Can Lymph Node Ratio Replace pN Categories in the Tumor-Node-Metastasis Classification System for Esophageal Cancer?

Zihui Tan,† Guowei Ma,*† Haoxian Yang,*† Lanjun Zhang,*† Tiehua Rong,*† and Peng Lin, PhD*†*

Background: We evaluated the prognostic value of lymph node ratio (LNR) in esophageal squamous cell carcinoma (ESCC) patients after tri-incisional esophagectomy by making comparisons with pN categories in the UICC/AJCC (International Union Against Cancer/American Joint Committee on Cancer) classification system (seventh edition).

Methods: Seven hundred ESCC patients underwent tri-incisional esophagectomy at our center (1988–2008) without neoadjuvant therapy. The adjusted X-tile cutoff values for LNR of 0 and 0.25 were compared with those in UICC/AJCC pN categories.

Results: Univariate and multivariate analyses identified LNR as a significant prognostic factor regardless of the number of retrieved LNs. Spearman's correlation analysis showed close linear correlations between the number of examined and metastatic LNs ($r = 0.205$, $p < 0.001$), but not between the number of examined LNs and LNR ($r = 0.058$, $p = 0.123$). Significant prognostic differences were seen among LNR categories in all pT categories ($p < 0.05$), but not in pN categories stratified by tumor status (except T3: $p < 0.001$). Significant prognostic difference was seen among LNR categories in all pN categories ($p < 0.05$), but not between pN categories in all LNR categories ($p > 0.05$). Significant differences in 5-year cancer-specific survival rates were found among retrieved-node groups in the same pN category (except N2+3: $p = 0.733$), but not within the same LNR category (except N0: $p < 0.001$).

Conclusions: LNR is an independent prognostic factor after tri-incisional esophagectomy, regardless of the number of retrieved LNs. In ESCC, LNR might reduce stage migration, have more potential for predicting patient outcomes, and compensate for deficiencies in UICC/AJCC pN categories.

*State Key Laboratory of Oncology in South China; and †Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China.

Zihui Tan and Guowei Ma contributed equally to this work.

This work was supported by a grant from Sun Yat-sen University Clinical Research 5010 plan (2007044), the Fundamental Research Funds for the Central Universities (No. 09YKPY51), the Science and Technology Planning Project of Guangdong Province, China (No. 2010B31500010), and the National High Technology Research and Development Program of China (863 Program; No. 2009AA02Z421).

Disclosure: The authors declare no conflict of interest.

Address for Correspondence: Peng Lin, PhD, Department of Thoracic Surgery, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, China. E-mail: linpeng3439@126.com

ISSN: 1556-0864/14/0908-1214

Key Words: Esophageal cancer, Lymph node ratio, pN categories, UICC/AJCC TNM classification

(*J Thorac Oncol.* 2014;9: 1214–1221)

Esophageal carcinoma is an aggressive malignancy and a major cause of cancer-related deaths worldwide.[1] Lymph node (LN) metastasis is a significant prognostic factor in patients with resected esophageal cancer; thus, accurate categorization of LN metastasis or optimization of pN classification is helpful to make decisions regarding their postoperative treatment.[2,3] The International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have proposed an updated classification (seventh edition) for N categories based on the number of metastatic LNs (pN),[4] which provides a more accurate estimation of prognosis than the sixth edition.[5] Some authors have pointed out the superiority of the new UICC/AJCC classification system on the grounds of its simplicity, reliability, and stratification, but have also mentioned some problems such as stage migration.[6] The new system addresses instances in which evaluation of an inadequate LN number leads to downstaging and subsequent underestimation of disease severity. Meanwhile, several reports have indicated that the accuracy of staging and survival in esophageal cancer increases proportionally with the number of retrieved LNs.[6–8]

Recently, a new prognostic tool, LN ratio (LNR)—a ratio of the number of metastatic LNs to the total number of examined LNs—was proposed. This ratio reflects the degree of LN metastasis and may help resolve stage migration. However, few studies have reported the prognostic significance of LNR in esophageal cancer[9–13] and no relevant publications are available for thoracic esophageal squamous cell carcinoma (ESCC) after tri-incisional esophagectomy. Thus, whether LNR is optimal for ESCC prognosis or whether LNR staging is better than the current pN system remains unknown.

This retrospective study evaluated the prognostic value of LNR in ESCC patients after tri-incisional esophagectomy in comparison with pN according to the seventh edition of the UICC/AJCC classification system.

