Variation in Lymph Node Examination After Esophagectomy for Cancer in the United States

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Objectives: To evaluate the quality of lymph node examination after esophagectomy for cancer in the United States based on current treatment guidelines (≥15 nodes) and to assess the association of patient, tumor, and hospital factors with the adequacy of lymph node examination.


Setting: National cancer database.

Patients: Patients with stage I through III esophageal cancer undergoing esophagectomy and not treated with neoadjuvant chemoradiotherapy.

Main Outcome Measure: Rate of adequate lymph node examination (≥15 nodes).

Results: A total of 13,995 patients were identified from 639 hospitals. Overall, 4,014 patients (28.7%) had at least 15 lymph nodes examined, which increased from 23.5% to 34.4% during the study period. At the hospital level, only 45 centers (7.0%) examined a median of at least 15 lymph nodes. In the most recent period (2005-2007), at least 15 nodes were examined in 38.9% of patients at academic centers vs 28.0% at community hospitals and in 44.1% at high-volume centers vs 29.3% at low-volume centers. On multivariable analysis, hospital type, surgical volume status, and geographic location remained significant predictors of having at least 15 lymph nodes examined.

Conclusions: Fewer than one-third of patients and fewer than 1 in 10 hospitals met the benchmark of examining at least 15 lymph nodes. Hospitals should perform internal process improvement activities to improve guideline adherence.


See Invited Critique at end of article

Esophageal malignant neoplasms continue to pose substantial diagnostic and therapeutic challenges with a generally poor prognosis. In 2010, 16,640 new cases and 14,500 deaths occurred secondary to this disease.1 One of the most important predictors of survival for patients undergoing esophagectomy for cancer is the presence of lymph node metastasis.2,3 Reflecting the prognostic implications of lymph node involvement, the current edition of the American Joint Committee on Cancer staging guidelines now separates the number of nodal metastasis into 4 distinct groups (N0-N3).2,4,6 The number of lymph nodes examined during surgical resection therefore considerably affects staging accuracy.7 Staging is clearly an important prognostic factor for patients and physicians, treatment decisions, and stratification in clinical trials. In addition, evidence suggests that the extent of lymphadenectomy could be a surrogate of other unmeasured factors such as surgical technique, more thorough pathologic examination, or both.8

As such, the importance of adequate lymphadenectomy is now appreciated as a performance indicator across many gastrointestinal malignant neoplasms. The National Comprehensive Cancer Network currently specifies that at least 15 lymph nodes should be examined after esophagectomy.9 However, despite the current evidence, little is known regarding the quality of lymph node sampling in the United States. Therefore, our objectives were to examine the adequacy of lymph node examination after esophagectomy for cancer in a national cohort of patients and to assess the association of patient, tumor, and hospital factors with the adequacy of lymph node examination.
PATIENT SELECTION AND EXCLUSION CRITERIA

From the NCDB, 38,741 patients who underwent a major surgical resection for esophageal or gastroesophageal junction cancer diagnosed from 1998 to 2007 using International Classification of Disease for Oncology second and third revision codes (C15.1, C15.2, C15.4, C15.5, C15.8, C15.9, C16.0) were identified.12 Patients were excluded from the analysis if they had cervical esophagus lesions (n = 741) or stage IV disease (n = 9185), if they were not treated at the reporting facility (n = 5045), or if insufficient data were available on the number of examined lymph nodes after resection (n = 832). In addition, because neoadjuvant therapy is known to reduce lymph node counts and because the number of nodes that should be evaluated in these patients is not established, patients receiving neoadjuvant therapy were excluded from the analysis (n = 3372). Patients with International Classification of Disease for Oncology second and third revision code C16.0 who underwent gastrectomy alone without esophagectomy were also excluded from the study (n = 3581). Three periods were created to evaluate lymph node examination time trends; hospitals were excluded if they did not report at least 1 esophagectomy during each period, thus further reducing the study population (n = 2086). The final study cohort included 13,995 patients.

NUMBER OF LYMPH NODES EXAMINED

The primary purpose of this study was to examine nodal evaluation by quantifying the total number of lymph nodes examined after esophagectomy. Because National Comprehensive Cancer Network guidelines, based on systematic review of the literature and consensus recommendations by experts, recommend that at least 15 lymph nodes be examined after esophagectomy for cancer, this cut point was used to define an adequate lymphadenectomy. To evaluate lymph node examination performance, we analyzed both the proportion of patients with at least 15 lymph nodes removed and median lymph node counts after surgical resection. Analysis was performed at both the patient level (patient as the unit of analysis) and the hospital level (hospital as the unit of analysis); however, owing to small sample sizes at the hospital level, hospitals were compared based on median lymph node counts.

