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Original Article

Prognostic value of the number of lymph nodes resected in patients with lymph-node-negative esophageal squamous cell carcinoma

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Abstract: No consensus has been achieved regarding the optimal extent of lymph node (LN) dissection for node-negative ESCC patients. This study aimed to determine the optimal extent of LN dissection for node-negative ESCC patients. We retrospectively reviewed 481 ESCC patients with node-negative resection and no preoperative therapy. Overall survival (OS) was evaluated by the log-rank test and multivariate Cox regression. The 5-year OS was 51.7% and 64.7% for patients with 1-5 and ≥6 negative LNs resected, respectively (P<0.001). However, there was no significant survival difference between patients with 6-12 negative LNs resected and patients with over 12 negative LNs resected (P=0.205). Multivariate analysis indicated that the negative LN count was independently associated with better survival. In the subgroup analysis, no optimum lymphadenectomy was defined for T1; the minimum number of LNs that needed to be resected was 6 nodes for T2 and 7 nodes for T3. No survival benefit was observed when extensive lymphadenectomy was performed. The nomogram, including the number of LNs examined, T stage, and histologic differentiation, had more predictive power than TNM staging. The results of our study suggest that ESCC patients with LN-negative tumors should have at least 6 LNs examined for T2 and 7 LNs for T3, but extensive lymphadenectomy is not recommended. The nomogram, including the number of LNs examined, T stage, and histologic differentiation, is a useful clinical tool.

Keywords: Esophageal carcinoma, node-negative, prognosis, lymphadenectomy

Introduction

Esophageal cancer is highly malignant, with the highest incidence in China. The majority of esophageal cancer in China is esophageal squamous cell carcinoma (ESCC), with the fourth highest ranking cancer-associated mortality rate among all malignant tumors [1]. The lymph node (LN) status is the most important prognostic factor in predicting the survival of esophageal carcinoma [2, 3]. According to the 7th American Joint Committee on Cancer (AJCC) staging system for esophageal cancer, the status of LN metastases is classified into four groups: N0 disease for patients without involvement of regional LNs, N1 disease for those with 1 or 2 regional LN metastases, N2 disease for those with 3-6 regional LN metastases and N3 disease for those with more than 6 regional LN metastases. Over 50% of the patients with node-negative esophageal carcinoma survive 5 years after diagnosis, compared with less than 10% of the patients with LNs involved [4, 5].

The significance of the negative LN count in predicting the postoperative survival of patients with ESCC remains unclear. Because of the important prognostic significance of LN metastases in patients with esophageal cancer, the relationship between a negative LN count and prognosis is confounded by the prognostic effect of the number of positive LNs. To exclude the influence of such confounding factors, we conducted a retrospective study from a Chinese population in a single institutional surgical database to determine the prognostic significance of a negative LN count and the minimum number of LNs needed to be resected in node-negative ESCC for sufficient nodal staging and the improvement of survival.

Table 1. Distribution of clinicopathologic characteristics for three categories by the number of lymph nodes examined

Variable	No. of nodes examined (n)			*P*
	0-5	6-12	≥13	
Sex				0.722
Male	121 (25.2)	140 (29.1)	92 (19.1)	
Female	41 (8.5)	56 (11.6)	31 (6.4)	
Age (years)				0.022
<60	87 (18.1)	80 (16.6)	49 (10.2)	
≥60	75 (15.6)	116 (24.1)	74 (15.4)	
Tumor location				0.719
Upper third	12 (2.5)	14 (2.9)	7 (1.5)	
Middle third	114 (23.7)	127 (26.4)	82 (17.0)	
Lower third	36 (8.1)	55 (11.4)	34 (7.1)	
Histologic differentiation				0.546
Well	18 (3.7)	15 (3.1)	7 (1.5)	
Moderate	86 (17.9)	105 (21.8)	70 (14.6)	
Poor	58 (12.1)	76 (15.8)	46 (9.6)	
Pathologic T category				0.060
Tis	4 (0.8)	5 (1.0)	3 (0.6)	
T1	54 (11.2)	70 (14.6)	31 (6.4)	
T2	36 (7.5)	65 (13.5)	37 (7.7)	
T3	65 (13.5)	51 (10.6)	51 (10.6)	
T4	3 (0.6)	5 (1.0)	1 (0.2)	
AJCC stage				0.481
0	4 (0.8)	5 (1.0)	3 (0.6)	
I	55 (11.4)	71 (14.8)	32 (6.7)	
II	100 (20.8)	115 (23.9)	87 (18.1)	
IIIA	3 (0.6)	5 (1.0)	1 (0.2)	
Total	162	196	123	481

