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Effects of preoperative radiotherapy on survival of patients with stage II and III esophageal squamous cell carcinoma

A population-based study

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Abstract

The impact of preoperative radiotherapy (PRT) on survival in patients with stage II and III esophageal squamous cell carcinoma (ESCC) remains controversial. The aim of this study was to explore the effect of PRT on survival of these patients.

Patients with stage II and III ESCC who underwent chemotherapy ± PRT were identified and retrieved from the SEER database from 2010 to 2015. Cox regression analysis was used to identify independent prognostic factors in patients. Subgroup analysis stratified by T stage and N stage was performed. Kaplan–Meier survival analysis was performed to assess disease specific survival (DSS).

A total of 1160 patients were retrieved, of whom 289 (24.9%) underwent PRT plus chemotherapy, and 871 (75.1%) did not receive PRT. In multivariate analysis, PRT plus chemotherapy was a favorable prognostic factor for patients with stage T2 (hazard ratio [HR], 0.364, 95% CI, 0.202–0.658; $P < .001$), T3 (HR, 0.536, 95% CI, 0.413–0.695; $P < .001$) and T4 (HR, 0.318, 95% CI, 0.125–0.805; $P = .016$), but PRT plus chemotherapy was not statistically significant on DSS in patients with T1 disease (HR, 0.556, 95% CI, 0.262–1.179; $P = .126$). All 3 different N stages (N0, N1, and N2 + N3) were statistically significant ($P < .05$) in chemotherapy with or without PRT.

In conclusion, patients with stage II and III ESCC at the T2-T4 stage gained significant survival benefit from PRT plus chemotherapy.

Abbreviations: DFS = disease-free survival, DSS = disease specific survival, ESCC = esophageal squamous cell carcinoma, HR = hazard ratio, OS = overall survival, PRT = preoperative radiotherapy.

Keywords: esophageal cancers, radiochemotherapy, SEER database, squamous cell carcinoma

1. Introduction

Esophageal cancer is the eighth most common type of cancer worldwide and the sixth leading cause of cancer-related deaths globally.[1] In 2018, an estimated 570,000 new cases of esophageal cancer were diagnosed worldwide. With an increasing incidence, the overall 5-year survival of esophageal cancer patients ranged from 15% to 25%.[2,3] The treatment is multidisciplinary, and furthermore, surgery and radiotherapy have always been the mainstay of treatment for esophageal cancer. Despite the advances in multidisciplinary treatment strategies, the prognosis of esophageal cancer patients is still poor, especially in patients with stage II / III disease. Recent studies found that neoadjuvant therapy could improve prognosis of patients with locally advanced esophageal cancer as compared to surgery alone.[4,5]

The CROSS-trial laid the groundwork for multimodality treatment of esophageal cancer, which indicated that neoadjuvant chemoradiation was a standard treatment for patients with locally advanced esophageal cancer.[6] However, esophageal squamous cell carcinoma (ESCC) patients made up a relatively small fraction of all patients in the CROSS trial (84/368). Thus, novel therapeutic strategies remain to be further explored for neoadjuvant therapies of ESCC.

In an earlier study, 286 ESCC patients (with stage T1N0, T1N1, T2N0, T2N1, or T3N0 disease) were divided into 2 groups, preoperative chemoradiotherapy plus surgery group and

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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surgery alone group. It was shown that Cisplatin monotherapy for 2 cycles combined with radiotherapy did not improve overall survival (OS), as compared with surgery alone. However, Cisplatin combined with radiotherapy significantly increased disease-free survival and local disease-free survival of patients, and decreased T staging, N staging and the mortality rate. The perentage of patients undergoing preoperative radiotherapy (PRT) was 26%. Notably, radiotherapy dosing up to 37Gy for 10 fractions increased the risk of postoperative death.[7] This might explain why there was no difference in OS between the 2 groups in contrast to markedly lowered tumor-related mortality in patients receiving preoperative chemoradiotherapy. In addition, Song et al. have suggested that (neo-) adjuvant radiotherapy might improve the OS compared to surgery alone in patients with T3N0M0 stage esophageal adenocarcinoma.[8]

Radiotherapy plays an important role in the comprehensive treatment of esophageal cancer. A meta-analysis showed that postoperative radiotherapy was promising in improving OS and reducing the locoregional recurrence rate.[9] The aim of our study was to search for aggressive PRT programs and improve the overall outcome and survival in ESCC patients.

2. Methods

In this retrospective study, we retrieved data from the SEER database using SEER*STAT 8.3.8 software (NCI). Permission to access the custom data file in the SEER Program was obtained (reference number 11169-Nov2020). Because this study used established data, and did not involve interactions with patients, Institutional Review Board approval was waived.

We collected the data of ESCC patients from 2010 to 2015, and this study included patients that were diagnosed as having stage II / III (AJCC 7th edition) ESCC who received chemotherapy ± PRT. We sequentially excluded subjects with unknown race (n = 6), unknown grade (n = 314), TX (n = 23) and NX (n = 5). Of remaining 1494 patients, only subjects whose tumor locations were upper third of the esophagus (n = 219), middle third of the esophagus (n = 518) and lower third of the esophagus (n = 426) were included. Furthermore, 3 patients with OS less than 1 month were removed. Ultimately, 1160 patients were included in the present study.