PATIENTS AND METHODS

Study Design and Patients

This retrospective study was approved by the Ethics Committee of the Sun Yat-sen University Cancer Center

(Guangzhou, Guangdong, China). The records of all patients who underwent tri-incisional esophagectomy for ESCC at the Sun Yat-sen University Cancer Center between January 1988 and December 2008 were collected. Patients eligible for this cohort study had pathologically confirmed ESCC and were treated by primary esophagectomy. Patients were not eligible if tumors were located at the cervical esophagus or esophagogastric junction, or had other histological subtypes of esophageal cancer besides ESCC. Patients who underwent R1/R2 resection and received neoadjuvant radiotherapy or chemotherapy were also excluded.

Preoperative Evaluation

Initially, all patients were clinically staged on the basis of barium esophagography, cervical ultrasonography, computed tomography (CT) of the chest and upper abdomen, upper gastrointestinal endoscopy, and tumor biopsy. Endoscopic ultrasound and positron emission tomography were later added to the staging workup. Patients were considered for surgical resection if preoperative evaluation revealed no evidence of distant metastases and there was no evidence of direct invasion of the airway or major vascular structures. All patients had a Karnofsky performance status of ≥80. Patients with pulmonary and/or cardiac diseases were considered ineligible for resection.

Surgical Resection

The surgical techniques of tri-incisional esophagectomy and lymphadenectomy have been described elsewhere.[14] All resections were performed using a tri-incisional approach involving an initial right-sided posterolateral thoracotomy to allow resection of the esophagus and mediastinal lymphadenectomy, followed by midline laparotomy for mobilization of the stomach and a left-sided cervicotomy for anastomosis. Definitions of lymphadenectomy were based on the 1994 consensus conference of the International Society for Diseases of the Esophagus.[15] The alimentary tract was reconstructed using the gastric pull-up technique. After the mobilized stomach was pulled up to the neck through the retrosternal or posterior mediastinal route, anastomosis was performed through a left cervical incision. The surgeons identified LN sites perioperatively and recorded their numbers during specimen dissection postoperatively. All resected specimens were submitted for pathological examination and LN involvement was classified according to the 2009 UICC/AJCC Tumor-Node-Metastasis (TNM) classification system.[4] LN station spread was determined according to Casson's LN drainage map.[16]

Follow-Up

Patients were recommended for follow-up examinations at our outpatient department every 3 months for the first 2 years, every 6 months during the next 3 years and annually thereafter. Patients were subjected to the following during follow-up examinations: history taking, physical examination, barium esophagography, chest radiography, abdominal ultrasonography, cervical ultrasonography, and neck-abdomen CT scans. Patients underwent endoscopy and/or positron emission tomography-CT, if necessary. The last contact month to calculate the survival rate was June 2012. The median time from the operation to the last censoring date was 101.5 months (43–282 months). Mean follow-up time was 38 months. Lost of follow-up accounts for 15.18%.

Statistical Analysis

Optimal cutoff values of LNR were determined using X-tile software (http://www.tissuearray.org/rimmlab),[17] which were 0.03 and 0.24 in our series. X-tile, an objective method, not only can divide the cohort into three subsets, but also determine two optimal cutoff values by using the minimum p value. For the sake of convenience in clinical interpretation and application, these were adjusted to 0 and 0.25. Thus, three LNR subgroups (LNR0, 0%; LNR1, 1–25%; LNR2, 26–100%) were evaluated in the present study. Meanwhile, the cutoff values for the number of retrieved LNs were calculated at eight and 15 using X-tile. The 2012 National Comprehensive Cancer Network guidelines for ESCC recommended that at least 15 LNs should be retrieved for adequate nodal staging. Thus, the cutoff value was 15 in our study. Spearman's correlation coefficient was used to assess the correlation between the number of retrieved and metastatic LNs, and the number of retrieved LNs and LNR. Survival curves were constructed using the Kaplan-Meier method and the log-rank test was used to assess differences in survival between groups. Multivariate analysis was carried out with a Cox proportional hazards model. A two-sided p value less than 0.05 was considered significant. Survival time was measured from the date of the operation to the date of death or the last follow-up. Patients who were lost during follow-up were censored at the last time of contact for data analysis, and so were those alive at the end of the study. Patients who died from causes other than cancer relapse were censored on the date when the cancer-specific survival (CSS) rate was calculated. Operative deaths were included as cancer-specific deaths. Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL).