HOSPITAL TYPE AND SURGICAL VOLUME CLASSIFICATION

Facilities in the NCDB Participant Use Data File are classified on the basis of the American College of Surgeons Commission on Cancer accreditation program as academic/research centers (includes all National Cancer Institute–designated cancer centers) and community centers based on a variety of structural and service-related factors.10 Academic centers are hospitals that must be affiliated with a teaching and research institution, meet annual case volume requirements, provide a wide range of services such as access to specialists and cancer-specific diagnostic- and treatment-related services, and per-
form a number of specified quality improvement activities such as multidisciplinary tumor boards and clinical trial participation. Community cancer centers also provide a broad range of diagnostic and treatment needs but have lower overall annual cancer volumes (<650 cancer cases/y) and may not be equipped to perform certain diagnostic tests and treatments. Hospitals were further divided into average annual surgical volume quartiles by ranking all hospitals based on increasing median surgical case volumes and then creating 4 separate volume categories containing roughly equal numbers of patients in each group. The middle quartiles were then combined, leaving 3 surgical volume groups for analysis: 12 or more cases/y, 3 to 11 cases/y, and fewer than 3 cases/y.

PATIENT- AND TUMOR-SPECIFIC VARIABLES

Variables collected by the NCDB are defined by the Facility Oncology Registry Data Standards (2003-2011) and Registry Operations and Data Standards (1998-2002). Three periods were studied to evaluate time trends: 1998 to 2001, 2002 to 2004, and 2005 to 2007. Data from 2007 were the most recent available for analysis. In 2003, the NCDB began collecting data on up to 6 preexisting conditions, defined using International Classification of Disease ninth revision codes. Among patients diagnosed in 2003 or later, we evaluated comorbidity severity by calculating a modified Charlson Comorbidity Index score. The patient’s primary cancer and any treatment complications from the index primary cancer were not included in the modified score. Geographic location was evaluated based on US census region of the reporting hospital. Geography was categorized into 4 mutually exclusive groups based on US census regions: Northeast, Midwest, West, and South. Additional patient-level covariates evaluated were age (≤55, 55-69, or ≥70 years), sex, race/ethnicity (white, black, Hispanic, Asian, or other), income (<$46,000 or ≥$46,000), and payer (private, Medicare, Medicaid, uninsured, or other). Tumor-related covariates were tumor location (middle esophagus, lower esophagus, or gastroesophageal junction), tumor grade (low, intermediate, or high), pathologic American Joint Committee on Cancer stage (stage I, II, or III), and histologic subtype (adenocarcinoma or squamous cell carcinoma).

STATISTICAL ANALYSIS

For categorical variables, descriptive statistics were compared using the χ² test and the Cochran-Armitage test for trend; for continuous variables, the Mann-Whitney U test was used to compare medians. Multivariable analysis was performed with generalized linear mixed models with the hospital as the random effect to evaluate predictors of at least 15 lymph nodes examined. Variables were chosen for the models if they had a univariate association with the outcome variable at a P < .05 level. The final model included the following covariates: age, sex, race/ethnicity, region, Charlson Comorbidity Index score, hospital type, surgical volume status, tumor characteristics, and tumor stage. The threshold for statistical significance was set at P = .05, and P values were based on 2-sided tests. All statistical analysis was performed using SAS version 9.2 statistical software (SAS Institute, Inc.). The Northwestern University Institutional Review Board approved this study.

RESULTS

From the NCDB (1998-2007), 13,995 patients who underwent esophagectomy for cancer from 639 hospitals were identified (1998-2001: 4197 patients; 2002-2004: 5864 patients; 2005-2007: 3934 patients). Patient and tumor characteristics are shown in Table 1. Overall, 4014 patients (28.7%) had at least 15 lymph nodes examined and 9981 patients (71.3%) had fewer than 15 lymph nodes examined (Figure 1). The proportion of patients with at least 15 lymph nodes examined increased from 23.5% (median, 8 patients) in 1998 to 2001 to 34.4% (median, 12 patients) in 2005 to 2007 (test for trend, P < .001). In addition, at the hospital level, 45 centers (7.0%) examined a median of at least 15 lymph nodes.

