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ORIGINAL ARTICLE

Prognostic value of the number of negative lymph nodes in esophageal carcinoma without lymphatic metastasis

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Keywords
Esophageal neoplasm; lymphatic metastasis; surgical procedure; metastasis.

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Abstract

Background: The impact of the number of negative lymph nodes (LNs) on survival in patients with esophageal cancer remains a controversial issue. This study investigated the association between the number of resected LNs and the prognosis of patients with node-negative esophageal carcinoma.

Methods: A retrospective review was performed of the data of 429 patients who underwent esophagectomy with modern two-field lymphadenectomy for the treatment of esophageal cancer between January 1998 and December 2008. Histopathology showed no LN involvement in the patient sample. The prognostic impact of the number of negative LNs and the clinicopathological factors were analyzed.

Results: The overall median survival time and the one, three, and five-year overall survival rates were 63.0 months and 78.5%, 64.0%, and 51.2%, respectively. Survival analysis confirmed that the number of negative LNs and the depth of tumor invasion were independent prognostic factors. Patients with a high number of negative LNs had a better overall survival rate than patients with a low number of negative LNs ($P < 0.001$). Patients with dissected LNs > 14 for pT1 tumors ($P < 0.001$) and > 19 for pT2–3 tumors ($P < 0.001$ and $P = 0.001$, respectively) had better long-term survival outcomes.

Conclusions: The number of negative LNs is an independent prognostic factor for node-negative esophageal carcinoma. Extended LN dissection is recommended to improve the survival of patients with node-negative esophageal carcinoma.

Introduction

Esophageal carcinoma ranks sixth worldwide among the causes of malignancy-related mortality,[1] and esophageal squamous cell carcinoma (ESCC) is the most common histological type of this cancer in Asian countries.[2] The presence of lymph node (LN) metastasis is an important prognostic factor and a critical determinant of the management of esophageal carcinoma.[3,4] Many studies have investigated the impact of the number of metastatic LNs and the ratio of metastatic LNs to the total number of resected lymph nodes (RLNs) on the survival of patients with esophageal cancer throughout the past decade and reported that higher numbers and a higher ratio are indicative of a poor prognosis.[5–9] The seventh edition of the American Joint Committee on Cancer (AJCC) staging system emphasized the significance of the number of RLNs and incorporated this into ESCC staging.[10] However, the minimum number of LNs requiring resection and the prognostic effect of this number on postoperative survival for patients with LN-negative ESCC remains undetermined.

Many studies have examined the impact of the number of negative LNs on the survival of patients with gastric cancer, and a higher number of negative LNs is associated with a better prognosis.[11–14] However, few studies have considered the relationship between the number of negative LNs and survival in patients with LN-negative ESCC.[15,16] In this study, we investigated the prognostic significance of the number of negative LNs on survival in 429 LN-negative ESCC patients after esophagectomy at a single institution.

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Methods

From January 1998 to December 2008, a total of 429 patients were diagnosed with LN-negative ESCC. The independent ethics committee approved the study and informed consent was waived.

Patient selection and staging

A retrospective review was performed of the data of 429 patients with negative LNs who had undergone transthoracic esophagectomy with modern, two-field lymphadenectomy for ESCC between January 1998 and December 2008. We verified and updated the clinical data in the patient records through June 2013 using the database. The patients were selected based on the following eligibility criteria: (i) a diagnosis of thoracic ESCC; (ii) postoperative pathologic staging of pT1-3N0M0; (iii) transthoracic esophagectomy with a modern, two-field lymphadenectomy (total mediastinal and perigastric lymph nodes) had been performed; and (iv) R0 resection occurred. Patients were excluded based on the following criteria: (i) distant metastasis was discovered during the operation, or pT4 was proven after the operation; (ii) neoadjuvant chemotherapy or radiotherapy was administered; (iii) R1 and R2 resection occurred; and (iv) medical records were incomplete.

All of the patients were interviewed about their medical history and underwent physical examinations. Chest radiographs, barium swallow tests, electrocardiograms, lung function tests, Doppler ultrasound examinations of the abdomen, computed tomography (CT) scans from the chest to the upper abdomen, endoscopic biopsies, complete blood counts, blood biochemistry analyses, and liver and renal function evaluations were performed.

We categorized patients into two groups according to the different number of LNs: patients with 1–19 LNs and patients with ≥ 20 LNs. Clinical data were collected, including gender, age, location, length, depth of invasion, differentiation, number of LNs, adjuvant chemotherapy, adjuvant radiotherapy, LN dissection, and postoperative complications.