AJCC: American Joint Committee on Cancer.

Patients and methods

Patients

Radical esophagectomy patients with ESCC at our institution were retrospectively reviewed from January 2002 to January 2012. This study, according to the 1975 Declaration of Helsinki, was approved by our Institutional Review Board for the review of the medical records and pathological material with informed consent from all patients.

All patients included for analysis met the following inclusion criteria: (1) ESCC, (2) received R0 resection, and (3) negative LNs. Patients with LN metastases, incomplete resection, or no esophagectomy were excluded.

Surgery

All patients received transthoracic en bloc esophagectomy with two-field LN dissection. Resected LNs were retrieved from the en bloc specimen by the surgeons or the pathologists. The remaining LNs were identified and recorded from the fresh specimen and the formalin-fixed specimens.

Follow-up

Systematical evaluation, including clinical history, physical examination, laboratory analysis, upper gastrointestinal endoscopy, ultrasound, and chest and abdomen computerized tomography, was performed in the follow-up. The telephone interview, approved by the Institutional Review Board, was performed to ascertain the patient's disease status at the end of follow-up.

Statistical analysis

The statistical analysis was performed by SPSS and GraphPad Prism 6.0. Survival curves were obtained using the log-rank test. Cox regression analysis was used for multivariate analysis, including clinicopathologic characteristics. Cutoff values of the optimal number of negative LNs (which were 6 LNs for the entire cohort and the T2 subgroup, 7 LNs for the T3 subgroup and none for the T1 subgroup) were determined by X-tile software (http://www.tissuearray.org/rimmlab) [6].

Results

Patient characteristics

A total of 481 patients with pN0 ESCC were included in this study. The median age of the patients was 61 years (range, 37-95 years). The 5-year overall survival and the median survival time were 60.4% and 55.3 months, respectively. Patient characteristics are summarized in **Table 1**. The number of resected LNs ranged from 1 to 38 (median 10). The result of assess-

Table 2. Log-rank and Cox analysis of overall survival of 481 esophageal squamous cell carcinoma patients after operation (n=481)

Factors	Log-rank analysis			Cox analysis		
	Median (ms)	At 5 years (%)	*P*	HR	95% CI	*P*
Sex			0.026			0.092
Female	Not reached	67.4		1		
Male	87.7	57.9		1.352	0.9-1.9	
Age (years)			0.540			0.077
<60	Not reached	61.7		1		
≥60	105.0	59.4		1.292	0.9-1.716	
Tumor location			0.606			0.934
Upper third	93.0	63.5		1		
Middle third	110.2	58.8		0.935	0.5-1.6	
Lower third	Not reached	63.9		0.895	0.5-1.7	
Histologic differentiation			<0.001			0.002
Well	Not reached	89.7		1		
Moderate	110.2	62.8		2.965	1.1-8.2	
Poor	67.8	50.7		4.277	1.5-11.9	
Pathologic T category			<0.001			<0.001
Tis-T1	Not reached	80.1		1		
T2	Not reached	62.7		1.818	1.2-2.8	
T3	47.0	42.2		2.815	1.9-4.1	
T4	38.5	33.3		4.237	1.9-9.6	
No. of examined LNs			<0.001			<0.001
0-5 LNs	69.8	51.7		1		
≥6 LNs	Not reached	64.7		0.509	0.4-0.7	
AJCC stage			<0.001			-
0-I	Not reached	79.9		-	-	
II	64.0	50.6		-	-	
III	38.5	33.3		-	-	

AJCC: American Joint Committee on Cancer, 95% CI: 95% confidence interval, LN: lymph node.

ing the number of LNs resected was that, compared with the node-positive patients, the number of resected LNs was less in the node-negative patients. In addition, there was no statistically significant difference in the distribution of sex, tumor location, histologic differentiation, pathologic T category or AJCC staging among the three groups with different numbers of negative LNs examined; however, there was a statistically significant difference in age among the groups (**Table 1**).

