Influence of Metastatic Status and Number of Removed Lymph Nodes on Survival of Patients With Squamous Esophageal Carcinoma

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Abstract: The aim of this study was to determine the impact of lymph node (LN) metastasis conditions on the prognosis of patients with esophageal squamous carcinoma and the minimum number of LNs that should be removed to maximize overall postoperative survival among patients with this specific pathologic subtype.

In this study, 312 patients with thoracic squamous esophageal carcinoma who received in-patient thoracic surgery by the same surgeon in our hospital from August 1, 2003 to December 31, 2009 were recruited. Subsequently, Kaplan-Meier methods were used to determine associations between LN metastasis conditions and mortality and between the numbers of LNs removed during esophagectomy and mortality. Cox regression models were used to adjust for potential confounding covariates.

According to Kaplan-Meier analyses, the number of metastatic LNs was a good predictor for the prognosis of patients with esophageal squamous carcinoma and the dissection of ≥29 LNs during thoracic surgery significantly improved patient survival (P = 0.011).

Lymph node metastasis rates may be a significant predictor for the prognosis of patients with esophageal squamous carcinoma. The number of LNs removed during esophagectomy is an independent predictor for the survival of patients with esophageal squamous carcinoma with maximal postoperative survival after the removal of ≥29 LNs.

METHODS AND PATIENTS

Inclusion and Exclusion Criteria

Eligibility criteria included primary esophageal squamous cell carcinoma tumor located in the thoracic esophagus, no distant metastasis, no LN larger than 1 cm around the celiac trunk or in the neck, and esophagectomy prescribed as a suitable curative surgical procedure.

Exclusion criteria included postoperative pathologic subtype other than squamous carcinoma, inoperable lesions even after neoadjuvant therapy (including invasion into the adjacent aorta, trachea, vertebra, or pulmonary structures), distant metastatic disease (including LN spread), no visible tumors after neoadjuvant therapy (chemotherapy or radiotherapy), or perioperative death.

Surgical Procedures

Patients were treated using Sweet, Ivor-Lewis, or Mckeon esophagectomy during the study period according to tumor characteristics and the surgeon’s preference.

All patients received double-lumen tracheal intubation and combined general and regional anesthesia with a thoracic epidural catheter. The dissection of intrathoracic esophagus included the en bloc resection of esophageal cancer and surrounding tissue. The proximal margin was at least 5 cm from the lesion and frozen sections were routinely obtained to secure tumor-free margins. The distal edging was 5 to 8 cm from the lesion according to character. The proximal margin was at least 5 cm from the lesion and frozen sections were routinely obtained to secure tumor-free margins. The distal edging was 5 to 8 cm from the lesion according to character.
TABLE 1. Status of the Patients Included

| Variable                | Cases (312) |
|-------------------------|-------------|
| Sex                     |             |
| Male                    | 239         |
| Female                  | 73          |
| Age                     | 59.01 ± 8.66 (35–77) |
| Preoperative treatment  |             |
| Chemotherapy            | 17          |
| Radiochemotherapy       | 1           |
| Postoperative treatment |             |
| Chemotherapy only       | 58          |
| Radiotherapy only       | 12          |
| Radiochemotherapy       | 32          |
| Neoplasm location       |             |
| Upper                   | 76          |
| Middle                  | 154         |
| Lower                   | 82          |
| Staging                 |             |
| T1                      | 44          |
| T2                      | 46          |
| T3                      | 193         |
| T4                      | 29          |
| N1                      | 151         |
| N2                      | 82          |
| N3                      | 61          |
| Stage I                 | 36          |
| Stage II                | 123         |
| Stage III               | 153         |

abdominal) lymph-node dissection, and stations were defined according to American Thoracic Society criteria.

Follow-up

Disease recurrence and survival was generally monitored at 1 month postoperatively, at 3-month intervals for 2 years, at 6-month intervals for the subsequent 3 years, and then at 1-year intervals. The last follow-up was performed in January 2012 and overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up.