Patients who met the following criteria were included in this study:

1. age ≥18 years;
2. pathologically confirmed ESCC (histologic types selected were coded as 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8083, and 8094);
3. diagnosis of stage II/III ESCC according to the 7th edition of the AJCC Cancer Staging Manual;
4. first malignant primary indicator;
5. complete record of radiotherapy and chemotherapy information (patients who received chemotherapy with or without PRT).

Clinical and demographic features were compared between patients who received PRT and those who received other therapies using the Chi-Squared test. In addition, the endpoint of interest for our study was death from ESCC. The survival analysis was performed using Kaplan–Meier curves, and *P* value was determined using the log-rank method. Hazard ratio (HRs) along with 95% CI were calculated using univariate and multivariate Cox proportional hazards models. Statistical analysis was performed using the statistical packages R version 4.0.3 (R Foundation for Statistical Computing). All statistical tests were 2-sided, and $P < .05$ was considered statistically significant.

3. Results

A total of 1160 patients who met inclusion criteria were included in this study (Fig. 1). Of those, 289 patients received PRT. The proportion of the patients differed by age and primary tumor site ($P < .001$). No significant difference was found in sex, race, year of diagnosis, pathologic grade, T stage and N stage (Table 1).

Univariate survival analysis was performed on all patients. PRT plus chemotherapy and other race category were favorable prognostic factors. Other-race category included American Indian or Native Alaskan, Asian, or Pacific Islander. Adverse prognostic factors included male sex, higher T stage and higher N stage. Univariate survival analysis of the patients with T1, T2, T3, and T4 stages showed that PRT plus chemotherapy was an advantageous factor for the prognosis of patients with stage T2, T3, and T4 disease, whereas PRT plus chemotherapy did not have a significant effect on survival of patients with T1 disease (Table 2).

Multivariate survival analysis of all patients showed that male sex and higher N stages were independent risk factors for prognosis, indicating shorter survival. PRT plus chemotherapy and age (≥60 years) were favorable prognostic factors which were related to longer survival. We conducted a subgroup multivariate survival analysis according to T stages. The results showed that PRT plus chemotherapy predicted better outcomes for ESCC patients with T2, T3, and T4 stages (HR, 0.364; 95% CI, 0.202–0.658; $P < .001$, HR, 0.536; 95% CI, 0.413–0.695; $P < .001$, and HR, 0.318; 95% CI, 0.125–0.805; $P = .016$, respectively), but had no significant impact on T1 stage disease (Table 3).

All the 1160 patients were divided into 2 groups, based on whether they had received PRT. The results showed that a great survival was seen in patients receiving PRT (median disease specific survival [DSS], 69 vs 19 months; $P < .001$) (Fig. 2A).

There was no significant difference in survival of patients with stage T1 ESCC based on whether they received PRT ($P = .344$). A Kaplan–Meier plot for patients with stage T1 was presented in Figure 2B. A total of 107 ESCC patients with T1 disease was divided into 2 groups, based on whether they were exposed to PRT. No significant differences were noted in median survival time between the 2 groups. Median survival time of patients who received PRT was 22 months, slightly longer than that (20 months) of patients who did not.

In addition, 142 ESCC patients with stage T2 did not receive PRT. Median survival time of patients who received PRT plus chemotherapy was significantly longer than that of patients who received chemotherapy alone (not attained vs 33 months; $P < .001$) (Fig. 2C). The median survival time of patients who received PRT plus chemotherapy was 68 months, remarkably longer, as compared with those who did not (median DSS, 20 months; $P < .001$) (Fig. 2D), among the 696 patients with T3 stage. As for patients with ESCC at the T4 stage, median DSS was significantly shorter in those who received chemotherapy alone than in those who received PRT plus chemotherapy (11 months vs not attained; $P = .004$) (Fig. 2E).

In present study, lymph node metastases were present in all T1 patients, as all patients enrolled in this study had stage II / III ESCC. Meanwhile, the rates of lymph node metastasis of patients

