Determination of the Minimum Number of Lymph Nodes to Examine in Esophagectomy Specimens to Maximize Survival in Patients with Esophageal Carcinoma: Data from the Surveillance Epidemiology and End Results Database

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Abstract:

Objective: We used a population-based cancer registry to examine the association between lymph node counts and survival in order to determine the minimum number of lymph nodes that should be examined as part of esophageal resection.

Methods: Using the Surveillance Epidemiology and End Results (SEER) database, we identified patients who underwent esophagectomy for invasive esophageal carcinoma from 1988 through 2005 and who had a known number of lymph nodes examined pathologically. After stratifying patients into groups (0, 1 to 11, 12 to 29, and 30 or more lymph nodes examined) based on a recursive partitioning analysis, we assessed the association between lymph nodes counts and survival using the Kaplan-Meier method. To adjust for potential confounding covariates, we used a Cox proportional hazards regression model.

Results: Of the patients in the SEER database with esophageal cancer, 4,882 met our inclusion criteria. We noted a significant difference between the lymph node groups with regards to unadjusted overall ($p < 0.0001$) and cancer-specific survival ($p = 0.004$). After adjusting for geographical location (cancer registry), patient factors, tumor characteristics, and timing of radiation therapy, we noted a significant difference between the lymph node groups with regards to overall and cancer-specific survival. As compared with patients who had no lymph node evaluation, only patients who had more than 12 lymph nodes examined had a significant improvement in survival. Patients who had 30 or more lymph nodes examined had significantly better survival rates than the other groups.

Conclusion: In order to maximize overall and cancer-specific survival, esophageal cancer patients should have at least 30 lymph nodes examined pathologically as part of esophageal resection.

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Introduction:

Esophageal cancer is an important public health problem. Since 1975, the incidence rate of esophageal cancer in the United States has been climbing faster than a number of other common malignancies, including colon cancer, lung cancer, and breast cancer [1]. Establishing evidence-based treatment guidelines is essential to ensure optimal care for all cancer patients, including those with esophageal cancer. The gold standard for treating patients with resectable disease is an esophagectomy [2]. There is debate in the literature regarding the optimal approach to esophageal resection [3-6] and the necessary extent of lymphadenectomy (i.e., 2-field vs. 3-field lymphadenectomy) [7-9].

Though the underlying mechanisms are incompletely understood, multiple studies on a variety of malignancies have demonstrated a strong association between the number of lymph nodes identified within a surgical specimen and survival. Given this association, other investigators have sought to identify a minimum number of lymph nodes that should be examined pathologically to maximize survival for patients with colorectal cancer [10], pancreatic cancer [11], gastric cancer [12], and non-small cell lung cancer [13]. However, there is no standard of care regarding the minimum number of lymph nodes that should be examined to maximize survival in esophageal carcinoma patients undergoing esophagectomy. As such, there are wide variations in practice patterns, as demonstrated by a recent analysis of data from the American College of Surgical Oncology Group Z0060 Trial [14]. Published recommendations on a minimum lymph node count to maximize *survival* vary from 6 to more than 40 lymph nodes [15-20].

Similarly, despite important prognostic [15] and therapeutic implications [2], there is no standard of care regarding the minimum number of lymph nodes that should be

examined in an esophagectomy specimen to maximize the *accuracy of cancer staging*. The current American Joint Committee on Cancer (AJCC) staging manual recommends that at least 6 lymph nodes should be evaluated [15]. Other studies suggest that more lymph nodes are needed [21]. Furthermore, it is unclear whether the minimum number of lymph nodes that should be examined to maximize survival is the same as the minimum number needed for accurate cancer staging.

We utilized a large population-based cancer registry to (1) determine the minimum number of lymph nodes that should be identified within an esophagectomy specimen and examined by a pathologist to maximize overall and cancer-specific survival in patients with esophageal carcinoma and (2) ascertain if this number is the same as the minimum number of lymph nodes needed for accurate nodal staging. We hypothesized that (1) higher total lymph node counts are associated with improved survival to a point, after which higher counts confer no significant incremental improvement in survival and (2) the minimum number of lymph nodes needed to maximize survival is different than the minimum number needed for accurate cancer staging.

Methods:

The Human Subjects Committee of the University of Minnesota determined that this study was exempt from formal review by the Institutional Review Board.

Data:

The Surveillance, Epidemiology, and End Results (SEER) database is a population-based cancer registry that was founded in 1973 by the National Cancer Institute (Bethesda, MD) and has been a valuable resource for oncology outcomes research. Other investigators have used SEER to examine racial differences (in cancer treatment [22], tumor size [23], and rates of lymph node metastasis [23]), associations between hospital volume and survival [24], and national trends in cancer incidence [25] and treatment [26]. SEER has also been widely utilized to examine the association between lymph node counts and survival from a number of malignancies, including colorectal cancer [10], pancreatic cancer [11], gastric cancer [12], and non-small cell lung cancer [13].

Currently, 17 United States cancer registries, selected in order to encompass a diverse sample (about 26%) of the national population, participate in the SEER program. We used the SEER database that was based on the November 2007 submission, which provides data through December 31, 2005 [27]. SEER registries began collecting lymph node data in 1988; therefore, this study represents data collected by the SEER registries from 1988 through 2005. Because of the negative impact of Hurricane Katrina on data collection by the Louisiana SEER registry, we excluded information obtained by that registry in 2005.

We collected information on patient characteristics (i.e., age, race, and gender), geographical location (i.e., SEER cancer registry), primary tumor characteristics (i.e., histology, grade, tumor location, depth of invasion, and lymph node status), and treatment regimens (i.e., esophagectomy, number of lymph nodes examined, and timing of radiation therapy).

Inclusion Criteria:

We selected patients from the SEER database for inclusion in our study using the following International Classification Disease for Oncology, 3rd Edition (ICD-O3) [28] topography codes (in parenthesis) for each anatomic location in the esophagus: proximal esophagus (15.0 and 15.3; lower border of the cricoid cartilage to the tracheal bifurcation), mid-thoracic esophagus (15.1 and 15.4; tracheal bifurcation to midway between the tracheal bifurcation and the gastroesophageal junction [GEJ]), distal esophagus (15.2 and 15.5; midway between the tracheal bifurcation and the GEJ to the GEJ), overlapping lesions (15.8) and esophageal lesions, not otherwise specified (NOS) (15.9).

We only included patients over the age of 18 who underwent esophagectomy for invasive esophageal carcinoma and who had a known number of lymph nodes examined (pathologically). The following carcinoma histologic subtypes were included in our analysis (ICD-O3 morphology codes in parenthesis) and were categorized as follows: **1. Adenocarcinomas:** papillary carcinoma, NOS (8050 to 8052), basaloid carcinoma (8123), adenocarcinoma (8140 to 8147), adenocarcinoma in an adenomatous polyp (8210), tubular adenocarcinoma (8211), adenocarcinoma with mixed subtypes (8255),

papillary adenocarcinoma (8260 to 8263), clear cell adenocarcinoma (8310), mucinous adenocarcinoma (8480 to 8481), signet cell carcinoma (8490), acinar adenocarcinoma (8550), and adenocarcinoma with other features (8570 to 8575); **2. Squamous cell carinomas:** spindle cell carcinoma (8032), squamous cell carcinoma (8070 to 8077), basaloid squamous carcinoma (8083), and basosquamous cell carcinoma (8094).

