The Prognostic Value of the Number of Negative Lymph Nodes in Esophageal Cancer Patients After Transthoracic Resection

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Background. Although the number of positive lymph nodes (LN), the total number of resected LN, and the proportion of positive LN have been reported to be associated with survival in patients with esophageal cancer, little is known about the prognostic impact of the number of negative LN.

Methods. A retrospective review of 754 patients receiving transthoracic esophagectomy for cancer between January 1995 and September 2011 was performed. The prognostic impact of the number of negative LN was analyzed. Log rank testing was used to compare survival curves, and Cox regression analysis was performed to identify significant prognostic factors.

Results. A total of 707 patients were included. The mean follow-up time was 28.4 ± 30.9 months. The 5-year overall survival for the entire cohort was 30.1%. Patients with a high number of negative LN (≥19) had better overall survival than patients with a low number of negative LN (5-year survival rate 33.4% versus 26.4%, p = 0.005). Stratified analysis showed that the impact of the number of negative LN was significant in patients with T3/4 (p = 0.027) and node-positive (p = 0.002) esophageal cancers but not in patients with less advanced tumors. Multivariate Cox regression analysis demonstrated that the number of negative LN (in addition to age, sex, T stage, N stage, tumor length, and surgical approach) was an independent prognostic factor.

Conclusions. A higher number of negative LN is associated with better overall survival of esophageal cancer patients after resection. The correlation of a high number of negative LN (≥19) with survival was more prominent in patients with advanced (T3/4 stage, node-positive) tumors.

Patients and Methods

Study Population
A retrospective review was performed on 754 patients who had undergone transthoracic esophagectomy for cancer at the Taipei Veterans General Hospital between January 1995 and September 2011. The Institutional Review Board of the Taipei Veterans General Hospital approved this study and granted a waiver of the informed consent process. The preoperative work-up and postoperative follow-up protocol were as described previously [2]. Before 2010, patients were considered for resection if there was no evidence of distant metastasis and if there were no signs of extensive locoregional invasion that obliterated the normal tissue planes. Since 2010, we used a multidisciplinary team approach in the treatment of esophageal cancer and followed the National Comprehensive Cancer Network guidelines: esophageal cancers in the upper third of the esophagus or with locally advanced disease were considered for neoadjuvant chemoradiation followed by esophagectomy.

Surgical Methods
The surgical methods of resection included open and thoracoscopic triple incisional esophagectomy (McKeown type). In each approach, esophagectomy and infracarinal mediastinal lymph node plus right paratracheal lymph node dissection were performed during the thoracic portion of the operation. Esophageal substitute mobilization and dissection of the paracardial nodes (and any enlarged celiac axis nodes) were performed during the abdominal portion of the operation. Once mobilized, the gastric tube was pulled up through the thoracic cavity for cervical anastomosis (the cervical stage). Cervical lymph node sampling was also completed in this cervical stage of the operation.

Surgical Specimen Pathology Review
The pathologic tumor stage was determined according to the seventh edition of the AJCC TNM classification. Each dissected node group was labeled by the operator. All lymph nodes were cut into slices of 5-μm thickness at several levels along the long axis and each slice was embedded in paraffin and sectioned for hematoxylin and eosin staining. The lymph node number was counted under low-power field microscopy. Description of the lymph nodes (number of involved and examined lymph nodes in each station) was recorded. The TLN was determined from the sum of the number of lymph nodes collected at the cervical, thoracic, and abdominal regions. To study the prognostic impact of the number of negative LN, patients were divided into four groups based on quartiles—a set of values that divide the dataset into four equal groups—of the number of negative LN.

Statistics
A χ² test was used to compare categorical variables. Analysis of variance was used for comparison of continuous variables. The survival curves were plotted by the Kaplan-Meier method and compared using the log rank test. Cox regression analysis was performed to identify significant prognostic factors. All calculations were performed using SPSS 15.0 software (SPSS, Chicago, IL) and a p value of less than 0.05 was considered significant.

Results
After excluding patients who did not receive intraoperative lymphadenectomy (n = 38) and patients lost during postoperative follow-up (n = 15), 707 patients were included for analysis. The mean TLN was 24 (SD 14.8) and the median TLN was 21 (range, 2 to 97). The number of negative LN was examined as a categorical variable based on quartiles. This resulted in the following distribution: 167 patients in group 1 (negative LN ≤11), 166 patients in group 2 (negative LN 12 to 18), 189 patients in group 3 (negative LN 19 to 28), and 185 patients in group 4 (negative LN ≥29). The relationships between patient demographics and the number of negative LN is shown in Table 1. The clinical and pathologic factors (including age, sex, histology type, TNM stages, grade of differentiation, tumor length, and surgical margin status) were comparable among the four groups. However, esophageal resection of tumors of the middle third of the esophagus yielded higher counts of negative LN (p = 0.008). The thoracoscopic esophagectomy technique also yielded higher counts of negative LN than open esophagectomy (p = 0.004).