RESULTS

Clinicopathological Characteristics of Patients

This study examined 700 consecutive ESCC patients (median, 57 years; range, 28–88 years) who underwent potentially curative resection at our institution between January 1988 and December 2008. The median number of examined and metastatic LNs was 16.4 (range, 1–78) and 1.2 (range, 0–31), respectively. Patients' clinical and pathological data and 5-year CSS rates are summarized in Table 1.

Univariate and Multivariate Survival Analyses

In univariate analysis, gender, surgical period, pT category, number of LNs retrieved (<15 versus ≥15), pN category (number of metastatic LNs), number of metastatic LN stations, and LNR were found to be significant prognostic factors (Table 1). In multivariate analysis, only pT category and LNR were independent prognostic factors (Table 2).

TABLE 1. Clinicopathological and Survival Data of 700 Esophageal Squamous Cell Carcinoma Patients

Variable	No. of Patients	5-Year CSS Rate	p[a]
Sex			
Male	491	36.3%	<0.001
Female	209	50.8%	
Surgical period			
1988–1998	140	27.6%	0.003
1999–2008	560	44.1%	
Tumor length			0.357
<3 cm	164	43.7%	
3–5 cm	327	41.2%	
>5 cm	209	38.3%	
Tumor location			0.205
Upper	225	36.1%	
Middle	436	41%	
Lower	39	68.8%	
Grade			0.147
Good	187	44.3%	
Moderate	340	41.1%	
Poor	173	33.2%	
T stage			<0.001
T1	75	61.1%	
T2	196	47.1%	
T3	362	35.9%	
T4	67	24.9%	
No. of metastatic LNs[b]			<0.001
N0	404	51.7%	
N1	199	31.2%	
N2	69	18.1%	
N3	28	11.2%	
No. of metastatic LN stations			<0.001
0	404	51.7%	
1	172	32.3%	
≥2	124	19.5%	
No. of fields of metastatic LNs			0.434
0	404	51.7%	
1	233	27.1%	
≥2	63	22.5%	
M stage			0.09
0	660	41%	
1	40	32.3%	
LNs retrieved			<0.001
<15	376	34.9%	
≥15	324	48%	
LNR[c]			<0.001
0	404	51.7%	
1	204	34.7%	
2	92	7.6%	

[a]Log-rank test.
[b]LNs: lymph nodes.
[c]LNR: lymph node ratio.
CSS, cancer-specific survival.

TABLE 2. Cox Regression Multivariate Analysis of the Prognostic Factors for Esophageal Squamous Cell Carcinoma Patients After Tri-incisional Esophagectomy

	Relative Risk	95% CI	p[a]
Sex	0.736	0.516–1.048	0.089
Surgical period	1.208	0.791–1.846	0.382
T stage	1.399	1.104–1.773	0.005
No. of metastatic LNs	1.266	0.927–1.731	0.138
No. of stations of metastatic LNs	1.054	0.717–1.551	0.789
LNs retrieved	0.790	0.561–1.112	0.177
LNR	1.849	1.258–2.718	0.002

[a]Cox regression multivariate analysis.
LNR, lymph node ratio; LN, lymph nodes.

Comparison of Survival Rates among Different T Stages

Analyses of the entire cohort showed that esophageal CSS rate was significantly worse with increasing LNR and pN categories ($p < 0.001$; Fig. 1). The observed 5-year CSS rates for groups LNR0, LNR1, and LNR2 were 51.7%, 34.7%, and 7.6%, respectively. Similarly, patients in lower LNR categories had considerably better CSS rates when stratified by tumor status ($p < 0.05$; Table 3). In contrast, no significant differences were observed among different pN categories stratified by tumor status (except T3: $p < 0.001$; Table 4).

Correlation Between LN Metastasis and Retrieved LNs

Spearman's correlation analysis showed that the number of metastatic LNs was significantly correlated to that of retrieved LNs (r = 0.205, $p < 0.001$; Fig. 2*A*), but LNR was not correlated to the number of retrieved LNs (r = 0.058, $p = 0.123$; Fig. 2*B*).

