

ORIGINAL ARTICLE

Radical esophagectomy for stage II and III thoracic esophageal squamous cell carcinoma followed by adjuvant radiotherapy with or without chemotherapy: Which is more beneficial?

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Keywords

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Abstract

Background: This retrospective study compared the efficacy and side effect profile between postoperative adjuvant radiotherapy and chemoradiotherapy in stage II or stage III thoracic esophageal squamous cell carcinoma (TESCC) patients who underwent curative (R0) esophagectomy.

Methods: A total of 272 TESCC patients who underwent radical esophagectomy from 2007 to 2016 were included in this retrospective analysis. All cases were pathologically confirmed with stage II or III disease and 148 patients received postoperative chemoradiotherapy (CRT), while the remaining 124 patients received postoperative radiotherapy (RT) alone.

Results: In CRT and RT groups, the three-year overall survival rates were 51.3 versus 31.5% ($P < 0.01$) and the median overall survival (OS) was 39 months (95% CI, 31.6 to 46.3 months) and 30 months (95% CI, 21.0 to 38.9 months), respectively ($P = 0.213$). Three-year disease-free survival rates (DFS) were 30.5% versus 15.9% ($P = 0.008$), while the median DFS times were 26 months (95% CI, 17.7 to 34.3 months) and 19 months (95% CI, 16.4 to 21.6 months), respectively ($P = 0.156$). Univariate and multivariate analyses showed AJCC (American Joint Committee on Cancer seventh edition) stage and N stage were independent prognostic factors for overall survival, while the N stage was an independent prognostic factor for disease-free survival.

Conclusions: Postoperative chemoradiotherapy led to one- and three-year overall survival benefits along with an obvious increase in treatment side effects for stage II to III TESCC patients, with no further improvement in five-year survival. However, the chemoradiotherapy benefits mainly favor stage III, number of resected lymph nodes less than 15, younger (less than 60 years old) and smoking patients.

Introduction

Concurrent chemoradiotherapy before dissection has been recommended by the latest National Comprehensive Cancer Network (NCCN) guidelines, whilst observation and follow-up have been recommended for esophageal squamous cell carcinoma (ESCC) patients, instead of postoperative therapies. There is no high-quality evidence to

evaluate the effect of post-operative treatment approaches and adjuvant treatments are the optimal choices with the purpose of reducing local recurrence and distant metastasis for radical ESCC patients in China. Moreover, it is still controversial whether adjuvant therapy should be applied after radical surgery because the conclusions of existing research on adjuvant therapy of ESCC are inconsistent.^{1–7}

As an important regional treatment, radiotherapy can eliminate the residual tumor cells around the tumor beds and local lymphatic drainage areas, thereby reducing the local recurrence rate.⁸ However, subclinical metastases outside the radiotherapy area may be a source of future recurrence and metastasis.⁹ As a proven method, chemotherapy may theoretically reduce the rate of metastasis.⁹ To some extent, postoperative adjuvant chemoradiotherapy has its theoretical advantages. Therefore, adjuvant therapy has been extensively and intensively researched by scholars worldwide. At present, numerous worldwide studies have confirmed the satisfying curative effect of postoperative adjuvant radiotherapy or chemoradiotherapy in ESCC.⁹⁻¹⁷ Although both adjuvant radiotherapy and chemoradiotherapy show better survival in contrast with surgery alone, the survival benefit for postoperative CRT compared to RT remains controversial.^{9,18-21}

Currently, it is necessary to clarify the benefits of CRT and the role of RT in the cohort of patients with TESCC. In this retrospective study, we varied the design and selection criteria considered in earlier studies. The present study attempts to assess the survival benefit of CRT by comparing with RT alone. We discovered factors contributing to poor prognosis in patients with stage II and III TESCC after tumor resection.

