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Postoperative chemoradiotherapy improves survival in esophageal squamous cell cancer with extracapsular lymph node extension

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In esophageal squamous cell carcinoma (ESCC), extracapsular extention (ECE) in metastatic lymph nodes portends high rate of recurrence and poor prognosis. To our knowledge, the effectiveness of postoperative chemoradiotherapy (CRT) in these patients has never been investigated. In this retrospective study, we compared the outcomes of surgery with or without postoperative chemoradiotherapy in ESCC patients with ECE. From 2008 to 2009, 90 ECSS patients with ECE were included. Among those patients, 47 only received curative surgery alone, and 43 received additional postoperative concurrent CRT which consisted of radiotherapy (median dose 50 Gy) and chemotherapy (5-fluorouracil 1000 mg/m^2, days 1-4 and 29-32; cisplatinum 25 mg/m^2, days 1-3 and 29-31). Patients treated with postoperative CRT had significantly more T3/4 tumors (p=0.023). Based on log-rank stratified by T stage, postoperative adjuvant CRT significantly improved the overall survival (p=0.017) and progression free survival (p=0.002). In multivariate analysis, adjuvant CRT was identified as an independent prognostic factor (HR=0.494, CI 0.290-0.844, p=0.010). Compared with surgery alone, the CRT group had significantly fewer cases of regional recurrence (P=0.048) and overall recurrence (P=0.024). However, there was no significant difference in distant metastasis between two groups (P=0.755). In conclusion, our data suggest that the postoperative adjuvant CRT might be beneficial in selected subgroups of ESCC patients with ECE. To further verify these results, a prospective trial with a large sample size is needed.

Key words: esophageal squamous cell cancer, adjuvant treatment, chemoradiotherapy, extracapsular extension

Esophageal cancer is an aggressive malignancy with a poor prognosis. It is the eighth most common malignant tumor and sixth most common cause of cancer deaths worldwide [1]. In China, the majority of cases are esophageal squamous cell carcinoma (ESCC) [2]. Surgery may be the initial treatment; however, patients with stages beyond T1b should undergo multidisciplinary evaluation and be considered for multimodality therapy. Surgery alone to treat esophageal cancer results in high rates of locoregional recurrence and distant metastasis [3]. Therefore, multimodal therapy that includes radiotherapy (RT), chemotherapy (CT), and surgery has been increasingly used in the treatment of esophageal cancer. Adjuvant RT has been evaluated in several randomized controlled trials [4-8]. Disappointingly, most of them failed in improvement of OS with the addition of RT to surgery. The high rate of recurrence and poor prognosis still make us believe that some high-risk subgroups of patients with ESCC may benefit from adjuvant therapy.

It is well known that extracapsular extention (ECE) of metastatic lymph nodes is associated with a poor prognosis in multiple tumor types, such as head and neck squamous cell carcinoma (HNSCC) and gastrointestinal malignancies [9-11]. Moreover, ECE in HNSCC is not only a prognostic factor, but also an adjuvant therapy determinant, because adjuvant chemoradiotherapy (CRT) has been demonstrated to improve locoregional control and survival of HNSCC patient with ECE in several multicenter randomized studies [12]. The role of ECE as a prognostic factor has also been well established in ESCC [13-16]. However, unlike the ECE positive HNSCC which has a higher local recurrence rate than the ECE negative ones, the recurrence pattern of ESCC patients with ECE is still controversial. Some studies [13,15] reported that ECE in ESCC

patients was an indicator of distant organ recurrence, whereas others [14] found local and distant recurrence rates were equally high. All in all, in ECE positive ESCC local recurrence is no longer the sole focus of attention, as the distant recurrence is also important. The CRT which combined RT and CT may play a role in both local and systematic disease and seems to be a good treatment option for the ESCC patients with ECE. For these reasons, we infer that adjuvant CRT may reduce recurrence and improve the survival in patients with ECE positive ESCC. To our knowledge, no previous studies have investigated the effect of adjuvant treatment on the ECE positive ESCC so far. In this retrospective study, we investigate the therapeutic impact of adjuvant CRT in ESCC patients with ECE.