The surgical methods of resection included McKeown esophagectomy for upper esophageal cancer and Ivor Lewis esophagectomy for middle or lower esophageal carcinoma. In addition, the AJCC 7th edition Tumor Node Metastasis (TNM) staging system for esophageal carcinoma was used to stage all patients. The surgeon labeled each dissected node and each dissected node group. The LNs examined also included those embedded in en bloc specimens that were not labeled by the surgeons but were identified by pathologists. The total number of RLNs was determined from the sum of the number of LNs collected and histopathologically confirmed by two pathologists.

Follow-up

Patient follow-up was conducted every four months for one year, every six months for two years, and annually thereafter. Each follow-up evaluation included a clinical examination and a CT scan of the chest and abdomen. An endoscopic biopsy was performed when there was clinical or radiographic evidence that suggested local recurrence. When a patient was diagnosed as having metastasis or recurrence during postoperative follow-up, the diagnosis and the site of metastasis or recurrence were recorded. Postoperative recurrence and metastasis were classified into local recurrence and distant metastasis. Adjuvant therapy was recommended to all stage T2–3 patients.

Statistical analysis

Analysis of variance was performed for the comparison of continuous variables. The survival duration was calculated from the date of discharge to the time of death or the follow-up visit. Kaplan–Meier plots were used to determine the survival distribution. A log-rank test was used to evaluate survival differences. Multivariate analysis of survival was performed using Cox regression to identify the independent prognostic variables. The level of significance was set at $P < 0.05$. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

The study group consisted of 282 men and 147 women with LN-negative ESCC, with a median age of 65 years (range: 42 –81). Primary lesions were most commonly found in the middle third of the thoracic esophagus (227/429, 52.9%). According to the 7th AJCC TNM classification, this study included 109 T1 patients, 148 T2 patients, and 172 T3 patients.

A total of 11 534 LNs were resected, and the mean total number of metastatic LNs was 26.8 (range: 6–41). The number of negative LNs was examined as a categorical variable, which resulted in the following distribution: 56 patients in group 1 (negative LN ≤ 14); 136 patients in group 2 (negative LN 15–19); 113 patients in group 3 (negative LN 20–24); and 124 patients in group 4 (negative LN ≥ 25).

We assessed the relationship between prognosis and the clinicopathological features of the patients, which included age, gender, tumor location, tumor length, depth of invasion, differentiation, number of LNs, and adjuvant therapies. In univariate analysis, we found that the depth of

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invasion, tumor length, and number of LNs were significantly correlated with prognosis (Table 1). In multivariate analysis, the depth of tumor invasion and number of LNs were independent prognostic factors of LN-negative ESCC patients ($P < 0.001$, $P < 0.001$, respectively).

When we compared the incidence of postoperative complications with different numbers of LNs, we found that the overall incidence of postoperative complications in patients with ≤ 19 LNs was lower than in patients with ≥ 20 LNs ($P = 0.04$). However, there was no difference in the morbidity rate of pneumonia, laryngeal nerve palsy, arrhythmia, chylothorax, anastomotic leakage, or perioperative death in patients with ≤ 19 and ≥ 20 LNs ($P > 0.05$) (Table 2).

By December 2008, after a mean follow-up period of 55.0 months (range: 1–137), 402 patients had been examined at follow-up visits (93.7%). The overall median survival time (MST) was 63.0 months, and the one, three, and five-year overall survival (OS) rates were 78.5%, 64.0%, and 51.2%, respectively. In T1 patients, the overall MST was 78.0 months, and the one, three, and five-year OS rates were 92.7%, 83.5% and 77.1%, respectively. In T2 patients, the overall MST was 61.0 months and the one, three, and five-year OS rates of patients were 79.1%, 65.5% and 53.4%, respectively. In T3 patients, the overall MST was 39.0 months, and the one, three, and five-year OS rates were 73.8%, 56.4% and 39.0%, respectively. The MST of 78.0 months (95% confidence interval [CI] 71.6–84.4) in patients with T1 staging was superior to that of patients with T2 and T3 staging ($P < 0.001$) (Fig 1). Furthermore, the MST of patients with > 25 RLNs was superior to that of patients with < 25 RLNs ($P < 0.001$) (Fig 2).