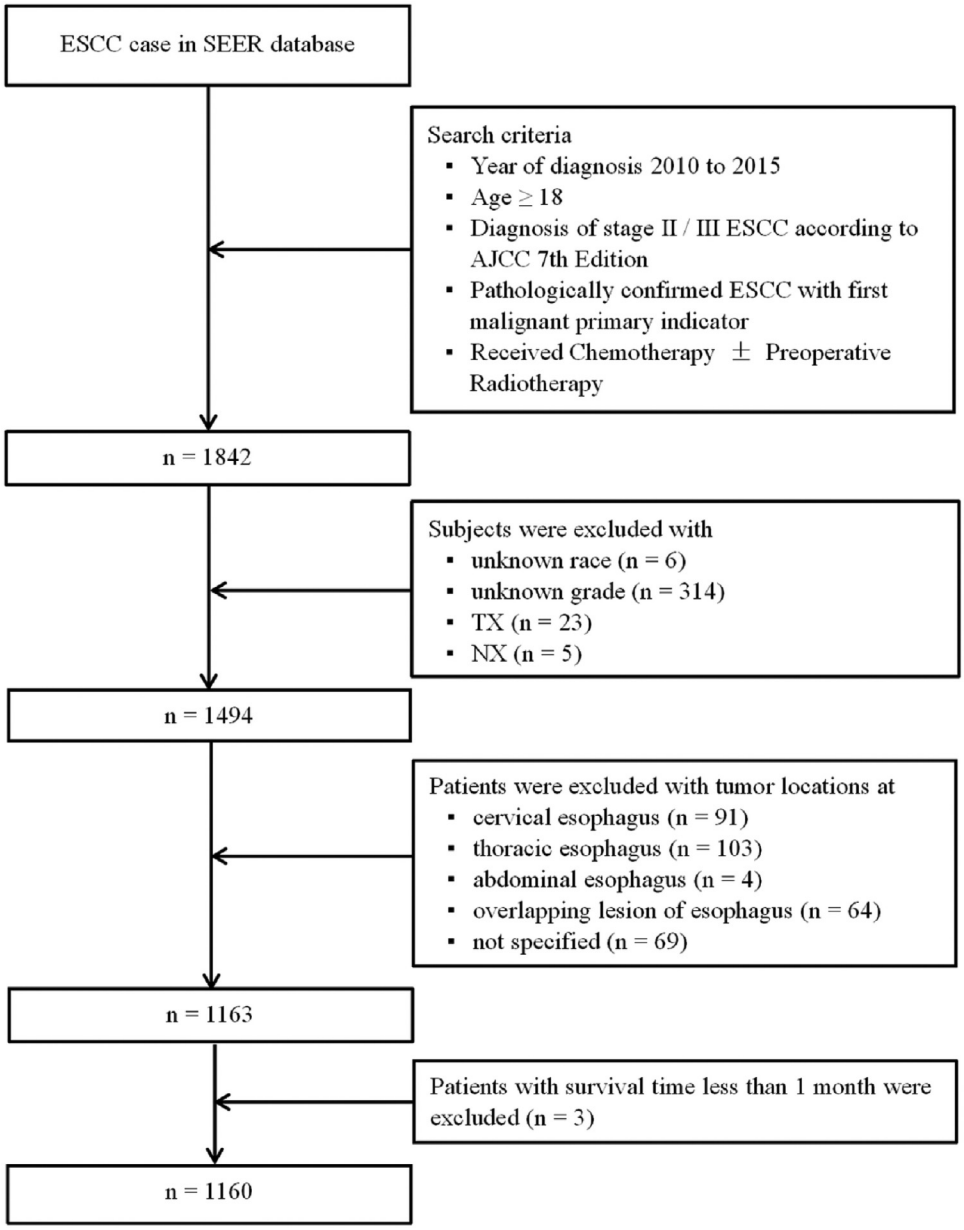

Figure 1. Patients selection. ESCC = esophageal squamous cell carcinoma.

with T2, T3, and T4 stages were 49.26% (100/203), 67.96% (473/696) and 63.64% (98/154), respectively. Therefore, we conducted further exploratory analysis according to N stages, and performed univariate and multivariate analyses (Tables 4 and 5). The results suggested that PRT plus chemotherapy had a better impact on the prognosis of the patients at stage N0, N1, and N2 + N3. They were grouped according to whether patients with different N stages were undergoing PRT. We found that patients with stage N0 (median DSS, not attained vs 28 months; $P < .001$), N1 (median DSS, 69 vs 16 months; $P < .001$) and N2 + N3 (median DSS, 26 vs 13 months; $P = .027$) who received PRT had significantly better survival than those who did not (Fig. 3). The results of multivariate survival analysis revealed that T2 patients had a survival advantage over those with T1 disease (HR, 0.611, 95% CI, 0.443–0.842; $P = .003$), and patients with T4 stage had poor prognosis (HR, 1.383, 95% CI, 1.019–1.877; $P = .038$).

4. Discussion

The survival rate is low, with a 5-year survival rate of approximately 20% in II and III stage esophageal cancer patients.[10,11] Approximately 63% of esophageal cancer patients suffers from local region or systemic recurrence within 2 years of radical treatment.[12] In recent years, studies have found that preoperative chemoradiotherapy and surgical resection combined with preoperative chemotherapy as important neoadjuvant regimens are needed to improve the outcome in esophageal

Table 1

Correlation between parameters and preoperative radiotherapy.

