

## RESEARCH ARTICLE

# Surgical Treatment for Early Esophageal Squamous Cell Carcinoma

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### Abstract

More studies are needed to clarify treatments and prognosis of early esophageal squamous cell carcinoma (ESCC). This retrospective study was designed to review the outcome of surgical treatment for early ESCC, evaluate the results of a left thoracotomy for selected patients with early ESCC, and identify factors affecting lymph node metastases and survival. The clinicopathological data of 228 patients with early ESCC who underwent transthoracic esophagectomy with lymphadenectomy without preoperative adjuvant treatment were reviewed. The  $\chi^2$  test or Fisher's exact test were used to detect factors related to lymph node metastasis. Univariate and multivariate analyses were performed to identify prognostic factors. There were 152 males and 76 females with a median age of 55 years. Two hundred and eight patients underwent a left thoracotomy, and the remaining 20 patients with lymph nodes in the upper mediastinum more than 5 mm in short-axis diameter by computed tomography scan underwent a right thoracotomy. No lymph node metastasis was found in the 18 patients with carcinoma in situ, while lymph node metastases were detected in 1.6% (1/62) of patients with mucosal tumours and 18.2% (27/148) of patients with submucosal tumours. Only 7 patients showed upper mediastinal lymph node metastases in the follow-up. The 5- and 10-year overall survival rates were 81.4% and 70.1%, respectively. Only histologic grade ( $P<0.001$ ) and pT category ( $P=0.001$ ) significantly correlated with the presence of lymph node metastases. In multivariate analysis, only histologic grade ( $P=0.026$ ) and pT category ( $P=0.008$ ) were independent prognostic factors. A left thoracotomy is acceptable for selected patients with early ESCC. Histologic grade and pT category affected the presence of lymph node metastases and were independent prognostic factors for early ESCC.

**Keywords:** Esophageal squamous cell carcinoma - early cancer - surgery - prognosis

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### Introduction

Early esophageal cancer (EEC) was defined as tumor limited to the mucosa or submucosa and not extending into the muscular wall of the esophagus. This definition also included patients who had resection for high-grade dysplasia (HGD), now termed intraepithelial neoplasia (HGIEN) (Schlemper et al., 2000). The incidence of patients with EEC has been increasing because of recent advances in endoscopic examinations and awareness of the clinical importance of Barrett's esophagus (Ishikawa et al., 2005; Stein et al., 2005; Westerterp et al., 2005; Tachibana et al., 2006; Saha et al., 2009; Barbour et al., 2010; DeMeester, 2010). Radical esophagectomy with lymphadenectomy are still the mainstay of curative treatment for patients with EEC at many centers, especially for patients with submucosal diseases (Stein et al., 2005). However, surgery has been challenged due to high morbidity and mortality rates related to the procedure

and the low rate of lymph node metastases in EEC. Less invasive approach such as limited surgical resection, organ-preserving treatment and endoscopic therapy have been developed and applied in clinic (Stein et al., 2005; Westerterp et al., 2005; Tachibana et al., 2006; Saha et al., 2009; Barbour et al., 2010; Watanabe et al., 2010).

A left thoracotomy with 2-field lymphadenectomy is widely adopted in China for surgical treatment of esophageal cancer, but may be less practiced in the rest of the world. Although the common hepatic nodes, celiac nodes, and upper right mediastinal nodes were difficult to remove via this operative route, lower rate of complications was observed in this procedure than a right thoracotomy. The results for patients with EEC received left thoracotomies have not been well studied.

In the current study, we present data of 228 patients with early ESCC who underwent surgical resection with systematic lymphadenectomy from a single cancer center at Chaoshan area, where is the only coastal region with

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a high incidence of esophageal cancer in China. Most of the patients in this study received left thoracotomies, with some selected patients received right thoracotomies. We investigate the long-term survival in these patients and factors associated with the presence of lymph node metastases, and further analyze factors associated with long-term survival.

