Prediction of prognosis by the extent of lymph node involvement in squamous cell carcinoma of the thoracic esophagus

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Abstract

Objectives: Current criteria of the N-category in the TNM staging system for carcinoma of the esophagus needs further subgrouping due to its simplicity in mixing together patients with different prognosis. Method: A retrospective cohort study of 186 patients (176 men and ten women; mean age, 59.9 years) with squamous cell carcinoma (SCC) of the thoracic esophagus who underwent esophagectomy followed by two-field lymphadenectomy and cervical lymph node sampling between 1992 and 1999 was conducted. A proposed N-category which involved dividing the nodal status into N0 (no nodal involvement), N1 (≤4 nodes or ≤20% nodal involvement), and N2 (>4 nodes, or >20%, or non-regional nodal involvement) subgroups was used for survival analysis. Results: The overall 5-year cumulative survival rate was 27%. Lymph node metastases were identified in 101 (54.3%) patients. Cumulative survival rates were 46% at 4 years in the N0 group and 21% at 4 years in the N1 group, whereas no patients in N2 group survived longer than 3 years (P < 0.01). A multivariable analysis revealed that independent prognostic factors included the depth of tumor invasion (P < 0.01), nodal involvement (P < 0.01), and organ metastasis (P < 0.01). Conclusion: In addition to the location of nodes, the extent of nodal involvement in SCC of the thoracic esophagus also plays an important role in prognosis prediction. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Esophagus; Carcinoma; Metastasis

1. Introduction

The current staging system for esophageal cancer groups all regional nodal positive patients together regardless of the number, and extent of nodes involved. It also puts positive nodes into different category according to their location (N1 vs. M1a and M1b). Furthermore, patients with N1 status are divided into different stages (IIb and III) according to the depth of tumor invasion [1]. Cumulative data have indicated that patients with nodal metastasis usually have dismal outcomes even though the primary lesion is small [2–4]. In addition, intrathoracic and extrathoracic nodal metastases may have different influences on survival [5,6]. The inadequacies of the current TNM staging system have prompted many to propose revisions based on large series retrospective analyses [7–9]. However, these reports have grouped together cancer of the esophagus with cancers of different anatomical locations and of different pathologies. We analyzed our experience in treating a homogenous group of patients with squamous cell carcinoma (SCC) of the thoracic esophagus by surgical resection, focusing on nodal involvement and its clinical significance. A proposal for revision of the current staging criteria for the N-category in SCC of the esophagus will be discussed.

2. Patients and methods

Between January 1, 1992, and June 30, 1999, 582 new cases of esophageal cancer were treated at Taichung Veterans General Hospital. The exclusion criteria included: (1) cervical esophageal cancers, (2) adenocarcinomas, (3) inoperable cases, (4) inadequate lymphadenectomy (total node number < 12), (5) transhiatal esophagectomy, and (6) patients who received preoperative radiotherapy or chemotherapy. Two hundred patients who underwent three-phase esophagectomy and two-field lymphadenectomy (with cervical node sampling) fit the above criteria. After the exclusion of 14 hospital mortalities (7.0%), 186 patients were included in this study for survival analysis. There were 176 men and ten women. The mean age at diagnosis was 59.9 years (range 36–78 years). The demographic data of the patients are shown in Table 1. A proposed N-category which involved dividing the nodal

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status into N0 (no nodal involvement), N1 (either > 4 nodes or > 20% nodal involvement), and N2 (either > 4 nodes, or > 20% nodal involvement, and non-regional nodal involvement) subgroups was used for survival analysis. Our definition for a non-regional lymph node (M1a or M1b) was the same as that described in the 1997 version of the AJCC Cancer Staging Manual [1]. The preoperative work-up included a plain chest roentgenogram, fiberesophagoscopy, a chest CT scan, liver sonography, a whole body bone scan, and pulmonary function testing. If possible, postoperative radiotherapy was implemented when intrathoracic lymph nodes were involved or tumor invasion was beyond the muscular layer.

Survival analyses by the Kaplan–Meier method, data comparison by log-rank test, and test of association by Cox’s proportional hazard model for categorical variables were performed using SPSS statistical software. Differences were considered significant if the two-tailed $P$ value was less than 0.05.

3. Results

3.1. Overall survival

As of December 31, 1999, 65 patients were still alive, 105 patients had expired, and 16 patients were lost during follow up. The cumulative survival rates of the entire series at 1 year, 3 years, and 5 years were 61, 32, and 27%, respectively (see Fig. 1). Cumulative survival curves according to the current TNM staging system [1] are shown in Fig. 2.

3.2. N-factor analysis

Altogether 4557 lymph nodes were resected for analysis (mean per patient, 24.5; range 12–56). As shown in Table 2, Cox’s proportional hazard model revealed that nodal metastasis was the most significant independent negative prognostic factor in this series ($P < 0.01$). The cumulative survival curves according to the status of nodal involvement are shown in Fig. 3 ($P < 0.01$).