Methods

Patients' selection

The medical records of all patients with TESCC who had undergone radical esophagectomy at the West China Hospital of Sichuan University between January 2007 and December 2016 were retrospectively reviewed. Patients were included in the present study if they met all the following criteria: (i) Patients had undergone radical esophagectomy with a systematic mediastinal lymphadenectomy and were pathologically confirmed with stage II/III thoracic ESCC (American Joint Committee on Cancer seventh edition); (ii) patients who received adjuvant chemoradiotherapy or postoperative radiotherapy alone; (iii) Eastern Cooperative Oncology Group (ECOG) performance status <2; (iv) normal liver, kidney, and bone marrow functions demonstrated by blood tests; Cardiopulmonary functions were approximately normal, and patients were supposed to be able to tolerate chemoradiotherapy; and (v) patients aged 18–80 years old. Patients were excluded from the study for the following reasons. (i) The pathological type of esophageal cancer was not pure squamous cell carcinoma or with cancer diagnosed at another site; (ii) patients with positive operative margins, defined as the microscopic positive margin of the International Union Against Cancer (UICC) criteria; (iii) patients had received preoperative chemotherapy or radiotherapy and patients who received postoperative chemotherapy only;

(iv) patients who had died within 30 days of operative complications and (v) patients with any concurrent disease such as serious diabetes, uncontrolled hypertension, or serious chronic obstructive pulmonary disease.

A total of 272 patients who satisfied the inclusion criteria were finally included in the study. Of these patients, 148 cases received postoperative chemoradiotherapy (CRT group), while 124 patients received postoperative radiotherapy alone (RT group).

Surgical procedure

In our study, all the patients underwent left- or right-sided thoracotomy for esophagectomy followed by two- or three-field lymph node dissection and mediastinal lymphadenectomy dissection for curative intent, while perigastric lymph node resection was carried out in patients whose tumors were located in the middle or lower thorax, and an intrathoracic supra-aortic esophagogastric anastomosis was then performed.

Postoperative therapies

Adjuvant therapies were started three to four weeks after the operation. Radiotherapy was given with a 6-MV-X-Ray linear accelerator. A total dose of 40–50 Gy (1.8–2 Gy/fraction/day, five fractions a week) was delivered to patients. Radiation methods include three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT). The clinical target volume (CTV) for treatment generally encompassed the mediastinum (in terms of the anatomic landmarks of a perioperative CT scan). The planning target volume (PTV) was determined as the CTV plus 0.8 cm margins.

There were 148 patients who received concurrent or sequential chemoradiotherapy. Platinum-based chemotherapies were administrated with a median of four cycles (range 2–6) and a combination of cisplatin (25 mg/m² intravenously on days 1–3) plus paclitaxel (135–175 mg/m² intravenously on day 1) or cisplatin (25 mg/m² intravenously on days 1–3) plus 5-fluorouracil (5-FU) (500 mg/m² intravenously on days 1–5), repeated every 21 days.

Follow-up

Follow-ups were once every three months within the first two years, once every half year from the third to fifth year and once every year thereafter. Patients were instructed to carry out follow up evaluations including physical examination, blood test, esophagogram, chest CT scan, and abdominal CT scan or ultrasound, endoscopy, bone scanning, and/or cerebral MRI was performed if clinically indicated.

Definitions and statistical analysis

The long-term outcome was determined from medical records and follow-up information. OS was defined as the time from operation to death (or the last follow-up visit), and DFS was defined as the time from operation to first

disease failure, including locoregional recurrence, distant metastasis and combined recurrence (or death from any cause). Diagnoses of locoregional recurrence were based on regrowth of cancer within the area of the previous resection, including local anastomotic sites and local nodal