Statistical Analysis

The Institutional Review Board at the Peking University Cancer Hospital approved this retrospective study and the requirement of patient consent was waived.

Overall survival was estimated using the Kaplan-Meier method and differences were compared using the log-rank test. Lymph node retrieval and staging were compared between 2 groups using Student t test or Mann-Whitney U test for analyses of normally or non-normally distributed data, respectively. Pearson χ² test or the Fisher exact test were used to compare proportions as required and differences were considered significant when P < 0.05.

RESULTS

Prognostic Factors Identified Using Cox Regression Models

Cox regression analyses indicated that T and N classifications by the 2010 AJCC staging system, the numbers of dissected LNs, and the receipt of postoperative radiochemotherapy were significant predictors of patient survival.

Prognostic Effects of Lymph Node Metastases

The current cases were divided into groups according to the numbers of LN metastases using the 2010 AJCC staging system as follows: N0, no LNs metastasis, n = 151; N1, 1 to 2 LN metastases, n = 82; N2, 3 to 6 LNs metastasis, n = 61; and N3, 7 or more LN metastases, n = 18.

Kaplan-Meier analysis (Fig. 1) indicated significant differences between groups of patients with and without LN metastases (P < 0.001). No significant differences, however, were observed between N1, N2, and N3 groups (P = 0.312).

In further analyses, LN metastasis rates were calculated as numbers of metastatic LNs/numbers of dissected LNs, and prognostic factors were evaluated according to the staging criteria and patient groups shown in Table 2.

Kaplan-Meier analyses indicated significant differences between all patient groups stratified by LN metastasis rates (Fig. 2; P < 0.001), and between N1, N2, and N3 groups (P = 0.001).

Numbers of Dissected Lymph Nodes and Prognosis

Cox regression analyses indicated that the number of dissected LNs is predictive of survival among patients with thoracic esophageal squamous carcinoma. Thus, patients were grouped according to the numbers of dissected LNs and comparisons of postoperative survival were made. Although, no effects were observed with the initial threshold of 10, the dissection of >17 LNs (thoracic plus abdominal field) significantly improved postoperative survival (P = 0.045). No further differences, however, were observed using higher thresholds (from 17 to 28) until comparisons were made with patients who underwent the removal of ≥29 LNs. At this threshold, postoperative survival was significantly improved (P = 0.011; Fig. 3).

To identify maximally prognostic criteria, patients were divided into 3 groups of <17, 17 to 28, and ≥29 removed LNs during esophagectomy. Subsequent Kaplan-Meier analyses showed significantly improved survival rates among patients who underwent the removal of ≥29 LNs (P = 0.018). The statistical difference exist only between group 17 ≤ LNs < 29 versus LNs ≥29 (P = 0.011), whereas P = 0.221 between group LNs < 17 and 17 ≤ LNs < 29 (Fig. 3).

To assess ≥29 removed LNs as an independent prognostic factor, χ² test were performed with pathologic staging and

FIGURE 1. Kaplan-Meier estimates of mortality base on the number of lymph nodes involved. Significant difference is shown by Kaplan-Meier analyses between groups of patients with and without lymph node metastases (P < 0.001), whereas no significant differences were observed between N1, N2, and N3 groups (P = 0.312).
agreement, Peyre et al8 demonstrated significant prognostic absolute numbers of involved LNs as prognostic criteria. In

postoperative treatments as covariates, but no significant effects of these covariates were identified (P = 0.733 and P = 0.486, respectively; Table 3).

**DISCUSSION**

**Locations and Differentiation States of Neoplasms**

In comparison with former editions, the 2010 AJCC staging system includes carcinoma locations and differentiation states as prognostic factors according to recent clinical studies. The current Cox regression analyses, however, eliminated these 2 factors, potentially reflecting the low rate of upper esophageal carcinomas (25% of patients). Hence, because the current staging system is based on both adenocarcinomas and squamous carcinomas of the esophagus, larger patient numbers may be required to demonstrate locations and differentiation states as significant prognostic factors.

