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***Retrospective Study***

**Developing a lymph node ratio-based staging system for esophageal squamous cell carcinoma**

Chen SB *et al*. LNR based staging system in ESCC

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**Data sharing:** Technical appendix, statistical code, and dataset available from the corresponding author at [stchenyp@hotmail.com](mailto:zsdxzhangxu@yahoo.com.cn)

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**Abstract**

**AIM:** To analyze a modified staging system utilizing lymph node ratio (LNR) in patients with esophageal squamous cell carcinoma (ESCC).

**METHODS:** Clinical data of 2011 patients with ESCC who underwent surgical resection alone between January 1995 and June 2010 at the Cancer Hospital of Shantou University Medical College were reviewed. The LNR, or node ratio (Nr) is defined as the ratio of metastatic lymph node number compared with the total resected node number. Overall survivals between groups were compared with the log-rank test. The cutoff points of LNR were established by grouping patients with 10% increment in node ratio, and then combining the neighborhood survival curves using the log-rank test. A new TNrM staging system, was constructed by replacing the American Joint Committee on Cancer (AJCC) N categories with the Nr categories in the new TNM staging system. The time-dependent receiver operating characteristic curves was used to evaluate the predictive performance of the seventh edition AJCC staging system and the TNrM staging system.

**RESULTS:** The median number of resected lymph nodes was 12 (range: 4–44), and 25% and 75% interquartile range was 8 and 16. Patients were classified into four Nr categories with distinctive survival differences (Nr0: LNR = 0; Nr1: 0% < LNR ≤ 10%; Nr2: 10% < LNR ≤ 20%; and Nr3: LNR > 20%). From N categories to Nr categories, 557 patients changed their lymph node stage. The median survival time (MST) for the four Nr categories (Nr0-Nr3) was 155.0 mo, 39.0 mo, 28.0 mo, and 19.0 mo, respectively, ant the 5-year overall survival was 61.1%, 41.1%, 33.0%, and 22.9%, respectively (*P <* 0.001). Overall survival was significantly different for the AJCC N categories when patients were subgrouped into 15 or more *vs* fewer than 15 examined nodes, except for the N3 category (*P =* 0.292). However, overall survival was similar when the patients in all four Nr categories were subgrouped into 15 or more *vs* fewer than 15 nodes. Using the time-dependent receiver operating characteristic, we found that the Nr category and TNrM stage had higher accuracy in predicting survival than the AJCC N category and TNM stage.

**CONCLUSION:** A staging system based on LNR may have better prognostic stratification of patients with ESCC than the current TNM staging system, especially for those undergoing limited lymphadenectomy.

**Key words:** Cancer staging; Esophagectomy; Esophageal squamous cell carcinoma; Lymph node ratio; prognosis

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**Core tip:** The lymph node ratio (LNR), or node ratio (Nr) has been found to be an independent prognostic factor in esophageal cancer patients. In the current study, we evaluate a lymph node ratio-based staging system in patients with esophageal squamous cell carcinoma (ESCC) and compare with the seventh edition AJCC staging system. We propose optimal Nr categories for ESCC, and demonstrate that a TNrM staging system bases on LNR may have better prognostic stratification of patients than the AJCC staging system. The application of this new staging system may aid oncologists in improved prediction of prognosis.

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**INTRODUCTION**

Esophageal cancer is the seventh leading cause of cancer mortality worldwide[1]. An estimated 18170 people will be diagnosed and 15450 people will eventually die of their disease in the United States in 2014[2].Surgical resection is the mainstay of therapy for patients with resectable diseases[3]. Varied types of surgical procedures (transhiatal, left thoracotomy, right thoracotomy, and minimally invasive surgery) are acceptable for esophagectomy in patients with resectable disease, leading to a significant variability in the extent of lymphadenectomy and the number of lymph nodes resected.

The American Joint Committee on Cancer (AJCC) revised and published the seventh edition TNM staging system for esophageal cancer in 2010. This staging system presents a significant improvement for N categories by stratifying patients according to the numbers of positive lymph nodes[4].However, this system does not specify the adequate number of examined lymph nodes for an accurate nodal staging. In patients with inadequate number of lymph nodes being examined, stage migration may occur, and lead to understaging of the diseases[5].