The 30-day in-hospital mortality was 4.1% (29 of 707). The mean follow-up time was 28.4 months (SD 30.9). The median survival of the entire cohort was 23.0 months (95% confidence interval [CI]: 19.5 to 26.5). The overall 1-, 3-, and 5-year survival rates were 69.5%, 38.0%, and 30.1%, respectively. According to the Kaplan-Meier survival curves, the patients in groups 3 and 4 had better overall survival than the patients in groups 1 and 2 (Fig 1A). Therefore, we classified patients as either high (groups 3 and 4) or low (groups 1 and 2) negative LN groups in the subsequent analyses. The high negative LN group had a median survival period of 28.0 months (95% CI: 22.8 to 33.2) and a 5-year survival rate of 33.4%, whereas the low negative LN group had a median survival period of 20.0 months (95% CI: 15.6 to 24.4) and a 5-year survival rate of 26.4% (log rank p = 0.005; Fig 1B).

The impact of negative LN on overall survival was examined after stratification by T (tumor) stage. In patients with T3 or T4 stage tumors, a high negative LN number was significantly associated with better overall survival (log rank p = 0.027; Fig 2B). In contrast, the correlation was attenuated in patients with T1 or T2 stage tumors (log rank p = 0.256; Fig 2A). Stratification according to N (node) stage showed similar results. Whereas a high number of negative LN was a significant prognostic factor in patients with concomitant LN metastasis (log rank p = 0.002; Fig 3B), a similar effect was not observed in patients with stage N0 (log rank p = 0.215; Fig 3A).

To correct any possible bias caused by inadequate lymph node staging due to sampling of an inadequate number of nodes for pathological review, we performed an additional analysis that included only patients who...
had received adequate node staging. Patients with TLN less than 15 were defined as having inadequate node staging according to the NCCN guideline criteria and were excluded [1]. Among the 499 patients with adequate node staging, there were 374 patients in the high negative LN group and 125 patients in the low negative LN group.
The 5-year overall survival rate and median survival period were 33.4% and 28.0 months (95% CI: 22.8 to 33.2), respectively, for the 374 patients with a high number of negative LN. The 5-year overall survival rate and median survival period were 23.4% and 17.0 months (95% CI: 13.6 to 20.4), respectively, for the 125 patients with a low number of negative LN. The Kaplan-Meier plot also indicated a better survival among patients with a high number of negative LN (log rank $p = 0.002$; Fig 4).

In the Cox regression univariate analysis (Table 2), TLN did not affect outcome. In the same analysis, however, the number of negative LN was a significant prognostic factor when examined either as a continuous variable ($p = 0.008$) or as a categorical variable after classification into high and low negative LN groups ($p = 0.005$). Other significant prognostic factors included age, sex, T stage, N stage, grade of differentiation, margin status, tumor length, and surgical approach (open versus thoracoscopic esophagectomy). In the multivariate analysis incorporating covariates that were significant in the univariate analysis, the following variables were independent factors for poor survival: older age, T3/4 stage tumors, lymph node

![Fig 1.](image1) (A) There are significant survival differences between group 1 (negative lymph nodes [LN] ≤11 [blue line]), group 2 (negative LN = 12 to 18 [green line]), group 3 (negative LN = 19 to 28 [yellow line]), and group 4 (negative LN ≥29 [red line]). (B) Patients with 19 or more negative LN (groups 3 and 4 [red line]) had significantly better survival rates than patients with less than 18 negative LN (groups 1 and 2 [blue line]).

![Fig 2.](image2) After stratification by T stage, (A) no survival difference between high negative (red lines) and low negative (blue lines) lymph node (LN) groups was noted in patients with T1/2 stage tumors. (B) However, a significant survival difference was noted in patients with T3/4 stage esophageal cancers.
metastasis, and longer tumor length. In contrast, the following variables were significant prognosticators for increased survival: female sex, a higher number of negative LN, and thoracoscopic esophagectomy (Table 2).

Comment

We demonstrate that a high number of negative LN is associated with better overall survival in esophageal cancer patients after transthoracic resection. Our findings are compatible with results from previous studies [4, 8, 11, 12]. Schwarz and colleagues [11] analyzed the SEER database and examined LN data from more than 5,600 patients who underwent esophagectomy between 1973 and 2003. They found that a higher number of negative LN ($\geq 15$) was associated with the best overall survival ($p < 0.0001$) and the lowest mortality ($p < 0.0001$). In their study, the impact of negative LN was invariably observed in both N0 and N1 stage groups [11]. However, such population-based studies have some inherent bias: information on the exact surgical techniques used and the methods of histopathology examination are lacking. There have also been several studies showing significant associations between a higher number of negative LN and increased survival in patients with node-negative esophageal cancer [4, 8, 12]. However, most were based on adenocarcinoma-predominant populations. The stratified analysis in the study by Greenstein and coworkers [12] even showed that the effect of the number of negative LN on survival was not present in patients with squamous cell carcinoma [12]. In contrast, more than 90% of the patients in our cohort had squamous cell carcinoma and the number of negative LN was shown to be a significant prognostic factor regardless of the type of histology ($\log rank p = 0.009$ for squamous cell carcinoma; $p = 0.05$ for non-squamous cell carcinoma).