Exclusion Criteria:

We excluded patients with more than 1 primary tumor. Due to the potential for confounding, we also excluded those patients who were unlikely to have received aggressive cancer treatment: patients with metastatic disease and those patients with a hospice/nursing home, autopsy or death certificate as their only reporting source.

Statistical Analysis:

Data was analyzed using SAS version 9.1 (SAS Institute, Cary, N.C.). For all statistical testing, we used a two-sided significance level (alpha) of 0.05. We stratified patients into lymph node groups with homogenous survival rates using a recursive partitioning analysis based on the log-rank statistic [29]. A sensitivity analysis was performed to confirm that our choice of cut-points did not change our study findings.

Descriptive statistics were collected. Where appropriate, results are reported as mean ± standard deviation for normally distributed variables and median (range in parenthesis) for non-parametric variables. Between-group comparisons were made using a two-sample *t*-test or an analysis of variance for normally distributed continuous

variables, a Wilcoxon rank-sum or Kruskal-Wallis test for nonparametric continuous variables, and a chi-square test for categorical variables.

To compare unadjusted *all-cause* morality (death from any cause) and *cancer-specific* mortality rates (death from cancer) between each lymph node group, we used the Kaplan-Meier method. We adjusted for the following potential confounding covariates using a Cox proportional hazards regression model: patient characteristics (age, race, and gender), geographical location (cancer registry), tumor characteristics (histology, grade, AJCC pathological tumor [pT] stage [15], and anatomic location), and timing of radiation therapy. With the exception of *pathological* T stage, all of these covariates are known by the surgeon prior to esophagectomy. Because only 12% of our cohort had longer-term follow-up, we censored our survival analyses at 5 years. After testing the proportional hazards assumption, we generated log-log survival plots to subjectively assess homogeneity of the hazard ratios (HRs) over time. After adjusting alpha using the Bonferroni correction, we used a multiple comparisons test to compare HRs between lymph node groups. We validated our model by taking out a 33% random sample of our cohort and repeating our survival analysis with that random sample.

Total lymph counts (our principal explanatory variable) are highly correlated with the number of positive lymph nodes, which in turn are highly correlated with the AJCC lymph node (N) stage. Therefore, we did not include number of positive lymph nodes (or N stage) in our model in order to avoid multicollinearity, which could reduce the precision of the parameter estimates in our model. Instead, we adjusted for the potential confounding influence of lymph node metastasis by performing a stratified survival analysis.

We also assessed for interactions between other tumor characteristics (i.e., pT stage, histology, and grade) and lymph node counts, and we repeated our survival analysis after stratifying by these characteristics to assess for consistency of our results across these strata. Due to concern for interaction between lymph node counts and timing of radiation therapy (since radiation therapy may be associated with lower lymph node counts), we also stratified our results by timing of radiation therapy. We hypothesized that neoadjuvant radiation therapy was associated with lower lymph counts.

The current AJCC staging system for esophageal cancer dichotomizes nodal status – N0 (absence of lymph node metastasis) and N1 (presence of lymph node metastasis). Therefore, to assess whether the number of lymph nodes needed to optimize survival was consistent with the number needed to optimize accurate nodal staging, we plotted the frequency of patients with at least 1 positive lymph node for each lymph node count using locally weighted least squares (LOWESS) smoothing. We compared the odds of finding lymph node metastasis in each lymph node group using a logistic regression model adjusted for the same covariates as our Cox proportional hazards regression model.

Results:

Descriptive Statistics:

Of 7,323 patients in the SEER database (1988 to 2005) who underwent an esophagectomy for invasive esophageal cancer and had a known number of lymph nodes examined, 4882 met our inclusion criteria (Figure 1).

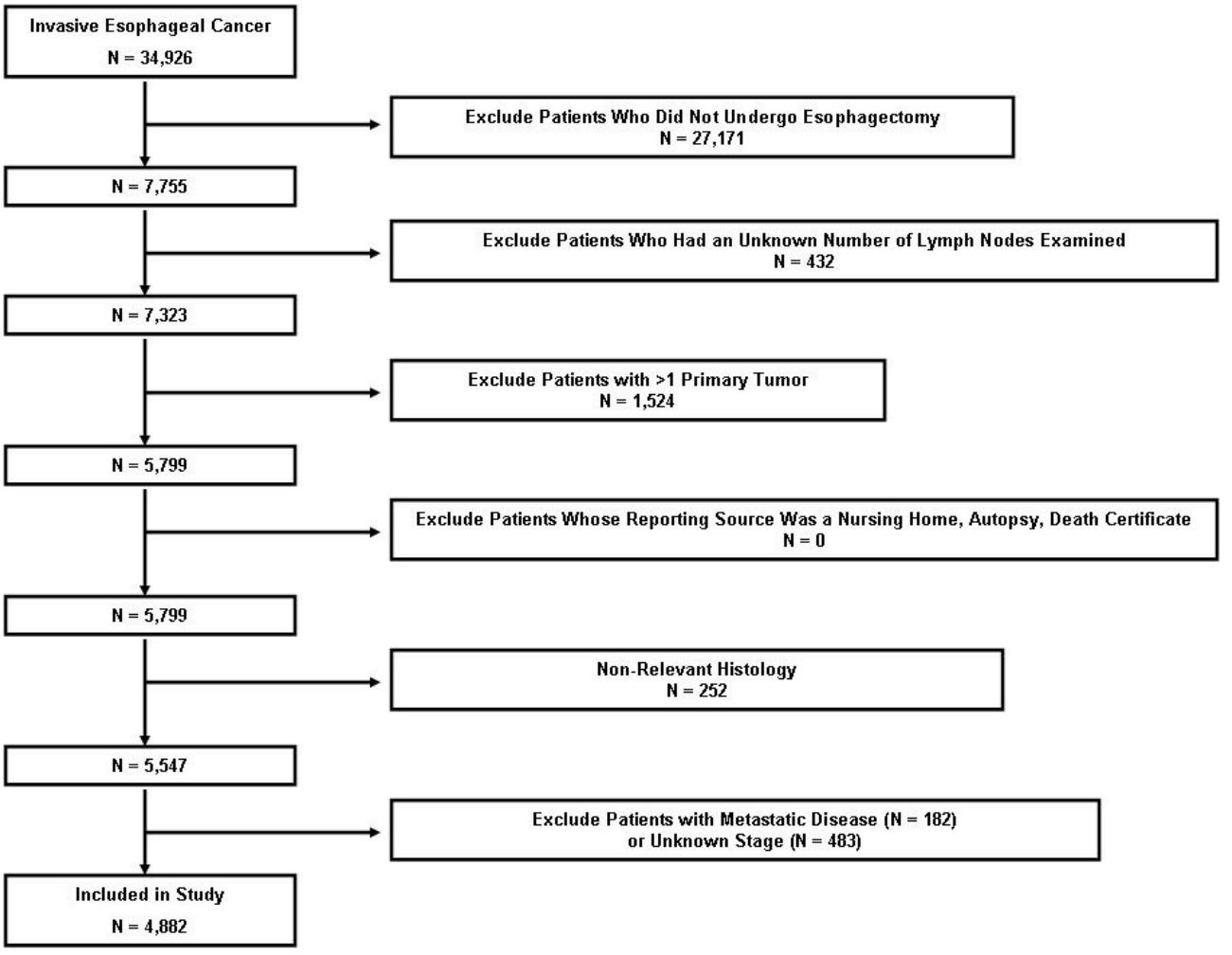


Figure 1: Patients in the Surveillance Epidemiology and End Results Database who were included in and excluded from our study.