Parameters	CT n (%)	CT + PRT n (%)	All patients	*P*
Age at diagnosis				<.001
<60 y	249 (67.8%)	118 (32.2%)	367	
≥60 y	622 (78.4%)	171 (21.6%)	793	
Sex				.211
Female	309 (72.9%)	115 (27.1%)	424	
Male	562 (76.4%)	174 (23.6%)	736	
Race				.079
Black	212 (79.7%)	54 (20.3%)	266	
White	553 (73.1%)	204 (26.9%)	757	
Other	106 (77.4%)	31 (22.6%)	137	
Year of diagnosis				.597
2010	127 (72.2%)	49 (27.8%)	176	
2011	138 (78.0%)	39 (22.0%)	177	
2012	138 (71.9%)	54 (28.1%)	192	
2013	174 (74.4%)	60 (25.6%)	234	
2014	154 (77.8%)	44 (22.2%)	198	
2015	140 (76.5%)	43 (23.5%)	183	
Primary tumor site				<.001
Upper third of esophagus	197 (90.0%)	22 (10.0%)	219	
Middle third of esophagus	385 (74.8%)	130 (25.2%)	515	
Lower third of esophagus	289 (67.8%)	137 (32.2%)	426	
Pathologic grade*				.123
I/II	514 (73.4%)	186 (26.6%)	700	
III/IV	357 (77.6%)	103 (22.4%)	460	
T stage				<.001
T1	87 (81.3%)	20 (18.7%)	107	
T2	142 (70.0%)	61 (30.0%)	203	
T3	501 (72.0%)	195 (28.0%)	696	
T4	141 (91.6%)	13 (8.4%)	154	
N stage				.020
N0	284 (74.3%)	98 (25.7%)	382	
N1	434 (73.1%)	160 (26.9%)	594	
N2 + N3	153 (83.2%)	31 (16.8%)	184	

PRT = preoperative radiotherapy.

* Pathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated.

cancer patients.[4,13,14] Patients with esophageal cancer may have a longer OS with the above neoadjuvant therapies. However, whether esophageal cancer patients can benefit from PRT combined with surgery remains unclear.[15]

Zheng et al reported that no marked difference was found in survival of patients undergoing preoperative chemotherapy with or without PRT.[16] A study based on the SEER database found that PRT significantly improved the survival outcomes for patients with esophageal cancer compared to postoperative radiotherapy.[17] Moreover, Thumallapally et al revealed that compared to adjuvant radiotherapy, neoadjuvant radiotherapy resulted in a better 5-year relative survival in patients with squamous cell neoplasms and/or T3, Tx stage disease.[18] The results of the randomized controlled CROSS trial suggested that the OS benefit of patients with locally advanced resectable esophageal or junctional cancer who received preoperative chemoradiotherapy according to CROSS persisted for more than 10 years, which strongly indicated that patients with locally advanced resectable esophageal or junctional cancer could benefit from preoperative neoadjuvant chemoradiotherapy.[19]

Because of the anatomical characteristics, esophageal cancer is more likely to invade into large vessels, trachea, bronchus and other tissues. Esophageal cancer is also prone to be accompanied with lymph node metastasis. Theoretically, PRT could effectively reduce the tumor volumes and the rate of local recurrence, alleviate invasion into the surrounding tissues, and improve the efficacy of surgery. Schwer et al demonstrated a survival advantage of PRT plus surgery versus surgery alone locally for advanced esophageal cancer patients (n = 1033) with respect to median OS (27 months vs 18 months) and 3-year survival rate (43% vs 30%).[20]

Based on our retrospective analysis of a large population, we attempted to answer the clinical question of whether PRT prolongs survival time for patients with stage II / III ESCC under the condition that patients received chemoradiation therapy. Although our study was retrospective, and bias was inevitable, and we tried to minimize this bias through a large data analysis. Among patients with stage T2–T4, we found that PRT could lead to an obvious improvement of survival time compared with chemotherapy plus surgery only. For patients with T1 disease who did not receive PRT, however, no statistical differences were detected in DSS of those with or without PRT.

In addition, we found that a survival advantage for patients with stage T2 as compared with patients with T1 disease in the subgroup stratified by different N stages ($P = .003$). That was largely because of patients with stage II / III and T1 accompanying with lymph node metastasis, and the lymph node metastasis rate of patients with stages T1 and T2 were 100% and 49.26%, respectively. This might suggest that patients with stage II / III ESCC, when presenting with lymph node metastasis at T1 stage, were associated with more aggressive and higher metastatic potential, which might contribute to a poor prognosis. This may also be the reason why no survival difference was observed between T1 stage patients with or without PRT.

Overall, PRT has become a hot spot in the field of locally advanced ESCC treatment.[21] After ESCC patients experienced surgical resection and reconstructed the digestive tract, most of postoperative patients with ESCC have a poor physical status and severe nutritional status. Preoperative neoadjuvant therapy is considerably easier to tolerate than postoperative adjuvant therapy. This difference has distinct advantages such as reduction of the lesion, decreasing difficulty in the surgery, improvement of the R0 resection rate and eradication of micro-metastatic foci. Moreover, the radio-sensitivity of tumor cells is related to the blood supply and oxygen content of the tumor. Chemo-radiotherapy sensitivity may permit superior efficacy, in the case of rich blood supply and enough oxygen supply before operation. In addition, it is noteworthy that evaluation of the sensitivity to radiotherapy and chemotherapy can be done in the presence of solid tumors.

Based on SEER database, this study was a retrospective analysis, and lacked systematic and prospective data. However, the large sample size in our study reduced the potential for confounding. The results of this study have several practical implications.

5. Conclusions

Our study provided more evidence for the application of PRT in patients with stage II and III ESCC based on a population-based cohort. PRT was associated with survival benefit in patients with ESCC at the T2–T4 stage, but not in patients with T1 stage.

Table 2

Univariate analysis of clinical features affecting prognosis of ESCC patients with T stage.