Comparison of Survival Rates Between Patient Subsets in Either LN Classification

There was significant difference in 5-year CSS rates among different LNR categories within the same pN stages ($p < 0.05$; Table 5), but not among different pN stages within the same LNR stage ($p > 0.05$; Table 6). Significant differences in 5-year CSS rates were also found between different retrieved-node groups within the same pN category ($p < 0.05$; except N2+3: $p = 0.733$; Table 7), but not within the same LNR category ($p > 0.05$; except N0: $p < 0.001$; Table 7)

Regarding pN classification, the 5-year CSS rate of stage N0 and N1 patients was significantly shorter when less than 15 LNs (group 1) were retrieved compared with when greater than or equal to 15 LNs (group 2) were retrieved (N0, 42.4% versus 64%, $p < 0.001$; N1, 19.6% versus 39.5%, $p = 0.007$), whereas no significant difference was observed in N2+N3 patients between groups 1 and 2. When LNR classification was applied, differences in CSS rates between groups 1 and 2 were maintained for LNR0 (which is identical to N0), whereas no significant differences were observed between groups LNR1 and LNR2. Five-year CSS rates of LNR1 and

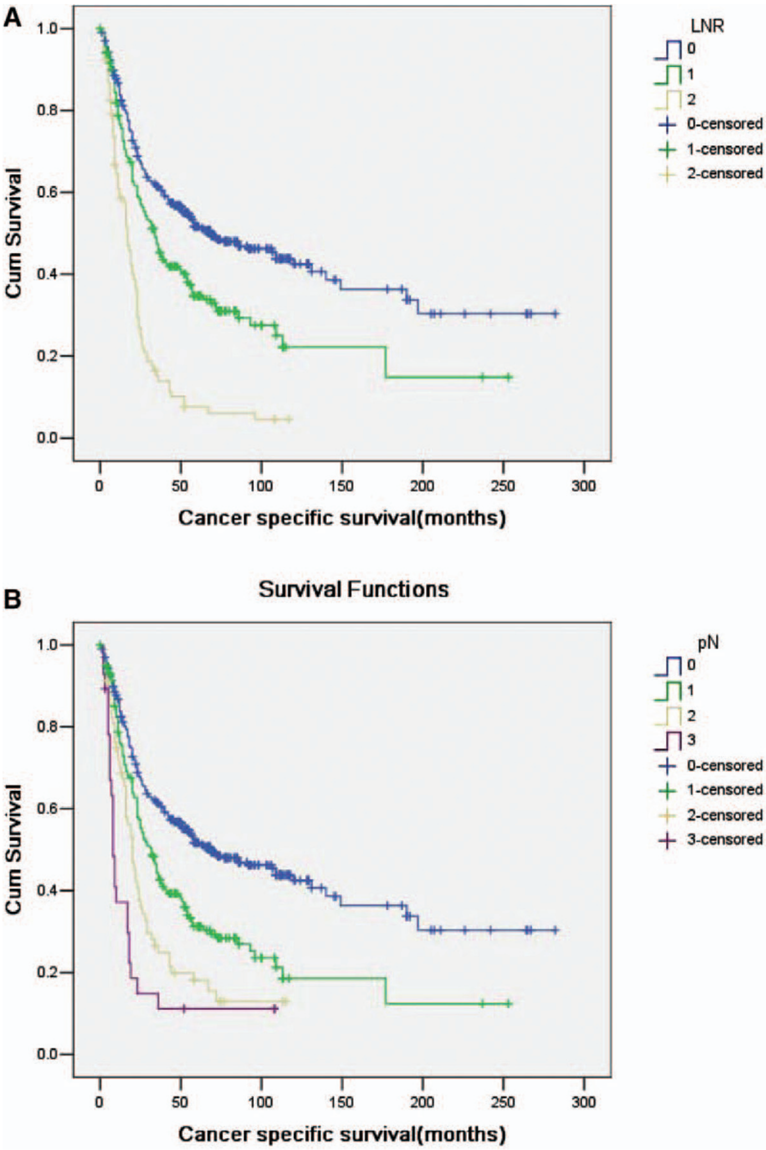

FIGURE 1. *A*, Esophageal cancer-specific survival (CSS) according to the LNR category. (*B*) Esophageal CSS according to the pN category.

LNR2 patients were 24.8% versus 30.9% (p = 0.291) and 6.8% versus 4.9% (p = 0.121) in groups 1 and 2, respectively.

