Log Odds of Positive Lymph Nodes Predicts Survival in Patients After Resection for Esophageal Cancer

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Background. **The number of lymph node metastases (LNMs) and the positive lymph node ratio (LNR) have been shown to be significant independent prognostic factors in predicting overall survival in patients with esophageal cancer. Our aim was to evaluate whether a novel prognostic indicator—the log odds of positive lymph nodes (LODDS)—predicts survival in esophageal cancer.**

Methods. **Patients who underwent esophagectomy for esophageal cancer between 1988 and 2007 were identified from the Surveillance, Epidemiology, and End Results (SEER) database of 18 registries, and a Chinese patient cohort was subjected to validation. The prognostic efficacy of LNM, LNR, and LODDS was compared. Prognostic performance was measured using Harrell's C-index statistic, Schemper's proportion of explained variation, and the Akaike information criterion (AIC).**

Results. **A total of 4,123 patients in the SEER database and 134 patients in the Chinese cohort met our criteria in this study. LODDS gave a better prognostic performance than either LNM or LNR in both the SEER database and the Chinese cohort. Multivariate analyses showed significant values for LNM, LNR, and LODDS as prognostic factors ($p < 0.001$). However, only LODDS was a significant prognostic factor regardless of the number of lymph nodes retrieved ($p = 0.677$). Furthermore, after stratification of patients with no nodes involved or all nodes involved, the values of LODDS still distinguished the heterogeneity efficiently.**

Conclusions. **LODDS predicts survival more accurately than either LNM or LNR in patients undergoing resection for esophageal cancer, especially for patients with an insufficient number of lymph nodes retrieved.**

(Ann Thorac Surg 2016;■:■–■)

Esophageal cancer is one of the most aggressive malignancies worldwide, causing more than 400,000 deaths each year [1]. Regional lymph node status is currently considered to provide the most reliable prognostic and therapeutic implications [2, 3]. Although an updated number of lymph node metastases (LNM) based on the International Union Against Cancer/American Joint Committee on Cancer Tumor Node Metastasis (UICC/AJCC TNM) staging system (seventh edition) has been well established for lymph node categories [4], some researchers have indicated that the new system is significantly influenced by the number of lymph nodes retrieved and is susceptible to stage migration [5].

Recently, the ratio of positive retrieved lymph nodes to total number of retrieved lymph nodes—known as the positive lymph node ratio (LNR)—has been shown to be a superior indicator of survival in esophageal cancer, especially when an insufficient number of lymph nodes are retrieved [5–7]. However, its prognostic superiority to LNM is still controversial; in particular, when no nodes or all nodes involved are used, neither of the two node classifications is able to distinguish heterogeneity.

The log odds of positive lymph nodes (LODDS) is another novel prognostic indicator and is defined as the natural logarithm of the ratio between the probability of a lymph node being positive and the probability of it being negative when only a single lymph node is retrieved [8]. Several authors have found that LODDS is more accurate for the prediction of prognosis than LNM and LNR in patients with gastric, colon, and pancreatic cancer [8–12]. Until now, the value of LODDS in predicting the prognosis for patients with esophageal cancer has seldom been determined.

In this study, we used the Surveillance, Epidemiology, and End Results (SEER) cancer registry, a population-based cancer database, and a Chinese patient cohort to evaluate the efficacy of LODDS as a prognostic indicator to predict survival in patients undergoing resection for

The Supplemental Figures and Tables can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2016.03.030] on http://www.annalsthoracicsurgery.org.

Accepted for publication March 8, 2016.

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Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.03.030

esophageal cancer and compare this prognostic value with those of LNM and LNR.