	T1 (n = 107)			T2 (n = 203)			T3 (n = 696)			T4 (n = 154)			All Patients (n = 1160)		
Parameters	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Treatment															
CT		Ref			Ref			Ref			Ref			Ref	
CT + PRT	0.726	0.370–1.422	.351	0.402	0.234–0.692	.001	0.537	0.418–0.689	<.001	0.295	0.120–0.725	.008	0.467	0.380–0.574	<.001
Age at diagnosis															
<60 y		Ref			Ref			Ref			Ref			Ref	
≥60 y	0.491	0.301–0.802	.004	1.134	0.689–1.867	.621	0.929	0.749–1.153	.506	1.000	0.683–1.463	.998	0.867	0.736–1.022	.089
Sex															
Female		Ref			Ref			Ref			Ref			Ref	
Male	1.582	0.920–2.72	.097	1.346	0.878–2.063	0.172	1.477	1.183–1.844	<.001	1.459	0.958–2.223	.079	1.512	1.277–1.790	<.001
Race															
Black		Ref			Ref			Ref			Ref			Ref	
White	0.531	0.237–1.190	.124	0.995	0.413–2.400	0.991	1.102	0.777–1.561	.587	0.78	0.412–1.474	.444	0.949	0.725–1.244	.706
Other	0.623	0.370–1.050	.076	1.069	0.626–1.827	0.807	0.755	0.589–0.967	.026	0.886	0.586–1.34	.567	0.757	0.630–0.909	.003
Year of diagnosis															
2010		Ref			Ref			Ref			Ref			Ref	
2011	1.915	0.910–4.031	.087	1.286	0.647–2.554	0.473	1.105	0.774–1.578	.582	1.103	0.583–2.088	.762	1.162	0.894–1.511	.262
2012	0.917	0.442–1.904	.816	0.714	0.331–1.543	0.392	1.008	0.703–1.446	.964	0.564	0.290–1.097	.091	0.876	0.668–1.149	.338
2013	1.119	0.497–2.517	.786	0.953	0.459–1.978	0.896	1.163	0.833–1.625	.375	0.858	0.474–1.552	.613	1.073	0.831–1.384	.589
2014	1.325	0.584–3.005	.501	1.316	0.636–2.725	0.459	1.013	0.701–1.463	.946	0.907	0.475–1.73	.766	1.044	0.794–1.373	.756
2015	0.750	0.265–2.119	.587	0.606	0.212–1.731	0.350	1.260	0.863–1.839	.231	0.536	0.240–1.195	.127	0.961	0.709–1.305	.800
Pathologic grade*															
I/II		Ref			Ref			Ref			Ref			Ref	
III/IV	1.404	0.863–2.283	.172	1.224	0.792–1.891	0.363	1.117	0.908–1.373	.296	0.944	0.643–1.386	.770	1.133	0.967–1.327	.122
Primary tumor site															
Upper Third of Esophagus		Ref			Ref			Ref			Ref			Ref	
Middle Third of Esophagus	0.944	0.547–1.626	.834	0.888	0.564–1.398	0.609	1.203	0.961–1.505	.106	1.002	0.623–1.611	.993	1.097	0.920–1.306	.302
Lower Third of Esophagus	0.883	0.441–1.768	.726	1.002	0.517–1.943	0.995	0.911	0.67–1.239	.552	1.485	0.925–2.382	.101	1.132	0.908–1.41	.271
N stage															
N0	–	–	–		Ref			Ref			Ref			Ref	
N1		Ref		1.463	0.933–2.295	0.097	1.470	1.152–1.875	.002	1.184	0.780–1.798	.428	1.490	1.240–1.791	<.001
N2 + N3	1.251	0.694–2.257	.456	2.810	1.461–5.402	0.002	1.895	1.407–2.554	<.001	1.045	0.593–1.841	.880	1.897	1.503–2.395	<.001

* Pathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated.

Table 3

Multivariate analysis of clinical features affecting prognosis of ESCC patients with T stage.