Patients and methods

Patients. The eligibility criteria were as follows: (1) patients had histologically proven ESCC with at least one ECE positive lymph node; (2) patients had received transthoracic esophagectomy with extensive lymphadenectomy, using either two-field or three-field approach and achieved R0 status; (3) at least 15 lymph nodes had been removed; (4) patients had not received preoperative cancer therapy; (5) karnofsky performance status was ≥70. (6) patients had received curative surgery alone or surgery plus adjuvant CRT.

Surgery. Three different procedures were used. For patients with tumors in the upper third of the thoracic segment, a standard esophagectomy was performed by a three-phase abdominothoracic McKeown method, and three-field (thoracoabdominal and cervical) lymph node dissection was also performed if indicated. For tumors in the mid and lower third, Ivor-Lewis or left thoracoabdominal esophagectomy techniques were employed and two-field (thoracoabdominal) lymph node dissection was performed. In each case, lymph nodes were removed as completely as possible.

Postoperative adjuvant chemoradiotherapy. Radiation therapy started 3 to 6 weeks after surgery. Treatment was delivered on linear accelerators using 6-15 MV photon beams. Either a two-dimensional (2D) or a conformal three-dimensional treatment (3D) planning was used for delivery of therapy based on the preference of the radiation oncologist. The field borders were defined based on pretreatment investigations and imaging, correlated with the patient's postoperative anatomy. The RT field included a minimum 5-cm margin from the superior and inferior margins of the tumor bed and a width of 6–8 cm. For tumors in the upper third of thoracic esophagus, supraclavicular fossae was included in the field, while the celiac lymph nodes were included for lower thoracic tumors. The total dose was 45-54 Gy (median dose 50 Gy) in 20-25 fractions within 5 weeks. In 2D, radiation was given through anteroposterior fields first at 40 Gy (1.8-2 Gy per fraction), followed by parallel opposing oblique fields at 5-14 Gy to avoid the spinal cord. For 3D planning total spinal cord radiation dose was limited to 4500 cGy and the double lung V20 dose was <30%.

In the same period during RT, two cycles of CT were performed. The CT regimen comprised protracted 5-fluorouracil infusion (1000 mg/m^2, days 1-4 and 29-32) and a 2-hour infusion of cisplatinum (25 mg/m^2, days 1-3 and 29-31). A prophylactic antiemetic was given during CT, and supportive care and symptomatic treatment were provided as well.

Follow-Up. Patients were routinely evaluated for tumor control every 3-4 months for the first year, every 6 months for the next 2 years, and then annually thereafter. Procedures included a careful clinical examination, routine blood tests, barium swallow, thoracic computer tomography (CT), and abdominal ultrasound. Further evaluations were carried out only if clinical findings suggested a progression of the disease.

Outcome. The primary endpoint was overall survival (OS), defined as the time from the date of surgery to the date of death for any cause or the last known date that the patient was alive. Progression free survival (PFS) was the secondary endpoint which was defined as time from the date of diagnosis until the earliest date of locoregional recurrence, distant metastasis, death from any cause, or the date of last follow-up. The pattern of recurrence was also recorded. Recurrence was classified as local recurrence, regional lymph node recurrence, or distant recurrence. Because of the manner of tumor spread through the lymphatic system, cervical, celiac axis and paraaortic node metastases were classified as lymph node recurrence in this study. Treatment-related toxicities were assessed according to version Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (1992) criteria [17].