HOSPITAL TYPE

Of the 13,995 patients studied, 7646 (54.6%) were treated at academic centers (n=206 centers) and 6349 (45.4%) at community centers (n=433 centers). The proportion of patients treated at academic centers increased from 50.9% in 1998 to 2001 to 58.4% in 2005 to 2007 (test for trend, P < .001). Among academic centers, the number of patients with at least 15 lymph nodes examined increased by an absolute percentage of 11.5% during the study period (test for trend, P < .001), while community centers demonstrated a slightly smaller increase at 9.7% (test for trend, P < .001). From 1998 to 2007, the median number of nodes examined increased from 9 to 12 at academic centers and from 8 to 10 at community centers (Table 2). In the most recent period (2005-2007), 38.9% of patients at academic centers and 28.0% of patients at community centers had at least 15 nodes examined (Figure 2). At the hospital level, the number of hospitals examining a median of at least 15 lymph nodes was 18 (8.7%) at academic hospitals and 27 (6.2%) at community hospitals (Table 3).

SURGICAL VOLUME STATUS

Of the 3 average annual surgical volume groups, 2935 patients were treated at low-volume centers (n=315 centers), 7151 at intermediate-volume centers (n=282 centers), and 3909 at high-volume centers (n=42 centers). Among the 206 academic centers, 56 (27.2%) were low volume, 111 (53.9%) were intermediate volume, and 39 (18.9%) were high volume. In contrast, of the 433 community centers, 259 (59.8%) were low volume and 171 (39.5%) were intermediate volume, while only 3 (0.7%) were high-volume hospitals.

During the study period, the proportion of patients with at least 15 lymph nodes examined increased by an absolute percentage of 9.6%, 9.2%, and 13.0% at low-, intermediate-, and high-volume centers, respectively (test for trend, all P < .001); in the most recent period (2005-2007), patients treated at high-volume centers had substantially more patients with at least 15 lymph nodes examined (high volume, 44.1%; intermediate volume, 34.4%; low volume, 24.6%).
30.5%; and low volume, 29.3%) (Figure 2). The median number of lymph nodes examined increased across all study periods and surgical volume groups (all $P < .001$).

From 2005 to 2007, high-volume centers examined the most lymph nodes (median, 13 lymph nodes) (Table 2). At the hospital level, the number of hospitals examining a median of at least 15 lymph nodes was 7 (16.7%) at high-volume centers, 15 (5.3%) at intermediate-volume centers, and 23 (7.3%) at low-volume centers (Table 3).

### MULTIVARIABLE ANALYSIS

Patients were more likely to have at least 15 lymph nodes examined if treated at academic or high-volume centers or if they had stage II or III tumors. Patients were less likely to have at least 15 lymph nodes examined if they were treated in the South or Midwest, had more severe comorbidities, or had tumors located in the

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**Table 2. Patient-Level Time Trends in the Median Number of Lymph Nodes Examined by Hospital Type and Hospital Surgical Volume Status in 13 995 Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lymph Nodes Examined by Period, Median (IQR), No.</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>9 (5-15) 10 (5-16) 12 (7-18)</td>
<td>.001</td>
</tr>
<tr>
<td>Community</td>
<td>8 (4-13) 9 (5-14) 10 (5-15)</td>
<td>.001</td>
</tr>
<tr>
<td>Hospital volume status$^a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>10 (6-17) 11 (6-18) 13 (8-20)</td>
<td>.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8 (4-13) 9 (5-15) 11 (6-16)</td>
<td>.001</td>
</tr>
<tr>
<td>Low</td>
<td>8 (4-13) 8 (4-14) 10 (5-16)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

$^a$Volume was defined as the average annual surgical volume: high volume, 12 cases/y or more; intermediate volume, 3 to 11 cases/y; and low volume, fewer than 3 cases/y.
lower esophagus (Table 4). There was no significant association in the number of lymph nodes examined by patient age, sex, race/ethnicity, histologic subtype, or tumor grade.

**COMMENT**

This study sought to evaluate the variation in the adequacy of lymph node examination after esophagectomy for cancer in a national cohort of patients. We found that overall only 28.7% of patients had an adequate lymphadenectomy, which was only marginally improved in the most recent period (2005-2007) at 34.4%. In addition, at the hospital level, only 45 of the 639 centers (7.0%) examined a median of at least 15 lymph nodes. The likelihood of achieving this 15–lymph node threshold was significantly increased if treatment occurred at academic hospitals and high-volume centers. To our knowledge, this is the first study reporting the adequacy of lymph node examination after esophagectomy for cancer on a national scale.