Of those patients in the SEER database with invasive esophageal carcinoma, we noted significant differences between patients that we included and patients that we excluded from our study with regards to patient characteristics, tumor characteristics, and timing of radiation therapy (Table 1). Patients who underwent esophagectomy (and had a known number of lymph nodes examined) that we excluded from our study were more likely to be older, to have an unknown T-stage, and an undifferentiated or unknown tumor grade. They also had fewer lymph nodes examined and were less likely to undergo radiation therapy (Table 1). Patients who were included in our study did not have significantly different all-cause (log-rank, $p = 0.43$) or cancer-specific (log-rank, $p = 0.56$) survival rates than patients who we excluded, suggesting that selection bias likely had a minimal impact on our results.

Table 1: Characteristics of Patients Included vs. Patients Excluded From Inclusion in Our Study.

Variable	Patients Included	Patients Excluded	*p*-value
Number of Patients	4882	2667	
Age at Diagnosis	62.5 ± 10.3	64.7 ± 10.4	<0.0001
Race			0.42
Caucasian	87.0%	86.8%	
African American	7.9%	8.5%	
Other	5.1%	4.7%	
Gender			0.35
Men	81.1%	80.2%	
Women	18.9%	19.8%	
Tumor Location			<0.0001
Proximal	3.5%	6.3%	
Mid-thoracic	18.4%	18.3%	
Distal	71.0%	66.1%	
Overlapping	3.4%	3.3%	
Unknown	3.7%	6.0%	
Histology			<0.0001
Adenocarcinoma	67.9%	52.7%	
Squamous Cell Carcinoma	32.1%	33.1%	
Other	0%	14.2%	
Grade:			<0.0001
Well-Differentiated	6.5%	4.9%	
Moderately Differentiated	37.2%	30.9%	
Poorly Differentiated	45.4%	40.5%	
Undifferentiated	2.0%	3.8%	
Unknown	8.9%	19.9%	
T Stage			<0.0001
T1	21.1%	18.5%	
T2	16.8%	16.0%	
T3	36.8%	30.5%	
T4	12.1%	11.1%	
Unknown	13.2%	23.9%	
Median Number of Nodes Examined	7 (range, 0 to 90)	5 (range, 0 to 90)	<0.0001
Median Number of Positive Nodes Retrieved	0 (range, 0 to 35)	0 (range, 0 to 46)	0.56
Timing of Radiation Therapy			<0.0001
None	53.4%	61.1%	
Preoperative	30.4%	24.8%	
Postoperative	16.2%	14.1%	

* Groups did not differ significantly by cancer registry ($p = 0.62$; data not shown)

A recursive partitioning survival tree analysis identified the following lymph node groups with significantly differently survival rates: 0, 1 to 11, 12 to 29, and 30 or more lymph nodes examined. These groups were used in our survival analysis. There were significant differences between these lymph node groups with regards to number of potentially important prognostic factors: age, race, geographic location (SEER registry), tumor grade, tumor location, tumor histology, T stage, and timing of radiation therapy (Table 2). We adjusted for these variables in our multivariate survival analysis.

Table 2: Characteristics of Patients Included in Our Study.

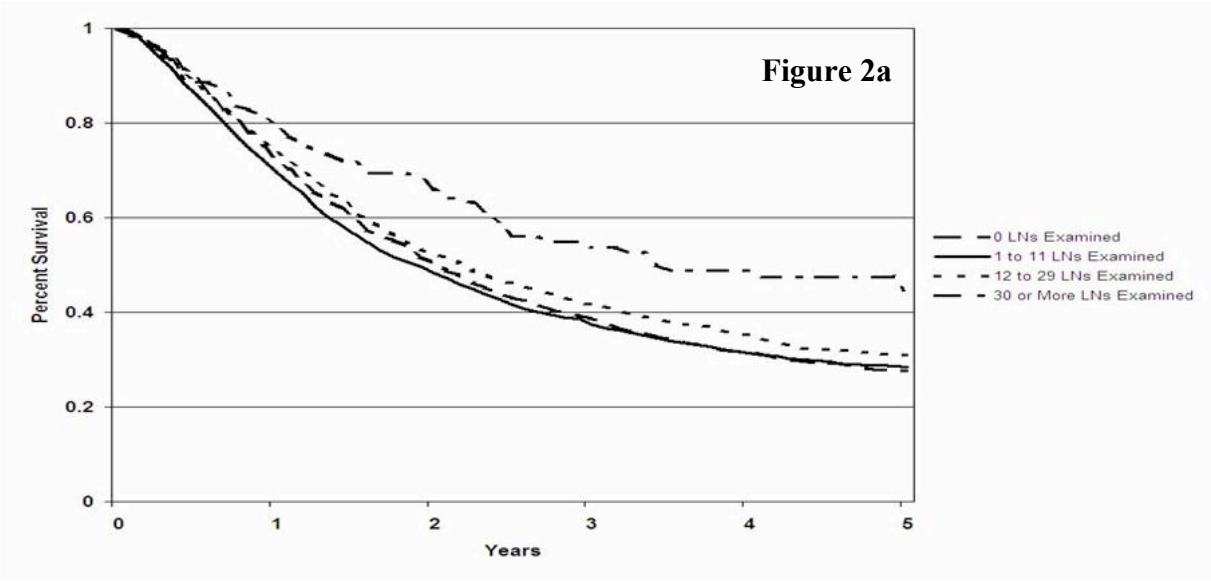
	Number of Lymph Nodes Examined				
	0	**1 to 11**	**12 to 29**	**≥ 30**	***p*-value***
Number of Patients	906	2555	1263	158	
Age at Diagnosis (Years)					0.0019
< 50	21.1%	47.3%	28.2%	3.4%	
50 to 64	19.4%	50.1%	26.9%	3.6%	
≥ 65	17.1%	55.7%	24.4%	2.8%	
Race					0.0002
Caucasian	17.8%	52.7%	26.3%	3.2%	
African American	26.9%	51.7%	18.5%	2.9%	
Other	19.2%	47.6%	29.2%	4.0%	
Gender					0.21
Men	18.3%	52.4%	26.3%	3.0%	
Women	19.8%	52.1%	24.1%	4.0%	
Tumor Location in Esophagus					<0.0001
Proximal	28.9%	43.9%	20.2%	6.4%	
Mid-thoracic	22.9%	51.8%	22.5%	2.8%	
Distal	16.3%	53.0%	27.6%	3.1%	
Overlapping	26.7%	46.0%	20.0%	7.3%	
Unknown	22.6%	56.4%	19.9%	1.1%	
Histology					<0.0001
Adenocarcinoma	16.3%	52.7%	27.7%	3.3%	
Squamous Cell Carcinoma	23.3%	51.6%	22.0%	3.1%	
Grade:					<0.0001
Well-Differentiated	19.4%	53.4%	23.4%	3.8%	
Moderately Differentiated	17.4%	54.0%	25.4%	3.2%	
Poorly Differentiated	17.5%	51.9%	27.1%	3.5%	
Undifferentiated	12.5%	44.8%	37.5%	5.2%	
Unknown	29.6%	48.4%	20.9%	1.2%	
T stage					<0.0001
T1	17.2%	56.3%	23.9%	2.6%	
T2	14.9%	56.0%	26.2%	2.9%	
T3	10.6%	54.9%	30.9%	3.6%	
T4	19.8%	48.7%	27.1%	4.4%	
Unknown	46.7%	37.5%	13.5%	2.3%	
Timing of Radiation Therapy					<0.0001
None	13.6%	55.0%	27.6%	3.8%	
Preoperative	29.4%	48.4%	20.1%	2.1%	
Postoperative	14.7%	51.7%	29.9%	3.7%	