## Materials and Methods

This study was undertaken at the Cancer Hospital of Shantou University Medical College (CH-SUMC) and was approved by the Ethics Committee of that hospital. A total of 3,883 cases with esophageal carcinomas underwent surgical resection in the CH-SUMC between January 1995 and December 2011. Excluding patients after neoadjuvant radiotherapy or chemoradiotherapy, histopathologic workup of the specimens identified 238 patients with EEC (6.13%, 238/3883). We excluded ten patients with other histologic type (one case of leiomyosarcoma, one case of small cell carcinoma, three cases of basaloid squamous cell carcinoma, and five cases of carcinosarcoma) and studied the remaining 228 patients with early ESCC.

All patients were questioned about their medical history and underwent physical examinations. Chest radiograph, barium meal, contrast enhanced computed tomography scan of the chest, Doppler ultrasound examination of the abdomen, esophagoscopy biopsy, complete blood count, blood biochemistry analyses, and liver and renal function evaluations were also performed. Unless clinically indicated, brain magnetic resonance imaging and radioactive isotope bone scans were not performed.

### Surgical procedure

Via a left or right thoracotomy, a surgical resection of a transthoracic en bloc esophagectomy with an end-to-side esophagogastric anastomosis was performed. A right thoracotomy was only performed for patient with lymph nodes in the upper mediastinum more than 5 mm in short-axis diameter by computed tomography scan. Two hundred and eight patients (91.2%) underwent a left thoracotomy, and the remaining 20 patients underwent a right thoracotomy. The anastomosis was constructed in the neck through a separate cervical incision in 205 patients (90.0%), and the upper chest in 23 patients. In all patients, a standard abdominal lymphadenectomy (left and right paracardial regions, along the lesser curve and the left gastric artery) and mediastinal lymphadenectomy (subcarinal, left and right bronchial, lower posterior mediastinum, pulmonary ligament, para-esophageal and thoracic duct) was performed. For patients who underwent a right thoracotomy, the paratracheal, left and right recurrent laryngeal nerve lymph nodes were also dissected. Cervical lymphadenectomy was not systematically undertaken.

### Histopathology

All resection specimens, including the lymph nodes, were assessed by two expert pathologists (Dr. Mingyao Wu and Dr. Dongping Tian). Specimen analysis was

performed in a standardized fashion with prospective documentation of all assessed parameters. The width of specimen for the pathologic examination is 2mm. Classification of the depth of tumor infiltration was performed according to standard criteria into carcinoma in situ (pTis category), carcinoma limited to the mucosa (pT1a category), and carcinoma invading the submucosal layer but not beyond (pT1b category).

### Follow-up

Follow-up was performed through clinical examinations every 3 months for the first year, every 6 months for the second year and every 6 to 12 months thereafter. Follow-up was continued up to July 2012 or until death if this occurred earlier. The mean follow-up was 60.3 months (range, 1-209 months). Six patients were lost to follow-up (2.6%).

Locoregional recurrence was defined as recurrence at the anastomosis or at any site within the operative field. Distant metastasis was defined as recurrence outside the operative field. Diagnosis of recurrent disease was made when pathologically or radiologically confirmed.

### Statistical Analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables were statistically compared using the  $\chi^2$  test or Fisher's exact test to detect factors related to lymph node metastasis. Overall survival time was calculated from the date of operation to the date of death or most recent follow-up. Univariate analysis of survival was performed using the Kaplan-Meier method to estimate survival probabilities in patient subgroups and the log-rank test for statistical comparisons. Patients who died of complications after surgery were not excluded from survival analysis. Factors identified at a significance level of  $P < 0.2$  in univariate analysis were selected for inclusion in a multivariate Cox proportional hazard regression model. All statistical tests were performed two-sided, and a  $P$ -value less than 0.05 was considered to be statistically significant.