**IMPORTANCE OF LYMPH NODE EXAMINATION**

The number of lymph nodes removed after oncologic surgery is important for staging accuracy and defining surgical and pathologic quality. Because the presence of cancer in lymph nodes remains an important prognostic factor and the basis for treatment decisions in patients with nonmetastatic malignant neoplasms, there has been a significant effort to define minimum lymph node sampling thresholds across many gastrointestinal cancers. For example, in colon cancer, a 12–lymph node cut point was endorsed by the National Quality Forum in 2007. In esophageal cancer, several reports in the past decade have also attempted to establish an optimal lymph node cut point. Results from these studies are variable and suggest lymph node cut points ranging from 10 to 40, possibly as a result of differing methods, patient selection, or both. Nevertheless, these reports all demonstrated a survival benefit with increasing nodal sampling in a variety of patient populations and cancer stages, likely owing to stage migration and possibly a therapeutic effect. Based on the literature and expert consensus opinion, the National Comprehensive Cancer Network suggests that at least 15 lymph nodes should be examined after esophagectomy for cancer, so this was chosen as the cut point in this study.

**HOSPITAL FACTORS**

The association of hospital type and surgical volume status on the adequacy of lymph node sampling was examined in this study on both a patient level and a hospital level. The table below shows the characteristics of hospitals examining a median of at least 15 and fewer than 15 lymph nodes by hospital type and hospital surgical volume status from 1998 to 2007.

### Table 3. Characteristics of Hospitals Examining a Median of at Least 15 and Fewer Than 15 Lymph Nodes by Hospital Type and Hospital Surgical Volume Status From 1998 to 2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Academic (n = 206)</th>
<th>Community (n = 433)</th>
<th>High (n = 42)</th>
<th>Intermediate (n = 282)</th>
<th>Low (n = 315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes, median (IQR), No.</td>
<td>8 (4–14)</td>
<td>6 (3–11)</td>
<td>10 (5–16)</td>
<td>8 (4–13)</td>
<td>6 (3–11)</td>
</tr>
<tr>
<td>Hospitals, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 Lymph nodes examined</td>
<td>18 (8.7)</td>
<td>27 (6.2)</td>
<td>7 (16.7)</td>
<td>15 (5.3)</td>
<td>23 (7.3)</td>
</tr>
<tr>
<td>&lt;15 Lymph nodes examined</td>
<td>188 (91.3)</td>
<td>406 (93.8)</td>
<td>35 (83.3)</td>
<td>224 (94.7)</td>
<td>272 (92.7)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

### Table 4. Predictors of Examining at Least 15 Lymph Nodes in 4375 Patients Undergoing Esophagectomy for Cancer From 2005 to 2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR (95% CI)a</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>1.34 (1.03-1.74)</td>
<td>.04</td>
</tr>
<tr>
<td>Community</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Hospital volume statusb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.59 (1.15-2.21)</td>
<td>.005</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.01 (0.82-1.24)</td>
<td>.93</td>
</tr>
<tr>
<td>Low</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Geographic location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>0.68 (0.52-0.89)</td>
<td>.006</td>
</tr>
<tr>
<td>South</td>
<td>0.68 (0.53-0.88)</td>
<td>.004</td>
</tr>
<tr>
<td>West</td>
<td>1.04 (0.77-1.40)</td>
<td>.82</td>
</tr>
<tr>
<td>Charlson Comorbidity Index score ≥2</td>
<td>0.60 (0.45-0.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEJ</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Middle third</td>
<td>0.84 (0.61-1.16)</td>
<td>.29</td>
</tr>
<tr>
<td>Lower third</td>
<td>0.85 (0.73-0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>Esophagus, NOS</td>
<td>0.60 (0.45-0.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AJCC stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 [Reference]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>II</td>
<td>1.93 (1.61-2.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>III</td>
<td>3.02 (2.51-3.63)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; GEJ, gastroesophageal junction; NOS, not otherwise specified; OR, odds ratio.

a Model was adjusted for age, sex, histologic subtype, and race/ethnicity.

b Volume was defined as the average annual surgical volume: high volume, 12 cases/y or more; intermediate volume, 3 to 11 cases/y; and low volume, fewer than 3 cases/y.
level. Our findings suggest that although there has been some improvement over time, the quality of lymph node examination based on a 15-lymph node threshold was marginal overall but more frequently achieved at academic and high-volume centers. In the most recent period (2005-2007) at the patient level, academic centers examined at least 15 lymph nodes approximately 34% more often than community centers, and high-volume centers examined at least 15 lymph nodes 59% more frequently than low-volume centers. At the hospital level, only 45 of the 639 centers examined a median of at least 15 lymph nodes, which was slightly more frequent at academic centers than community centers (8.7% vs 6.2%, respectively). In multivariable analysis, academic hospitals were 34% more likely and high-volume hospitals were 59% more likely to examine at least 15 lymph nodes compared with community and low-volume centers, respectively.