Table 1 The clinical characteristics of the patients

Characteristic	No. of patients (%)			χ^2	P-value
	Overall	CRT	RT		
Gender				0.211	0.646
Male	225 (82.7)	121 (81.8)	104 (83.9)		
Female	47 (17.3)	27 (18.2)	20 (16.1)		
Age (years)				3.584	0.167
<60 years	173 (63.6)	101 (68.2)	72 (58.1)		
60 ≤ years < 70 years	79 (29.0)	39 (26.4)	40 (32.3)		
≥70 years	20 (7.4)	8 (5.4)	12 (9.6)		
Drinking				2.252	0.133
Yes	171 (62.9)	99 (66.9)	72 (58.1)		
No	101 (37.1)	49 (33.1)	52 (41.9)		
Smoking				1.395	0.238
Yes	196 (72.1)	111 (75.0)	85 (68.5)		
No	76 (27.9)	37 (25.0)	39 (31.5)		
Tumor location				1.462	0.481
Upper	27 (9.9)	12 (8.1)	15 (12.1)		
Middle	146 (53.7)	83 (56.1)	63 (50.1)		
Lower	99 (36.4)	53 (35.8)	46 (37.8)		
Depth of invasion				1.645	0.649
pT1	9 (3.3)	5 (3.4)	4 (3.2)		
pT2	37 (13.6)	22 (14.9)	15 (12.1)		
pT3	167 (61.4)	93 (62.8)	74 (59.7)		
pT4	59 (21.7)	28 (18.9)	31 (25.0)		
LN involved				5.941	0.015
pN0	87 (32.0)	38 (25.7)	49 (39.5)		
pN1-3	185 (68.0)	110 (74.3)	75 (60.5)		
No. of resected nodes				0.658	0.417
≥15	184 (67.6)	97 (65.5)	87 (70.2)		
<15	88 (32.4)	51 (34.5)	37 (29.8)		
Differentiation				1.846	0.397
G1	5 (1.8)	3 (2.0)	2 (1.6)		
G2	113 (41.5)	56 (37.8)	57 (46.0)		
G3	154 (56.7)	89 (60.2)	65 (52.4)		
Pathological stage				0.063	0.802
II	90 (33.1)	48 (32.4)	42 (33.9)		
III	182 (66.9)	100 (67.6)	82 (66.1)		
Vascular cancer embolus				0.226	0.635
Yes	26 (9.6)	13 (8.8)	13 (10.5)		
No	246 (90.4)	135 (91.2)	111(89.5)		
Chemotherapy regimen					
PF		89 (60.1)	0		
TP		59 (39.9)	0		
Chemotherapy cycles					
2-3		77 (52.0)	0		
4-5		63 (42.6)	0		
6		8 (5.4)	0		

CRT, postoperative chemoradiotherapy; G, histopathological grading; LN, lymph nodes; No., number; PF, cisplatin plus 5-fluorouracil; RT, postoperative radiotherapy; TP, paclitaxel plus cisplatin.

clearance. Recurrence beyond those sites was considered distant progression. The diseases with simultaneous locoregional and distant recurrences were named combined recurrence.

All statistical analyses were performed using IBM SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). Survival analysis was performed using the Kaplan-Meier method, and the log-rank test was used to detect survival differences between the two groups. Categorical variables were compared by using the chi-square test. Multivariate analysis was carried out by the method of Cox regression. Statistical significance was defined as $P < 0.05$.

Results

Patients' characteristics

Patients' characteristics are presented in Table 1. There was a total of 272 patients, 124 cases (45.6%) received postoperative adjuvant radiotherapy alone, while 148 (54.4%) received postoperative chemoradiotherapy. Because of potential bias in the clinician's treatment selection, the percentage of patients with positive lymph nodes in CRT group was higher than in the RT group ($P = 0.015$).

Overall survival and disease-free survival

Overall survival rates for the entire population of 272 patients were 88.24% at the first year, 42.28% at the third year, and 21.69% at the fifth year, respectively, with a median OS of 35.0 months (95% CI 28.5–41.5). The three-year OS rate was 51.4% versus 31.5 ($P < 0.001$) for group CRT and RT, respectively (Table 2). The median OS was 39.0 months (95% CI 31.6–46.3) in the group CRT versus 30.0 months (95% CI 21.0–38.9) in the group RT ($P = 0.213$; HR, 0.69) (Fig 1).

The median DFS of the whole cohort of 272 patients was 23.0 months (95% CI 19.4–26.6). DFS rates for the whole group were 66.8% at the first year, 23.9% at the third year, and 13.9% at the fifth year, respectively. The one year, three-, and five-year DFS rates were 70.2% versus 62.8%, 30.5% versus 15.9 and 17.6% versus 9.3% for group CRT