The lymph node ratio (LNR), or node ratio (Nr), is defined as the ratio of metastatic lymph node number compared with the total resected node number. Most previous studies have found that LNR is another independent prognostic factor in esophageal cancer patients[6-20]. However, fewer studies have examined whether the LNR has an improved ability to predict survival compared with the absolute number of positive nodes as stratified by the new staging criteria. Moreover, the optimal cutoff points of LNR are still controversial. The differences in study sizes, inclusion criteria, and statistical methods will lead to different results.

In a previous study[21], we have found that the N categories of the seventh AJCC staging system does not well represent survival characteristics in ESCC patients in China. We use the data from this study to propose optimal Nr categories, and try to compare the predictive ability of these Nr categories with the N categories in the current study. We further evaluate the predictive performance of a TNrM staging system compared with the current TNM staging system.

**MATERIALS AND METHODS**

***Patient population***

This study was approved by the Ethics Committee of Cancer Hospital of Shantou University Medical College (CH-SUMC). 3375 patients with esophageal carcinoma underwent esophagectomy in CH-SUMC from January 1995 to June 2010, and only patients of ESCC with neither neoadjuvant nor adjuvant therapy (esophagectomy alone) were enrolled in this study.

The surgical procedure has been described in our previous report and is summarized below[21]. A transthoracic en bloc esophagectomy was performed *via* a left or right thoracotomy. A standard two-field lymphadenectomy (abdominal and thoracic lymphadenectomy) was performed in all patients. When patients underwent a right thoracotomy, the paratracheal, left and right recurrent laryngeal nerve lymph nodes were also resected. Cervical lymphadenectomy was not systematically undertaken.

All operations were performed or closely supervised by two senior surgeons (Chen YP and Yang JS), and all resection specimens, including the lymph nodes, were assessed by two expert pathologists (Wu MY and Tian DP) in a standardized fashion.

***Follow-up***

Patients were followed with a clinical examination every 3 mo for the first year, every 6 mo for the second year and every 6 to 12 mo thereafter. The routine examination during the follow-up included a clinical evaluation, blood biochemistry examination, ultrasonography, and X-ray examination. Computed tomography was performed every 6 mo. Endoscopic examinations were performed when necessary. Follow-up was continued up to June 2011 or until death, whichever occurred earlier.

***Statistical Analysis***

The NCCN guidelines recommend at least 15 lymph nodes to be removed for adequate nodal staging for patients undergoing surgical resection without neoadjuvant therapy in the version 1.2014. We stratified all patients into two groups for analysis: adequate lymphadenectomy (≥ 15 lymph nodes) and inadequate lymphadenectomy (< 15 lymph nodes).

Overall survivals between groups were compared with the log-rank test. The cutoff points of LNR were established by grouping patients into 10% increment in node ratio, and then combining the neighborhood survival curves using the log-rank test. A new TNrM staging system, was constructed by replacing the AJCC N categories with the Nr categories in the new AJCC staging system.

The time-dependent receiver operating characteristic (ROC) is an extension of the classic ROC, which permits an evaluation of the diagnostic performance of biomarkers at all time points of interest[22,23]. To assess the predictive ability of the TNM staging system and TNrM staging system, we compare the time-dependent ROC curves for these two staging systems and use the area under the ROC curve (AUC) as the criterion. A larger AUC indicates better predictability of time to event. An AUC of 0.5 indicates no predictive ability, whereas a value of 1 represents perfect predictive ability.

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, United States), while time-dependent ROC analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were performed two-sided, and a *P* value less than 0.05 was considered to be statistically significant.

**RESULTS**

***Patient characteristics***

The patient characteristics had been summarized in our previous report[21]. A total of 2011 patients with a median age of 55 years (range: 30-82 years) were enrolled in this study, including 1456 males and 555 females. The R1 resection rate was 4.1% (83/2011), and R2 resection rate was 3.1% (63/2011). The overall postoperative 30-d mortality was 1.2% (24/2011). The median number of resected lymph nodes was 12 (range: 4–44), and 25% and 75% interquartile range was 8 and 16.