* Lymph node groups also differed by cancer registry ($p < 0.0001$; data not shown)

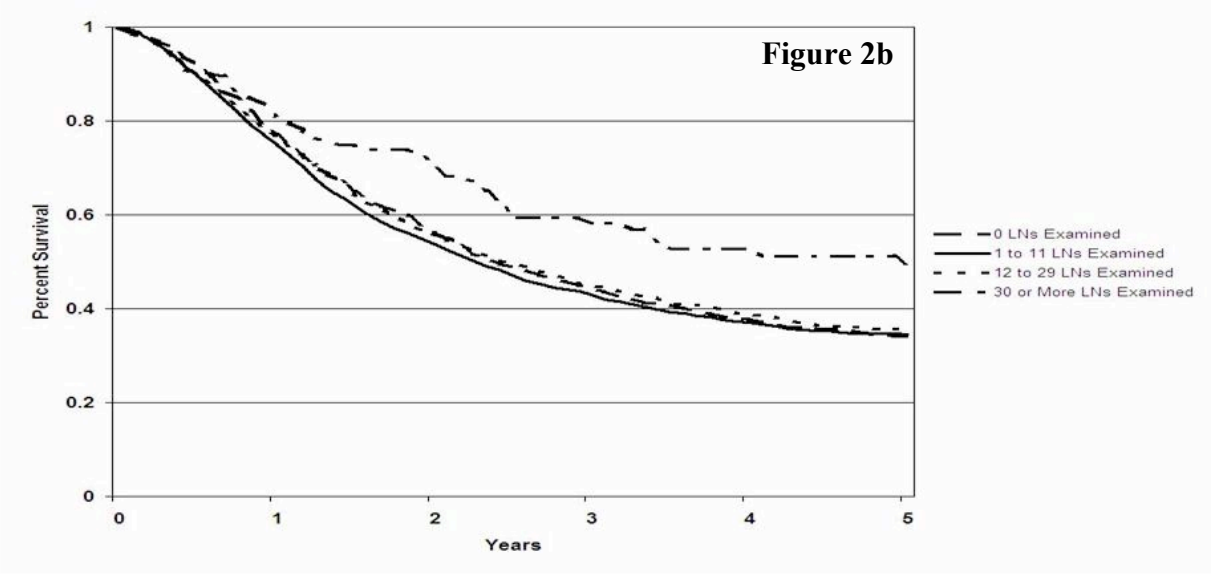
Kaplan-Meier Survival Analysis:

We found a significant difference between the lymph node groups with regards to all-cause (Wilcoxon test, $p < 0.0001$) (Figure 2a) and cancer-specific survival (Wilcoxon test, $p = 0.004$) (Figure 2b). Patients who had 30 or more lymph nodes examined had the best survival rates.

Figure 2a



0 LNs						
Number at Risk	**906**	**631**	**414**	**294**	**215**	**163**
Survival	**100%**	**72.2%**	**50.4%**	**38.8%**	**31.7%**	**27.7%**
CI		**(69.1% - 75.0%)**	**(47.0% - 53.7%)**	**(35.5% - 42.1%)**	**(28.5% - 34.9%)**	**(24.5% - 30.9%)**
1 – 11 LNs						
Number at Risk	**2555**	**1606**	**948**	**629**	**427**	**304**
Survival	**100%**	**69.7%**	**48.3%**	**37.5%**	**31.8%**	**28.5%**
CI		**(67.8% - 71.4%)**	**(46.2% - 50.3%)**	**(35.5% - 39.6%)**	**(29.7% - 33.8%)**	**(26.5% - 30.6%)**
12 – 29 LNs						
Number at Risk	**1263**	**796**	**461**	**295**	**208**	**145**
Survival	**100%**	**73.9%**	**52.4%**	**41.7%**	**35.6%**	**30.9%**
CI		**(71.3% - 76.4%)**	**(49.3% - 55.4%)**	**(38.5% - 44.8%)**	**(32.4% - 38.8%)**	**(27.7% - 34.2%)**
More than 30 LNs						
Number at Risk	**158**	**112**	**78**	**46**	**34**	**25**
Survival	**100%**	**81.6%**	**68.6%**	**55.0%**	**48.8%**	**47.4%**
CI		**(74.3% - 87.0%)**	**(60.1% - 75.6%)**	**(45.6% - 63.4%)**	**(39.1% - 57.8%)**	**(37.5% - 56.5%)**