**Lymph Node Metastasis**

This revised 2010 AJCC staging classification is based on risk-adjusted random forest analyses of data from the Worldwide Esophageal Cancer Collaboration, including 13 institutions and 4627 patients who were treated with primary esophagectomy alone.7 This edition of N classification used absolute numbers of involved LNs as prognostic criteria. In agreement, Peyre et al8 demonstrated significant prognostic values of the numbers of LNs in 1053 patients from 9 esophageal centers. Although some other studies support further subdivision of absolute numbers of involved LNs,9–12 all previous analysis were based on data from combined cohorts of patients with squamous carcinomas and adenocarcinomas. In the current study, only patients with squamous carcinomas were included and N staging contributed significantly to the predictions of OS only for N0 and N1 groups.

In further analyses, the prognostic value of LN metastasis rates were assessed according to the numbers of metastatic LNs/numbers of dissected LNs. Previous studies also report use of LN metastasis rates using ratios of 0.113,14–0.315 or 0.216–18 as decisive criteria, and in comparisons of patients with lymph metastasis rates lower and higher than 0.2, 5-year survival rates were decreased from 54% to 22%, and the risk of recurrence was increased from 44% to 59%.

In the current analyses, patients were divided into 4 groups (N0–N3) according to LN metastasis rates, and Kaplan-Meier analyses showed significant differences only between N1 to N3 groups. According to this result, we conclude that if dissected LNs are adequate for staging, LN metastasis rates may be more predictive of survival than absolute numbers of metastatic LNs. Hence, more a thorough dissection of LNs may lead to the identification of more normal and metastatic LNs; therefore, the improved accuracy of LN metastasis rates and higher prognostic value were achieved.

**Optimal Numbers of Dissected Lymph Nodes**

The required number of LNs that should be dissected to achieve the best staging assessments and outcomes for patients with esophageal squamous carcinoma remains controversial. In agreement with previous studies, the numbers of pathologically examined LNs removed at the time of esophagectomy were significantly associated with prognosis in the current cohort.19 Moreover, although the underlying mechanisms remain unknown, the dissection of ≥15 LNs is currently recommended by the National Comprehensive Cancer Network official guidelines for the surgical treatment of esophageal carcinoma.

Rizk et al20 analyzed 4627 patients from the Worldwide Esophageal Cancer Collaboration database, and suggested that the extent of lymphadenectomy was positively associated with survival among all patients with pN0 and pN(+) cancers, and recommended more LN dissections for patients with higher T status. Moreover, Groth et al21 used surveillance epidemiology and end results data from 4882 patients to determine the minimum number of LNs required to maximize survival, and indicated that the large numbers of LNs (30 or more) should be examined regardless of the surgical technique. Peyre et al24 also
published a retrospective international multi-institutional study of 2303 patients who received R0 resections for esophageal carcinoma. These authors concluded that the number of removed LNs is an independent predictor of survival after esophagectomy for cancer, and a minimum of 23 regional LNs must be removed to achieve the maximum survival benefit. Finally, smaller studies also support this view, but the recommended thresholds vary between 12 and 30.

All of the previous studies on degrees of lymphadenectomy in esophageal cancer included both patients with adenocarcinoma and squamous carcinoma, and all report a preponderance of adenocarcinomas. Because the pathogenesis and biologic behaviors of these carcinomas may differ, further larger studies are required to examine prognostic factors in patients with only squamous carcinomas.

In summary, we analyzed survival rates among patients who underwent the dissection of 10 to 30 LNs, and used Kaplan-Meier analyses to show that postoperative survival differed between patients with <29 and ≥29 dissected LNs (P = 0.011). Cox proportional hazards models, however, failed to show other significant prognostic differences between these 2 groups. Hence, the number of removed LNs during esophagectomy is an independent predictor of survival among patients with esophageal squamous carcinoma, and ≥29 LNs should be dissected to maximize postoperative survival.

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