## Results

### Patient Characteristics

The distribution of EEC and early ESCC patients in different periods was shown in Table 1. The detection rate of EEC rose significantly in the past, especially the past five years. Between the year 2007 and 2011, nearly

**Table 1. Distribution of Patients with EC, EEC and Early ESCC in Different Periods**

Years	No. Patients		
	EC	EEC (%)	Early ESCC (%)
1995-2000	1173	53 (4.5)	52 (4.4)
2001-2006	1476	71 (4.8)	68 (4.6)
2007-2011	1234	114 (9.2)	108 (8.8)
Total	3883	238 (6.1)	228 (5.9)

EC, Esophageal cancer; EEC, Early esophageal cancer; ESCC, Esophageal squamous cell carcinoma

**Table 2. Univariate Analysis for the Prognosis of the 228 Patients with Early Esophageal Squamous Cell Carcinoma**

Variable	No. Patients (%)	Survival (%)		P value
		5-yr	10-yr	
Gender				0.62
Male	152(66.7)	81.5	68.3	
Female	76(33.3)	81.3	72.5	
Age (yr)				0.03
≤60	168(73.7)	83.3	75.0	
>60	60(26.3)	75.1	50.3	
Tumor location				0.31
Upper third	38(16.7)	80.0	63.0	
Middle third	170(74.6)	81.6	73.9	
Lower third	20(8.8)	81.5	57.0	
Tumor length				0.22
<3cm	118(51.8)	86.7	75.8	
≥3cm	110(48.2)	76.5	63.9	
Histologic grade				<0.01
Well (G1)	113(49.6)	89.3	85.4	
Moderate (G2)	99(43.4)	77.8	59.9	
Poor (G3)	16(7.0)	48.5	32.3	
pT category				<0.01
pTis	18(7.9)	100.0	100.0	
pT1a	62(27.2)	95.9	90.3	
pT1b	148(64.9)	72.5	58.3	
pN category				0.10
pN0	200(87.7)	83.0	71.8	
pN+	28(12.3)	67.2	56.0	
R-category				0.44
R0	226(99.1)	81.2	69.7	
R1	2(0.9)	100.0	-	

ten percent of the patients with esophageal carcinomas underwent surgical resection in our hospital were pathologically diagnosed as EEC.

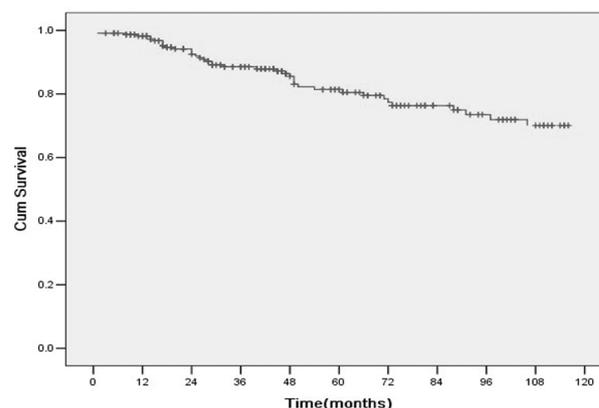
The clinicopathological features of the 228 patients with early ESCC are shown in Table 2. There were 152 males and 76 females with a median age of 55 years (range 35-77 years). The primary lesions were most often found in the middle third of the thoracic esophagus and had a median length of 2.5cm (0.5~10.0cm). An R0 resection (complete tumor resection) was achieved in 226 patients (99.1%), R1 resection (microscopically positive margins) in 2 patients (0.9%).

There were 14 cases of serious postoperative complications, including seven cases of anastomotic leakage, three cases of pneumothorax, three cases of pneumonia combined with anastomotic leakage, one case of empyema, and one case of pneumonia. One patient with pneumonia died three days after surgery, and another patient with pneumonia died nine days after surgery. The overall postoperative 30-day mortality was 0.9% (2/228).