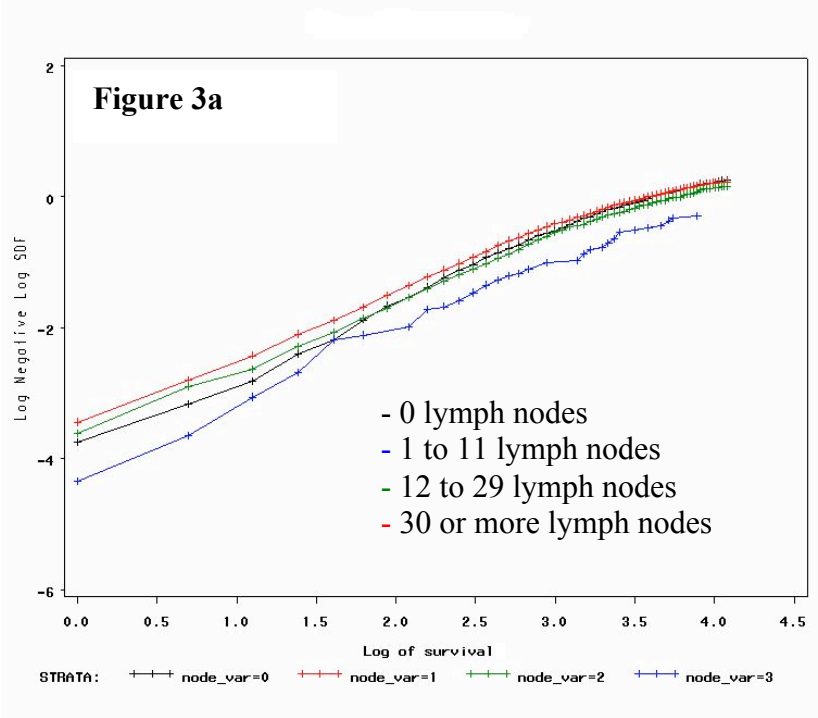


0 LNs						
Number at Risk	**898**	**625**	**411**	**293**	**215**	**162**
Survival	**100%**	**77.1%**	**56.4%**	**44.8%**	**38.1%**	**34.3%**
CI		**(74.1% - 79.7%)**	**(52.8% - 59.7%)**	**(41.2% - 48.3%)**	**(34.6% - 41.7%)**	**(30.8% - 37.9%)**
1 – 11 LNs						
Number at Risk	**2538**	**1599**	**942**	**626**	**425**	**304**
Survival	**100%**	**74.8%**	**53.7%**	**43.0%**	**37.1%**	**34.7%**
CI		**(73.0% - 76.5%)**	**(51.5% - 55.8%)**	**(40.8% - 45.2%)**	**(34.8% - 39.4%)**	**(32.3% - 37.0%)**
12 – 29 LNs						
Number at Risk	**1254**	**793**	**459**	**293**	**206**	**145**
Survival	**100%**	**76.5%**	**55.7%**	**45.1%**	**38.8%**	**35.8%**
CI		**(73.9% - 78.9%)**	**(52.6% - 58.8%)**	**(41.8% - 48.3%)**	**(35.4% - 42.2%)**	**(32.3% - 39.2%)**
More than 30 LNs						
Number at Risk	**153**	**108**	**77**	**46**	**34**	**25**
Survival	**100%**	**83.5%**	**73.0%**	**59.5%**	**52.8%**	**51.3%**
CI		**(76.2% - 88.7%)**	**(64.6% - 79.8%)**	**(49.8% - 67.9%)**	**(42.6% - 62.0%)**	**(40.9% - 60.7%)**

Figure 2: Kaplan-Meier curves for all-cause (Figure 2a) and cancer-specific survival (Figure 2b) for each lymph node group.
LN: Lymph Node
CI: Confidence Interval

Cox Proportional Hazards Regression Model:

After generating log-log survival plots for all-cause (Figure 3a) and cancer-specific mortality (Figure 3b), we noted the plots to be relatively homogenous over time; there was only a minor deviation at later periods of follow-up.



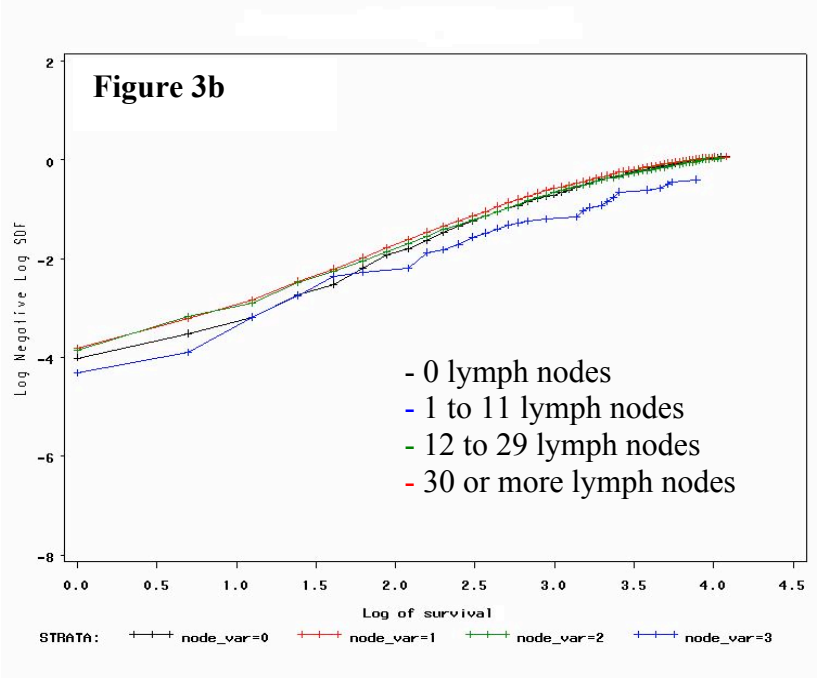


Figure 3: Log-log all-cause (Figure 3a) and cancer-specific mortality plots (Figure 3b) for each lymph node group.

These plots supported our hypothesis that the lymph node groups were different. Though the proportional hazards assumption was violated (the log-log plots are not perfectly parallel; they tangle at a few points), the relative homogeneity of these plots suggests that the violation is of minimal importance. Therefore, we chose to exclude a time-dependent interaction term from our final model (to adjust for the proportional hazards violation) since including the term would have significantly increased the complexity of our analysis, with little improvement in accuracy.

When modeled as a continuous variable, we noted a significant relationship between lymph node counts and all-cause ($p < 0.0001$) and cancer-specific mortality ($p = 0.0002$) – survival improves as the number of lymph nodes examined increases.

To determine the minimum number of lymph nodes that should be examined, we also modeled lymph node counts as a categorical variable (using the groups defined by our recursive partitioning survival tree analysis). Only patients who had at least 12 lymph nodes evaluated had significantly lower all-cause and cancer-specific mortality rates than patients who had no lymph nodes examined. Similar to our Kaplan-Meier analysis, we found that patients who had 30 or more lymph nodes examined had the lowest mortality rates (Table 3). Even after excluding patients who died within 30 days of esophagectomy, our results were unchanged. To validate our model, we repeated our survival analysis using a 33% random sample of our cohort and found that our results were unchanged.

Because SEER does not mandate endoscopic verification of tumor location, we reclassified tumor location into broader groups (cervical, thoracoabdominal and

overlapping) and repeated our Cox proportional hazards regression survival analysis. Our results were unchanged.

Table 3: Cox Proportional Hazards Regression Models for All-Cause and Cancer-Specific Mortality.