Statistical methods. Categorical variables were expressed as numbers and percentages and quantitative variables as the mean or median with interquartile range. The differences in clinical factors between groups were assessed by X^2 test or Fisher's exact test. The Kaplan–Meier method was applied for outcome analysis of OS and PFS. Statistical significance was tested by stratified log-rank test. Cox regression was used to identify the independent predictors of outcome. Two-sided p values <0.05 were considered statistically significant. The statistical analyses were performed using SPSS (version 16.0 for Windows).

Results

Characteristics of patients. From 2008 to 2009, a total of 90 patients from two centers met the eligibility criteria. Of them, 47 (52.2%) received curative surgery alone and 43 (47.8%) received adjuvant CRT after surgery. Characteristics of the patients were summarized in table 1. There was no difference in the baseline characteristics between the surgery and adjuvant treatment groups except T stage. The number of patients with the T4 stage was larger in the adjuvant treatment group (P=0.023).

Survival. The median follow-up time was 26.5 months, ranging from 6.5 to 70 months. For the entire cohort of patients, the overall survival rates at 1, 3, and 5 years were

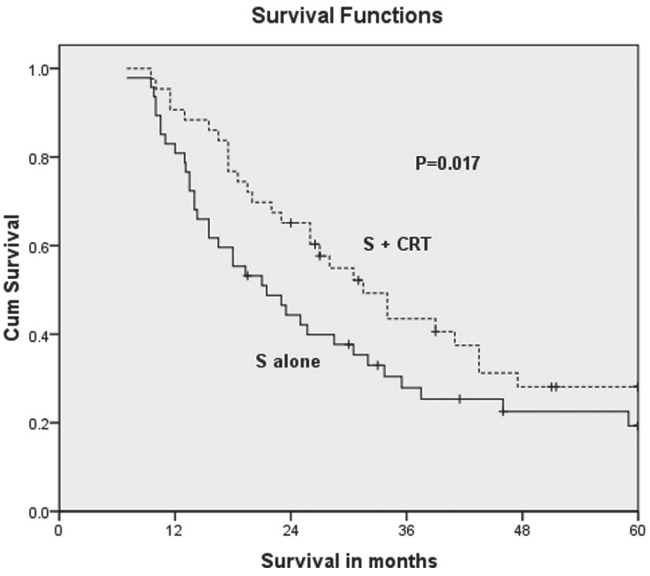

Figure 1. Overall survival of patients with extracapsular extension positive esophageal squamous cell carcinoma received either surgery plus postoperative chemoradiotherpay(CRT) or surgery (S) alone.

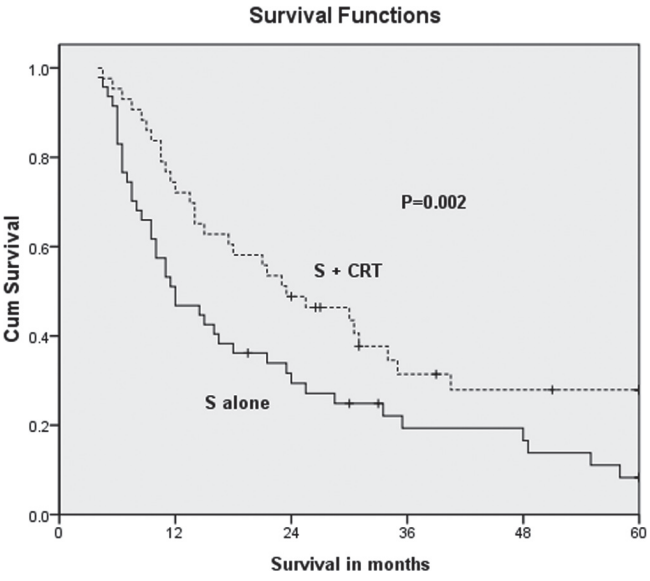

Figure 2. Progression free survival of patients with extracapsular extension positive esophageal squamous cell carcinoma received either surgery plus postoperative chemoradiotherpay (CRT) or surgery (S) alone.