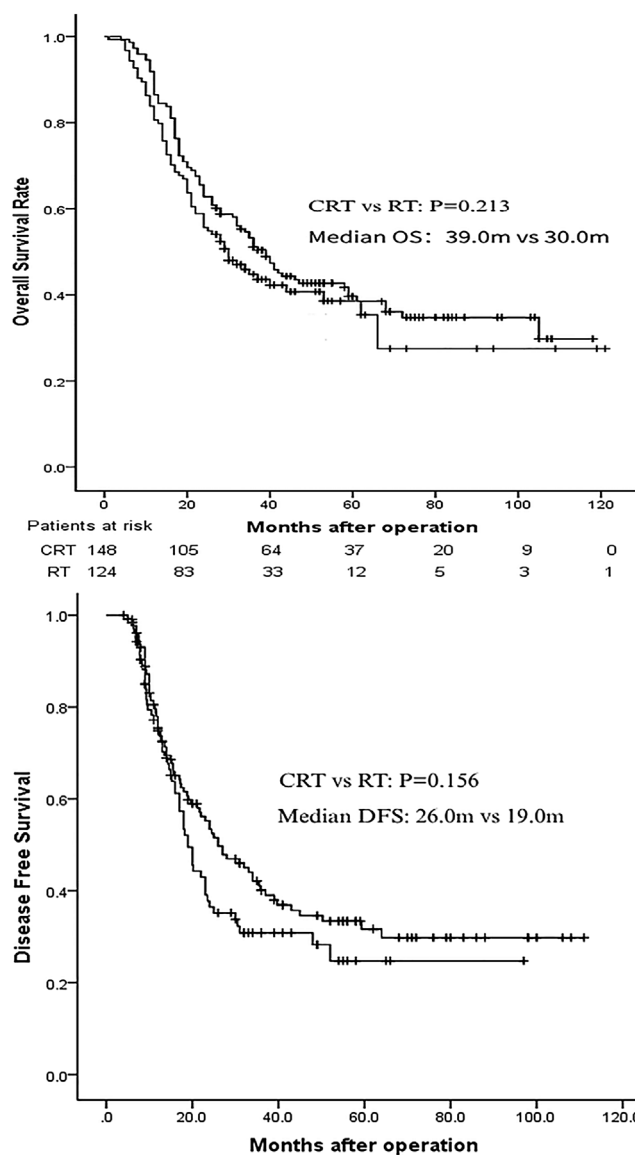


Figure 1 Effects of different postoperative adjuvant therapies on OS and DFS in all 272 patients. CRT group, patients who received postoperative adjuvant chemoradiotherapy; RT group, patients who received postoperative adjuvant radiotherapy alone.

Table 2 The OS rate and DFS rate of CRT group and RT group

		CRT group (n = 148)	RT group (n = 124)	χ^2	P-value
OS rate	One year	136 (91.9)	104 (83.9)	4.182	0.041
	Three years	76 (51.4)	39 (31.5)	10.948	0.001
	Five years	37 (25.0)	22 (17.7)	2.092	0.148
DFS rate	One year	104 (70.2)	78 (62.8)	1.654	0.198
	Three years	45 (30.5)	20 (15.9)	7.561	0.06
	Five years	26 (17.6)	12 (9.3)	3.495	0.62

and CT, respectively. The median DFS of the CRT group and RT group in our study was 26.0 months (95% CI 17.7–34.3) and 19.0 months (95% CI 16.4–21.6), respectively ($P = 0.156$; HR, 0.69) (Fig 1).

Subgroup statistical analysis showed that in patients who were younger than 60 years old and whose resected lymph nodes by surgeons during the operation were less than 15, postoperative CRT was much more effective than RT at improving OS and DFS. There was an obvious difference in OS and DFS between the CRT and RT group in patients younger than 60 years old (median OS: 41.0 vs. 29.0 months; $P = 0.04$; median DFS: 32.0 vs. 20.0 months; $P = 0.02$, respectively) and whose resected lymph nodes by surgeons during the operation were less than 15 (median OS: 41.0 vs. 20.0 months; $P = 0.006$; median DFS: 37.0 vs. 14.0 months; $P = 0.006$, respectively)(Fig 2).