Survival analyses

Univariate log-rank analysis for the entire cohort demonstrated that the 5-year survival rate was higher in the patients with ≥6 LNs resected than in the patients with <6 LNs resected (64.7% vs. 51.7%, *P*<0.001) (**Table 2**; **Figure 1A**). We also performed multivariate analysis to evaluate whether the number of negative LNs resected was associated with OS. As shown in **Table 2**, patients with ≥6 negative LNs resected had significantly higher OS after adjusting for sex, age, tumor location, histologic differentiation, and pathologic T category (*P*< 0.001). A previous study showed that patients with over 12 LNs resected have more opportunity for LN metastasis detection than patients with less than 12 LNs examined [7], and the 7th AJCC staging system recommended that at least 12 LNs should be examined for accurate staging [8]. However, no significant survival difference was observed between the patients with 6-12 LNs resected and the patients with more than 12 negative LNs resected (5-year OS rate, 66.6% vs. 61.8%, *P*=0.205, **Figure 1B**).

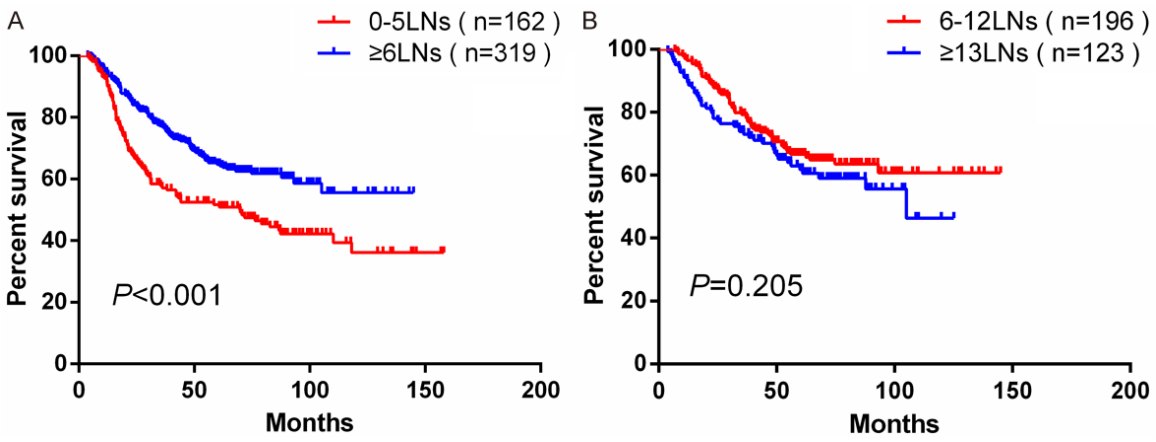

Figure 1. A. Overall survival for patients with less than 6 LNs examined and for patients with at least 6 LNs examined in the entire cohort of 481 patients (5-year OS rate, 51.7% for <6 LNs examined vs. 64.7% for ≥6 LNs examined, *P*<0.001). B. Overall survival for patients with 6-12 LNs examined and for patients with over 12 LNs examined (5-year OS rate, 66.6% for 6-12 LNs examined vs. 61.8% for over 12 LNs examined, *P*=0.205).