Variable	All-Cause Mortality HR (95% CI)*‡	Cancer-Specific Mortality HR (95% CI)*‡
Number of Lymph Nodes Examined*		
0	1.00 (Reference) [a]	1.00 (Reference) [a]
1 to 11	0.98 (0.88, 1.08) [a]	0.99 (0.88, 1.11) [a]
12 to 29	0.85 (0.75, 0.95) [b]	0.90 (0.79, 1.02) [a]
≥ 30	0.55 (0.42, 0.72) [c]	0.58 (0.44, 0.78) [b]
Age at Diagnosis (Years)		
<50	1.00 (Reference) [a]	1.00 (Reference) [a]
50-64	1.14 (0.99, 1.31) [a]	1.08 (0.94, 1.25) [a]
≥ 65	1.51 (1.32, 1.73) [b]	1.37 (1.19, 1.58) [b]
Race		
Caucasian	1.00 (Reference) [a]	1.00 (Reference) [a]
African American	1.24 (1.08, 1.44) [b]	1.23 (1.05, 1.44) [a]
Other	0.93 (0.76, 1.12) [a]	1.00 (0.82, 1.23) [a]
Gender		
Female	1.00 (Reference) [a]	1.00 (Reference) [a]
Male	1.21 (1.10, 1.35) [b]	1.21 (1.09, 1.35) [b]
Tumor Location in Esophagus		
Proximal	1.00 (Reference) [abc]	1.00 (Reference) [a]
Mid-thoracic	1.23 (0.99, 1.51) [ac]	1.29 (1.02, 1.62) [b]
Distal	0.99 (0.81, 1.22) [bc]	1.01 (0.81, 1.27) [a]
Overlapping	1.20 (0.91, 1.58) [c]	1.21 (0.90, 1.64) [a]
Unknown	1.19 (0.89, 1.58) [c]	1.16 (0.84, 1.60) [a]
Histology		
Adenocarcinoma	1.00 (Reference) [a]	1.00 (Reference) [a]
Squamous Cell Carcinoma	1.13 (1.02, 1.25) [b]	1.12 (1.01, 1.25) [b]
Grade		
Well-Differentiated	1.00 (Reference) [a]	1.00 (Reference) [a]
Moderately Differentiated	1.58 (1.30, 1.91) [b]	1.82 (1.45, 2.29) [b]
Poorly Differentiated	1.99 (1.65, 2.41) [c]	2.40 (1.92, 3.01) [c]
Undifferentiated	2.04 (1.51, 2.77) [c]	2.41 (1.71, 3.39) [c]
Unknown	1.28 (1.02, 1.62) [d]	1.49 (1.14, 1.96) [d]
T Stage		
T1	1.00 (Reference) [a]	1.00 (Reference) [a]
T2	2.16 (1.87, 2.49) [b]	2.52 (2.14, 2.96) [b]
T3	2.93 (2.58, 3.34) [c]	3.43 (2.96, 3.98) [c]
T4	3.78 (3.26, 4.39) [d]	4.60 (3.90, 5.43) [d]
Unknown	2.22 (1.90, 2.58) [b]	2.47 (2.08, 2.95) [b]
Timing of Radiation Therapy		
None	1.00 (Reference) [a]	1.00 (Reference) [a]
Preoperative	0.74 (0.67, 0.81) [b]	0.75 (0.68, 0.83) [b]
Postoperative	0.90 (0.81, 0.99) [c]	0.95 (0.85, 1.06) [a]

* Hazard ratios adjusted for cancer registry (data not shown)

‡ ***a,b,c*** Hazard ratios that do not share a letter are significantly different ($p < 0.05$); hazard ratios that share a letter are not significantly different.

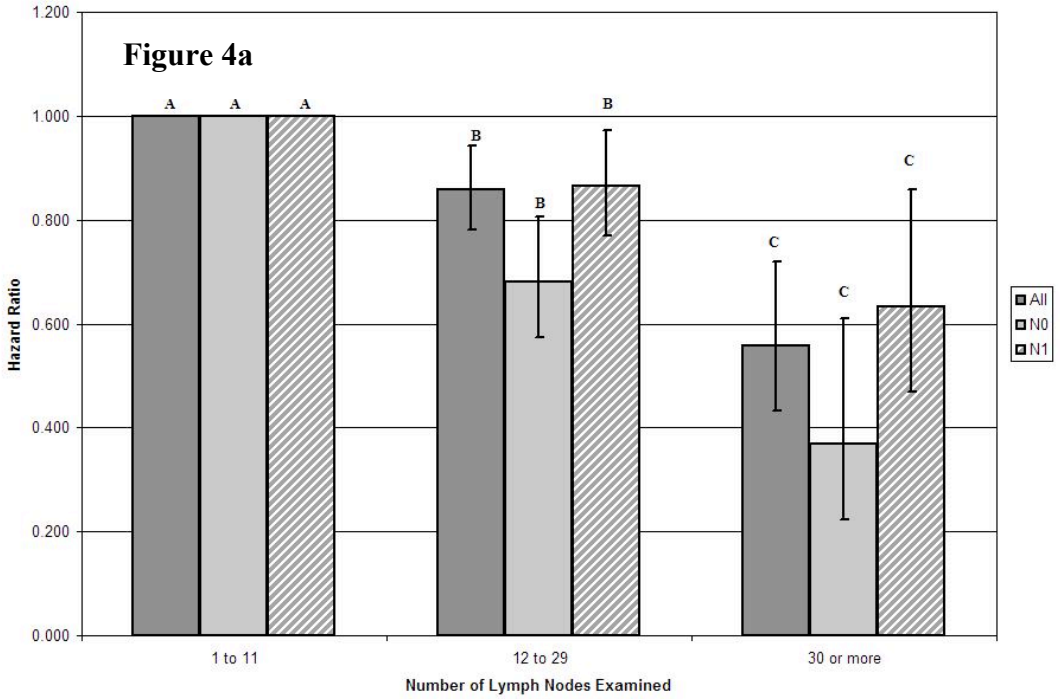
HR: Hazard Ratio

CI: Confidence Interval

Our multivariate analysis also revealed that patients who were older (65 and older), men, African Americans, had squamous cell carcinomas, higher grade tumors, and more advanced T stage tumors had the worst all-cause and cancer-specific mortality rates (Table 3). Patients with mid-thoracic tumors (where squamous cell carcinomas predominate) had worse cancer-specific mortality and a non-significant trend towards worse all-cause mortality as compared with patients with tumors in other locations. Neoadjuvant radiation therapy had a protective effect. As compared with patients who did not undergo radiation therapy, patients who underwent adjuvant radiation therapy had slightly lower all-cause mortality rates; however, cancer-specific mortality was not improved (Table 3).

Due to concern for multicollinearity, we did not include the number of positive lymph nodes in our multivariate survival model. Instead, we adjusted for the potential confounding influence of lymph node metastasis on survival by stratifying our multivariate analysis for all-cause (Figure 4a) and cancer-specific survival (Figure 4b) by lymph node status: all patients, N0 (node negative) patients, and N1 (node positive) patients. For this analysis, we excluded those patients in which their nodal status was unknown (i.e., those with no lymph nodes examined). The hazard ratios were adjusted for the same covariates as our full model.

Regardless of lymph node status, we found that patients who had 30 or more lymph nodes examined had the lowest all-cause (Figure 4a) and cancer-specific mortality rates (Figure 4b).