	T1 (n = 107)			T2 (n = 203)			T3 (n = 696)			T4 (n = 154)			All Patients (n = 1160)		
Parameters	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Treatment															
CT		Ref			Ref			Ref			Ref			Ref	
CT + PRT	0.556	0.262–1.179	.126	0.364	0.202–0.658	<.001	0.536	0.413–0.695	<.001	0.318	0.125–0.805	.016	0.475	0.384–0.587	<.001
Age at diagnosis															
<60 y		Ref			Ref			Ref			Ref			Ref	
≥60 y	0.424	0.231–0.779	.006	1.072	0.616–1.865	.806	0.845	0.676–1.058	.142	1.117	0.746–1.672	.592	0.844	0.713–0.999	.049
Sex															
Female		Ref			Ref			Ref			Ref			Ref	
Male	1.767	0.932–3.352	.081	1.244	0.799–1.938	.334	1.450	1.155–1.821	.001	1.340	0.856–2.097	.201	1.492	1.258–1.770	<.001
Race															
Black		Ref			Ref			Ref			Ref			Ref	
White	0.968	0.395–2.374	.943	0.998	0.383–2.603	.997	0.941	0.659–1.343	.736	0.810	0.410–1.601	.545	0.876	0.667–1.152	.345
Other	0.898	0.501–1.609	.717	1.245	0.686–2.260	.471	0.790	0.612–1.019	.069	0.851	0.544–1.331	.479	0.817	0.677–0.985	.034
Year of diagnosis															
2010		Ref			Ref			Ref			Ref			Ref	
2011	1.938	0.843–4.457	.119	1.111	0.536–2.303	.778	1.152	0.803–1.654	.441	1.363	0.687–2.703	.376	1.200	0.921–1.564	.177
2012	0.817	0.346–1.929	.645	0.810	0.372–1.764	.596	1.002	0.696–1.442	.991	0.767	0.378–1.558	.463	0.935	0.711–1.228	.627
2013	1.579	0.644–3.867	.318	0.897	0.418–1.926	.780	1.130	0.806–1.582	.479	1.010	0.543–1.878	.975	1.096	0.849–1.415	.483
2014	1.676	0.705–3.983	.242	1.256	0.592–2.663	.552	1.006	0.693–1.460	.975	1.118	0.557–2.242	.754	1.065	0.808–1.403	.655
2015	1.038	0.347–3.106	.946	0.720	0.247–2.104	.548	1.229	0.832–1.815	.300	0.624	0.271–1.433	.266	0.993	0.729–1.352	.963
Pathologic grade*															
I/II		Ref			Ref			Ref			Ref			Ref	
III/IV	1.599	0.921–2.776	.096	1.050	0.646–1.706	.845	1.130	0.912–1.400	.265	0.871	0.571–1.328	.521	1.124	0.957–1.320	.154
Primary tumor site															
Upper Third of Esophagus		Ref			Ref			Ref			Ref			Ref	
Middle Third of Esophagus	0.912	0.506–1.643	.759	0.957	0.586–1.565	.862	1.177	0.937–1.478	.161	0.906	0.545–1.506	.704	1.081	0.906–1.291	.386
Lower Third of Esophagus	0.953	0.425–2.135	.906	0.786	0.386–1.603	.508	0.823	0.597–1.134	.233	1.346	0.816–2.220	.245	0.989	0.789–1.241	.926
N stage															
N0	–	–	–		Ref			Ref			Ref			Ref	
N1		Ref		1.691	1.065–2.685	.026	1.573	1.228–2.015	<.001	1.251	0.813–1.924	.308	1.570	1.305–1.890	<.001
N2 + N3	1.044	0.525–2.075	.903	3.318	1.615–6.817	.001	1.723	1.267–2.343	<.001	0.966	0.540–1.727	.906	1.795	1.418–2.272	<.001

* Pathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated.