Pattern of failure

The failure patterns of all patients in the two groups are detailed in Table 3. There were no significant differences

Table 3 Failure patterns of patients between two groups

Failure pattern	CRT group ($n = 148$)	RT group ($n = 124$)	<i>P</i> -value
Supraclavicular	36 (24.3)	27 (21.8)	0.62
Mediastinum	18 (12.2)	12 (9.7)	0.51
Abdominal cavity	9 (6.1)	7 (5.6)	0.88
Tumor bed	6 (4.1)	8 (6.5)	0.37
Distant organ metastasis	28 (18.9)	26 (20.9)	0.67
Mixed	15 (10.1)	18 (14.5)	0.27
Overall	112(75.6)	98(79.0)	0.51

between the two groups for recurrence and metastasis rate, with an overall recurrence and metastasis rate of 75.6% and 79.0% for group CRT and RT, respectively ($P = 0.51$).

Univariate and multivariate analyses of prognostic factors

The extent of lymph node involvement, number of positive lymph nodes and AJCC stage were significantly associated with both OS and DFS in a univariate analysis, while the

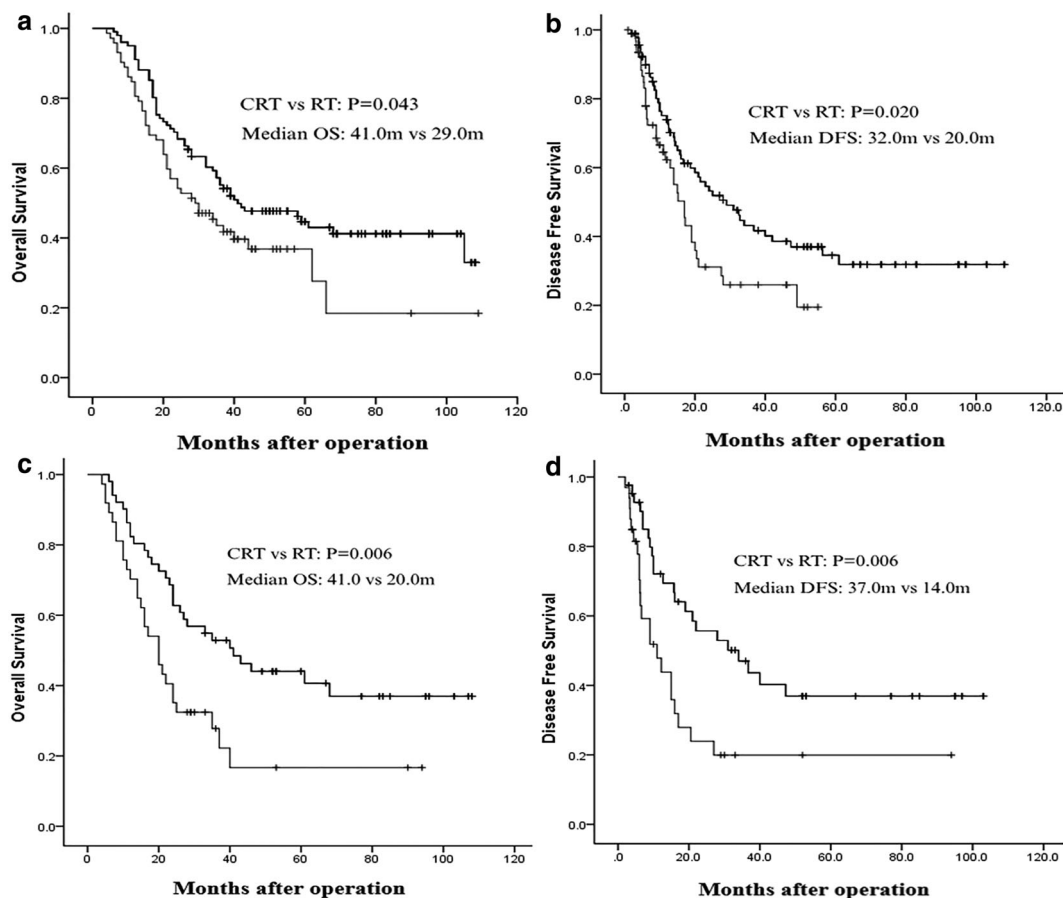


Figure 2 (a) Overall survival for patients younger than 60 years old and (c) patients with number of resected lymph nodes less than 15; (b) Disease-free survival for patients younger than 60 years old and (d) patients with number of resected lymph nodes less than 15.