Once the nodes were involved, patients with more than four positive nodes had poorer prognoses than patients with four or less positive nodes (Fig. 4, $P < 0.01$). When more than 20% of dissected lymph nodes were involved, a negative influence on survival was observed ($P < 0.03$).
4. Discussion

Esophageal cancer is notorious for its poor prognosis due to early lymphatic spreading or distant metastasis at diagnosis. Complex submucosal and periesophageal lymphatic interconnections have been well demonstrated [10]. The tumor cells can spread along the submucosal lymphatic channel for a long distance before entering the periesophageal lymph nodes or can spread circumferentially by penetrating the esophageal wall and invading the periesophageal lymphatic system. A more thorough understanding of patterns of lymphatic spreading in esophageal cancer is crucial for determination of treatment and prediction of outcome.

The Japanese experience has demonstrated an improved outcome in cancer of the esophagus after surgical resection and three-field lymphadenectomy [2,11]. Even though the reported mortality rate is acceptable (2.9–10.4%), the associated morbidity rate is very high (31.1–65.1%) [3–6,11]. The improved surgical results may be due to stage migration phenomenon or to the early stage of the patients at diagnosis [2,11]. In this series, we performed two-field lymphadenectomy and cervical lymph node sampling (along the left common carotid artery and jugular vein) during neck exploration. More than half (54.2%) of the patients presented with stage III or stage IV disease. The composition of the patients and the overall 5-year survival rate of 27% in this series were similar to those reported by Roder et al. [12].

Multivariable analysis revealed that the predictive prognostic factors of esophageal cancer included the depth of tumor invasion (T-factor), the presence of nodal involvement (N-factor), and organ metastasis (M-factor). Among these factors, the nodal status had the strongest influence on survival ($P < 0.01$). Further analysis of the influence of the T-factor on nodal negative patients showed a better prognosis in T1N0 patients as compared with T2–4N0 patients ($P < 0.01$). However, the T-factor did not influence the prognosis significantly once lymph nodes were involved ($P = 0.28$). This suggested that once the lymph nodes become involved, further separation of the patients into different stages or groups according to their T-status may not be necessary.

The impact of lymph node metastasis on survival depends on three factors, which include the number of nodes involved, the extent of nodal involvement, and the location of nodal metastasis. The importance of quantitative analysis of nodal metastasis in esophageal cancer has been suggested by many researchers [3–6,13–16]. The extent of nodal metastasis can be estimated either by analyzing the number of nodes involved or the percent of nodes involved. Various cutoff values had been chosen in previous series, and we found that once the number of involved nodes was greater than four or the percentage was greater than 20%, significant survival differences could be demonstrated ($P < 0.01$ and $P < 0.03$, respectively). We chose these two cutoff values simply because they are adequate and did not cause further
uneven distribution of the patient groups. If adequate lymphadenectomy were performed, we believe that using the number of nodes involved is simpler and more practical than using the percentage of nodal involvement. Even though the current TNM staging system [1] does not consider the extent of nodal involvement as a prognostic factor, we strongly recommend that this factor be included in the next version of TNM staging system for esophageal cancer.

The current TNM staging system [1] divides non-regional and distant nodal involvement into M1a and M1b categories according to the location of the primary lesion. Bias may exist because sometimes it is difficult to categorize the location of the tumor once it occupies more than two esophageal regions. Furthermore, separation of the celiac lymph node from the perigastric lymph node is determined subjectively by the surgeon or pathologist which also leads to bias. Non-regional nodal metastasis was identified in 14 (7.5%) of our patients. In an attempt to avoid the above-mentioned biases, we categorized these patients into the so-called N2 group. As shown in Fig. 2, significant survival differences are demonstrated between each N group.

In Asian countries, adenocarcinoma of the esophagus is less common than in North America. Different cancer etiologies may play an important role in this phenomenon. Subsequently, different cancer origins even with same pathology, as presented in our previous report, may influence the pattern of lymphatic spreading [17]. Recent reports from North America have focused on the revision of the current TNM staging criteria for esophageal cancer. However, in these series, cancer of the esophagus has included two different pathological entities [7–10]. Our series represented a homogeneous group of patients with the same pathology (squamous cell carcinoma), which is important for data analysis. Our experiences in treating adenocarcinoma of the esophagus, especially from Barrett’s esophagus, are limited. These tumors may behave more like cancer of the gastric cardia. Further study is necessary to clarify the appropriateness of current criteria in grouping of the regional and distant lymph nodes for adenocarcinoma of the esophagus.

Based on the above findings, we suggest that in addition to the location of nodes, the extent of nodal involvement in SCC of the thoracic esophagus also plays an important role in prognosis prediction. Future revision of the TNM staging system for esophageal cancers should take this into consideration. Furthermore, squamous cell carcinoma and adenocarcinoma of the esophagus may have to be staged using different criteria due to different tumor etiologies and behaviors.

References