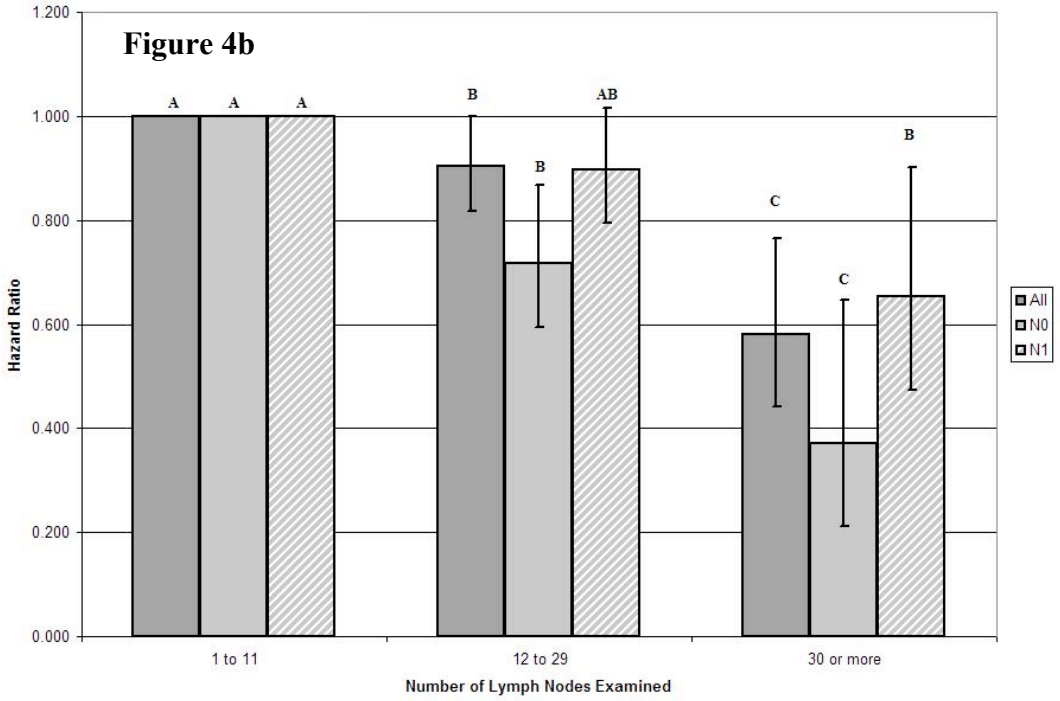
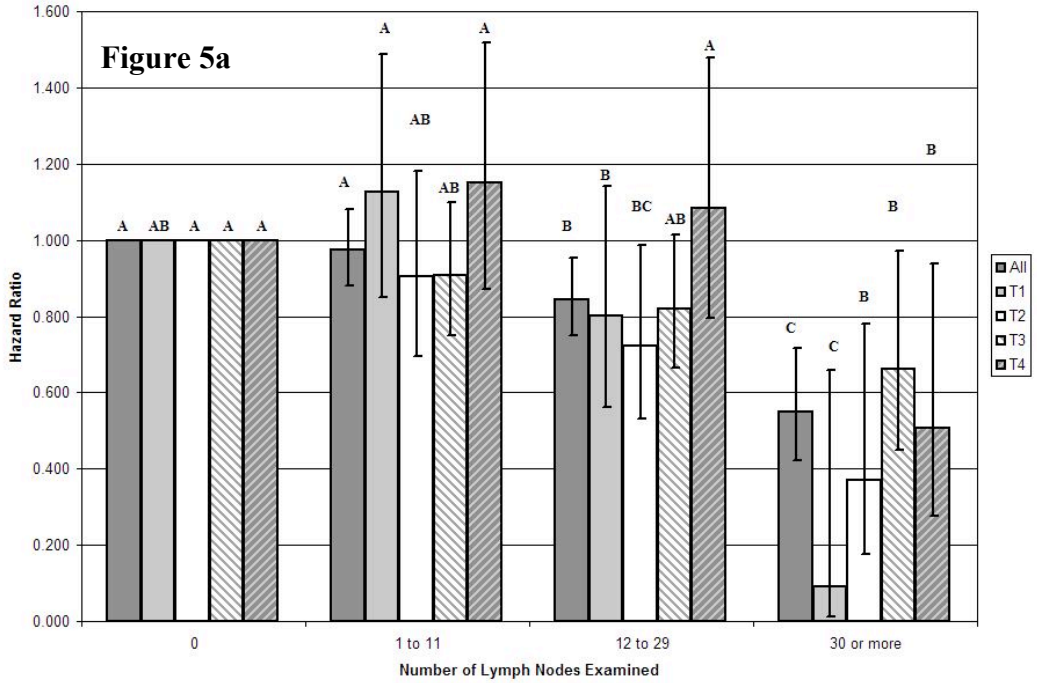


Figure 4: Hazard ratios for all-cause (Figure 4a) and cancer-specific mortality (Figure 4b) stratified by lymph node status and adjusted for the same covariates as the full model.
A,B,C: Hazard ratios that do not share a letter are significantly different ($p < 0.05$); hazard ratios that share a letter are not significantly different.

We also assessed for interactions between lymph node counts and other tumor characteristics and stratified our results by these characteristics (after adjusting for the same covariates as our full model) to assure that our pooled estimates were consistent across these strata. The test for heterogeneity across T stage strata was significant ($p < 0.0001$). However, after stratifying our analysis by T stage, our results were similar to our full model (Figure 5). Though the parameter estimates T3 and T4 tumors with 30 or more lymph nodes examined were lower than the other lymph node groups, this difference was not significantly different, likely due to a lack of statistical power given the small sample sizes in these groups. Nonetheless, the overall trend that we noted in our full model was unchanged – patients with 30 or more lymph nodes examined had the lowest all-cause (Figure 5a) and cancer-specific (Figure 5b) mortality rates.