The impact of the number of negative LNs on the five-year survival rate was examined after stratification by T

Table 1 Univariate and multivariate Cox regression analysis of ESCC patient prognoses

Characteristics		Univariate analysis			Multivariate Cox regression analysis	
	No. of patients	MST, months (95% CI)	Five-year survival (%)	*P*	HR (95% CI)	*P*
Gender				0.326	—	0.483
Male	282	65.0 (58.8–71.2)	53.5			
Female	147	60.0 (45.0–75.0)	47.2			
Age (years)				0.348	—	0.543
≤ 65	189	63.0 (56.8–69.2)	51.5			
> 65	240	62.0 (52.8–71.2)	51.2			
Location				0.439	—	0.615
Upper	80	60.0 (42.8–77.2)	49.8			
Middle	227	60.0 (51.5–68.5)	47.2			
Lower	120	68.0 (62.7–73.3)	60.0			
Length				< 0.001	—	0.074
≤ 3 cm	304	66.0 (60.7–71.3)	55.1			
> 3 cm	125	50.0 (37.4–62.6)	42.0			
Depth of invasion				< 0.001	1.506 (1.315–1.725)	< 0.001
T1	109	78.0 (71.6–84.4)	75.1			
T2	148	61.0 (52.7–69.3)	50.4			
T3	172	39.0 (29.9–48.1)	37.0			
Differentiation				0.081	—	0.519
G1	130	68.0 (60.5–75.5)	57.6			
G2	225	60.0 (50.1–69.9)	48.7			
G3	74	60.0 (48.6–71.4)	48.4			
No. of LNs				< 0.001	0.769 (0.692–0.855)	< 0.001
0–14	56	36.0 (18.4–53.6)	28.5			
15–19	136	60.0 (46.0–74.0)	47.7			
20–24	113	69.0 (60.4–77.6)	56.4			
≥ 25	124	69.0 (62.4–75.6)	60.4			
Adjuvant chemotherapy				0.830	—	0.484
Yes	165	46 (30.8–61.2)	44.0			
No	264	66 (61.2–70.8)	55.9			
Adjuvant radiotherapy				0.209	—	0.315
Yes	115	55 (37.9–72.1)	45.7			
No	314	66 (59.9–72.1)	53.4			

$P < 0.05$ was considered statistically significant. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; LNs, lymph nodes; MST, median survival time.

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Table 2 Comparison of postoperative complications of patients with different numbers of LNs

No. of LNs	0–19 (*n* = 192)	≥ 20 (*n* = 237)	*P**
Overall postoperative complications	31 (16.1%)	59 (24.9%)	0.04
Pneumonia	18 (9.4%)	35 (14.8%)	0.12
Laryngeal nerve palsy	16 (8.3%)	29 (12.2%)	0.25
Arrhythmia	16 (8.3%)	33 (13.9%)	0.09
Chylothorax	10 (5.2%)	22 (9.3%)	0.16
Anastomotic leakage	8 (4.2%)	17 (7.2%)	0.27
Perioperative death	1 (0.5%)	1 (0.4%)	0.89

**P* <0.05 was considered statistically significant. LNs, lymph nodes.

staging. The five-year survival of each staging group with a statistically significant number of LNs was compared. In patients with T1 staging, a high negative LN number (> 14) was significantly associated with a better five-year survival rate ($P < 0.001$) (Fig 3). Similarly, in patients with T2 and T3 staging, a high negative LN number (> 19) was significantly associated with a better five-year survival rate (both $P = 0.001$) (Figs 4–5).

Of the 429 patients who completed follow-up, 189 patients developed local recurrence or distant metastasis. Of these 189 patients, 32 developed recurrence at the anastomosis, 135 patients developed LN metastasis, 92 patients developed distant organ metastasis, 18 patients had anastomotic recurrence and LN metastasis, and 52 patients had LN and distant organ metastases. There were no significant differences in the incidence of anastomotic recurrence among the four groups ($P > 0.05$), but higher LN and distant organ metastases were significantly