Table 4 Univariate and multivariate analyses of OS and DFS

Variable	OS						DFS						
	UVA			MVA			UVA			MVA			
	Median OS	95% CI	P-value	HR	95% CI	P-value	Median DFS	95% CI	P-value	HR	95% CI	P-value	
Treatment method	CRT	39.0	31.6–46.4	0.213	0.679	0.491–0.939	0.019*	26.0	17.74–34.26	0.156	0.687	0.485–0.973	0.034*
	RT	30.0	21.0–38.9	—	—	—	—	19.0	16.35–21.65	—	—	—	—
AJCC stage	II	66.0	58.8–73.1	0.000*	0.524	0.342–0.801	0.003*	34.0	11.72–56.28	0.001*	—	—	—
	III	26.0	20.8–31.2	—	—	—	—	18.0	14.81–21.20	—	—	—	—
Tumor location (thoracic esophageal)	Upper	68.0	40.9–95.1	0.149	—	—	—	34.0	0.682–67.32	0.258	—	—	—
	Middle	32.0	23.2–40.8	—	—	—	—	19.0	13.97–24.03	—	—	—	—
	Lower	36.0	25.6–46.4	—	—	—	—	23.0	16.75–29.25	—	—	—	—
Lymph nodes involved	Yes	30.0	23.5–36.5	0.044*	—	—	—	19.0	15.01–22.99	0.012*	—	—	—
	No	53.0	35.0–70.9	—	—	—	—	32.0	8.78–55.22	—	—	—	—
Drinking	Yes	29.0	21.7–36.3	0.021*	1.335	0.949–1.878	0.097	20.0	15.88–24.12	0.067	—	—	—
	No	58.0	36.8–79.2	—	—	—	—	30.0	20.41–40.60	—	—	—	—
Gender	Male	35.0	28.1–41.9	0.270	—	—	—	23.0	18.98–27.02	0.47	—	—	—
	Female	40.0	30.1–46.3	—	—	—	—	23.5	11.48–35.52	—	—	—	—
Smoking	Yes	34.0	27.2–40.8	0.260	—	—	—	20.0	16.35–23.65	0.115	—	—	—
	No	41.0	13.1–68.9	—	—	—	—	27.0	18.92–35.08	—	—	—	—
Age (years)	<60y	37.0	29.4–44.6	0.425	—	—	—	23.5	17.23–29.77	0.649	—	—	—
	60 ≤ y < 70	31.0	15.4–46.7	—	—	—	—	21.2	14.96–27.44	—	—	—	—
	≥70y	26.0	14.3–37.7	—	—	—	—	16.0	2.62–29.38	—	—	—	—
Differentiation	G1	105.0	0.000–237.6	0.843	—	—	—	28.3	20.44–35.06	0.586	—	—	—
	G2	37.0	27.0–46.9	—	—	—	—	24.0	20.90–27.10	—	—	—	—
	G3	32.0	25.0–38.9	—	—	—	—	20.2	14.79–25.61	—	—	—	—
Depth of invasion	T1	—	—	0.165	—	—	—	—	—	0.136	0.148	0.035–0.628	0.010*
	T2	46.0	14.7–77.3	—	—	—	—	24.0	14.28–33.72	—	0.576	0.315–1.053	0.073
	T3	33.0	24.6–41.4	—	—	—	—	23.0	18.26–27.74	—	0.690	0.452–1.051	0.084
	T4	30.0	20.2–39.8	—	—	—	—	17.0	11.71–22.29	—	—	—	—
No. of positivelymph nodes	N0	53.0	35.0–70.9	0.000*	0.353	0.160–0.780	0.010*	32.0	12.50–51.50	0.032*	0.249	0.113–0.546	0.001*
	N1	35.0	25.8–44.2	—	0.347	0.169–0.712	0.004*	18.8	13.57–24.04	—	0.463	0.220–0.977	0.043*
	N2	26.0	19.8–32.2	—	0.418	0.195–0.896	0.025*	19.7	13.77–25.63	—	0.407	0.178–0.933	0.034*
	N3	12.0	10.9–13.0	—	—	—	—	11.2	10.62–11.78	—	—	—	—
No. of resected lymph nodes	≥15	39.0	29.1–48.9	0.120	0.645	0.464–0.897	0.009*	23.0	18.46–27.54	0.643	—	—	—
	<15	25.0	16.1–33.9	—	—	—	—	20.0	13.57–26.43	—	—	—	—
Vessel carcinoma embolus	Yes	29.0	13.1–44.9	0.370	—	—	—	20.0	10.66–29.34	0.363	—	—	—
	No	36.0	28.6–43.4	—	—	—	—	23.0	18.90–27.10	—	—	—	—
Chemotherapy regimens	PF	36.0	24.5–47.5	0.199	1.565	0.983–2.492	0.059	24.0	17.25–30.75	0.499	—	—	—
	TP	40.0	30.6–49.7	—	—	—	—	33.1	22.14–44.10	—	—	—	—
Chemotherapy cycles	2–3	36.0	28.8–43.2	0.320	—	—	—	26.0	16.60–35.39	0.234	—	—	—
	4–5	43.0	0.000–90.8	—	—	—	—	39.7	16.64–62.76	—	—	—	—
	6	27.0	7.6–46.4	—	—	—	—	17.4	15.24–19.56	—	—	—	—