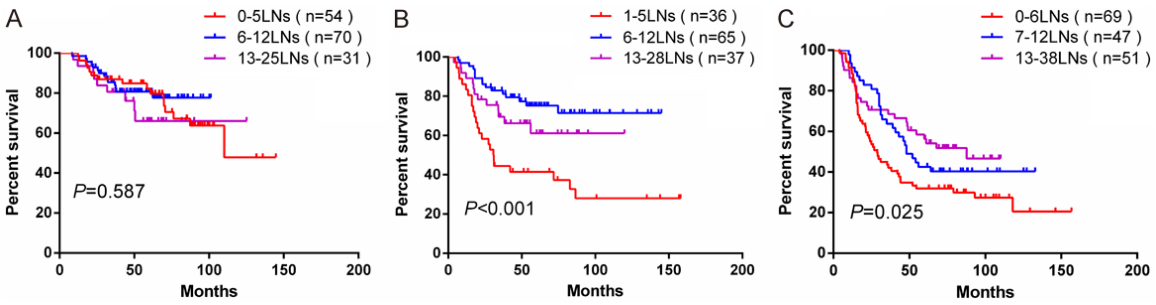

Figure 2. A. Overall survival for 3 groups stratified according to the number of negative LNs examined in pathologic stage T1 patients (n=155). Among the 3 groups, *P*=0.586; Group 1 (1-5 LNs examined) vs. Group 2 (6-12 LNs examined), *P*=0.651; Group 1 (1-5 LNs examined) vs. Group 3 (over 12 LNs examined), *P*=0.475; Group 2 (6-12 LNs examined) vs. Group 3 (over 12 LNs examined), *P*=0.296. B. Overall survival for 3 categories of patients according to the number of the LNs examined in pathologic stage T2 patients (n=138). Among the 3 groups, *P*<0.001; Group 1 (1-5 LNs examined) vs. Group 2 (6-12 LNs examined), *P*<0.001; Group 1 (1-5 LNs examined) vs. Group 3 (over 12 LNs examined), *P*=0.021; Group 2 (6-12 LNs examined) vs. Group 3 (over 12 LNs examined), *P*=0.185. C. Overall survival for 3 categories of patients according to the number of the LNs examined in pathologic stage T3 patients (n=167). Among the 3 groups, *P*=0.024; Group 1 (1-6 LNs examined) vs. Group 2 (7-12 LNs examined), *P*=0.047; Group 1 (1-6 LNs examined) vs. Group 3 (over 12 LNs examined), *P*=0.021; Group 2 (7-12 LNs examined) vs. Group 3 (over 12 LNs examined), *P*=0.458.

Stratified analyses

In the subgroup analysis stratified by T stage, patients with a higher number of negative LNs resected in the T2 and T3 subgroups had better survival than those in the T1 subgroup (**Figure 2A-C**). The 5-year survival rate in T1 patients was 82.3% for patients with 1-5 LNs resected, 80.7% for patients with 6-12 LNs resected, and 66% for patients with over 12 LNs resected (*P*=0.586). No significant survival difference was found among the three groups in T1 patients (**Figure 2A**). In the T2 subgroup, the patients with at least 6 negative LNs resected had better survival than the patients with less than 6 negative LNs resected (5-year survival rate, 70.2% vs. 41.5%, *P*<0.001). Moreover, there was no difference in survival between the patients with 6-12 LNs resected and the patients over 12 LNs resected (5-year survival rate, 75.2% vs. 61.1%, *P*=0.185, **Figure 2B**). In the T3 subgroup, the patients with no less than 7 negative LNs resected had better survival than the patients with less than 7 negative LNs resected (5-year survival rate, 49.6% vs. 31.9%, *P*=0.008). Additionally, similar to the result observed in the T2 subgroup, there was no difference in survival between the patients

Table 3. Multivariate analysis of factors related to the survival of patients with ESCC, grouped by T stage (n=460)