There are two possible explanations for our finding that improved survival is related to the number of negative LN removed. One possibility is that the improved survival is due to stage migration, meaning that a proportion of the patients staged as N0 may in fact have had cancer disseminated to regional lymph nodes [4, 5, 11, 12]. As the number of examined LN increases, the probability of missing a positive lymph node and erroneously classified with an earlier stage cancer decreases. However, while the stage migration phenomenon may affect patients with N0 disease, it does not hold true in patients with node-positive cancers. Thus, the “stage

Fig 3. After stratification by N stage, (A) no survival difference between high negative (red lines) and low negative (blue lines) lymph node (LN) groups was noted in patients with N0 stage tumors. (B) However, a significant survival difference was noted in patients with node-positive esophageal cancers.

Fig 4. Among patients with adequate lymph node (LN) staging (TLN $\geq 15$), patients with a high number of negative LN (red line) had significantly better survival than patients with a low number of negative LN (blue line).
A second explanation is that an increase in the number of negative LN may contribute to a reduction of unrecognized tumor cells [13]. There are immunohistochemistry-based studies that have shown that a high rate of node-negative patients actually have nodal metastases that were missed during routine pathology examination [13, 14]. In the study of Thompson and colleagues [14], immunohistochemical staining identified occult nodal metastases in 31 of 119 esophageal cancer patients (26.1%) who were classified as node-negative. The presence of occult metastases in negative lymph nodes might explain enhanced patient survival by the following mechanism: removal of more negative LN (that may potentially harbor occult cancer) could eliminate residual tumor cells and reduce the potential for subsequent oncologic progression.

In addition to the number of negative LN, we also identified that age, sex, T stage, N stage, tumor length, and the type of surgical approach were significant prognostic factors. It should be noted that the type of surgical approach influenced patient survival in our study. Previous reports have demonstrated that thoracoscopic esophagectomy offers advantages over open thoracotomy, including an easier mediastinal lymph node dissection, reduced postoperative pain, decreased postoperative pulmonary complication rates, and shorter hospital stays [15]. There are also studies showing trends toward better overall survival with thoracoscopic esophagectomy. For example, Lazzarino and associates [16]...
found that the patients undergoing thoracoscopic esophagectomy had better 1-year survival rates than patients receiving open procedures (odds ratio 0.68, \( p = 0.058 \)). In our study, thoracoscopic esophagectomy was also associated with better overall survival (hazard ratio 0.544, \( p = 0.034 \)). A possible explanation may be related to the magnified vision provided by a thoracoscope. Improved vision may facilitate mediastinal lymph node dissection and increase the extent of dissection. That, in turn, may allow harvesting of a higher number of negative LN, improve local disease control, and prolong patient survival [16]. However, owing to the small number of patients in the thoracoscopic group, the retrospective nature of the current study, and possible selection bias, careful interpretation of our results is mandated.

There were some other limitations and shortcomings in this study. First, we included patients receiving primary resection as well as preoperative chemoradiation therapy. The current analysis reflects our experience and may be applied to all patients undergoing esophagectomy (rather than to a highly selected population). We understand that chemoradiation may affect tumor and lymph node status. However, the number of patients in the preoperative chemoradiation group was small. A subgroup analysis was not feasible. We believe that further studies are needed to evaluate the impact of negative LN in patients receiving neoadjuvant chemoradiation followed by surgical resection. Second, we included patients with TLN less than 15 to broaden the applicability. In the Worldwide Esophageal Cancer Collaboration database, a high proportion of patients who underwent esophagomyectomy had low TLN. The TLN distribution shown in the report by Rizk and coworkers [17] demonstrated that nearly 60% of the patients had TLN less than 15. If we had excluded patients with TLN less than 15, the results would lose applicability to more than 60% of population in the Worldwide Esophageal Cancer Collaboration database. Our analysis showed that the results were the same in both the entire cohort and in patients with TLN of 15 or more. Third, we understand that it is inappropriate to set an arbitrary or subjective cutoff value for the number of disease-free lymph nodes. Instead, we used quartiles to demonstrate such a trend. Although we demonstrated that 19 or more negative LN was positively associated with survival, the impact of negative LN was not an all-or-none phenomenon. We recognized a gradient correlation: the number of negative LN continued to be a prognostic factor when modeled as a continuous variable in the Cox regression analysis.

In summary, we demonstrate that a high number of negative LN is associated with better overall survival in esophageal cancer patients after transthoracic resection. The correlation of a higher number of negative LN and increased survival was more prominent in patients with advanced tumors. A high number of negative LN (in addition to age, sex, T stage, N stage, tumor length, and thoracoscopic approach) remained an independent prognostic factor in multivariate analysis. One of the strengths of our study is that by having a large cohort of squamous cell carcinoma patients from a single institution using relatively standard surgical techniques, we were able to avoid the possible bias that occurs in population-based studies. Moreover, we showed that the number of negative nodes also plays a role in patients with advanced esophageal squamous cell carcinoma (T3/4 stage or positive nodal involvement). Future studies based on larger populations are needed to validate our findings and to explore the potential mechanisms underlying the prognostic implications of negative lymph nodes.

References