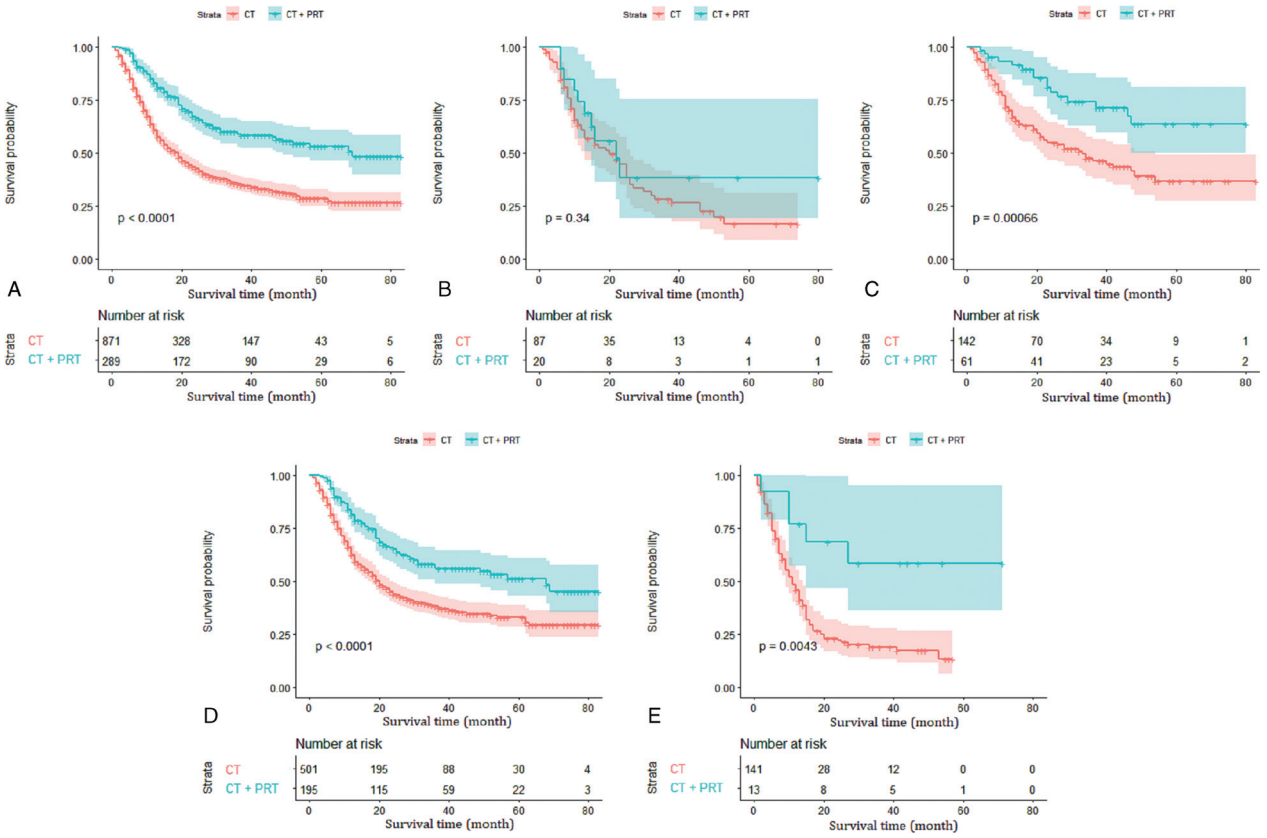

Figure 2. Disease specific survival curves of patients with stage II / III ESCC compared according to treated with CT versus CT + PRT. (A) All patients;(B) Patients with T1 stage;(C) Patients with T2 stage;(D) Patients with T3 stage;(E) Patients with T4 stage. The shaded regions represent 95% CI. CI = credibility interval, CT = chemotherapy, ESCC = esophageal squamous cell carcinoma, PRT = preoperative radiotherapy.

Table 4

Univariate analysis of clinical features affecting prognosis of ESCC patients with N stage.

	N0 (n = 382)			N1 (n = 594)			N2 + N3 (n = 184)			All patients (n = 1160)		
Parameters	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Treatment												
CT		Ref			Ref			Ref			Ref	
CT + PRT	0.425	0.281–0.641	<.001	0.470	0.359–0.615	<.001	0.564	0.336–0.946	.030	0.467	0.380–0.574	<.001
Age at diagnosis												
<60 y		Ref			Ref			Ref			Ref	
≥60 y	0.945	0.683–1.307	.733	1.155	0.923–1.446	.209	0.847	0.589–1.217	.368	0.867	0.736–1.022	.089
Sex												
Female		Ref			Ref			Ref			Ref	
Male	1.418	1.025–1.961	.035	1.446	1.156–1.809	.001	1.995	1.292–3.082	.002	1.512	1.277–1.790	<.001
Race												
Black		Ref			Ref			Ref			Ref	
White	1.009	0.570–1.785	.976	0.859	0.594–1.240	.416	0.824	0.466–1.458	.507	0.949	0.725–1.244	.706
Other	0.809	0.571–1.145	.231	0.716	0.558–0.918	.008	0.732	0.475–1.127	.156	0.757	0.630–0.909	.003
Year of diagnosis												
2010		Ref			Ref			Ref			Ref	
2011	0.853	0.523–1.393	.525	1.408	0.995–1.993	.053	1.581	0.750–3.333	.228	1.162	0.894–1.511	.262
2012	0.672	0.398–1.134	.137	0.898	0.630–1.282	.554	1.443	0.681–3.056	.338	0.876	0.668–1.149	.338
2013	1.060	0.650–1.728	.817	0.987	0.708–1.376	.937	1.492	0.725–3.069	.277	1.073	0.831–1.384	.589
2014	1.117	0.685–1.822	.658	0.882	0.597–1.303	.527	1.653	0.808–3.384	.169	1.044	0.794–1.373	.756
2015	0.801	0.430–1.492	.484	0.806	0.521–1.248	.334	1.703	0.823–3.524	.152	0.961	0.709–1.305	.800
Pathologic grade*												
I/II		Ref			Ref			Ref			Ref	
III/IV	0.961	0.703–1.315	.806	1.296	1.046–1.605	.018	0.887	0.618–1.273	.515	1.133	0.967–1.327	.122
Primary tumor site												
Upper Third of Esophagus		Ref			Ref			Ref			Ref	
Middle Third of Esophagus	0.914	0.649–1.289	.609	1.253	0.990–1.585	.061	1.106	0.734–1.668	.630	1.097	0.920–1.306	.302
Lower Third of Esophagus	1.176	0.785–1.763	.432	1.066	0.773–1.469	.697	1.267	0.794–2.023	.321	1.132	0.908–1.410	.271
T stage												
T1	–	–	–		Ref			Ref			Ref	
T2		Ref		0.648	0.429–0.978	.039	0.965	0.446–2.091	.929	0.549	0.400–0.754	<.001
T3	1.298	0.889–1.894	.177	0.845	0.625–1.143	.274	0.879	0.497–1.555	.659	0.751	0.580–0.973	.030
T4	3.114	1.964–4.938	<.001	1.664	1.146–2.416	.007	1.160	0.575–2.341	.678	1.462	1.081–1.977	.014

* Pathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated.

Table 5

Multivariate analysis of clinical features affecting prognosis of ESCC patients with N stage.

