RESEARCH ARTICLE

Prognostic Value of Subcarinal Lymph Node Metastasis in Patients with Esophageal Squamous Cell Carcinoma

Ji-Feng Feng[1,2]*, Qiang Zhao[1,2], Qi-Xun Chen[1,2]

Abstract

Purpose: The 7th edition of the American Joint Committee on Cancer Staging Manual for esophageal cancer (EC) categorizes N stage according to the number of metastatic lymph nodes (LNs), irrespective of the site. The aim of this study was to determine the prognostic value of subcarinal LN metastasis in patients undergoing esophagectomy for esophageal squamous cell carcinoma (ESCC). Methods: A retrospective analysis of 507 consecutive patients with ESCC was conducted. Potential clinicopathological factors that could influence subcarinal LN metastasis were statistically analyzed. Univariate and multivariate analyses were also performed to evaluate the prognostic parameters for survival. Results: The frequency of subcarinal LN metastasis was 22.9% (116/507). Logistic regression analysis showed that tumor length (>3cm vs ≤3cm; *P*=0.027), tumor location (lower vs upper/middle; *P*=0.009), vessel involvement (Yes vs No; *P*=0.001) and depth of invasion (T3-4a vs T1-2; *P*=0.012) were associated with 2.085-, 1.810-, 2.535- and 2.201- fold increases, respectively, for risk of subcarinal LN metastasis. Multivariate analyses showed that differentiation (poor vs well/moderate; P=0.001), subcarinal LN metastasis (yes vs no; *P*=0.033), depth of invasion (T3-4a vs T1-2; *P*=0.014) and N staging (N1-3 vs N0; *P*=0.001) were independent prognostic factors. In addition, patients with subcarinal LN metastasis had a significantly lower 5-year cumulative survival rate than those without (26.7% vs 60.9%; *P*<0.001). Conclusions: Subcarinal LN metastasis is a predictive factor for long-term survival in patients with ESCC.

Keywords: Esophageal cancer - lymph node - prognostic factor - survival

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Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, with 482,000 new cases estimated in 2008, and the sixth most common cause of death from cancer with 407,000 deaths (Ferlay et al., 2010). In China, EC is the fourth most common cause of mortality and is frequently located in the thorax, while 95% of EC is pathologically diagnosed as squamous cell carcinoma (Ferlay et al., 2010; Mao et al., 2011). Although advances have occurred in the multidisciplinary treatment, surgical resection remains the modality of choice.

Lymph node (LN) metastasis is the single most important prognostic factor in EC (Ferguson et al., 1997; Mao et al., 2011). Accurate N staging of EC is crucial, as it will impact on choice of management, the need for chemoradiotherapy, choice of surgical approach, and aid in predicting prognosis (DeMeester et al., 2006; Kunisaka et al., 2010; Kayani et al., 2011; Mirinezhad et al., 2012). Many scholars believed that the prognosis in patients with EC depended on the number, but not the site, of metastatic LNs after curative esophagectomy (Greenstein et al., 2008; Peyre et al., 2008). Moreover, the 7th edition of the American Joint Committee Cancer Staging Manual for EC categorizes N stage according to the number of metastatic LNs, irrespective of the site (Rice et al., 2010). However, the 10th edition of the Japanese Classification of Esophageal Cancer categorizes N stage according to both the site and the number of metastatic LNs (Japanese Society for Esophageal Disease, 2008).

Subcarinal LN metastasis is common in EC. However, to date, few data regarding subcarinal LN metastasis in EC are available (Gotohda et al., 2005; Hsu et al. 2005; Li et al., 2012; Liu et al., 2012). Moreover, its relationship with prognosis has never been studied. The aim of this study was to determine whether subcarinal LN metastasis is associated with survival after esophagectomy for patients with esophageal squamos cell carcinoma (ESCC).