Table 1. Characteristics of patients in each group

Characteristic	No. of patients (%)		X^2	*P* value
	Surgery Only	Surgery + CRT		
Sex			0.045	0.833
Male	38(80.9.0)	34(79.1)		
Female	9(19.1)	9(20.9)		
Age			1.683	0.195
<60	22(46.8)	26(60.5)		
≥60	25(53.2)	17(39.5)		
Primary tumor stage			7.504	0.023
T1,2	12(25.5)	3(7.0)		
T3	30(63.8)	29(67.4)		
T4	5(10.6)	11(25.6)		
Nodal stage			0.124	0.940
N1	18(38.3)	15(34.9)		
N2	18(38.3)	17(39.5)		
N3	11(23.4)	11(25.6)		
Disease stage			5.828	0.120
IIB	9(19.1)	2(4.7)		
IIIA	10(21.3)	13(30.2)		
IIIB	15(31.9)	11(25.6)		
IIIC	13(27.7)	17(30.5)		
Tumor location			1.468	0.226
Upper, middle	27(57.4)	30(69.8)		
Lower	20(42.6)	13(30.2)		
Differentiation			0.551	0.458
Well, moderate	34(72.3)	34(79.1)		
Poor	13(27.7)	9(20.9)		

Abbreviations: CRT, chemoradiotherapy.

85.6%, 35.4%, and 23.4%, respectively. Median survival time was 26.0 months. The overall survival curves for patients treated with surgery alone or combined modality are shown in Figure 1. 5-year survival rates were 19.3% for the surgery only group and 28.1% for the surgery plus postoperative CRT group. Postoperative CRT showed a statistically significant better overall survival (p=0.017, log-rank test stratified by T stage). The 1-year, 3-year and 5-year PFS rates were 58.9%, 25.1% and 17.0% for the whole group, and the median PFS was 16.5 months. The 5-year PFS rate was 27.9% in the combined modality group, while in the surgery alone group, the 5-year PFS rate was 8.3%. CRT provided more benefit in PFS compared to surgery alone (p=0.002, log-rank test stratified by T stage).

Univariate and multivariate analyses factors. The clinical characteristics of patients were evaluated to determine the prognostic value in terms of OS (Table 2). Univariate analysis showed that overall survival was significantly associated with N stage (p<0.001), differentiation (p=0.011), and adjuvant CRT (p=0.017). In multivariate analysis, T stage (p=0.024), N stage (p=0.001), and adjuvant CRT (p=0.010) were identified as independent prognostic factors.

Patterns of failure. In the surgery alone group, progression in regional lymph nodes was observed in 25 (53.2%) patients, distant relapse was observed in 19 (40.4%) patients, and both occurred in 4 (8.5%) patients; however, in the surgery plus postoperative CRT group, 14 (32.6%) patients had progression in regional lymph nodes, and 16 (38.9%) patients had progression at distant sites. Compared with surgery alone group, the surgery plus CRT group had significantly decreased the number of cases in regional recurrence (P=0.048) and overall

Table 2. Univariate analysis of the prognostic factors for overall survival

Characteristic	Univariate analysis				
	3-y survival rate (%)	5-y survival rate (%)	MST (moth)	X^2	*P* value
Sex				0.349	0.555
Male	35.7	22.3	25.7		
Female	34.0	27.2	33.7		
Age				0.000	0.986
<60	35.6	21.6	27.0		
≥60	35.1	24.6	25.7		
T stage				3.987	0.136
T1,2	58.7	44.0	59.0		
T3	32.9	20.7	23.5		
T4	22.5	15.0	26.0		
Nodal stage				16.482	<0.001
N1	41.9	33.9	33.7		
N2	40.2	24.1	28.5		
N3	8.3	8.3	17.5		
Differentiation				6.432	0.011
Well+ moderate	41.9	30.0	30.5		
Poor	15.6	5.2	17.5		
Treatment				5.682	0.017
Surgery only	27.9	19.3	21.5		
Surgery+ CRT	43.5	28.1	31.5		

Abbreviation: MST, Median survival time; CRT, chemoradiotherapy.

recurrence (*P*=0.024) (Table 3). However, there was no difference in distant metastasis between two groups (*P*=0.755).

