Radical Lymph Node Dissection in Primary Esophagectomy for Esophageal Squamous Cell Carcinoma

Chen-Sung Lin, MD, PhD, Chih-Tao Cheng, MD, DrPH, Chao-Yu Liu, MD, Ming-Yuan Lee, MD, Mu-Chi Hsiao, MD, Chih-Hsun Shih, MD, MS,* and Chia-Chuan Liu, MD*

Faculty of Medicine, National Yang-Ming University, Taipei; National Defense University, Taipei; Division of Thoracic Surgery, Far Eastern Memorial Hospital, New Taipei City; Division of Thoracic Surgery, Taipei Hospital, Ministry of Health and Welfare, New Taipei City; and Department of Pathology and Divisions of Thoracic Surgery and Psychiatry, Koo-Foundation Sun Yat-sen Cancer Center, Taipei, Taiwan

Background. Subtotal esophagectomy with radical lymph node dissection (RLND) remains an effective therapeutic strategy for localized esophageal squamous cell carcinoma (ESCC). However, controversy exists regarding the extent to which RLND should be performed. We reappraised the prognostic impact and accurate nodal staging of RLND in ESCC.

Methods. The data from 101 ESCC patients (mean age, 57.5 years; 93 men) who underwent primary subtotal esophagectomy were retrospectively collected. Candidate variables, including the number of total dissected lymph nodes (TDLN [subgrouped into TDLN less than 13, TDLN 13 to 40, and TDLN more than 40]), were evaluated to determine their prognostic impacts and hazard ratio (HR).

Results. Fewer TDLN ($p < 0.001$; HR 9.011, 2.449, and 1.000 for TDLN less than 13, TDLN 13 to 40, and TDLN more than 40, respectively), tumor length exceeding 3.5 cm ($p < 0.001$; HR 3.321), resection margin invasion ($p < 0.001$; HR 14.493), and positive nodal status ($p = 0.002$; HR 2.730) were independent predictors of a poor prognosis. Considering the 54 node-negative patients, more TDLN correlated with improved survival ($p = 0.001$). Risk analysis demonstrated that one fewer TDLN could contribute to an increased HR of 1.047 ($p = 0.014$). However, RLND involving more TDLN appeared to lose the prognostic impact for the 47 node-positive patients ($p = 0.072$). Furthermore, the number of positive dissected lymph nodes remained at approximately 4 if the number of TDLN exceeded 20.

Conclusions. For N-negative or N-positive ESCC patients undergoing primary surgical resection, the number of TDLN influenced their prognosis or nodal staging accuracy, respectively. At least 20 TDLN were necessary for N-positive patients.

(Ann Thorac Surg 2015;100:278–87)
© 2015 by The Society of Thoracic Surgeons

Esophageal squamous cell carcinoma (ESCC) is a highly lethal malignancy with a poor prognosis, and several prognostic variables have been evaluated [1, 2]. Clinically, tumor (T) status, node (N) status, metastasis (M) status, and cancer stage as defined by the American Joint Committee on Cancer (AJCC) manual are the gold standards for making survival predictions and developing tailored therapeutic strategies for ESCC patients [3, 4]. Concerning the alterations of N status to differentiate survival (AJCC sixth to seventh edition), the emphasis on positive nonregional lymph nodes has been shifted to the number of positive dissected lymph nodes (PDLN) [4]. The extent of radical lymph node dissection (RLND), which is represented and quantified by the number of total dissected lymph nodes (TDLN), is crucial for N status determination. To distinguish N-negative and N-positive ESCC patients and further subgroup N-positive patients, RLND with sufficient TDLN appears to be mandatory. Although some researchers have emphasized that RLND can achieve better local-regional control, eliminate undetectable lesions, and perhaps prolong survival, others believe that ESCC is a systemic disease and that RLND may increase the risk of postoperative comorbidities without improving survival [5–7]. Because of these controversies, the role of RLND in ESCC deserves reappraisal. In this study, we aimed to reappraise the roles of RLND/TDLN compared with other prognostic variables in ESCC patients who underwent primary esophagectomy.