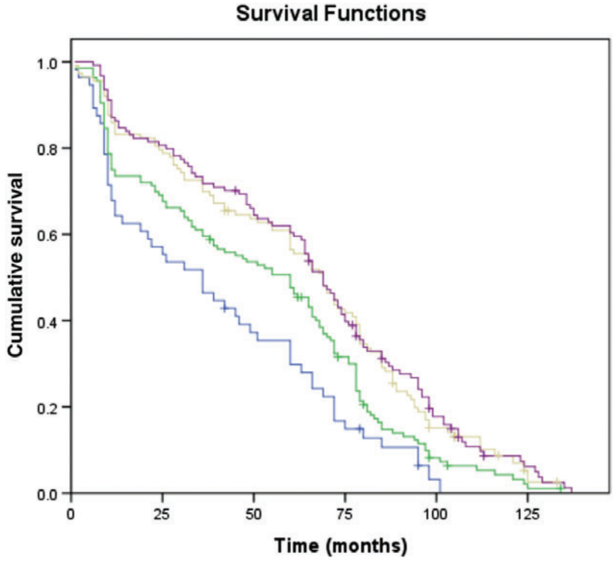

Figure 2 Kaplan–Meier curve of survival in esophageal squamous cell carcinoma patients with different numbers of lymph nodes (LNs) ($P < 0.001$). The number of LNs ( ) 0~14, ( ) 15~19, ( ) 20~24, ( ) ≥ 25, ( ) 0–14-censored, ( ) 15–19-censored, ( ) 20–24-censored, and ( ) ≥ 25-censored.

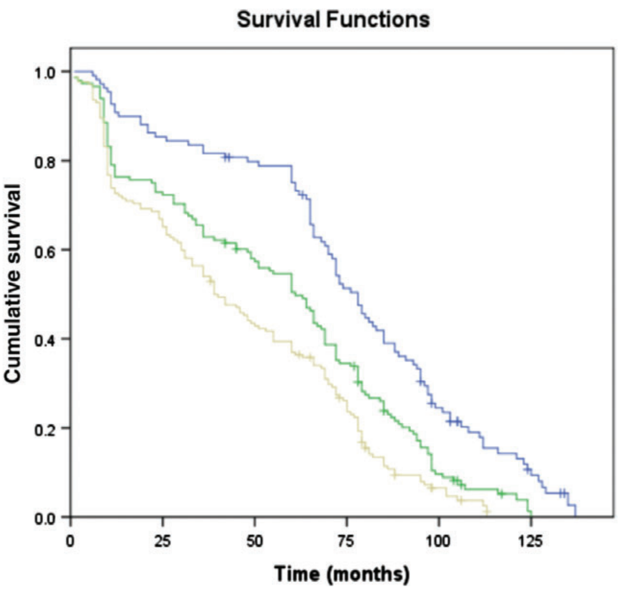

Figure 1 Kaplan–Meier curve of survival in esophageal squamous cell carcinoma patients with different depths of invasion ($P < 0.001$). T staging ( ) T1, ( ) T2, ( ) T3, ( ) T1-censored, ( ) T2-censored, and ( ) T3-censored.

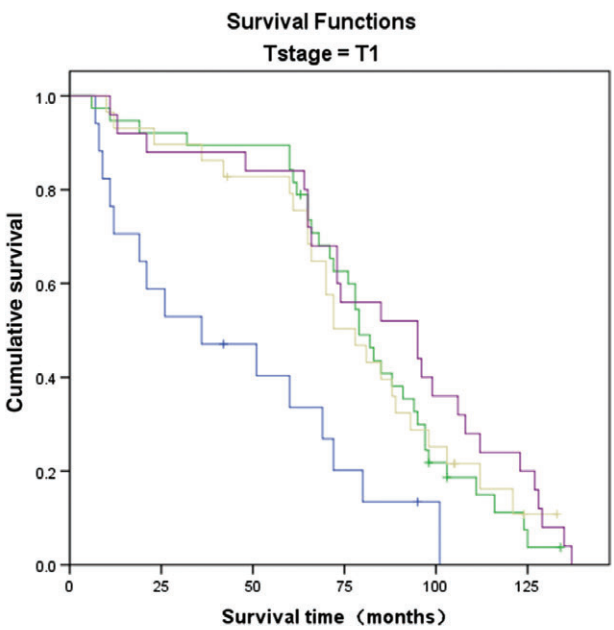

Figure 3 Kaplan–Meier curve of survival in T1 patients with different numbers of lymph nodes (LNs) ($P = 0.001$). The number of LNs ( ) 0–14, ( ) 15–19, ( ) 20–24, ( ) ≥ 25, ( ) 0–14-censored, ( ) 15–19-censored, ( ) 20–24-censored, and ( ) ≥ 25-censored.