Although there are no comparative reports in esophageal cancer, these findings are consistent with reports for other gastrointestinal malignant neoplasms. For example, using data from the NCDB, Bilimoria et al demonstrated that only 23.2% of patients with gastric cancer and 16.4% of patients with pancreatic cancer underwent adequate lymphadenectomy. In gastric cancer, community hospitals were more than 70% less likely and low-volume centers were nearly 60% less likely to examine at least 15 lymph nodes. Similarly, in pancreatic cancer, community hospitals were more than 60% less likely and low-volume centers were more than 50% less likely to examine at least 15 lymph nodes.

PATIENT- AND TUMOR-RELATED FACTORS

We also examined the association between hospital geography and lymph node examination and found wide variation by hospital region. On the patient level during the most recent period (2005-2007), patients treated in the Northeast were more likely to have at least 15 lymph nodes examined compared with other regions, especially the South, which examined at least 15 nodes nearly 20% less often. After controlling for confounding factors, compared with the Northeast, the South and Midwest were both 32% less likely to examine 15 nodes. In 2 separate studies in patients with colorectal and gastric cancer, data from the Surveillance Epidemiology and End Results database demonstrated substantial regional variations in lymph node sampling rates (colon, 33%-53%; gastric, 30%-56%).

We did not find that patient age, sex, race/ethnicity, histologic subtype, tumor grade, or tumor location was significantly associated with the number of lymph nodes examined during the most recent period (2005-2007). In gastric cancer, Bilimoria et al found that younger, female, or Asian patients were more likely to have at least 15 lymph nodes examined. These findings are consistent with a study by Baxter and Tuttle, who also found that being female, being Asian, and being younger than 65 years increased the likelihood of adequate lymph node examination in gastric cancer. In contrast, among patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma, Bilimoria and colleagues did not find that tumor- or patient-related factors were associated with the extent of lymphadenectomy. The reason for this variation across cancer and procedure types is not clear; however, it may reflect known differences in case mix or may be a result of other unmeasured confounding factors, such as obesity, not accounted for in these studies.

LIMITATIONS

This study should be considered with respect to certain limitations. First, specific operative details were not known, such as operative approach (ie, transhiatal or transhiobasic) or the location of the removed lymph nodes. Although these factors have definite implications on nodal harvest, we believe that a cut point of 15 lymph nodes represents a valid and achievable quality threshold regardless of such operative details. Second, this report used retrospective data from a large multi-institutional database; therefore, coding inconsistencies or errors could have affected the results. However, any systematic bias is unlikely as cancer registrars use standard definitions and are routinely audited to ensure data reliability. Third, it has been argued that the number of lymph nodes sampled during cancer surgery should not be considered a quality metric. Although not perfect, clearly cancer treatment decisions and prognostic information hinge on accurate staging, and at least a minimum number of lymph nodes should be examined to establish such information. Assessment of the adequacy of nodal counts should be used as part of wider hospital-level internal quality improvement efforts.

CONCLUSIONS

In this study of 13,995 patients who underwent esophagectomy for cancer, only 28.7% of patients had at least 15 nodes examined and only 7.0% of hospitals are meeting the National Comprehensive Cancer Network’s 15-lymph node recommendation. There is opportunity for improvement in lymph node staging at most hospitals in the United States regardless of hospital type, volume status, or geographic location.

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Lymphadenectomy as a Benchmark to Surgical Quality in Esophagectomy

Quality improvement processes are most relevant when they establish or compare to validated benchmarks. Metrics such as survival, perioperative events, extent of resection, and local recurrence are often associated with the quality of esophagectomy. However, most of these outcomes are also correlated with a patient's disease burden and demographic characteristics. To the extent that it is extremely difficult to compare patient populations between hospitals, other indicators of surgical quality such as the number of lymph nodes resected may serve as a better surrogate. Evidence-based data support the removal of between 10 and 50 lymph nodes (pT1-pT4) during esophagectomy for cancer.1,2

REFERENCES