Toxicities. Toxicities related to postoperative CRT are summarized in Table 5. Acute toxicities were common but manageable. There were 8 (18.6%) patients suffered from grade 3-4 hematological toxicities and 1 (2.3%) suffered a grade 4 esophagitis which developed an esophagus fistula. No patients developed grade 3 or worse late toxicities. Four (9.3%) patients developed mild pulmonary fibrosis, 2 (4.7%) suffered grade 1 cardiac toxicities and 1 (2.3%) had grade 2 esophageal stenosis. There were no toxic deaths.

Discussion

In present study, we first investigated the impact of post-operative CRT in ESCC patients with nodal ECE. Our results showed that postoperative adjuvant CRT significantly reduced local recurrence rates, improved the OS and PFS of the ESCC patients with ECE. Multivariate analysis demonstrated that T stage, N stage, and adjuvant CRT were independent prognostic factors. Regarding the safety, we found the concurrent CRT was well tolerated with rare unmanageable toxicities.

Five randomized controlled trials (RCT) [4-8] have evaluated the role of postoperative radiotherapy after surgery compared with surgery alone. Disappointingly, most of them

Table 3. Multivariate analysis of the prognostic factors for overall survival

Characteristic	HR	95%CI	*P* value
Sex			
Male	1		
Female	0.719	0.373-1.383	0.323
Age			
<60	1		
≥60	1.070	0.639-1.792	0.796
Primary tumor stage			
T1,2	1		
T3	2.793	1.195-6.526	0.018
T4	3.078	1.163-8.147	0.024
Nodal stage			
N1	1		
N2	1.075	0.569-2.032	0.824
N3	3.014	1.553-5.846	0.001
Differentiation			
Well, moderate	1		
Poor	1.610	0.913-2.840	0.100
Treatment			
Surgery only	1		
Surgery+CRT	0.494	0.290-0.844	0.010

Abbreviation: CRT, chemoradiotherapy.

Table 4. Sites of treatment failure

Site of recurrence	Patients (%)		X^2	P values
	Surgery Only (n=47)	Surgery + CRT (n=43)		
Regional lymph nodes	25(53.2%)	14(32.6%)	3.893	0.048
Cervical region	6(12.8%)	3(7.0%)		
Mediastinal region	13(27.7%)	8(18.6%)		
Celiac region	9(19.1%)	4(9.3%)		
Tumor bed	1(2.1%)	0(0%)	-	1.000*
Distant site	19(40.4%)	16(38.9%)	0.098	0.755
Mixed	4(8.5%)	1(2.3%)	-	0.363*
Overall	41(87.2%)	29(67.4%)	5.089	0.024

Abbreviations: CRT, chemoradiotherapy; * Fisher's exact test

Table 5. Toxicity reaction of chemoradiothapy

Toxicity	Patients (n=43)	%
Acute toxicities		
Hematological	38	88.4
Grade 1-2	30	69.8
Grade 3-4	8	18.6
Esophagus	27	62.8
Grade 1-2	26	60.5
Grade 4	1	2.3
Gastrointestinal		
Grade 1-2	26	60.5
Late toxicities		
Cardiac		
Grade 1	2	4.7
Pulmonary		
Grade1-2	4	9.3
Esophagus		
Grade 2	1	2.3