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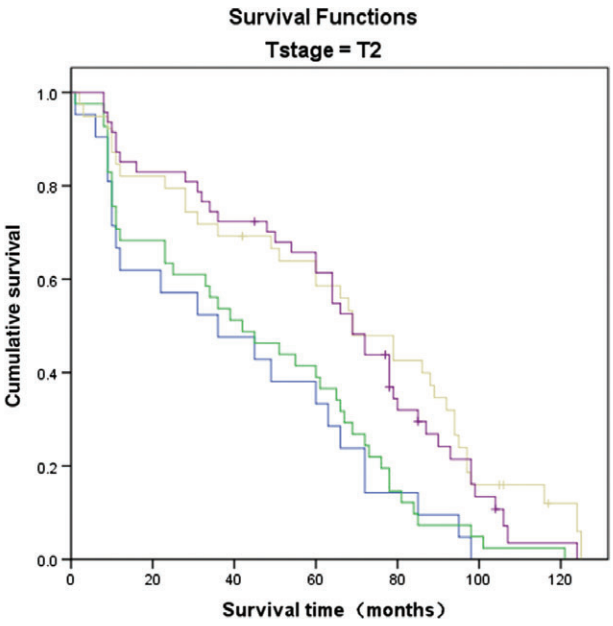

Figure 4 Kaplan–Meier curve of survival in T2 patients with different numbers of lymph nodes (LNs) (P = 0.001). The number of LNs (—) 0–14, (—) 15–19, (—) 20–24, (—) ≥25, (—+—) 0–14-censored, (—+—) 15-19-censored, (—+—) 20–24-censored, and (—+—) ≥ 25-censored.

associated with a low negative LN number (0–19, P = 0.002 and P = 0.020, respectively) (Table 3). Furthermore, of the 135 patients with LN metastasis, recurrent laryngeal LNs (46/135) and peritumoral LNs (44/135) most frequently exhibited recurrence.

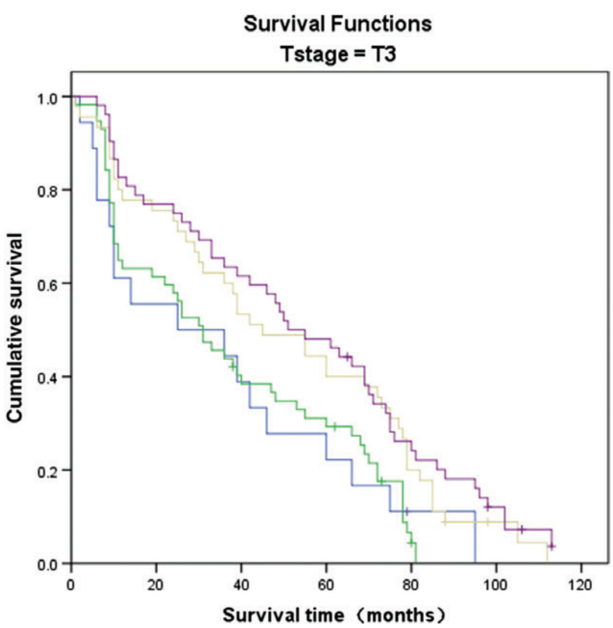

Figure 5 Kaplan–Meier curve of survival in T3 patients with different numbers of lymph nodes (LNs) (P = 0.006). The number of LNs (—) 0–14, (—) 15–19, (—) 20–24, (—) ≥ 25, (—+—) 0–14-censored, (—+—) 15-19-censored, (—+—) 20–24-censored, and (—+—) ≥ 25-censored.

Discussion

Lymph node status remains one of the most important survival factors for ESCC. A reasonable lymphadenectomy is an important procedure for accurate nodal staging and TNM classification, and can improve survival for patients with esophageal carcinoma.[14] Unfortunately, the current 7th AJCC staging system for esophageal carcinoma does not define the minimum number of RLNs necessary for adequate lymphadenectomy, which is in contrast to the recommendations for other solid tumors, such as gastric cancer.[11–14] In this study, we found that the number of LNs and the depth of tumor invasion were independent prognostic factors for patients with LN-negative ESCC. Furthermore, we analyzed the survival differences between groups with different numbers of examined LNs and found that better survival was associated with an increased number of examined LNs.

