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.

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

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

Table 1. Demographic Characteristics, Clinical Staging, and Histologic Diagnosis
lymph nodes, and age. Of these, only pN status and age independently predicted survival (Table 2).

Next, we analyzed lymph node evaluation. The median total number of dissected/analyzed lymph nodes was 8 (range, 0 to 63) for the entire cohort and also for the cohort of patients that were pN0. To identify a minimum number of dissected lymph nodes to prevent understaging, recursive partitioning analysis was performed on the 262 postinduction pN0 patients using postinduction pT status and the number of dissected lymph nodes as predictors. The most significant predictor of survival in this population was having at least 28 lymph nodes sampled, signified by group A (Fig 1), accounting for only 7 patients (2.7%). In this group, the range of lymph nodes dissected/analyzed was 28 to 63. As Figure 2 demonstrates, no ypN0 patient with 28 lymph nodes sampled died during follow-up. Within this group, 3 patients were T0, 2 were T1, and 5 were T2. For patients with fewer than 28 lymph nodes sampled, the most important predictor of survival was pT stage lower than 3, as signified by group B (Fig 1). This group accounted for 195 patients (74.4%), of which 131 were T0, 26 were T1, and 28 were T2, and 96 (49.2%) of these patients died during follow-up. The range of lymph nodes dissected/analyzed in this group was 0 to 27.

For ypT3-4 N0 patients, the most important predictor of survival was having at least 7 lymph nodes sampled. When compared with patients with more than 7 lymph nodes sampled (group C, Fig 1), a significant survival decrement was noted for patients with fewer than 7 lymph nodes sampled (group D, Figs 1 and 2). Group C accounted for 33 patients (12.6%), 16 (48.5%) of whom died during follow-up. Group D accounted for 27 patients (10.3%), 22 (81.5%) of whom died during follow-up. All patients in groups C and D were ypT3.

**Comment**

The American Joint Committee on Cancer Staging Manual states that an adequate lymphadenectomy requires resecting 12 to 22 nodes [14]. However, this range was derived from analyses of patients who received esophagectomy alone [6]. The extent of lymphadenectomy and its effect on staging in patients receiving induction chemoradiotherapy has not been adequately addressed. Because induction chemoradiotherapy is widely used, supported by randomized trials and recommended in guidelines for many patients with resectable esophageal cancer, we believe that such an analysis is extremely important [12, 17].

**Table 2. Cox Proportional Hazard Analysis (N = 395)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage</td>
<td>1.1 (0.97–1.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>N stage</td>
<td>1.3 (1.2–1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total lymph nodes</td>
<td>0.99 (0.96–1.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Age per year</td>
<td>1.03 (1.01–1.04)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.

In this study, we have demonstrated that age and nodal positivity strongly predict survival after induction chemoradiotherapy for locally advanced esophageal cancer. More importantly, our analysis of a cohort of 262 pN0 patients has shown that having 28 or more lymph nodes examined predicts significantly improved survival compared with patients who have had a smaller number of nodes harvested. Interestingly, the 7 patients in this group were alive at last follow-up and had significant nodal positivity.
downstaging with induction therapy. Of the pN0 patients without 28 lymph nodes examined, T stage lower than 3 is the next most important survival predictor on recursive partitioning analysis. T1 and T2 patients with fewer than 28 lymph nodes examined had an intermediate prognosis. Of the persistent T3 patients after induction therapy, 7 lymph nodes were enough to significantly stratify patients.

These data diverge from those generated from the Worldwide Esophageal Cancer Collaboration analysis in which optimum lymphadenectomy was defined as 10 nodes for T1 tumors, 20 nodes for T2 tumors, and 30 nodes for T3/T4 tumors [13]. The explanation for this is unclear. One explanation is that we have a much smaller cohort and could not use the random forest approach to analyze the patients. However, another probable explanation is that an interaction exists between postinduction T stage and the lymphadenectomy. If a patient has a poor response to induction therapy such that he or she is still T3, positive nodes are prevalent. In this situation, only a small number of nodes is necessary to prove that a patient is N0.

Only one other study has focused on adequacy of lymphadenectomy after induction therapy. Stiles and colleagues [13] analyzed 135 patients after chemotherapy or chemoradiotherapy and created a binary classifier for whether the patient had an “optimal” lymphadenectomy by Worldwide Esophageal Cancer Collaboration criteria. They then performed a Cox model to see whether this predicted survival. Although “optimal” lymphadenectomy predicted survival for the entire cohort, this result only trended toward significance on a T stage–per–T stage basis. Their study differs from ours in that many patients underwent induction chemotherapy without radiotherapy, and 70% of the patients underwent a three-field lymphadenectomy.