A mean of 15.7 (range 4-51) lymph nodes was dissected from each specimen. None of the 18 patients with carcinoma in situ had lymph node metastases. Only one of the 62 patients with mucosal tumor had lymph node metastases (1.6%), while twenty-seven of the 148 patients with submucosal tumor had lymph node metastases (18.2%). Four of the 20 patients (20%) underwent right thoracotomies showed lymph node metastases in the upper mediastinum. Of the 28 patients had lymph node metastases, 18 patients had only one positive node, while

**Table 3. Clinicopathological Variables Associated with Lymph Node Metastases for the 228 Patients with Early Esophageal Squamous Cell Carcinoma**

Variable	No. Patients	Lymph node		P value
		Positive	Negative	
Gender				0.89
Male	152	19	133	
Female	76	9	67	
Age (yr)				0.78
≤60	168	20	148	
>60	60	8	52	
Tumor location				0.07
Upper third	38	4	34	
Middle third	170	21	149	
Lower third	20	3	17	
Tumor length				0.88
<3cm	118	10	108	
≥3cm	110	18	92	
Histologic grade				<0.01
Well (G1)	113	4	109	
Moderate (G2)	99	19	80	
Poor (G3)	16	5	11	
pT category				<0.01
pTis	18	0	18	
pT1a	62	1	61	
pT1b	148	27	121	



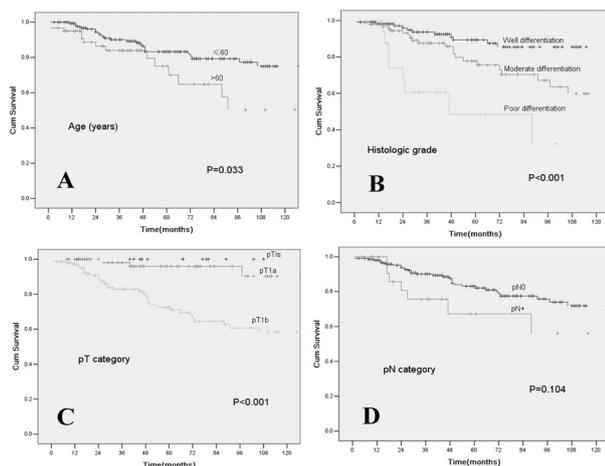
**Figure 1. Survival Curves for the 228 Patients with Early Esophageal Squamous Cell Carcinoma after Surgical Resection**

the other ten patients had 2 to 6 positive nodes. The most common site of lymphatic spread was to the locoregional nodes in the periesophageal region and along the lesser gastric curvature.

All patients underwent a radical operation without lymph node metastases were treated with surgery alone. Two patients underwent a R1 resection received postoperative radiotherapy with a total dose of 60 Gy. Of the 28 patients with lymph node metastases, 11 cases received postoperative radiotherapy, one case received postoperative chemoradiotherapy, one case received postoperative chemotherapy, and the other 15 cases received surgery alone. Therapeutic radiation was delivered using 6 or 8 MV photons. A total dose of 44-60 Gy (median 50 Gy) was delivered in 2 Gy fractions 5 days a week.

#### Survival and prognostic factors

The 1-, 3-, 5-, and 10-year overall survival rates were



**Figure 2. Kaplan-Meier Curves for Overall Survival of Patients with Early Esophageal Squamous Cell Carcinoma According to Different Clinopathological Features.** A: Kaplan-Meier curves for overall survival stratified by age ( $\leq 60$  yr versus  $>60$  yr). B: Kaplan-Meier curves for overall survival stratified by histologic grade (Well differentiation versus moderate differentiation versus poor differentiation). C: Kaplan-Meier curves for overall survival stratified by pT category (pTis versus pT1a versus pT1b). D: Kaplan-Meier curves for overall survival stratified by pN category (pN0 versus pN+)

**Table 4. Multivariate Cox Regression Analysis for the Prognosis of the 228 Patients with Early Esophageal Squamous Cell Carcinoma**

Prognostic factor	Hazard Ratio	95%CI	P value
Age	1.609	0.84-3.09	0.15
Histologic grade	1.893	1.08-3.32	0.03
pT category	3.884	1.42-10.6	<0.01
pN category	0.965	0.41-2.30	0.94

98.2%, 88.5%, 81.4%, and 70.1%, respectively (Figure 1).

Univariate analyses were performed to identify factors associated with the presence of lymph node metastases (Table 3). Only histologic grade ( $P<0.001$ ) and pT category ( $P=0.001$ ) showed significant differences.