*Significant difference. CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; MVA, multivariate analysis; PF, cisplatin plus 5-fluorouracil; RT, radiotherapy; TP, paclitaxel plus cisplatin; UVA, univariate analysis.

lower postoperative stage, without lymph node involvement (N-) and lower numbers of positive lymph nodes were significantly associated with improved survival (Table 4).

In multivariate analysis, postoperative chemoradiotherapy and the number of positive lymph nodes were significantly associated with improved OS and DFS. A comprehensive univariate and multivariate analysis showed that the number of positive lymph nodes and AJCC stage were independent prognostic factors for OS, and that the number of positive lymph nodes were independent prognostic factors for DFS (Table 4).

Toxicity

The most common side effects in the study were gastrointestinal reactions and myelosuppression. The other side effects included radiation-induced pneumonia, radiation-induced esophagitis, radiation skin damaged, diarrhea, poor appetite, dizziness, and so on. The adverse reactions were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE 3.0). Myelosuppression and gastrointestinal reactions were experienced significantly more frequently by patients in Group CRT than those in Group RT. However, there were no significant differences in the incidence of other adverse reactions. Grade 1–2 myelosuppression and grade 1–2 gastrointestinal reactions between CRT and RT group were 70.9% versus 37.9% ($P < 0.001$), 40.5% versus 8.1% ($P < 0.001$), while the grade 3–4 myelosuppression and grade 3–4 gastrointestinal reactions were 21.0% versus 7.3% ($P = 0.002$) and 10.1% versus 3.2% ($P = 0.026$), respectively. There were no treatment-related toxic deaths for the whole cohort.

Discussion

Although was no difference between the patients who received postoperative CRT and the adjuvant radiotherapy alone group in both the median OS and DFS, the three-year OS and DFS rates were obviously improved, which favored the group who received CRT, which is partially consistent with previous studies.^{13,14} In this study, the differences of three-year OS and DFS rate were statistically significant between the CRT and RT groups, but the survival analysis curve did not show statistically significant differences; the inconsistency of this conclusion may relate to the nature of the study, which includes a higher incidence of lymph node metastasis in the CRT group. However, the disease-free survival curves for patients who received chemoradiotherapy and for those who received radiotherapy shows a tendency of divergence from the follow-up time of approximately 16 months. This suggests that the potential improvement in DFS may be achieved by a therapeutic regimen of plus chemotherapy to

radiotherapy, and ultimately, to improvement in OS if the sample size is large enough. As to the one-year overall survival rates, the statistical difference was relatively mild and the difference of one-year DFS rate was not obvious while it became obvious in the third year. This may have been related to the timeliness of adjuvant therapy and postoperative tumor bed blood circulation disorders, which resulted from the operation damage that had not been completely rebuilt, thus leading to the increased proportion of hypoxic tumor cells.^{22,23} The increase in the proportion of hypoxic tumor cells was associated with decreased sensitivity to radiotherapy and reduced local delivery of chemotherapeutic drugs.^{24–27}