Materials and Methods

Patients

Five hundred and seven patients with ESCC who underwent curative esophagectomy in the Department of Thoracic Surgery of Zhejiang Cancer Hospital in China from January 2005 to December 2008 were included in the retrospective database for this study. Patients who had received pre/post-operative chemo¬therapy and/

[1]*Department of Thoracic Surgery, Zhejiang Cancer Hospital,* [2]*Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, Hangzhou, Zhejiang Province, China *For correspondence: Jifzhejiang@gmail.com*

Table 1. The Correlation in Patients with and Without Subcarinal LN Metastasis

	Cases (n=507)	Subcarinal LN metastasis (n, %)	*P* value
Age (years)			0.57
≤60	287	63 (22.0)	
>60	220	53 (24.1)	
Gender			0.086
Female	73	11 (15.1)	
Male	434	105 (24.2)	
Tumor length (cm)			<0.001
≤3	144	15 (10.4)	
>3	363	101 (27.8)	
Tumor location			0.002
Upper	24	3 (12.5)	
Middle	256	45 (17.6)	
Lower	227	68 (30.0)	
Differentiation			0.013
Well	76	8 (10.5)	
Moderate	341	82 (24.0)	
Poor	90	26 (28.9)	
Vessel involvement			<0.001
No	429	85 (19.8)	
Yes	78	31 (39.7)	
Perineural invasion			0.003
No	407	82 (20.1)	
Yes	100	34 (34.0)	
Depth of invasion			<0.001
T1	93	3 (3.2)	
T2	84	16 (19.0)	
T3	279	71 (25.4)	
T4a	51	26 (51.0)	

or radiotherapy were excluded. In addition, we also excluded patients with non-ESCC, gastroesophageal junction carcinoma, and patients who underwent surgical exploration but without esophagectomy. All subjects gave written informed consent to the study protocol, which was approved by the Ethical Committees of Zhejiang Cancer Hospital, China.

Based on the medical records, the following data were collected for each patient: age, gender, tumor location, tumor length, differentiation, depth of invasion, LN metastasis, N staging and other miscellaneous characterics. In our institute, patients were followed up at our outpatient department every 3 to 6 months for the first 2 years after resection, then annually. Recording of medical history, physical examination and CT of the chest were performed during the follow-up. Endoscopic examination was obtained in cases of clinically indicated recurrence or metastasis.

Surgery

The standard surgical approach consisted of a limited thoracotomy on the right side and intrathoracic gastric reconstruction (the Ivor Lewis procedure) for lesions at the middle/lower third of the esophagus. Upper third lesions were treated by cervical anastomosis (the McKeown procedure). In our institute, the majority of patients underwent two-field lymphadenectomy. In this cohort of patients, thoracoabdominal lymphadenectomy was performed, including the subcarinal, paraesophageal, pulmonary ligament, diaphragmatic and paracardial LNs, as well as those located along the lesser gastric curvature, the origin of the left gastric artery, the celiac trunk, the common hepatic artery and the splenic artery. Three-field lymphadenectomy was performed only if the cervical LNs were thought to be abnormal upon preoperative evaluation. All of the patients included in the study were staged according to the 7th edition of the American Joint Committee on Cancer Cancer Staging Manual (Rice et al., 2010).

Table 2. Factors Correlated to Subcarinal LN Metastasis

	P value	OR (95% CI)
Age (>60 years vs ≤60 years)	0.81	1.057 (0.673-1.660)
Gender (Male vs Female)	0.467	1.308 (0.634-2.695)
Tumor length (>3 cm vs ≤3 cm)	0.027	2.085 (1.088-3.998)
Tumor location (Lower vs Upper/Middle)	0.009	1.810 (1.157-2.832)
Differentiation (Poor vs Well/Moderate)	0.163	1.480 (0.853-2.567)
Vessel involvement (Yes vs No)	0.001	2.535 (1.481-4.337)
Perineural invasion (Yes vs No)	0.221	1.385 (0.822-2.333)
Depth of invasion (T3-4a vs T1-2)	0.012	2.201 (1.192-4.066)

OR, odds ratio; CI, confidence interval

Statistical analysis

Statistical evaluation was conducted with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The distribution of baseline characteristics between patients with and without subcarinal LN metastasis was compared by using the chi-square test. Significant factors were extracted for further analysis, which was conducted by using logistic regression. The overall cumulative probability of survival was calculated by the Kaplan-Meier method, and the difference was assessed by the log-rank test. Univariate and multivariate analyses of Cox regression proportional hazard model were performed to evaluate the prognostic parameters for survival. A *P* value less than 0.05 was considered to be statistically significant.

Results

Patient Characteristics

Among the 507 patients, 73 (14.4%) were women, and 434 (85.6%) were men. The mean age was 59.2 ± 7.9 years, with an age range from 34 to 80 years. A mean of 26.4 ± 10.8 LNs per patient was dissected during pathologic review (range: 6-61 LNs). The metastatic LNs per case was 1.7 ± 3.3 (range: 0-26 LNs).