Patients and Methods

Patient Population

Patients were selected from the latest version of the SEER program, SEER 18 (1973–2012), which was released in June 2015, using SEER*Stat, version 8.2.1 software [13]. All patients at least 18 years of age who were diagnosed with a unique microscopically confirmed invasive primary esophageal cancer from 1988 to 2007 were identified. Among these patients, we narrowed the focus to those who underwent an esophagectomy with the retrieval of at least one node that was examined pathologically. The histologic types in our study were limited to the International Classification of Disease—Oncology, third edition (ICD-O3) codes 8000 to 8576, 8940 to 8950, and 8980 to 8981 and to tumor site codes 150 to 155 and 158 to 159. The inclusion criteria were limited to active follow-up and survival of not less than 2 months after the operation. Patients were excluded from the study if they had received radiotherapy before the surgical procedure or if the infiltration depth and distant metastasis of the tumor were unknown. The program selection codes for the SEER database queries are shown in Supplemental S1. The variables used were year of diagnosis, age at diagnosis, sex, race, primary site, histologic type, tumor extension and size, number of positive nodes and number of nodes examined, grade, months of survival, metastasis at diagnosis, radiation sequence with operative treatment, and cause-specific classification of death. Survival time was defined as the time between diagnosis and the date of death, the last contact, or the cutoff date of December 31, 2012. Because SEER is a public-use database, no approval from the institutional review board was sought.

A Chinese cohort consisting of 134 patients who underwent esophagectomy for esophageal cancer between January 2005 and June 2010 at the first Affiliated Hospital of Zhejiang University was used as validation data. All patients had histologically confirmed disease using the same criteria of inclusions and exclusions. The study protocol was approved by the Ethical Committee and Institutional Review Board of the first Affiliated Hospital of Zhejiang University.

Node Classification

According to the seventh edition of the UICC/AJCC TNM staging system, LNM was classified as a value between 0 and 3 based on the number of positive nodes examined: 0 (LNM0), 1 to 2 (LNM1), 3 to 6 (LNM2), and greater than or equal to 7 (LNM3) nodes, respectively [14]. The LNR intervals range from 0 to 1, defined as the ratio of the number of positive retrieved lymph nodes to the total number of retrieved lymph nodes. LODDS was estimated by $\log_e [(pN + 0.5)/(nN + 0.5)]$ [15], where pN is the number of positive lymph nodes and nN is the number of negative lymph nodes; the latter value was calculated by subtracting pN from the total number of examined nodes and adding 0.5 to both the numerator and the denominator to avoid singularity.

Statistical Analysis

The optimal cutoff values for LNR and LODDS were determined using X-Tile software (http://www.tissuearray.org/rimmlab) and by the minimal p value approach [16]. Cancer-specific survival was calculated using the Kaplan-Meier estimator, and the statistical differences were identified by the univariate Cox-Regression analysis. The significance variables were included to identify the possible independent prognostic factors and the prognostic performance of node classifications in multivariate analyses.

To elucidate the classification characteristics and determine how the accuracy of LODDS contributed to node classification, the relationships between LODDS and LNM or LNR were plotted as scatter plots. The cubic spline function was also used to plot the association between the log hazard ratio and LNM, LNR, and LODDS.

The prognostic performance of each node classification was compared using the Harrell's C-index statistic with a bootstrapping variable selection algorithm, which is similar to the area under the receiver operating characteristic curve but more appropriate for censored data [17, 18]. The value of the Harrell's C-index statistic ranges from 0.5 (no discrimination) to 1 (perfect discrimination), and the highest value was chosen as the best prognostic prediction model [18]. To explain variation, Schemper's proportion of explained variation (PEV) measure was used to score the different Cox models. Schemper's PEV generally known as R^2, represents the amount of the survival variability that could be explained by a predictor or a model. Higher PEV values indicated a better prognostic model [19]. The power estimation was assessed by receiver operating characteristic analysis. Akaike information criterion (AIC) was also used as an additional measure for evaluating prognostic performance of the three node classifications. When the AIC value is lower, the model is more accurate [20].

Statistical analyses and graphics were performed using IBM SPSS statistics, version 20.0 (SPSS, Inc, Chicago, IL) and R version 3.1.2 (The R Project for Statistical Computing, Vienna, Austria; http://www.r-project.org) statistical packages of *Hmisc* and *rms* [21, 22]. For all of the analyses, p less than 0.05 was considered to be statistically significant.

Results

Patient Characteristics of the SEER Database and a Chinese Cohort

A total of 4,123 eligible patients who underwent an esophagectomy for esophageal cancer were identified from the SEER cancer registry. The median follow-up was 24 months (range, 2–296 months) and the overall 5-year survival rate of the entire cohort was 33%. The ratio of lymph node metastasis in the data set was 53.3%. Patient demographics and detailed information on tumor features are summarized in Table 1. The features of 134