The Prognostic Importance of the Number of Dissected Lymph Nodes After Induction Chemoradiotherapy for Esophageal Cancer

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Background. **Analyses of adequacy of lymph node dissection during resection of esophageal cancer are based on patients who have not undergone induction chemoradiotherapy. We sought to determine the minimum number of dissected lymph nodes necessary to ensure adequate staging after induction chemoradiotherapy.**

Methods. **A prospectively maintained thoracic surgery database was queried to identify consecutive patients undergoing postinduction esophagectomy from 1996 to 2010. Cox proportional hazard and recursive partitioning survival analyses were performed.**

Results. **Complete lymph node data were available for 395 patients. Mean age was 59.5 years, and 64 patients (16%) were female. The median number of dissected lymph nodes was 8 (range, 0 to 63). When pathologic (p)T stage, pN stage, and the number of dissected lymph nodes were used as predictors, only pN stage (odds ratio, 1.3; 95% confidence interval, 1.2 to 1.7) and age (odds ratio, 1.03; 95% confidence interval, 1.01 to 1.04) independently predicted survival. Recursive partitioning was performed on 262 pN0 patients using T stage and the number of dissected lymph nodes as predictors. No pN0 patient with 28 lymph nodes dissected died during follow-up. For patients with fewer than 28 lymph nodes dissected, the next prognostic factor was T stage. For pT1-2 N0 patients, the number of lymph nodes dissected did not affect survival. For pT3-4 N0 patients, a significant survival decrement was noted for patients with fewer than 7 lymph nodes dissected compared with those with more than 7 lymph nodes dissected.**

Conclusions. **T stage determines prognosis in postinduction pN0 patients with fewer than 28 lymph nodes evaluated. Postinduction pT3N0 patients with fewer than 7 lymph nodes evaluated are understaged.**

(Ann Thorac Surg 2015;99:265–9)
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The number of regional lymph nodes containing metastases is the most important prognostic factor in patients undergoing resection for esophageal cancer [1–5]. In the past several years, multiple groups have demonstrated the importance of an adequate lymph node dissection [3–11]. In general, the more lymph nodes resected, the better the survival, which may be due to improved staging or to a therapeutic effect of the lymphadenectomy itself. Most of the patients in these studies, however, were receiving a primary surgical intervention. Given that National Comprehensive Cancer Network (NCCN) guidelines now advocate chemoradiotherapy followed by surgical resection as a standard treatment option for patients with noncervical stages IB, II, III, and IVA esophageal cancer based on the results of several randomized trials [12], determination of the minimum number of lymph nodes required to accurately stage patients receiving multimodality therapy with induction chemoradiotherapy is important.

Recently, Stiles and colleagues [13] analyzed 135 patients who had undergone resection after induction chemotherapy or chemoradiotherapy. They found that optimal lymphadenectomy, as defined by Rizk and colleagues [6] and the Worldwide Esophageal Cancer Collaboration investigators in a noninduction cohort, might predict survival after induction therapy. However, many of these patients did not undergo radiotherapy, only about half were downstaged, and most underwent a three-field lymphadenectomy. To our knowledge, no study to define optimal lymphadenectomy has been performed in a large cohort of patients having undergone induction chemoradiotherapy followed by two-field resection. Therefore, the purpose of this study was to define optimal lymphadenectomy for esophageal cancer after induction chemoradiotherapy.

Patients and Methods

Acquisition of Clinical Data

After Institutional Review Board approval, a prospectively maintained thoracic surgery database was queried

Accepted for publication Aug 15, 2014.

Presented at the Sixtieth Annual Meeting of the Southern Thoracic Surgical Association, Scottsdale, AZ, Oct 30–Nov 2, 2013.

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Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2014.08.073

to identify consecutive patients undergoing esophagectomy after induction chemoradiotherapy at Duke University Medical Center from January 1996 to December 2010. Patients received various chemotherapy regimens during the study course and daily radiation dosing over 6 weeks for a total of 45 to 50 Gy. The analysis excluded patients who did not have survival information or complete lymph node data. We included patients who had adenocarcinoma or squamous cell carcinoma of the thoracic esophagus, with or without involvement of the gastroesophageal junction and gastric cardia. The data collected included patient demographics, the tumor histologic type and location, the depth of tumor invasion, and the number of all malignant and benign lymph nodes. Overall survival, as calculated from the time of operation, was confirmed from the Social Security Death Index. April 2011 was the censoring date for survival.