Subcarinal LN metastasis

LN metastasis were observed in 215 patients (42.4%), and subcarinal LN metastasis was found in 116 patients (22.9%). From the variables considered to be potentially associated with subcarinal LN metastasis, tumor length, tumor location, differentiation, vessel involvement, perineural invasion and depth of invasion were found to differ significantly between patients with and without subcarinal LN metastasis (Table 1).

A logistic regression analysis showed that tumor length (>3cm vs ≤3cm; *P*=0.027), tumor location (Lower vs Upper/Middle; *P*=0.009), vessel involvement (Yes vs No; *P*=0.001) and depth of invasion (T3-4a vs T1-2; *P*=0.012) were associated with 2.085-, 1.810-, 2.535- and 2.201- fold

Table 3. Univariate Analyses in Patients with ESCC

	Survival (%)	HR (95% CI)	*P* value
Age (years)			0.522
≤60	54	1	
>60	51.8	1.086 (0.841-1.403)	
Gender			0.051
Female	64.4	1	
Male	51.2	1.500 (0.998-2.255)	
Tumor length (cm)			<0.001
≤3	69.4	1	
>3	46.6	2.098 (1.512-2.911)	
Tumor location			0.059
Upper/Middle	57.5	1	
Lower	47.6	1.278 (0.991-1.648)	
Differentiation			0.003
Well/Moderately	55.6	1	
Poorly	41.1	1.578 (1.162-2.142)	
Vessel involvement			0.002
No	55.7	1	
Yes	38.5	1.654 (1.205-2.272)	
Perineural invasion			0.001
No	56.5	1	
Yes	39	1.643 (1.227-2.199)	
Subcarinal LN metastasis			<0.001
No	60.9	1	
Yes	26.7	2.636 (2.019-3.441)	
T grade			<0.001
T1-2	70.9	1	
T3-4a	43.3	2.396 (1.761-3.260)	
N staging			<0.001
N0	68.2	1	
N1-3	32.6	2.881 (2.217-3.744)	

HR, hazard ratio; CI, confidence interval

increase, respectively, for risk of subcarinal LN metastasis (Table 2).

Prognostic analysis

Univariate analyses showed that tumor length, differentiation, vessel involvement, perineural invasion, subcarinal LN metastasis, depth of invasion and N staging were predictive of survival (Table 3). Multivariate analyses were performed with the Cox proportional hazards model. In that model, we demonstrated that differentiation (Poor vs Well/Moderate; *P*=0.001), subcarinal LN metastasis (Yes vs No; *P*=0.033), depth of invasion (T3-4a vs T1-2; *P*=0.014) and N staging (N1-3 vs N0; *P*=0.001) were independent prognostic factors (Table 4).

Overall survival

The 5-year survival were 26.7% in patients with subcarinal LN metastasis and 60.9% in patients without subcarinal LN metastasis, a difference that was shown to be statistically significant between these two groups (*P*<0.001; Figure 1).

Discussion

ESCC is the most common pathological type in China, in contrast to the predominance of adenocarcinoma in the Western world. There are probably differences in the biologic behavior between adenocarcinoma and ESCC and also in the prevalence and pattern of lymphatic

Table 4. Multivariate Analyses in Patients with ESCC

	P value	OR (95% CI)
Age (>60 years vs ≤60 years)	0.497	1.096 (0.841-1.428)
Gender (Male vs Female)	0.155	1.354 (0.891-2.057)
Tumor length (>3 cm vs ≤3 cm)	0.282	1.220 (0.850-1.752)
Tumor location (Lower vs Upper/Middle)	0.402	1.120 (0.859-1.462)
Differentiation (Poor vs Well/Moderate)	0.001	1.669 (1.224-2.277)
Vessel involvement (Yes vs No)	0.692	1.071 (0.763-1.502)
Perineural invasion (Yes vs No)	0.296	1.179 (0.866-1.606)
Subcarinal LN metastasis (Yes vs No)	0.033	1.435 (1.029-2.002)
Depth of invasion (T3-4a vs T1-2)	0.014	1.582 (1.098-2.279)
N staging (N1-3 vs N0)	0.001	1.805 (1.275-2.555)