Some previous studies have reported that the number of metastatic LNs and the ratio of metastatic LNs to the total number of RLNs are independent prognostic factors.[5–9] Mariette *et al.* studied 536 patients who underwent esophagectomy and found that the number of LN metastases and the ratio of metastatic LNs to the total number of RLNs were the only prognostic factors.[17] Greenstein *et al.* reported significantly poorer outcomes for patients with a ratio of metastatic LNs to the total number of RLNs > 0.2.[8] However, the patients in these studies were from the United States and several Western European countries, and most had pathological adenocarcinoma. Greenstein *et al.* studied 838 esophageal cancer patients using data from the Surveillance, Epidemiology, and End Results (SEER) database; these patients had adenocarcinoma (60%), squamous cell carcinoma (34%), and other cell types (6%).[8] They reported that the survival advantage was limited to adenocarcinoma patients with a higher number of RLNs. In contrast, > 90% of the esophageal carcinoma patients in Eastern countries had ESCC, particularly in China.[4,15,16] In this study, all patients were diagnosed with ESCC and a similar result was found: the number of RLNs was a prognostic factor for the survival of patients with LN-negative ESCC.

There are two possible explanations for our finding that improved survival is related to the number of negative RLNs. First, the number of RLNs may be affected by underreporting the extent of lymphadenectomy, because the pathologists may not have examined all of the LNs from an en bloc-resected specimen; this would result in stage migration. When more LNs are examined, the detection of metastatic nodes is more likely.[18] Second, the

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Table 3 Comparison of patients with a significant number of LNs and distant metastasis

No. of LNs	0–19 (*n* = 192)	≥ 20 (*n* = 237)	*P**
LN metastasis	78 (39.1%)	57 (25.3%)	0.002
Distant organ metastasis	51 (26.6%)	26 (17.3%)	0.020

**P* <0.05 was considered statistically significant. LNs, lymph nodes.

number of negative LNs may contribute to a reduction in the frequency of unrecognized tumor cells. Immunohistochemical analyses have shown that a high rate of LN-negative patients have nodal metastases that were missed during routine pathology examinations.[19,20] Thus, removing more negative LNs that may harbor occult cancer could eliminate residual tumor cells and reduce the potential for subsequent tumor recurrence and metastasis.

There is no standard for an optimal lymphadenectomy. The primary methods of lymphadenectomy include traditional two-field lymphadenectomy (middle or lower mediastinal + abdominal regions), modern two-field lymphadenectomy (total mediastinal + abdominal regions), and three-field lymphadenectomy (cervical + total mediastinal + abdominal regions).[18] Rizk *et al.* examined 4627 patients with esophageal cancer who underwent esophagectomy and demonstrated that > 60% of the population had > 15 total RLNs.[21] In this study, the mean total number of RLNs was 26.8, and 86.9% (373/429) of the patients had ≥ 15 RLNs. Furthermore, we included patients who had < 15 RLNs (in order to maintain applicability). We included patients who underwent trans-right-thoracic esophagectomy and modern two-field lymphadenectomy, and excluded patients who underwent trans-left-thoracic esophagectomy. The primary reason for this exclusion is that trans-left-thoracic esophagectomy traditionally only has a two-field lymphadenectomy (middle or lower mediastinal + abdominal regions) without upper mediastinal lymphadenectomy, which reduces the accuracy of nodal staging and TNM classification.

The number of negative LNs and T staging are both well-established independent prognostic factors. When we analyzed the survival differences between the groups with different numbers of examined negative LNs for different T classifications, we observed an increased cancer-specific five-year survival rate as the number of examined negative LNs increased with different T classifications. In addition, the patient with > 20 LNs examined demonstrated greatly reduced LN and distant organ metastases compared to patients in whom fewer LNs were examined. Furthermore, we observed that examining > 19 LNs did not improve the survival of patients with ESCC. The depth of tumor invasion was determined prior to surgery, and the tumor-specific prognoses of the ESCC patients were decided. However, surgeons can increase the number of RLNs to improve the OS of ESCC patients by improving the quality and number of dissected LNs.

There were some limitations to this study. First, there was a potential for selection bias because of the retrospective nature of the study. Second, the number of RLNs may be affected by underreporting the extent of lymphadenectomy because pathologists may not examine all of the LNs from an en-bloc resected specimen. Third, all patients in our study received modern two-field lymphadenectomy, and no patients received three-field lymphadenectomy. Finally, none of the patients in this study received neoadjuvant therapy. We believe that future studies need to focus on this aspect.

In conclusion, we demonstrated that the number of negative LNs and the depth of tumor invasion influence the prognosis of patients with LN-negative ESCC. We recommend examining ≥ 15 LNs in stage T1 and ≥ 20 in stages T2–3 as the minimum number for accurate staging of operable ESCC. In addition, we suggest that surgeons should identify and label the LNs embedded in the en bloc specimen before sending them to the pathologist.

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Disclosure

No authors report any conflict of interest.

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