Material and Methods

Patient Recruitment

Between January 2001 and December 2013, 380 constitutive cases were newly diagnosed as ESCC in the

Abbreviations and Acronyms

AJCC	=	American Joint Committee on Cancer
ESCC	=	esophageal squamous cell carcinoma
HR	=	hazard ratio
NDLN	=	negative dissected lymph nodes
PDLN	=	positive dissected lymph nodes
PRDLN	=	positive rate of dissected lymph nodes
RLND	=	radical lymph node dissection
TDLN	=	total dissected lymph nodes

Koo-Foundation Sun Yat-sen Cancer Center. Among them, 101 ESCC patients who received surgery alone without preoperative chemotherapy, radiotherapy, or both as the primary therapeutic modality were retrospectively evaluated for analysis. None of these patients had detectable metastatic lesions during the preoperative work-up. The Institutional Review Board of Koo-Foundation Sun Yat-sen Cancer Center approved the study and waived the informed consent requirement.

Preoperative Work-Up

Panendoscopic examinations, chest radiographs, upper gastrointestinal series, thoracic computed tomography scans from the lower neck to the upper abdomen, and whole body bone scans were routinely arranged to determine the resectability and oncologic characteristics of the ESCC. Complete blood counts with cell differentials, routine urine tests, blood biochemistries, pulmonary function testing, and cardiac sonography were collected to evaluate the general condition of each patient. The patients underwent surgery after completing the preoperative workup and providing written informed consent.

Surgical Resection and Extended Two-Field RLND

The surgical modalities contained three-field approaches with extended two-field RLND by the following: (1) transthoracic subtotal esophagectomy and RLND along the periesophageal region, grouped N-T; (2) gastric tube reconstruction after gastric cardiectomy and RLND along the left gastric artery to the main celiac trunk, grouped N-A; and (3) esophagogastric anastomosis through a left cervical oblique incision and lymph node sampling if clinically suspected, grouped N-C.

Surgical Pathology Staging and Lymph Node Counting

Based on the surgical and pathologic findings, the ESCC cancer stages were determined according to the T status, N status, and M status as described in the AJCC manual, seventh edition [3]. Dissected lymph nodes (N-T, N-A, N-C) were labeled by the surgeon and then sent for pathology examination. The lymph node number was counted under low-power field microscopy. The number of TDLN was the sum of the number of N-T, N-A, and N-C collected during surgery. Similarly, the number of PDLN was the sum of the metastasis-involved lymph nodes found by N-T, N-A, and N-C. The number of negative dissected lymph nodes (NDLN) was equal to TDLN minus PDLN. A positive rate of dissected lymph nodes (PRDLN [%]) was defined as PDLN divided by TDLN for each patient.

Prognostic Variables

Candidate variables, including demographic data, the tumor characteristics, and the number of TDLN, were recorded in detail for analysis. The minimal requirement of TDLN for N-positive patients was also evaluated.

Statistical Analysis

The overall survival intervals were calculated from the date of surgery until death or the last follow-up in December 2013. Survival curves were plotted by the Kaplan-Meier method. The log rank (long-term) or Breslow (short-term) test was used to compare the differences in survival among the groups within each categorical variable. Variables associated with survival probability of 0.10 or less were considered in a univariate or multivariate Cox regression analysis under a continuous or categoric model. Categoric variables in two, three, or more groups were compared by χ^2 test or Fisher exact test or by linear association (χ^2 test for trend) when appropriate. Continuous variables in two, three, or more groups were compared by t test, Mann-Whitney U test, or analysis of variance or Kruskal-Wallis H test when appropriate. Relationships between two continuous variables (TDLN versus NDLN) were evaluated by Pearson's correlation and presented as the Pearson correlation coefficient (Pcc) and R square (R^2). Significance was defined as p less than 0.05.

Results

Demographic Data and Impact of TDLN

The demographic data of the 101 ESCC patients (93 men and 8 women; mean age, 57.5 years) are summarized in Table 1. The mean numbers of TDLN, NDLN, and PDLN were 32.4, 30.7, and 1.7, respectively. The mean survival was 80.7 months (median survival 72.5). The 1-, 2-, 3-, and 5-year survival rates were 85%, 72%, 62%, and 55%, respectively. Significantly, one fewer TDLN was able to contribute to an increased hazard ratio (HR) of 1.029 ($p = 0.011$; Table 2).

Impact of TDLN on Survival and HR

We tested various cutoff points for TDLN on receiver-operating characteristic curves, and 13 and 40 had the highest area under the curve coefficients (area under the curve = 0.6507). Using the cutoff values of 13 and 40, the patients who were found to have TDLN of 13 or less were classified as group I (TDLN $\leq$ 13, n = 10) and those with more than 40 as group III (TDLN > 40, n = 25). The remaining 66 patients were classified into group II (TDLN 13 to 40). Significantly, group III had the best mean survival of 110.0 months, followed by 78.1 months for group II and 31.0 months for group I