DISCUSSION

An accurate staging classification system based on internationally accepted guidelines is of crucial significance in cancer treatment. Not only does such a system provide prognosis, it also aids the clinician in planning treatment and evaluating treatment results between different centers.[18] For the first time, the number of involved metastatic LNs has been incorporated into the esophageal cancer AJCC TNM system.[4] However, the number of metastatic LNs identified may depend on the number of LNs retrieved and examined. When the number of LNs retrieved and examined is insufficient, potentially metastatic LNs may be overlooked. The resulting stage migration phenomenon is because of inappropriate UICC/AJCC staging and overestimating the patient's prognosis.[19–21] Meanwhile, significant association was reported between high total nodal counts and improvement in disease-free and overall survival rates in various gastrointestinal cancers.[6,7,22–24] Thus, a new prognostic parameter, LNR, has been proposed as a simple, convenient, and reproducible system that can be used to better identify subgroups of gastric, breast, and colon cancer patients with similar prognosis.[25–28]

The value of LNR is being gradually accepted, but there is no consensus on optimal thresholds for LNR in esophageal cancer. Thus, controversies may result from the difference in number of cases examined, inclusion criteria, and statistical methods used to determine reasonable cutoff values. Bogoevski et al.[10] assessed 255 patients by classifying LNR into four categories (0, <11%, 11%–33%, and >33%) and identified LNR as an independent prognostic factor for overall survival in esophageal carcinoma patients, which is consistent with our conclusion. Mariette et al.[9] analyzed 536 patients (including 276 patients who received neoadjuvant chemoradiation) to emphasize significant prognostic differences between three LNR categories (0%,

TABLE 3. Esophageal Cancer-Specific Survival (CSS) Among T1–T4 Patients According to the LNR Category (All $p < 0.05$)

	LNR0		LNR1		LNR2		
	No. of Patients	5-Year CSS (%)	No. of Patients	5-Year CSS (%)	No. of Patients	5-Year CSS (%)	p^a
T1	62	63.4	13	36.9			0.049
T2	124	52.4	66	38.5	26	18	0.005
T3	185	47.9	121	31.6	56	1.9	<0.001
T4	33	36.1	24	19.7	10	0	0.043

[a]Log-rank test.
LNR, lymph node ratio; LN, lymph nodes.

TABLE 4. Esophageal Cancer-Specific Survival (CSS) Among T1–4 Patients According to the pN Category (All $p > 0.05$ Except T3 $p < 0.001$)

	N0		N1		N2		N3		
	No. of Patients	5-Year CSS	No. of Patients	5-Year CSS	No. of Patients	5-Year CSS	No. of Patients	5-Year CSS	p^a
T1	62	63.4%	12	40%	0	/	1	0%	0.126
T2	124	52.4%	54	33.3%	13	14.4%	5	6%	0.055
T3	185	47.9%	119	28.8%	19	17.9%	39	0%	<0.001
T4	33	36.1%	14	17.1%	17	17.6%	3	0%	0.137

[a]Log-rank test.

1%–20%, and >20%). However, these authors did not describe a specific method for selecting the reported cutoff values. In our retrospective study conducted at a single institution using X-tile analysis, we found that the optimal cutoff values were 0%, 1%–25%, and >25%, similar to previous reports.[9,11] We considered X-tile to be one of the most objective methods and more convenient in clinical application than abovementioned approaches in other studies, which may be relatively more subjective and less validate in clinical interpretation. Furthermore, X-tile is a validated computer program to determine optimal cutoff values using minimum p values from log-rank statistics and provide a method of dividing a single cohort into training and validation subsets for p values estimation when separate training and validation cohorts are not available.[17,29]

A larger study[12] used the cancer registry database of the Surveillance, Epidemiology, and End Results Program of the US National Cancer Institute and classified 838 cases of node-positive esophageal cancer into three groups according to LNR (≤0.2, 0.21–0.5, and >0.5) and found that the 5-year CSS rates were 30%, 16%, and 13%, respectively. The survival curves for the latter two groups were split, but there was no significant difference between them. As a consequence, only the LNR cutoff value of 0.2 in their report, which is close to our value, should be considered. Also, most patients (60%) had adenocarcinomas in their series compared with ESCC (34%). According to the seventh edition of the UICC/AJCC system,[4] the survival rates in these two cancer types are regarded as two separate entities and should be staged separately. In this respect, the results from our data are more significant and accurate because these are solely from ESCC patients. Moreover, the surgical strategies, preoperative treatment strategies, cell types, ethnicity, and hospital volume may be different in different centers, which could yield heterogeneous characteristics in the database. This suggests that selection bias may occur when the Surveillance, Epidemiology, and End Results database is used to determine LNR and LN staging. However, in our study, we included patients who underwent tri-incisional esophagectomy only and used cancer-specific mortality as the endpoint event to avoid unrelated causes of death affecting survival. We also excluded patients with tumors originating from the cervical esophagus or esophagogastric junction and those who received neoadjuvant radiotherapy or chemotherapy to avoid the impact of these surgeries on survival. We believe that this design made our data more homogeneous, and our purpose was more focused on LNR as the prognostic factor of ESCC patients.