Characteristics	T1#			T2			T3		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex			0.082			0.781			0.290
Female	Ref			Ref			Ref		
Male	2.029	0.9-4.5		1.098	0.6-2.1		1.331	0.8-2.3	
Age (years)			0.766			0.127			0.314
<60	Ref			Ref			Ref		
≥60	1.113	0.5-2.3		1.578	0.9-2.8		1.223	0.8-1.8	
Tumor location			0.390			0.143			0.468
Upper third	Ref			Ref			Ref		
Middle third	0.513	0.2-1.5		0.428	0.1-1.5		1.445	0.7-3.2	
Lower third	0.425	0.1-1.5		0.730	0.2-2.6		1.131	0.5-2.8	
Differentiation			0.028			0.476			0.081
G1	Ref			Ref			Ref		
G2	3.144	0.7-14.1		2.664	0.3-20.5		1.335	0.2-9.7	
G3	5.753	1.3-25.4		2.041	0.3-15.9		2.074	0.3-15.1	
No. of LNs examined			0.467			<0.001			0.001
0-5 LNs	Ref			Ref			Ref		
≥6 LNs	0.774	0.4-1.5		0.280	0.2-0.5		0.514	0.3-0.8	

95% CI: 95% confidence interval; LN: lymph node; Ref: reference. #Tis and T4 were not analyzed because of the small number.

with 7-12 LNs resected and the patients with more than 12 LNs resected (5-year survival rate, 42.6% vs. 56.3%, *P*=0.458, **Figure 2C**). The results of multivariate Cox regression analysis (**Table 3**) showed that the number of negative LNs was an independent prognostic factor for predicting survival in patients with T2 and T3 stage ESCC but not in patients with T1 stage ESCC (**Table 4**). On multivariate analysis, the results also showed that the number of negative LNs was an independent prognostic factor for predicting survival in patients with moderately-differentiated and poor-differentiated ESCC (**Table 4**).

Nomogram

Based on Cox multivariate analysis (**Table 2**), we established a nomogram including the number of examined LNs, T stage, and histological differentiation for predicting the prognosis of patients with lymph-node-negative ESCC (**Figure 3**). For each independent variable, the score in **Figure 3** is a selected scoring standard or scale, and a vertical value is given at that point. The score in the figure is a selected scoring standard or scale. For each independent variable, a straight line perpendicular to the fractional axis (through a ruler) is made at that point, and the intersection point represents the score under the value of the independent variable. Then, we can obtain the scores corresponding to the indicators predicting ESCC prognosis of each variable, and the sum of each score is recorded as the total score. The corresponding number of the total score is the 3- and 5-year probability of survival. The bootstrap test is used to perform the consistency test of the predicted value and the actual value. The result indicates that the predicted value of the nomogram model coincides with the actual value (**Figure 4A** and **4B**). We then used the area under the ROC curve to compare the prediction ability of the nomogram and TNM staging. We found that the predictive power of the nomogram was significantly higher than that of TNM staging (**Figure 4C** and **4D**).

Discussion

Nodal status is the most important prognostic factor for patients with ESCC. The number of metastatic LNs [9-12], the total number of LNs resected [7, 13, 14], and the ratio of metastatic LNs to the total number of LNs resected [15-18] are independent prognostic factors for

Table 4. Multivariate analysis of factors related to the survival of patients with ESCC, grouped by differentiation grade (n=481)

Characteristics	Well			Moderate			Poor		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex			0.731			0.197			0.347
Female	Ref			Ref			Ref		
Male	1.729	0.1-39.0		1.386	0.8-2.3		1.283	0.8-2.2	
Age (years)			0.517			0.212			0.239
<60	Ref			Ref			Ref		
≥60	2.729	0.1-56.9		1.282	0.9-1.9		1.298	0.8-2.0	
Tumor location			0.564			0.272			0.291
Upper third	Ref			Ref			Ref		
Middle third	0.213	0.0-5.8		1.360	0.5-3.4		0.721	0.3-1.5	
Lower third	0.158	0.0-6.0		0.934	0.3-2.5		1.031	0.5-2.4	
Pathologic T category			0.379			0.002			<0.001
Tis-T1	Ref			Ref			Ref		
T2	5.0	0.2-124.9		2.478	1.4-4.5		1.161	0.6-2.2	
T3	5.6	0.3-112.5		3.024	1.7-5.4		2.731	1.6-4.6	
T4	-	-		2.767	0.8-9.6		6.476	2.1-19.8	
No. of LNs examined			0.235			0.002			0.001
0-5 LNs	Ref			Ref			Ref		
≥6 LNs	0.171	0.0-3.2		0.531	0.4-0.8		0.467	0.3-0.7	

95% CI: 95% confidence interval; LN: lymph node; Ref: reference.