***Determination of LNR cut-off points***

We firstly grouped all patients into 10% increment in node ratio to search for possible cutoff points. The patients with LNR > 50% were taken into a group as the small patient numbers (total 108 patients). So, seven Nr stages (LNR = 0, 0% < LNR ≤ 10%, 10% < LNR ≤ 20%, 20% < LNR ≤ 30%, 30% < LNR ≤ 40%, 40% < LNR ≤ 50%, LNR > 50%) were established for analyzing (Figure 1). Then we combined the neighborhood survival curves using the log-rank test, patients were stratified into four node ratio group (Nr0 to Nr3), based on the following intervals: Nr0: LNR = 0; Nr1: 0% < LNR ≤ 10%; Nr2: 10% < LNR ≤ 20%; and Nr3: LNR > 20%.

***AJCC N categories and Nr categories***

From N categories to Nr categories, 557 patients change their lymph node stage (Table 1). The median survival time (MST) for AJCC N categories (N0-N3) was 155.0 mo, 33.0 mo, 19.0 mo, and 14.0 mo, respectively, and the 5-year overall survival was 61.1%, 36.6%, 20.7%, and 20.0%, respectively (*P <* 0.001). However, the survival difference was not significant for N2 *vs* N3 category (*P =* 0.159) in a subgroup analysis (Figure 2A). When patients in the N0 to N3 categories were stratified into subgroups of adequate lymphadenectomy and inadequate lymphadenectomy, those with adequate lymphadenectomy had significantly better survival than those with inadequate lymphadenectomy (*P <* 0.05, Figure 3A-C), except for N3 category (*P =* 0.292, Figure 3D). But the patient number in the N3 category was only 86. The median survival time (MST) for the four Nr categories (Nr0-Nr3) was 155.0 mo, 39.0 mo, 28.0 mo, and 19.0 mo, respectively, ant the 5-year overall survival was 61.1%, 41.1%, 33.0%, and 22.9%, respectively (*P <* 0.001). The survival differences were significant in a separate subgroup analysis (*P* value for Nr0 *vs* Nr1: < 0.001, Nr1 *vs* Nr2: 0.021, Nr2 *vs* Nr3: 0.001; Figure 2B). No significant difference was observed in the 5-year overall survival when the Nr1, Nr2 and Nr3 categories were stratified into subgroups of adequate lymphadenectomy and inadequate lymphadenectomy (*P* > 0.05; Figure 3E-G).

***AJCC TNM staging system and TNrM staging system***

The predictive ability of the current TNM staging system and the TNrM staging system was further evaluated by using time-dependent ROC, which was performed by estimating the value of AUC according to time-dependent sensitivity and specificity. The AUCs for Nr categories were higher than those for N categories (Figure 4A), which indicated that Nr categories had better predictive value than N categories. The TNrM stage also had higher accuracy in predicting survival than the AJCC TNM stage (Figure 4B).

We further evaluated the predictive ability of these two staging systems in the subgroups of patient with adequate lymphadenectomy and inadequate lymphadenectomy. We also found in both of these two subgroups that the Nr categories and TNrM stage had a higher accuracy in predicting survival than the AJCC N categories and TNM stage (Figure 4).

***Overall survival***

The 5-year overall survival for the current TNM staging system is: stage 0 100%, stage IA 84.8%, stage IB 78.6%, stage IIA 66.5%, stage IIB 53.4%, stage IIIA 33.6%, stage IIIB 22.4%, stage IIIC 15%, and stage IV 0%. For the TNrM staging system, 5-year overall survival is as follows: stage 0 100%, stage IA 84.8%, stage IB 78.6%, stage IIA 66.5%, stage IIB 54.5%, stage IIIA 40.8%, stage IIIB 29.2%, stage IIIC 22.2%, and stage IV 0%. The cumulative survival curves according to these two staging systems were shown in Figure 5. All survival curves were well separated except for stage IA *vs* IB (*P* = 0.922).

**DISCUSSION**

An accurate staging classification for cancer, according to guidelines that are internationally accepted among surgeons, oncologists, and other physicians, is of crucial importance[13].An ideal cancer staging should not only provide an indication of prognosis and a framework for treatment decisions but should also allow evaluation of treatment with meaningful comparisons between patient cohorts across different institutions and locations[24,25].

The AJCC TNM staging system is now the most commonly used system for esophageal cancer to classify the severity of disease. In 2010, the AJCC published the latest edition TNM system for esophageal cancer. The most notable change for this new staging system is the reclassification of N categories by grouping patients based on the numbers of metastatic lymph nodes, which may have greater prognostic importance for esophageal cancer patients[26]. However, although this system advocates as extensive a lymphadenectomy as possible, it does not specify the adequate number of resected lymph nodes for an accurate nodal staging.