To the best of our knowledge, this is the first large-sample size study to (1) determine the cutoff values of LNR using an objective method and (2) assess the prognostic value of LNR in ESCC patients by making comparisons with pN staging (seventh edition). Significant prognostic difference was found among LNR categories in all pT categories, whereas no significant difference was observed in pN categories stratified by tumor status. Furthermore, there was significant prognostic difference among LNR categories in all pN categories. However, no significant prognostic difference was found among pN categories in any LNR category. These results indicate heterogeneity within each pN category, whereas survival was homogeneous in each LNR category.

If the number of LNs examined is inadequate, downstaging of patients will manifest in pN staging because the prognostic power is greatly affected by the number of examined LNs. For example, the 5-year CSS rate in stage N0 patients was significantly lower in group 1 than in group 2. Similarly, the CSS rate in group 1 was significantly different from that in group 2 in stage N1 cases. The reason for this finding may be that some cases classified as stage N0 would have turned

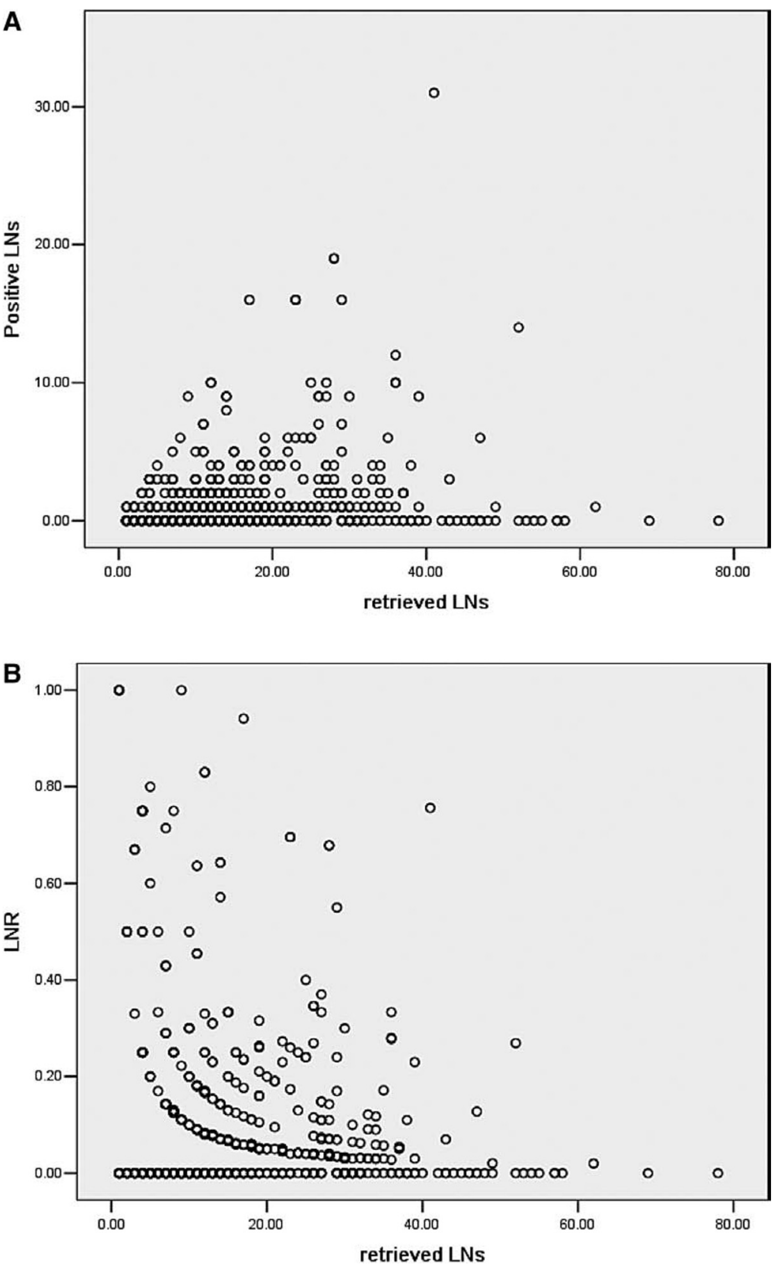

FIGURE 2. *A*, Spearman's correlation analysis showing significant correlation between positive lymph nodes (LNs) and retrieved LNs (r = 0.205, $p < 0.001$). (*B*) No significant correlation between LNR and the number of retrieved LNs (r = 0.058, $p = 0.123$).