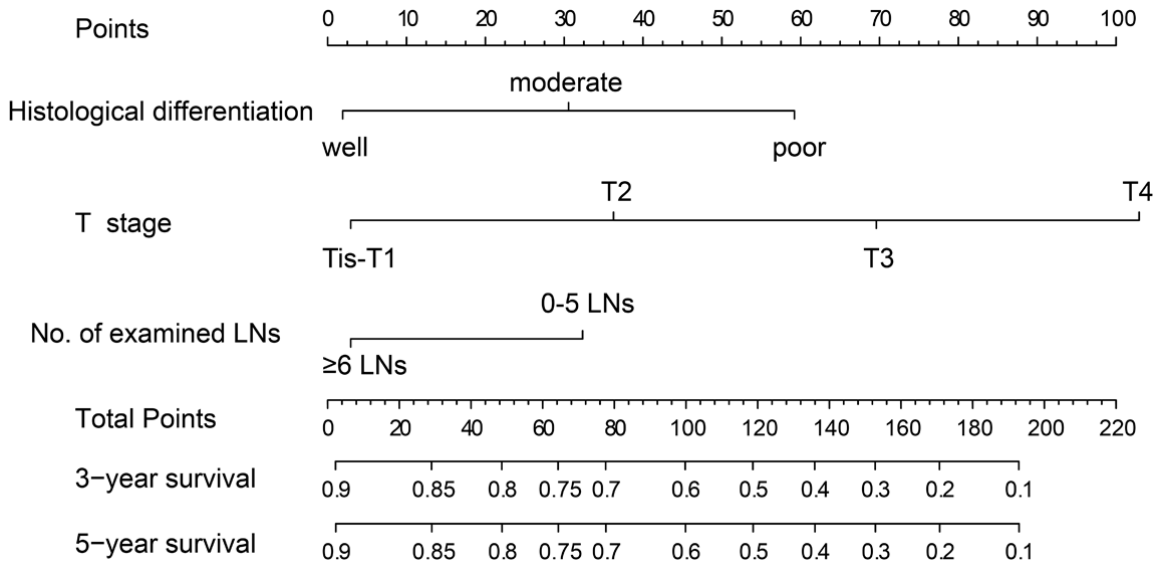

Figure 3. Nomogram integrating the number of examined LNs, T stage, and histologic differentiation in patients with lymph node-negative ESCC.

ESCC patient survival. However, the number of negative LNs for predicting prognosis remains controversial. For node-positive esophageal cancer, several studies reported that a high number of negative LNs was associated with an improved survival of esophageal cancer [13, 19, 20]. Their results can be explained by the fact that more negative LNs represented a lower positive LN ratio, which indicated a better prognosis in many previous studies. In contrast, for node-negative esophageal cancer, especially for ESCC, the significance of the