The extent of lymphadenectomy for esophageal cancer is still controversial[6-8,27]. There are varied types of surgical procedures for esophagectomy performed in different institutions, leading to a significant variability in the number of lymph nodes examined. Previous studies had shown that the total number of lymph nodes resected is an independent prognostic predictor for esophageal cancer patients underwent surgery[27,28]. Because the number of positive nodes is confounded by the total number of nodes examined, nodal categorization based on only the numbers of positive lymph nodes could not accurately classify all nodal status when insufficient lymphadenectomy existing. Our data show that when patients are categorized by the AJCC N categories, those with 15 or more nodes examined have significantly better survival than those with fewer than 15 nodes examined in a same N stage. This indicates that insufficient lymphadenectomy will lead to understaging of the disease. However, further studies are required to specify the minimum number of examined nodes to maximize survival.

LNR has been found to be another independent prognostic factor for esophageal cancer patients after surgery[6-20], and may stratify survival even better than the AJCC N category for certain cohorts of patients[15]. However, most previous studies were with small patient cohorts, and seldom specified what calculations were performed to retrieve the optimal cutoff point[12]. Moreover, few studies were concerned on the predictive performance of LNR in esophageal cancer patients with adequate lymphadenectomy and inadequate lymphadenectomy.

To our knowledge, our study is the largest ever single-center patient cohort of ESCC to evaluate the predictive ability of LNR. We propose optimal Nr categories for ESCC (Nr0: LNR = 0; Nr1: 0% < LNR ≤ 10%; Nr2: 10% < LNR ≤ 20%; and Nr3: LNR > 20%), which are different from previous studies[6-20].In our study, we found that the survival differences were significant in the four Nr categories in a separate subgroup analysis, while no survival difference was observed for the AJCC N categories of N2 *vs* the N3 (*P =* 0.159). We also found that the use of Nr categories significantly reduces the range of overall survival within patients with adequate lymphadenectomy and inadequate lymphadenectomy compared with that of the N categories, suggesting that the Nr categories are a better measure of the extent of regional lymph node involvement than N categories, particularly in patients with inadequate lymphadenectomy.

Few studies have compared the predictive performance of a TNrM staging system with the new AJCC staging system. One study by Hou *et al*[12] found that when replacing the N categories with Nr categories in the new AJCC staging system, the survival rate could be easily distinguished between patients. In the current study, we evaluate the predictive performance of a TNrM staging system for the first time using the time-dependent ROC curves, and find that Nr categories and TNrM stages predict survival better than the N categories and TNM stage. We can also confirm the same result in the subgroups of patient with 15 or more nodes and those with fewer than 15 nodes examined, indicating that Nr categories and TNrM stage may be a better discriminator. However, more studies are required to confirm these findings before true recommendations can be made.

Our study has some limitations. Firstly, this new TNrM staging system may be improved with better T, Nr, M classifications or other factors, such as a subdivision of T1 cancer into T1a and T1b. However, as the AJCC TNM staging system is now the most commonly used system for esophageal cancer, a TNrM staging system based on the TNM staging system may be of wider application. Secondly, it is a single-institution, retrospective study. Whether this new TNrM system is applicable in another data set or patients with adenocarcinoma still needs further validation. Thirdly, most of the patients underwent a standard two-field lymphadenectomy in this study. The examined lymph nodes number for each patient is limited (median 12 per case). So it may not be optimal for cohorts of patients in which more extensive lymphadenectomy are performed. A more extensive lymphadenectomy results in a greater number of uninvolved nodes removed, thereby driving down the LNR[29,30], so modification of the Nr intervals may be needed for such cohorts. However, our staging system may be more suitable for patients who undergo esophagectomy with limited lymphadenectomy. Finally, whether the TNrM staging system is applicable to patients with neoadjuvant or adjuvant therapy still needs further research, as all of our patients underwent surgical resection alone.

In conclusion, we propose optimal Nr categories (Nr0: LNR = 0; Nr1: 0% < LNR ≤ 10%; Nr2: 10% < LNR ≤ 20%; and Nr3: LNR > 20%) for ESCC in the current study, and demonstrate that a staging system based on LNR may have better prognostic stratification of patients with ESCC than the current TNM staging system, especially for those undergoing less extensive lymphadenectomy. Further studies are required to confirm our results.