The variables related to survival in univariate analysis were shown in Table 2. Only age, histologic grade, and pT category affected the overall survival ( $P<0.05$ , Figure 2). pN category did not show statistically significance ( $P=0.104$ ), although the 5- and 10-year overall survival rates of 83.0% and 71.8% for pN0 category patients were higher than those of 67.2% and 56.0% for pN+ category patients.

To identify independent prognostic factors predicting survival after surgery for early ESCC, Cox regression analysis was performed. The results were presented in Table 4. Only histologic grade and pT category were independent prognostic factors ( $p<0.05$ ). Age and pN category were not significantly correlated with survival ( $P>0.05$ ).

Twenty patients had complete recurrence and metastasis data. The first failure sites in these 20 cases included locoregional recurrences in nine cases, locoregional recurrences with distant metastases in three cases, and distant metastases in eight cases. Only 7 patients showed upper mediastinal lymph node metastases in the follow-up. The mean time from treatment to failure was

30.9 months (2-111 months).

## Discussion

The incidence of patients with EEC has been increasing because of recent advances in endoscopic examinations and awareness of the clinical importance of Barrett's esophagus (Ishikawa et al., 2005; Stein et al., 2005; Westerterp et al., 2005; Tachibana et al., 2006; Saha et al., 2009; Barbour et al., 2010; DeMeester, 2010). Chaoshan area in Guangdong province, located at the southeast of China, is the only coastal region with a high incidence of esophageal cancer in China. But no widespread population screening programs for esophageal cancer has been conducted in this area. Due to the improvement of endoscopy and staining methods, the detection rate of EEC in our hospital rose significantly in the past five years, and reached to nearly 10%. But the detection rate is still lower than that of 15%-30% in Japan and western countries (Natsugoe et al., 2004; Stein et al., 2005; Saha et al., 2009; Bogoevski et al., 2011; Dubecz et al., 2012).

In our study, none of the 18 patients with carcinoma in situ had lymph node metastases, and the 5-year overall survival rate was 100%. No lymph node metastases and systemic disease has been reported in patients with high-grade dysplasia before, and this is the only lesion from which patients can be assured that they have been cured with adequate therapy (DeMeester, 2010). But when the tumor infiltrates the basement membrane and enters the lamina propria, lymph node metastases can occur. The incidence of lymph node metastases in early ESCC was 0%-15.6% for mucosal tumor and 17.1%-48.7% for submucosal tumor (Sugimachi et al., 1989; Matsubara et al., 1999; Fujita et al., 2001; Endo et al., 2000; Stein et al., 2005; Bogoevski et al., 2011; Tanaka et al., 2012). In the current study, only one of the 62 patients with mucosal tumor had lymph node metastases (1.6%), while twenty-seven of the 148 patients with submucosal tumor had lymph node metastases (18.2%). Most of our patients underwent a left thoracotomy, the common hepatic nodes, celiac nodes, and upper right mediastinal nodes were difficult to remove via this operative route. This might contribute to the relatively low level of lymph node metastases in our study group.

Radical esophagectomy with lymphadenectomy are still the mainstay of curative treatment for patients with EEC at many centers, especially for patients with submucosal diseases (Stein et al., 2005). Previous studies even recommended an extended 3-field lymphadenectomy in early EEC patients as the lymph node metastases in the upper mediastinum and cervical region in up to 30% (Altorki et al., 2002; Lerut et al., 2004). However, the extent of lymphadenectomy should be balanced against the risk of complications. Although the lymph nodes in the upper mediastinum could not be removed via a left thoracotomy, lower rate of complications was observed in this procedure. At our center, left thoracotomies was performed for most of the patients with early ESCC while right thoracotomies was performed for those with lymph nodes in the upper mediastinum more than 5 mm in short-axis diameter by computed tomography

scan. Twenty of these 228 patients with early ESCC underwent right thoracotomies, and four of them (20%) had upper mediastinal lymph node metastases in postoperatively pathologic examinations. Only seven of these 228 patients showed upper mediastinal lymph node metastases in the follow-up, and the 5- and 10-year overall survival rates were 81.4% and 70.1%. Moreover, the postoperative morbidity and mortality were relatively low for our patients, with only 6.1% of serious postoperative complications (14/228) and 0.9% of postoperative 30-day mortality (2/228). We think that surgical resection via a left thoracotomy is acceptable for selected patient with early ESCC, while a right thoracotomy is recommended to patient with lymph nodes in the upper mediastinum more than 5 mm in short-axis diameter by computed tomography scan.