out to be N+, whereas stage N1 cases would have turned out to be N2 or N3, if more LNs had been examined in group 1. A higher LN count may therefore reduce stage migration and favorably influence survival. In contrast, there was no significant difference between the two groups in stage N2+3 diseases, suggesting that a survival benefit may not be achieved through extended lymphadenectomy for advanced stage cases. Conversely, LNR could discriminate subsets of patients with similar prognoses. In addition, Spearman's correlation analysis showed close linear correlations between the number of examined and metastatic LNs, but not between the number of examined LNs and LNR. These findings emphasize the ability of LNR classification to minimize potential clinician errors or bias and obviate possible confounding factors related to the number of LNs removed. Furthermore, multivariate analysis showed that LNR categories have more potential for predicting patient outcomes and may be superior to UICC/AJCC pN categories.

For the same number of metastatic LNs, higher survival benefit is obtained with optimal lymphadenectomy compared with suboptimal lymphadenectomy, because LNR decreases with optimal lymphadenectomy. This demonstrates that LNR not only reflects tumor staging but also considers the extent of LN dissection. In other words, it considers treatment efficacy and safety margin of the lymphatic drainage area. For patients with early or localized diseases, LN dissection should be as optimal as possible to yield low LNR, without increasing the occurrence of postoperative complications. However,

TABLE 5. Esophageal Cancer-Specific Survival (CSS) Based on pN Category According to the LNR Category

	LNR1		LNR2		
	No. of Patients	5-Year CSS	No. of Patients	5-Year CSS	p^a
N1	165	35.1%	34	6.6%	<0.001
N2+3	39	28%	58	5.4%	0.024

[a]Log-rank test.
LNR, lymph node ratio.

TABLE 6. Esophageal Cancer-Specific Survival CSS based on LNR category according to the pN category

	N1		N2		N3		
	No. of Patients	5-Year CSS	No. of Patients	5-Year CSS	No. of Patients	5-Year CSS	p^a
LNR1	165	36.2%	36	30.6%	3	0%	0.249
LNR2	34	6.6%	33	4%	25	12.6%	0.56

[a]Log-rank test.

TABLE 7. Cancer-Specific Survival (CSS) Rates Based on pN and LNR Category According to the Number of LNs Retrieved (<15 vs. ≥15)

pN	5-year CSS (%)	p^a	LNR	5-year CSS (%)	p^a
0	<15 (42.4)	<0.001	0	<15 (42.4)	<0.001
	≥15 (64)			≥15 (64)	
1	<15 (19.6)	0.007	1	<15 (24.8)	0.291
	≥15 (39.5)			≥15 (39)	
2+3	<15 (10.2)	0.733	2	<15 (6.8)	0.121
	≥15 (16.8)			≥15 (4.9)	

[a]Log-rank test.
LNR, lymph node ratio; LN, lymph nodes.

for patients with advanced diseases, we emphasize multidisciplinary therapy because surgery alone with excessive lymphadenectomy leads to subjectively low LNRs, which will further increase the incidence of postoperative complications and yield no survival benefit. A consensus on optimal lymphadenectomy for different disease stages is yet to be addressed; we have designed a prospective study that is currently underway. Moreover, in terms of a fixed number of metastatic LNs, excessive lymphadenectomy will subjectively decrease LNR and patients' outcome will therefore be overestimated. In this particular situation, LNR cannot completely replace pN staging, but can rather play a complementary role.

Our study had several limitations. Our data were retrospectively collected, so it was difficult to draw an absolute conclusion that LNR is superior to UICC/AJCC pN categories for patients with resectable ESCC. Furthermore, our conclusions are based on a single institutional study of 700 ESCC patients in China who underwent tri-incisional esophagectomy. As the cutoff values vary among different studies, whether our results and cutoff LNR values can be applied to other institutions remains to be demonstrated.