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**COMMENTS**

***Background***

The seventh edition American Joint Committee on Cancer (AJCC) staging system for esophageal cancer was published in 2010. This staging system presents a significant improvement for N categories by stratifying patients according to the numbers of positive lymph nodes. However, stage migration may occur in patients with inadequate number of lymph nodes being examined in this new system. A staging system based on the lymph node ratio (LNR) may be a compensation for the AJCC staging system.

***Research frontiers***

Previous studies have found that LNR is an independent prognostic factor in esophageal cancer patients. However, fewer studies have examined whether the LNR has an improved ability to predict survival compared with the new staging criteria. Moreover, the optimal cutoff points of LNR are still controversial. We reported one of the largest ever single-center patient cohort of ESCC to evaluate the predictive ability of LNR, and further evaluate the predictive performance of a TNrM staging system compared with the current TNM staging system.

***Innovations and breakthroughs***

We propose optimal Nr categories for ESCC in this study (Nr0: LNR = 0; Nr1: 0% < LNR ≤ 10%; Nr2: 10% < LNR ≤ 20%; and Nr3: LNR > 20%), which are different from previous studies. We also demonstrate that a staging system based on LNR may have better prognostic stratification of patients with ESCC than the current TNM staging system, especially for those undergoing less extensive lymphadenectomy

***Applications***

The use of this new TNrM staging system in our study may aid oncologists in improved prediction of survival, making treatment decisions, and comparing cohorts of patients, especially those undergoing more limited lymphadenectomy.

***Terminology***

A TNrM staging system bases on LNR may have better prognostic stratification of patients with ESCC than the AJCC TNM staging system, especially for those undergoing limited lymphadenectomy.

***Peer-review***

This is a good paper which reports a large series of patients who underwent esophagectomy for SCC without neoadjuvant treatment. The data analysis appears sound and a good case is made for using the lymph node ratio to determine prognosis.

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**Figure 1 Kaplan-Meier curves for overall survival according to different intervals of lymph node ratio.** The *P* value for LNR0 *vs* LNR1: < 0.001, LNR1 *vs* LNR2: 0.021, LNR2 *vs* LNR3: 0.031. No significant survival differences were observed between LNR3 to LNR6 (*P* > 0.05). LNR: Lymph node ratio.

**A**

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**Figure 2 Kaplan-Meier curves for overall survival according to American Joint Committee on Cancer N categories (A) and node ratio categories (B).** A: No significantly survival difference was observed for N2 *vs* N3 category (*P =* 0.159). B: The survival differences were significant in all subgroups analysis (*P* < 0.001). LNR: Lymph node ratio; Nr: Node ratio.

A

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**Figure 3** **Kaplan-Meier curves for overall survival according to American Joint Committee on Cancer N categories and node ratio categories, stratified by the number of examined nodes (< 15 and ≥ 15).** The survival differences were significant in the AJCC N categories (N0-N2, *P* < 0.05), except for N3 categories (*P =* 0.292). No significant difference was observed in the node ratio (Nr) categories (Nr1-N3).

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B

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**Figure 4** **Time-dependent receiver-operator characteristic curve analysis.** The figure shows the time-dependent area under curves (AUCs) for node ratio (Nr) categories and TNrM stage were higher than those for American Joint Committee on Cancer (AJCC) N categories and TNM stage in the total patient cohorts, and in patients with adequate lymphadenectomy or inadequate lymphadenectomy.

A

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**Figure 5 Kaplan-Meier curves for overall survival according to the seventh American Joint Committee on Cancer TNM stage (A) and TNrM stage (B).**

**Table 1 Cross-table analysis of changes in the lymph node stage grouping N categories to Nr categories of 2011 patients with esophageal squamous cell carcinoma (*n* = 2011)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Nr0** | **Nr1** | **Nr2** | **Nr3** | **Total** |
| N0 | 1136 | 0 | 0 | 0 | 1136 |
| N1 | 0 | 187 | 213 | 96 | 496 |
| N2 | 0 | 11 | 46 | 236 | 293 |
| N3 | 0 | 0 | 1 | 85 | 86 |
| Total | 1136 | 198 | 260 | 417 | 2011 |