup>[45]</sup> used real-time quantitative polymerase chain reaction (PCR) to detect CD1 expression, and the study showed that low or negative CD1 expression predicted sensitivity to neoadjuvant chemoradiotherapy in patients with EC. One researcher<sup>[46]</sup> proposed a combination of immunohistochemistry and PCR to detect mutations in the P53 gene. It is believed that no matter how the result of immunohistochemistry is, as long as the PCR test results show P53 gene mutation, patients with EC are not sensitive to neoadjuvant therapy. Hong et al<sup>[47]</sup> found that the down-regulated expression of miRNA-296 in histological specimens of patients with esophageal cancer could enhance the sensitivity of patients with esophageal cancer to chemotherapy drugs, and also found that patients with esophageal cancer with low miRNA-296 expression had better prognosis. Shimada et al<sup>[48]</sup> found that the expression level of vascular endothelial growth factor (VEGF) protein was an independent prognostic factor for EC patients receiving neoadjuvant therapy, while patients with positive expression of VEGF protein had poor prognosis. Therefore, the search for molecular markers to predict the efficacy of neoadjuvant therapy has become the key to individualized treatment of locally advanced esophageal cancer patients.

However, this paper also has some shortcomings. There is no clear time limit for chemotherapy, which poses difficulties and obstacles in establishing the accuracy of treatment strategies. Secondly, the esophageal cancer data in this paper are all from public databases, and we don't know much about the process of patient inclusion and exclusion. Therefore, in our future clinical practice, it is necessary to focus on observing and studying the quality of life and long-term survival rates of regimens using radiation prior to surgery combined with chemotherapy, for patients with esophageal cancer.

## 5. Conclusions

In conclusion, in the treatment of esophageal cancer, the combination of radiation prior to surgery and chemotherapy is better than no radiotherapy, perioperative radiotherapy, postoperative radiotherapy, or other combinations without chemotherapy. In addition, patient selection, optimization of an adjuvant chemo-radiotherapy regimen, and development of a low-toxicity regimen are still important directions for future development of esophageal cancer treatment.

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