

Proposed Modification of Nodal Staging as an Alternative to the Seventh Edition of the American Joint Committee on Cancer Tumor-Node-Metastasis Staging System Improves the Prognostic Prediction in the Resected Esophageal Squamous-Cell Carcinoma

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Introduction: The 7th American Joint Committee on Cancer (AJCC) tumor-node-metastasis staging system for esophageal cancer defined N classification based on the number of metastatic lymph nodes (LNs). However, this classification might neglect the extent of LNs metastasis. This study aimed to revise N classification based on the extent of LNs metastasis and propose a modification to the current AJCC staging system for better representing the prognostic characteristics of Chinese esophageal squamous-cell carcinoma (ESCC).

Methods: We retrospectively reviewed 1993 ESCC patients who underwent curative resection. The proposed N categories based on the number of LNs metastasis stations were compared with the current staging system by univariate and multivariate Cox regression analyses. Homogeneity, discriminatory ability, and monotonicity of gradients of two staging systems were compared using likelihood ratio χ^2 statistics and Akaike information criterion calculations.

Results: The survival differences were not significant for N2 versus N3 category ($p = 0.231$) and stages IIIB versus IIIC ($p = 0.713$) based on the 7th AJCC staging system. When the modified staging system was adopted, the survival difference for N2 versus N3 and IIIB versus IIIC could be well discriminated. Statistical analysis showed that the modified staging system had higher likelihood ratio χ^2 scores and smaller Akaike information criterion values than the 7th AJCC staging system, which represented the optimum prognostic stratification.

Conclusions: The modified staging system with the revised N categories based on the number of LNs metastasis stations better predicts

the survival of Chinese ESCC population than the 7th AJCC staging system. Further studies are required to confirm this result.

Key Words: Esophageal squamous-cell carcinoma, Lymph nodes metastasis stations, Prognosis, 7th American Joint Committee on Cancer staging system.

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Cancer staging system is commonly used to unify clinicopathological classification, guide treatment decision making, evaluate prognosis, and compare treatment results from different institutions.¹ Many studies have previously suggested that the number of metastatic lymph nodes (LNs) is the most important independent prognostic factor in esophageal cancer.^{2–12} The 7th version of the American Joint Committee on Cancer (AJCC) staging system for esophageal cancer, in which Nodal (N) categories are based on the number of metastatic LNs, is more reliable than before.^{13–15} However, this classification might have neglected the extent of LNs metastasis, an even more important factor in predicting prognosis.¹⁶ Moreover, the exact number of metastatic LNs is sometimes difficult to evaluate, when an enlarged LN is actually the coalescence of multiple positive LNs or when a single enlarged LN becomes broken during surgical dissection. Moreover, it was reported by several studies that the 7th edition of the AJCC staging system cannot satisfactorily distinguish the prognosis among different risk groups of patients with resected esophageal carcinoma, especially between N2 and N3 and between IIIB and IIIC.^{16,17}

The current AJCC staging system for esophageal cancer used global data from 4627 patients.¹ However, esophageal squamous-cell carcinoma (ESCC) patients only constitute 39.6% of the database (1834 of 4627) used to elaborate the 7th AJCC staging system for esophageal cancer.¹⁸ The most common pathological type of esophageal cancer in China is squamous-cell carcinoma type, which accounts for more than 90% of cases.¹⁹ We believe that more data from Chinese patients are essential to validate the N categories in the current staging system for ESCC.

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In this retrospective study, we present data from a large cohorts of Chinese patients in a single institution and aimed to revise N staging based on the extent of LNs metastasis and propose a modification to the current AJCC staging system in order to better represent the prognostic characteristics of ESCC after radical esophagectomy in Chinese population.