Surgical therapy for EEC has been challenged in recent years by endoscopic resection methods due to its lower morbidity rate and risk for procedure-related mortality. On the other hand, the potentially affected lymph nodes can not be removed in this method. Thus, identification of EEC patients with low risk of lymph node metastases gives them the best chance of being treated successfully by complete local excision and avoiding potential peri-operative complications. In our study, only histologic grade and pT category were associated with lymph node metastases. Patients with submucosal tumor (pT1b) have a high risk of lymph node metastases, in our series 18.2% (27 of 148), which makes them unsuitable for endoscopic treatment. Therefore, endoscopic resection is limited to patients with high-grade dysplasia or mucosal tumors (Korn, 2004), especially for patients with high-grade dysplasia, as no lymph node metastases and systemic disease reported. Most of the previous studies confirmed that lymph node metastases were rare in patients with mucosal tumor (Endo et al., 2000; Fujita et al., 2001; DeMeester, 2010; Bogoevski et al., 2011), but some studies reported a rate of higher than ten percent for lymph node metastases in mucosal tumor (Matsubara et al., 1999). It is hard to identify patients with high risk of lymph node metastases in mucosal tumor in our study as only one of the 62 patients with mucosal tumor had lymph node metastases (1.6%). According to the previous reports (Ancona et al., 2008; Barbour et al., 2010) and our finding, histologic grade was another factor associated with lymph node metastases in EEC. We think that for patients with poor differentiated mucosal tumors, careful selection should be made for patients to receive endoscopic treatment.

Histologic grade has been shown to be an independent prognostic factor for early ESCC (Tajima et al., 2000), and it has been added for stage grouping in the seventh edition of the American Joint Committee on Cancer (AJCC) staging system for esophageal cancer (Rice et al., 2009; Rice et al., 2010). Our study further confirmed its prognostic significance among patients with early ESCC. pT category was another independent prognostic factor for early ESCC in our study group, which was similar to those of many previous studies (Endo et al., 2000; Stein et al., 2005; Wijnhoven et al., 2007; Gertler et al., 2011). Previous studies recommended that T1 stage should be

subdivided according to the depths of infiltration rather than the histologic grade (Gertler et al., 2011), and we have confirmed this in our previous report (Chen et al., 2013).

The impact of lymph node metastasis on survival in patients with esophageal cancer has been recognized generally (Tanaka et al., 2012). The number of metastatic lymph nodes has also been shown to be one of the most important independent prognostic factors for patients with esophageal cancer after curative resection (Rice et al., 2009; Rice et al., 2010). Previous studies with EEC also showed that lymph node metastasis was a significant predictor for survival (Westerterp et al., 2005; Barbour et al., 2010); Natsugoe et al., 2004; Tajima et al., 2000; Grotenhuis et al., 2010). In our study, although the 5- and 10-year overall survival rates of 83.0% and 71.8% for pN0 category patients were higher than those of 67.2% and 56.0% for pN+ category patients, the difference was not statistically significant ( $P=0.104$ ). This might be due to the relatively small number of patients in the subgroup of pN+ category (n=28).

In conclusion, a left thoracotomy is acceptable for selected patients with early ESCC. The incidence of lymph node metastasis in submucosal tumors is relatively high while only histologic grade and pT category affected the presence of lymph node metastases in early ESCC. Histologic grade and pT category were independent prognostic factors for early ESCC. Further studies are required to select patients with early ESCC for endoscopic treatment.

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