In conclusion, our study reports that LNR is an independent prognostic factor in ESCC patients who underwent tri-incisional esophagectomy, regardless of the number of retrieved LNs. Furthermore, for these patients, LNR might reduce stage migration, have more potential for predicting patient outcomes, and compensate for deficiencies in UICC/AJCC pN categories.

ACKNOWLEDGMENTS

This work was supported by the grant "5010 plan" from Sun Yat-sen University, which focuses on randomized control studies with multidisciplinary therapy on esophageal carcinoma (Clinical Trial No.:NCT01137123). The authors thank the members of the Department of Thoracic, Pathology, Radiology and Epidemiology at the Sun Yat-sen University Cancer Center for their cooperation and assistance.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
2. Wu PC, Posner MC. The role of surgery in the management of oesophageal cancer. *Lancet Oncol* 2003;4:481–488.
3. Lin CS, Chang SC, Wei YH, et al. Prognostic variables in thoracic esophageal squamous cell carcinoma. *Ann Thorac Surg* 2009;87:1056–1065.
4. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17:1471–1474.
5. Greene FL, et al. Esophagus. In: *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*. 6th ed. New York: Springer; 2002:167–78.

6. Altorki NK, Zhou XK, Stiles B, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. *Ann Surg* 2008;248:221–226.
7. Peyre CG, Hagen JA, DeMeester SR, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. *Ann Surg* 2008;248:549–556.
8. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. *Cancer* 2008;112:1239–1246.
9. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg* 2008;247:365–371.
10. Bogoevski D, Onken F, Koenig A, et al. Is it time for a new TNM classification in esophageal carcinoma? *Ann Surg* 2008;247:633–641.
11. Wijnhoven BP, Tran KT, Esterman A, Watson DI, Tilanus HW. An evaluation of prognostic factors and tumor staging of resected carcinoma of the esophagus. *Ann Surg* 2007;245:717–725.
12. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Prognostic significance of the number of lymph node metastases in esophageal cancer. *J Am Coll Surg* 2008;206:239–246.
13. Kelty CJ, Kennedy CW, Falk GL. Ratio of metastatic lymph nodes to total number of nodes resected is prognostic for survival in esophageal carcinoma. *J Thorac Oncol* 2010;5:1467–1471.
14. Akiyama H, et al. *Surgery for Cancer of the Esophagus*. Baltimore: Williams & Wilkins; 1990:19–42.
15. Bumm R, Wang J. More or less surgery for esophageal cancer: extent of lymphadenectomy for squamous cell esophageal carcinoma-How much is necessary? *Dis Esophagus*.1994; 7:151–5.
16. Casson AG, Rusch VW, Ginsberg RJ, Zankowicz N, Finley RJ. Lymph node mapping of esophageal cancer. *Ann Thorac Surg* 1994;58:1569–1570.
17. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res* 2004;10:7252–7259.
18. Sobin LH. TNM: principles, history, and relation to other prognostic factors. *Cancer* 2001;91(8 suppl):1589–1592.
19. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985;312:1604–1608.
20. Sun Z, Zhu GL, Lu C, et al. The impact of N-ratio in minimizing stage migration phenomenon in gastric cancer patients with insufficient number or level of lymph node retrieved: results from a Chinese mono-institutional study in 2159 patients. *Ann Oncol* 2009;20:897–905.
21. Marchet A, Mocellin S, Ambrosi A, et al.; Italian Research Group for Gastric Cancer (IRGGC). The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. *Ann Surg* 2007;245:543–552.
22. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 1994;220:364–372; discussion 372.
23. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol* 2005;23:7114–7124.
24. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. *Ann Surg* 2010;251:46–50.
25. Peschaud F, Frédérique P, Benoist S, et al. The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in rectal cancer. *Ann Surg* 2008;248:1067–1073.
26. Rosenberg R, Engel J, Bruns C, et al. The prognostic value of lymph node ratio in a population-based collective of colorectal cancer patients. *Ann Surg* 2010;251:1070–1078.
27. Kong SH, Lee HJ, Ahn HS, et al. Stage migration effect on survival in gastric cancer surgery with extended lymphadenectomy: the reappraisal of positive lymph node ratio as a proper N-staging. *Ann Surg* 2012;255:50–58.
28. Rosenberg R, Friederichs J, Schuster T, et al. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3,026 patients over a 25-year time period. *Ann Surg* 2008;248:968–978.
29. Austin PC, Brunner LJ. Inflation of the type I error rate when a continuous confounding variable is categorized in logistic regression analyses. *Stat Med* 2004;23:1159–1178.