In this study, there were no differences in the overall recurrence and metastasis rates between the CRT and RT groups, which is opposite to the previous study. Chen *et al.* and other scholars showed that adjuvant chemoradiotherapy could reduce the overall recurrence rate, distant metastasis rate, and mixed metastasis rate compared with adjuvant radiotherapy alone.⁹ In our study, although the univariate analysis showed that adding chemotherapy based on radiotherapy could not reduce the recurrence and metastasis rates of TESCC patients, the multivariate analysis showed that compared with adjuvant radiotherapy alone, the risks of recurrence and metastasis could be reduced by 31.3% when extra chemotherapy was added. The possible reasons are expected to encourage further research.

Univariate and multivariate analysis in this study showed that postoperative AJCC stage and number of positive lymph nodes (N stage) were independent prognostic factors for OS, while N stage was an independent prognostic factor for DFS. In other words, the prognosis of patients diagnosed as stage II was better than those at stage III. One retrospective analysis which involved 1715 esophageal squamous-cell carcinoma patients who were treated after surgery, showed that the five-year survival rates of patients with stage I, IIA, IIB and III were 83.8%, 70.8%, 52.1% and 41.1%, respectively, which is consistent with our results.²⁸ Another study also showed that the one-, three-, five-year survival rates and median OS in patients with stage I + II was significantly longer than those with stage III, while the prognosis of patients with 0–1 positive lymph node involvement was better than patients with the number of positive lymph nodes greater than two.²¹ It means that the more positive lymph nodes pathologically confirmed after surgery means that it is easier for a patient to relapse a metastasis, and finally lead to shorter DFS and OS time, which is in accordance with the present results of ours study.

Subgroup analysis showed that patients aged younger than 60 years old, who smoked, with resected lymph nodes less than 15 and well-differentiated tumors were more likely to benefit from adjuvant chemoradiotherapy

compared with postoperative radiotherapy alone. The study by van Nistelrooij *et al.* showed that patients aged younger than 50 years were more likely to survive longer than 50 years older after esophagectomy, median OS was 33 months versus 23 months, and the five-year survival rate was 40.5% versus 31% ($P = 0.001$), respectively.²⁹ The results of the present study revealed that patients who received adjuvant CRT who were younger than 60 years old had a longer survival time compared to those older than 60, which was similar to the conclusion of the study by van Nistelrooij *et al.* ($P = 0.04$).²⁹ This may be associated with better organ function, stronger immunity, fewer complicated diseases, greater tolerance to radiotherapy and chemotherapy of young patients, and higher compliance and response to treatment. At present, the NCCN guidelines recommend that the number of lymph nodes is more than 15 in the radical resection of esophageal cancer. The risk of recurrence and metastasis will be greatly increased if the number of resected lymph nodes is less than 15. Adjuvant radiotherapy and chemotherapy may have a synergistic effect in eliminating cancer cells of local residual and distant micrometastasis.⁹ Those reports, as well as our analysis, suggested that patients with both older age and less than 15 resected lymph nodes were at higher risk of disease progression, and of diminished survival. Therefore, more potent treatment modalities such as additional chemotherapy should be used on these patients.

As for side effects, the incidence of gastrointestinal reactions and myelosuppression in the group CRT was significantly higher than those in the group RT, but most were alleviated after symptomatic treatment. Other treatment-related side effects were similar between the two groups, and most were grade 1–2; there were no treatment-related deaths and patients were able to tolerate treatment. This is consistent with the findings of Chen *et al.* and Chi *et al.* that CRT can significantly increase the incidence of toxic and side effects compared with RT.^{9,20}

In the present analysis, stage II to III ESCC patients were benefited from the postoperative chemoradiotherapy for the one- and three-year overall survival, while the benefits were disappeared for five-year survival. However, in our study, chemoradiotherapy mainly benefitted stage III patients, number of resected lymph nodes less than 15, younger (less than 60 years old) and smoking patients. Since this was a single centre retrospective study, larger and prospective randomized clinical trials are warranted to confirm these findings.

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Disclosure

No authors report any conflict of interest.

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