METHODS

Patients Selection

This study was undertaken according to the Declaration of Helsinki at the Third Affiliated Hospital of Soochow University with the approval of the ethics committee at our institution, which waived the requirement for written informed consent of individual patients owing to the retrospective nature of this study. None of stage IV patients according to the 7th edition tumor-node-metastasis (TNM) system was included because all the patients enrolled in this study underwent radical resection and had no distant metastasis. A total of 1993 resectable ESCC patients who underwent radical esophagectomy at our institution were retrospectively reviewed from January 2002 to December 2011. Among 1993 patients, 672 patients with either preoperative or postoperative radiotherapy and/or chemotherapy were excluded to eliminate the influence of adjuvant and neoadjuvant treatment. Then, 339 patients with less than 12 LN examined or supraclavicular LN involved were also excluded, as they were regarded as nonregional LN metastasis or insufficient LN dissection according to the suggestion of AJCC.²⁰ In the remaining 982 ESCC patients, 65 patients were excluded because of incomplete resection and/or perioperative death and/or lost to follow-up. Finally, 917 patients were included into this study. Clinical data, including age, gender, tumor location, staging, pathology, and survival outcomes, were collected. Description of the LNs (number of involved LNs and LNs metastatic station) was also recorded.

Surgery

All patients who were conformed to be resectable ESCC without distant metastasis by clinical and experimental examination received radical surgical resection of a transthoracic en-bloc esophagectomy with mediastinal and abdominal two-field lymphadenectomies. Mediastinal lymphadenectomies were performed to include subcarinal, left and right bronchial, lower posterior mediastinum, pulmonary ligament, and paraesophageal and thoracic duct nodes. Abdominal lymphadenectomies were performed to include the paracardial, lesser curvature, left gastric, common hepatic, celiac, and splenic nodes. The paratracheal and recurrent laryngeal nerve LNs were also dissected. Cervical lymphadenectomy was only performed in case of suspicious cervical lymphadenopathy. Each resected node group was labeled by the operator.

Staging

Tumor staging was performed according to the 7th AJCC staging system for ESCC.²⁰ According to Casson's LN drainage map, LN metastasis station (LMS) was grouped and shown in Table 1.²¹ Four revised N categories (r-N: r-N0, 0 station; r-N1, 1 station; r-N2, 2 stations; r-N3,

TABLE 1. The Station and Name of Regional LN Drainage for Esophageal Cancer

Station*	Name	Station	Name
2R	Right upper paratracheal nodes	9	Pulmonary ligament nodes
2L	Left upper paratracheal nodes	10R	Right tracheobronchial nodes
3P	Posterior mediastinal nodes	10L	Left tracheobronchial nodes
4R	Right lower paratracheal nodes	15	Diaphragmatic nodes
4L	Left lower paratracheal nodes	16	Paracardial nodes
5	Aortopulmonary nodes	17	Left gastric nodes
6	Anterior mediastinal nodes	18	Common hepatic nodes
7	Subcarinal nodes	19	Splenic nodes
8M	Middle paraesophageal LNs	20	Celiac node

*Supraclavicular lymph node was not included because of being regarded as nonregional LN metastasis.
LN, lymph node.

more than 2 stations) were classified by the number of LMS in this study. To compare the 7th edition AJCC TNM staging system, a modified TNM staging system with the revised N category based on the number of LMS was proposed as seven prognostically homogeneous classes of patients just as the 7th AJCC staging system (IA; IB; IIA; IIB; IIIA; IIIB; IIIC).

Follow-Up

All patients were followed up every 3 months for the first 2 years, every 6-month intervals until 5 years, and then annually. All patients underwent clinical, laboratory, imaging, and endoscopy examination for assessing recurrence or metastasis. The last follow-up of survivors was conducted at the end of July 2014. All patients were followed up by phone calls and regular mail. The observation time in this study was the interval from the date of surgical resection to death or last follow-up. Surviving patients were censored on the day of the last contact.

Statistical Analysis

Optimal cutoff values for the number of LMS (which were 0, 1, and 2 station in our series) were determined using X-tile software (<http://www.tissuearray.org/rimmlab>).²² All statistical analyses were performed using SPSS 13.0 software (SPSS, Inc., Chicago, IL). Survival was calculated using the Kaplan–Meier method, and the log-rank test was used to assess differences in survival between groups. In multivariate analysis, forward stepwise regression analysis was carried out with a Cox proportional hazards model. The likelihood ratio χ^2 test related to the Cox regression model was used for measuring the homogeneity. To compare prognostic systems with different staging system, the Akaike information criterion (AIC) value was applied to measure the discriminatory ability of each prognostic model.²³ AIC was defined as follows: $AIC = -2 \log \text{maximum likelihood} + 2 \times (\text{the number of parameters in the model})$. A smaller AIC value indicates a better model for predicting outcome. *p* Value less than 0.05 from the two-sided test was considered to be statistically significant.

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