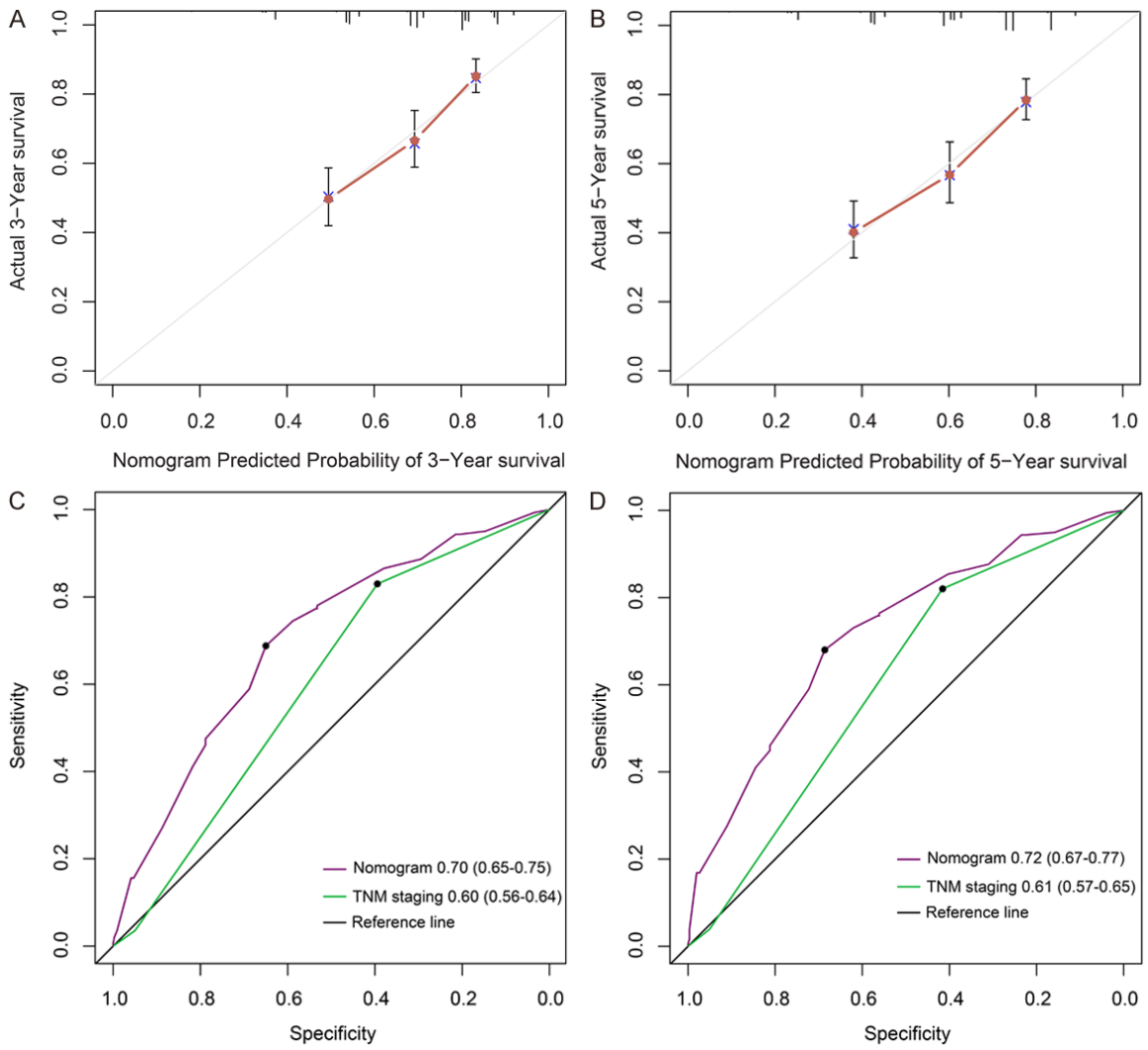

Figure 4. Calibration curve for predicting patient survival at 3 years (A) and 5 years (B). Time-dependent ROC curves by nomogram and TNM stage for 3-year (C) and 5-year (D) OS.

effect of the number of LNs resected on survival remains controversial. Greenstein et al. evaluated the effect of the number of lymph nodes removed on the postoperative survival of N0 esophageal cancer patients from the SEER database and found that the number of LNs sampled was not associated with the survival of ESCC patients [21]. In another study by Hsu and his colleagues that included 754 ESCC patients from a single institution, the results indicated that the association of a high number of negative LNs with survival was more prominent in locally advanced patients with node-positive ESCC but not in patients with node-negative ESCC [20]. Similar results were observed in the study by Baba et al., who suggested that node-negative ESCC patients with a high negative-LN count did not show a better prognosis than those with a low negative-LN count [19]. In our study, we found that a negative LN count was associated with survival in ESCC patients without LN metastases. Patient survival improved with the increased number of negative LNs resected. This is because the resection of less than 6 LNs will miss positive LNs and lead to incorrect staging. Some patients classified as having negative LNs may actually have occult metastatic LNs [22, 23].