Parameters	N0 (n = 382)			N1 (n = 594)			N2 + N3 (n = 184)			All patients (n = 1160)		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Treatment												
CT		Ref			Ref			Ref			Ref	
CT + PRT	0.461	0.298–0.712	<.001	0.502	1.991–0.380	<.001	0.506	0.277–0.926	.027	0.501	0.405–0.620	<.001
Age at diagnosis												
<60 y		Ref			Ref			Ref			Ref	
≥60 y	0.947	0.667–1.345	.762	1.162	0.861–0.921	.206	0.751	0.492–1.147	.185	0.862	0.727–1.021	.086
Sex												
Female		Ref			Ref			Ref			Ref	
Male	1.217	0.871–1.702	.251	1.399	0.715–1.112	.004	2.087	1.241–3.512	.006	1.430	1.206–1.696	<.001
Race												
Black		Ref			Ref			Ref			Ref	
White	1.067	0.587–1.940	.831	0.838	1.193–0.578	.353	0.683	0.339–1.375	.285	0.951	0.724–1.250	.720
Other	0.997	0.684–1.454	.987	0.788	1.268–0.610	.070	0.609	0.353–1.051	.075	0.863	0.715–1.042	.126
Year of diagnosis												
2010		Ref			Ref			Ref			Ref	
2011	0.898	0.542–1.489	.677	1.289	0.776–0.905	.159	1.368	0.568–3.292	.485	1.223	0.939–1.595	.136
2012	0.737	0.427–1.274	.275	0.862	1.160–0.602	.418	1.460	0.638–3.342	.371	0.932	0.709–1.226	.616
2013	1.000	0.611–1.637	.999	1.013	0.987–0.723	.940	2.010	0.886–4.562	.095	1.124	0.870–1.453	.371
2014	1.226	0.744–2.020	.425	0.881	1.135–0.593	.531	1.573	0.698–3.544	.275	1.097	0.833–1.444	.511
2015	0.831	0.441–1.565	.566	0.872	1.147–0.561	.543	1.586	0.663–3.795	.300	1.026	0.755–1.395	.869
Pathologic grade*												
I/II		Ref			Ref			Ref			Ref	
III/IV	0.858	0.621–1.186	.353	1.376	0.727–1.105	.004	0.704	0.444–1.116	.136	1.130	0.963–1.327	.134
Primary tumor site												
Upper Third of Esophagus		Ref			Ref			Ref			Ref	
Middle Third of Esophagus	0.892	0.625–1.271	.526	1.165	0.859–0.914	.219	1.092	0.659–1.811	.732	1.061	0.889–1.266	.513
Lower Third of Esophagus	0.924	0.603–1.418	.719	0.919	1.088–0.658	.620	1.390	0.783–2.465	.261	0.924	0.737–1.158	.492
T stage												
T1	–	–	–		Ref			Ref			Ref	
T2		Ref		0.754	1.327–0.495	.188	1.013	0.395–2.601	.979	0.611	0.443–0.842	.003
T3	1.277	0.867–1.881	.217	0.987	1.014–0.722	.933	1.149	0.551–2.394	.711	0.808	0.622–1.050	.111
T4	2.789	1.730–4.497	<.001	1.679	0.596–1.148	.008	0.991	0.391–2.516	.985	1.383	1.019–1.877	.038

* Pathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated.

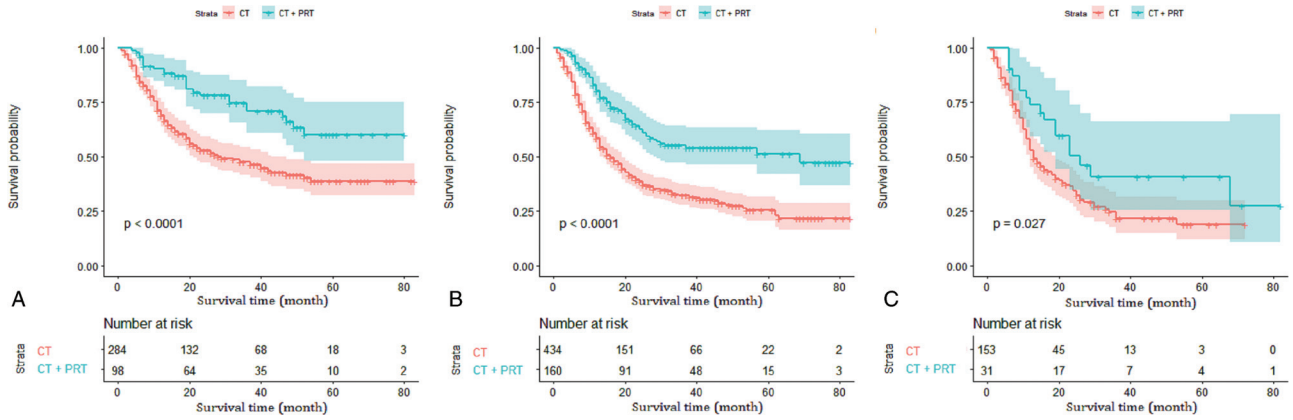

Figure 3. Disease specific survival curves of patients with stage II / III ESCC compared according to treated with CT versus CT + PRT. (A) Patients with N0 stage;(B) Patients with N1 stage;(C) Patients with N2 + N3 stages. The shaded regions represent 95% CI. CI = credibility interval, CT = chemotherapy, ESCC = esophageal squamous cell carcinoma, PRT = preoperative radiotherapy.

However, further prospective trials are needed to confirm our findings.

Author contributions

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Writing – review & editing: Shuchai Zhu.

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