failed to demonstrate any improvement in OS with the addition of RT to surgery. A study from France [5] reported that post RT did not provide any survival benefits to ESCC patients regardless of lymph node status. In our study, the total radiation dose was 45-54 Gy (median dose 50 Gy) in 20-25 fractions within 5 weeks. Teniere et al. employed a similar schedule using 5 fractions per week and 1.8 Gy per fraction to total doses of 45-55 Gy. It is appeared that the differences in outcomes between our study and that of Teniere et al. were not due to the radiation dose and frequency. We noticed that Teniere et al. included patients with positive celiac nodes (stage M1a, AJCC 2002). These patients represent a cohort at much higher risk for distant failure and therefore are less likely to benefit from adjuvant RT alone. However, the adjuvant treatment strategy in our study was CRT, rather than RT. The addition of CT to RT may not only have a radiosensitizing effect, but also play a role in systemic cancer progression. So, we speculate that different adjuvant treatment modalities may contribute to the different results and the combined modality therapy with radiotherapy and chemotherapy may be superior to radiotherapy alone. To our knowledge, the efficacy of adjuvant CRT has not been compared with surgery alone in a randomized trial in patients with ESCC. The positive result from our study supported the use of postoperative CRT in ESCC with ECE.

A RCT from China [7], Xiao and colleagues also found no survival benefit for the entire cohort with the addition of adjuvant RT. When stratifying based on stage, however, there was a significant survival benefit with adjuvant RT for stage III patients. In a series of retrospective studies, Chen and colleagues [18,19] analyzed some clinical data of a large sample of patients with ESCC, and reported that postoperative RT was associated with better survival for patients with node-positive ESCC. In further analysis, they found the main beneficiaries of postoperative RT were the patients with three or more positive nodes. In summary, the majority of the available evidence currently reveals that only selected locally advanced esophageal SCC are likely to benefit from adjuvant treatment. It should be noted that the ECE status was not investigated in all the studies. Our results suggested that ECE status was a new indicator for the post CRT of ESCC patients.

Sakai M et al [13] and Baba et al. [15] reported that the 5-year OS of the ESCC patients with ECE was 17.9% and 14%, respectively. In our study, the 5-year OS is 19.3% in the surgery only group, which was similar to those studies. Encouragingly, the use of postoperative CRT provided a significant improvement in OS compared with surgery alone and the absolute improvement in overall survival was 8.8% at 5 years. In the analysis of recurrence pattern, we found the loco-regional recurrence rate was significantly lower in patients received CRT than those received surgery alone, but there were no significant differences in distant metastases between the two groups. It seems that the prolonged OS in the CRT arms still largely benefits from the reduction in local-regional recurrence. This suggests that chemotherapy may fail to eradicate micro-metastases. Further studies are needed to identify more effective chemotherapy program. In addition, two studies [20,21] reported that ECE status of esophageal cancer was an independent negative prognostic factor not influenced by neoadjuvant CRT. It is also indicated that patients with ECE may need more effective or intensified adjuvant treatment.

In the analysis of safety, we found the risk of Grade 3 or 4 adverse events was rare except for the hematological toxicity with a rate of 18.6%. However, hematological toxicity currently is a manageable adverse effect, especially with the use of granulocyte colony-stimulating factor [22]. So, CRT was well tolerated by patients.

There are several potential limitations in our study. Firstly, because this is a retrospective study, some bias may be unavoidable. In the analysis of baseline characteristics, we found the T stages between two groups were not balanced. To overcome

this issue, the log-rank test stratified by T stage was used to compare PFS and OS. Furthermore, a Cox proportional hazards model was used to identify significant factors. As a result, both of the statistical methods identified the CRT as an independent prognostic factor. The consistency of the results across statistical methods suggested that the result is robust. Secondly, in this study, most patients received 2D conventional treatment. Compared with 3D-RT, 2D-RT may reduce the therapeutic effect and increase the therapeutic side effects. The third limitation of our present study is the small sample size which may limit the power of the analysis and suggesting that the results should be interpreted with some caution.

In conclusion, for the ESCC patients with nodal ECE, postoperative adjuvant CRT significantly reduced local recurrence rates and improved the PFS and OS compared with surgery alone. To further verify these findings, a prospective trial with a large sample size is needed.

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