Precise nodal staging for esophageal cancer plays an important role in treatment for predicting postoperative survival and guiding treatment strategy. According to the suggestion of the 7th AJCC staging system, at least 12 LNs

should be examined for accurate staging [8]. However, to our knowledge, there are no published guidelines defining an adequate lymphadenectomy for accurate staging and better survival in node-negative ESCC patients. Our results indicated that at least 6 LNs should be resected to improve prognosis in LN-negative ESCC patients. This result was coincident with the observation from Hu et al., who investigated 1098 patients with advanced ESCC [24]. They evaluated the influence of resected LN count on the prognosis of patients and recommended that a minimum of 6 LNs needed to be removed for improved survival in patients with negative LNs.

Previous studies according to the research results put forward different thresholds of the minimum LN dissection count. Both Liu et al. [25] and Yang et al. [26] indicated that at least 16 or 18 LNs need to be resected for negative-LN ESCC patients after curative resection. The minimum LN dissection number of the abovementioned studies was more than that of our study. A probable explanation for this finding is that the majority of patients with esophageal cancer in the abovementioned study were treated in the 1990s. Since then, great progress has been made in esophageal carcinoma operation, including a decreased risk of postoperative residual malignancy and an improved postoperative cure rate. Dutkowski and his colleagues reported that a maximum increase in the sensitivity in classifying pN occurred from 1 to 6 LNs examined [27]. Nevertheless, a limited improvement of sensitivity was shown when more than 12 LNs were examined; moreover, the incidence of complications may significantly increase. The 7th AJCC staging system also pointed out that the extent of lymphadenectomy should be balanced against the risk of complications, including anastomotic leakage, recurrent laryngeal nerve damage and respiratory complications [28, 29]. Moreover, the prevalence of lymph node metastases in early ESCC patients was very rare [30, 31]. As the reasons mentioned above, our study showed no survival difference in ESCC patients with 6-12 LNs resected compared with those with over 12 LNs resected. Extensive lymphadenectomy showed no improved prognosis in our study and may not be indicated for early stage LN ESCC patients who were diagnosed with negative LN by preoperative clinical examination and showed little probability of LN metastasis.

Rizk et al. analyzed 4627 esophageal cancer cases from the Worldwide Esophageal Cancer Collaboration database and found that the optimum lymphadenectomy should be modulated by T classification [32]. In pN0M0 cancers, the optimum lymphadenectomy threshold was 10 nodes for pT1, 15 for pT2, and ≥30 for pT3/T4. We also performed stratified analysis according to the invasion depth of the tumor. Only the cases with T1, T2 and T3 disease were included for subgroup analysis because the number of Tis (n=42) and T4 (n=12) subgroups were too small to be further stratified analyzed. In the T1 subgroup, survival did not improve with the increase in the number of LNs dissected. The most likely explanation is that the incidence of LN metastasis in the T1 stage is very low [30, 33]. Extensive lymphadenectomy, which increases the postoperative complication rates and postoperative systemic inflammatory response and influences prognosis, is not necessary for patients in the T1 stage [34, 35]. The minimum number of LNs needed to be resected for the T2 and T3 subgroups was 6 and 7 LNs, respectively. However, extensive lymphadenectomy in the T2 and T3 subgroups, such as over 12 LNs resected, showed no improvement in survival when compared with the patients with 6-12 LNs resected. The population of the study by Rizk et al. was mainly from western countries, and squamous cell carcinoma accounted for only 40% of the tumors. Therefore, their conclusions may not be suitable for Eastern populations in which squamous cell carcinoma is the most prominent.

In conclusion, according to the present results, we suggest that at least 6 LNs should be examined for improved survival in ESCC patients with negative LNs; however, more extensive lymphadenectomy, for example, over 12 LNs resected, did not improve survival.

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Disclosure of conflict of interest

None.

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