OR, odds ratio; CI, confidence interval

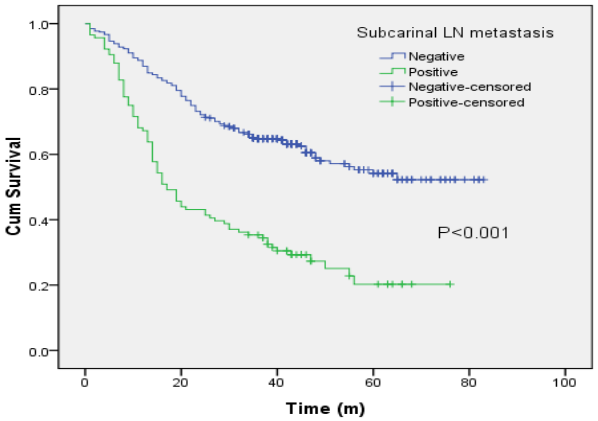

Figure 1. Patients with Subcarinal LN Metastasis had a Significantly Lower 5-year Cumulative Survival Rate than Those Without Subcarinal LN Metastasis (26.7% vs 60.9%; *P*<0.001)

spread (Siewert et al., 2001; Stein et al., 2005). Thus, in the present research, we enrolled patients with ESCC exclusively. In this study, we determine the prognostic value of subcarinal LN metastasis in ESCC patients. Our study showed that subcarinal LN metastasis is a predictive factor for long-term survival in patients with ESCC. To our knowledge, this may be the first study to determine the prognostic value of subcarinal LN metastasis in ESCC. In addition, we conclude that tumor length, tumor location, vessel involvement and depth of invasion are significant variables for identifying patients with subcarinal LN metastasis.

The frequency of subcarinal LN metastasis in patients with EC ranges from 6.8% to 23.8% (Gotohda et al., 2005; Hsu et al., 2005; Li et al., 2012; Liu et al., 2012). In our study, the frequency of subcarinal LN metastasis was 22.9%. We demonstrated that the subcarinal LN metastasis was rare in patients with upper ESCC and tumor location was found to differ significantly between patients with and without subcarinal LN metastasis. This observation is in line with data from Gotohda et al. (2005), but is contrary to the result of Liu et al. (2012), who suggested that subcarinal LN metastasis is not significant correlation with the tumor location. In addition, both Liu et al. (2012) and our study showed that longer tumor length and higher depth of invasion associated with a higher frequency of subcarinal LN metastasis.

Subcarinal LN metastasis is common in patients with EC. Thus, further clarification is necessary to identify which factors correlated to subcarinal LN metastasis. Liu et al. (2012) showed that tumor length, depth of invasion,

and histologic grade were independent factors correlated with subcarinal LN metastasis. In our study, we also concluded that tumor length, tumor location, and depth of invasion are significant variables for identifying patients with subcarinal LN metastasis. In addition, we also found that vessel involvement associated with a higher frequency of subcarinal LN metastasis. Based on these results, we conclude that individuals with longer tumor length, lower tumor location, vessel involvement or higher depth of invasion should be on high alert for the possibility of subcarinal LN metastasis.

In our study, patients with subcarinal LN metastasis had shorter survival than those without subcarinal LN metastasis (26.7% vs. 60.9%; $P<0.001$). Then multivariate analyses showed that differentiation (Poor vs Well/ Moderate; $P=0.001$), subcarinal LN metastasis (Yes vs No; $P=0.033$), depth of invasion (T3-4a vs T1-2; $P=0.014$) and N staging (N1-3 vs N0; $P=0.001$) were independent prognostic factors. From the database of 507 patients with ESCC who underwent surgery, our results clearly demonstrated that subcarinal LN metastasis can serve as an independent predictor of long-term survival for ESCC patients.

Our study has several limitations. It was a retrospective study with all the limitations that accompany such a study. In addition, because the study used data from a single institution but with different pathologists and different surgeons, there may have been a lack of uniformity. The LN dissection number was also not consistent, and we also excluded patients who had a dissected LN number of less than 6 (Greene et al., 2002; Sorbin et al., 2002), which may have influenced our analysis. Further studies are needed to explore its long-term effect.

In conclusions, subcarinal LN metastasis is a predictive factor for long-term survival in patients undergoing esophagectomy for ESCC. Patients with subcarinal LN metastasis had a poor prognosis. We conclude that tumor length, tumor location, vessel involvement and depth of invasion are significant variables for identifying patients with subcarinal LN metastasis.Larger prospective studies will need to be performed to confirm these preliminary results.

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The author(s) declare that they have no competing interests.

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