The lymph node yields in our analysis are lower than those in the Worldwide Esophageal Cancer Collaboration analysis and in the Stiles report. There are several potential reasons for this. First, we routinely perform a two-field rather than three-field lymphadenectomy. Also, radiation itself is known to reduce lymph node yield [18, 19]. Differences in pathologic assessment of lymph node packets may also be important. We have begun sending lymph nodes separately to pathology to optimize lymph node yield. Ultimately, all thoracic surgeons should strive to have as many lymph nodes as possible analyzed in each esophageal cancer case.

This study has several limitations. First, it is inherently biased because it is a single-center retrospective study. Second, we do not have reliable information on adjuvant treatment after surgical resection. Finally, this study is underpowered to evaluate the effect of histologic status, tumor differentiation, vascular and neural invasion, and extracapsular nodal invasion.

In conclusion, the number of involved lymph nodes is a powerful prognostic factor after induction chemo-radiotherapy. Persistent node-positive patients have a poor prognosis, and to prevent understaging, as many lymph nodes as possible should be evaluated. T stage determines prognosis in ypN0 patients with fewer than 28 lymph nodes evaluated, and ypT3N0 patients with fewer than 7 lymph nodes evaluated are most likely understaged. These results can be used for prognostic purposes and also, potentially, can be useful in guiding postresection surveillance strategies or even to guide adjuvant therapy decisions.

References
DISCUSSION

DR MITCHELL MAGEE (Dallas, TX): That was a nice study. I have to ask the obvious question, though. How do you determine number of lymph nodes? Because that varies a lot by the pathologist. Did you look at different pathologists and different surgeons? And also, different approach. Did you find that more lymph nodes are taken out by the McKeown approach vs the transhiatal or the Ivor Lewis?

DR HANNA: We did not look at differences between surgeon and between pathologists over that study period, but between approaches, the median number of lymph nodes was the same.

DR HIRAN FERNANDO (Boston, MA): Actually going along the line with the earlier discussions, what about differences between minimally invasive and open, or robotic and nonrobotic approaches? Did you analyze that in your group to see if there were differences in lymph node counts?

DR HANNA: This study did not incorporate patients that had robotic esophagectomies because that procedure was not done over this study period and not currently our practice. Therefore, this study only included esophagectomies that were done open or using a combination of both thoracoscopic and open techniques. Additionally, the focus of the study was not to look at differences in lymph node counts based on technique, but rather to analyze whether or not patients were being understaged based on how many lymph nodes were sampled.

DR FERNANDO: Did you analyze for differences between the open and the laparoscopic?

DR HANNA: No, as this was not the focus of the study.

DR ROBERT J. CERFOLIO (Birmingham, AL): It is a mistake to allow the pathologist to be a variable in this equation. So for the lung we do this: And it is a pain in the neck in the operating room for you, your nurses, but you know what, that is the job; some jobs are tough, and therefore, I literally take out every single node, and we do a report—paperwork—for each node. So, here is a 2R, here is a 2R, three paperworks go in; here is a 4R, here is a 4R, here is a 4R, three paperworks go in, and then we take the same thing with all the other nodes. So they are sent in, each one, individually. There is nothing for the pathologist to do. For every lymph node you give them with a piece of paper, they have to generate a report. That is how you get your lymph nodes up, and you are not contingent on a variable that does not share your culture, that does not share your culture, and that is important. The next thing is in the specimen itself. After I put the specimen in a bag and I will put it on the back table and I will take some 11s and 12s out from the specimen and give it to the nurse, and she has got to find five or six different little pieces of paper. That reduces that variable, and as Dr Howington said, it is a benchmark for us, and if it is going to be a benchmark for you, do you want somebody else counting them or do you want to be in control of them? So my advice is: do it yourself. We do the same for the esophagectomy.

DR HANNA: Our practice has evolved into individually labelling and packaging individual lymph nodes as well in order to reduce variability based on pathologist’s handling of the sample. The greater challenge arises in postinduction chemoradiation patients in which the lymph nodes are often matted and are therefore taken out in an en bloc fashion with the specimen, or in cases where there has been obliteration of a large amount of lymph nodes and lymph tissue, which decreases the overall lymph node count.

DR ALLAN PICKENS (Atlanta, GA): In continuation of the discussion of lymph node count, would the speaker, and the audience, comment on the use of lymph node volume or lymph node weight in the assessment of adequate lymph node removal?

DR HANNA: We do not do that at our institution because current data do not support that these methods of lymph node analyses are superior to absolute lymph node counts for accurately staging patients.

DR PICKENS: This is important because we need a better system for assessing lymph node removal, as pointed out by the author.

DR CERFOLIO: We tried it. We took a 10-cc beaker, tried to put a lymph node in and see how much water came out. It is cumbersome and I do not know what to do with the data. I do not know if it is practical.