TNM Classification

The T, N, and M descriptors and staging classification used for this analysis were those defined in the Seventh Edition of the American Joint Committee on Cancer Staging Manual [14]. The overall number of lymph nodes included the sum of all involved lymph nodes plus all benign lymph nodes found. The T stage was based on the depth of tumor invasion into the esophageal wall as described in the American Joint Committee on Cancer Staging Manual. Pathologic staging was obtained using standard light microscopy methods by board-certified pathologists.

Statistical Analysis

Patient characteristics are described with categoric variables, and means and ranges are used for continuous variables. Survival time was measured from the date of the operation to the date of death or the last follow-up. Survival curves were estimated by the Kaplan-Meier method. A Cox proportional hazard regression model using postinduction treatment pathologic (p) T status, pN status, number of dissected lymph nodes, and age was created to identify independent predictors of survival.

Recursive partitioning was used to determine the optimal cutoffs for lymph node numbers with respect to their prognosis (in this case, overall survival). Recursive partitioning is a simple regression model for prediction and explanation but is designed to be unbiased [15]. Instead of imposing many assumptions to arrive at a tractable statistical model, recursive partitioning simply seeks to accurately predict a response variable based on values of predictor variables. A two-stage algorithm is used: first, partition the observations by univariate splits in a recursive way, and second, fit a constant model in each cell of the resulting partition. This analysis performs an exhaustive search over all possible splits of every possible value of every possible feature within the data set and selects the covariate that shows the widest binary split. The result is that the data becomes split at each node into two independent groups, or nodes—this is partitioning. Once we have two new nodes (children nodes) linked to a previous node (parent node), we can repeat the process for each child node independently using only the observations present in that node, which is the recursive step. The process is halted once a maximum number of nodes in the tree is reached. The method outputs a decision tree depicting the predictor variables that were related to the response variable, along with the nature of the variables' relationships. Thus, this method partitions the patients recursively at each step into two groups on the basis of the covariate that gives the maximal separation with respect to their prognosis and accounts for interactions between factors. Cox proportional hazard (survival package) and recursive partitioning survival analyses (rpart package) were performed using R statistical software [16].

Results

Complete lymph node data were available for 395 patients. Of these, 262 were node-negative on pathologic analysis of the resected specimen after induction chemoradiotherapy. Demographic information is presented in Table 1. Patients were a mean age of 59.5 years (range, 34 to 83 years), and 64 (16.2%) were female. Operations performed included Ivor Lewis in 148 (37.5%), transhiatal in 115 (29.1%), and McKeown in 101 (25.6%). Pretreatment staging was determined by endoscopic ultrasound (EUS) imaging in 385 patients. As Table 1 demonstrates, patients who were pN0 were similar to the entire cohort, with the exception that the EUS nodal stage was lower in the pN0 group. Overall, of the 385 patients with pretreatment EUS results, 216 (56.1%) were downstaged, 91 (23.6%) were upstaged, and 78 (20.3%) remained the same stage on pathologic analysis after resection. Complete pathologic response occurred in 134 of 395 patients (33.9%).

To analyze factors contributing to survival of the entire cohort, a Cox proportional hazards model was developed. During follow-up, 228 patients died. Variables included in the model were pT status, pN status, number of dissected

Table 1. Demographic Characteristics, Clinical Staging, and Histologic Diagnosis

Characteristic	Entire Cohort (N = 395)	pN0 Cohort (n = 262)	*p* value
Age, mean ± SD y	59.5 ± 9.8	60.4 ± 9.7	0.26
Male gender, No. (%)	331 (83.8)	220 (84.0)	1
EUS T stage, No. (%)			0.6
T1	14 (3.5)	11 (4.2)	
T2	55 (13.9)	46 (17.6)	
T3	305 (77.2)	192 (73.3)	
T4	11 (2.8)	7 (2.7)	
EUS N stage			0.03
N0	152 (38.5)	123 (46.9)	
N1	233 (59.0)	133 (52.8)	
Histologic diagnosis, No. (%)			0.19
Adenocarcinoma	308 (78.9)	192 (73.3)	
Squamous	87 (21.1)	70 (26.7)	

EUS = endoscopic ultrasound; p = pathologic; SD = standard deviation.

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