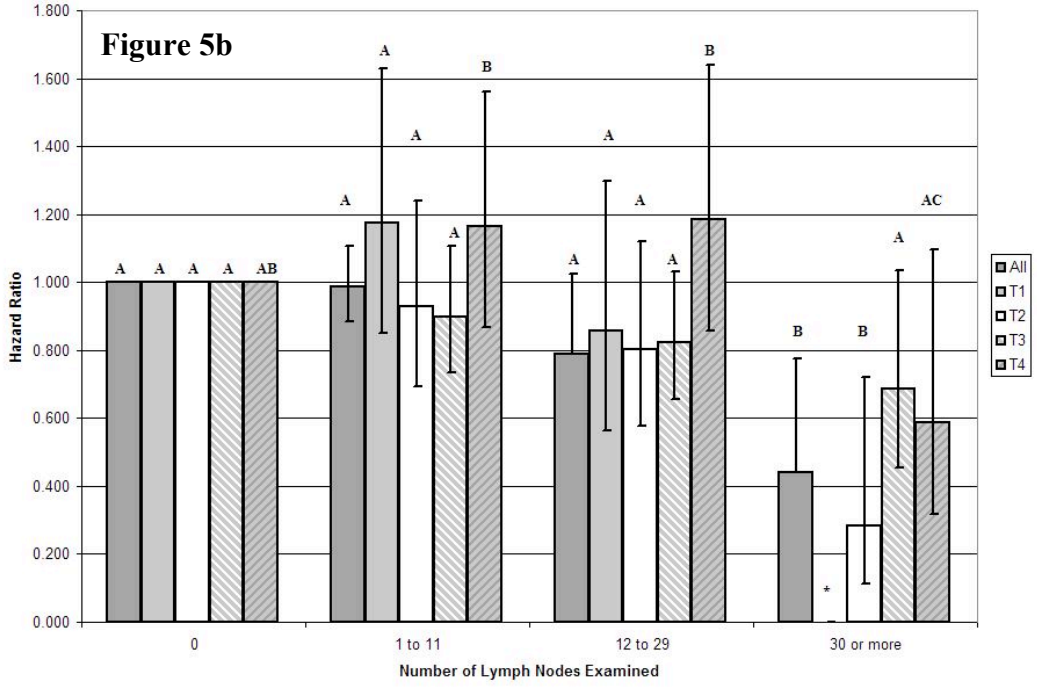
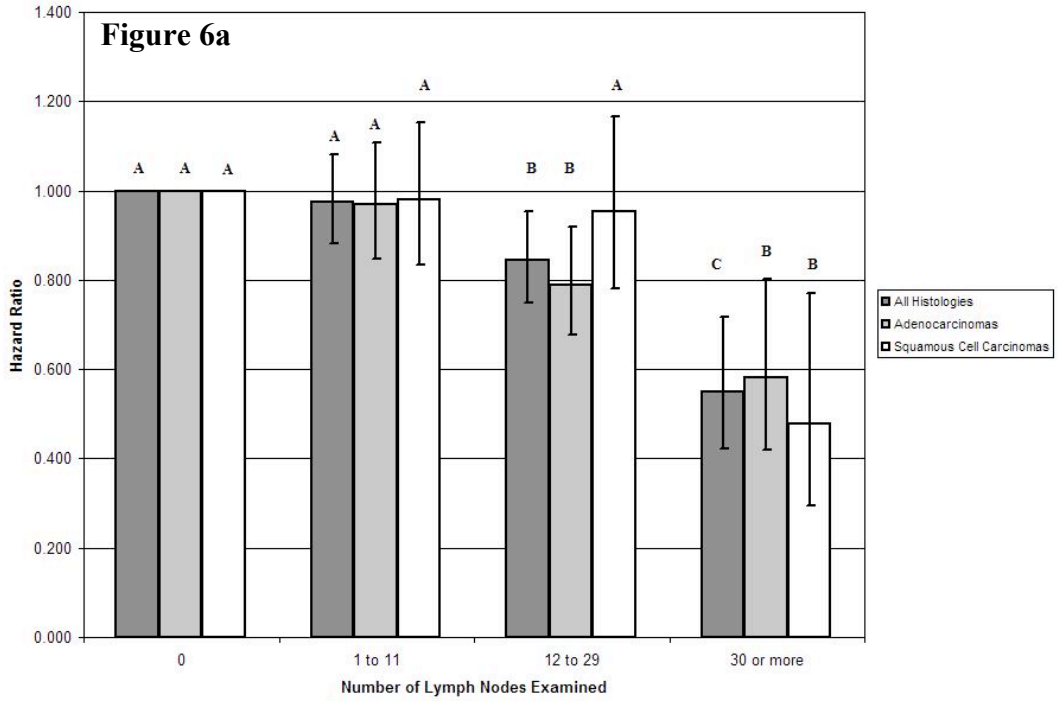


Figure 5: Hazard ratios for all-cause (Figure 5a) and cancer-specific mortality (Figure 5b) stratified by pT stage and adjusted for the same covariates as the full model.
A,B,C: Hazard ratios that do not share a letter are significantly different ($p < 0.05$); hazard ratios that share a letter are not significantly different.
***** Hazard ratio for cancer-specific mortality could not be assessed for T1 tumors with 30 or more lymph nodes examined due to small sample size.

We did not find significant heterogeneity across histology strata ($p = 0.16$), and our results were unchanged when we stratified by histology (Figure 6). Though the stratified parameter estimates for patients with 30 or more lymph nodes examined were lower than the other lymph node groups, this difference was not significantly different. The absolute benefit of examination of 30 or more lymph nodes is less for squamous cell carcinomas than for adenocarcinomas. Nonetheless, the overall trend was unchanged – patients with 30 or more lymph nodes examined had the lowest all-cause (Figure 6a) and cancer-specific (Figure 6b) survival rates.



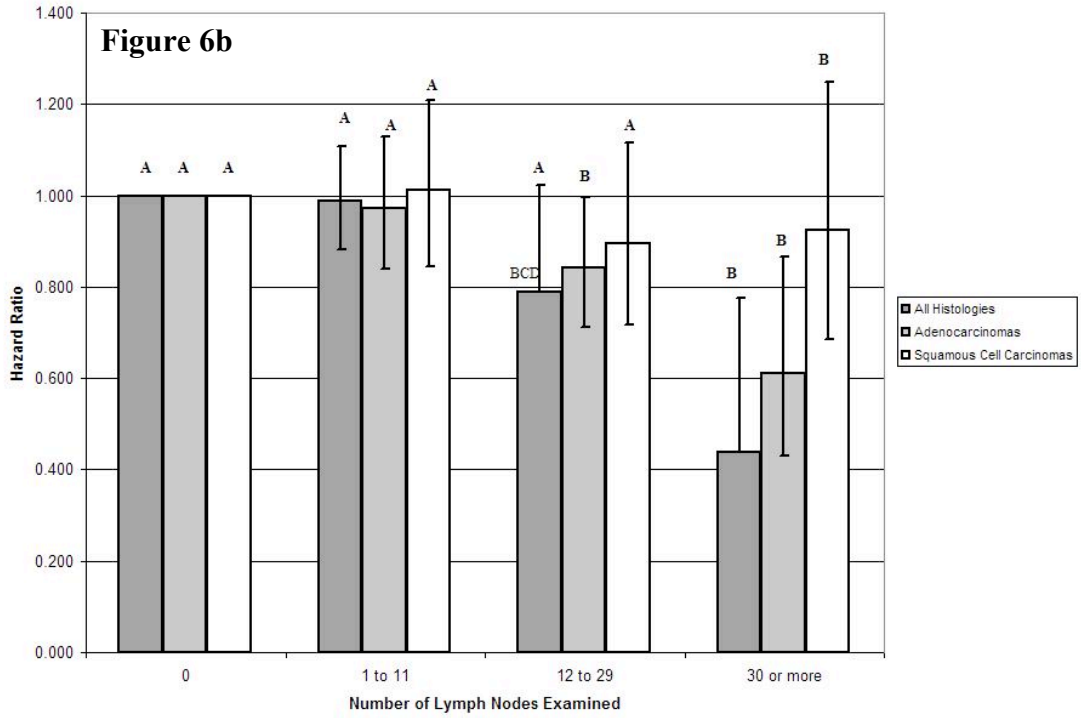
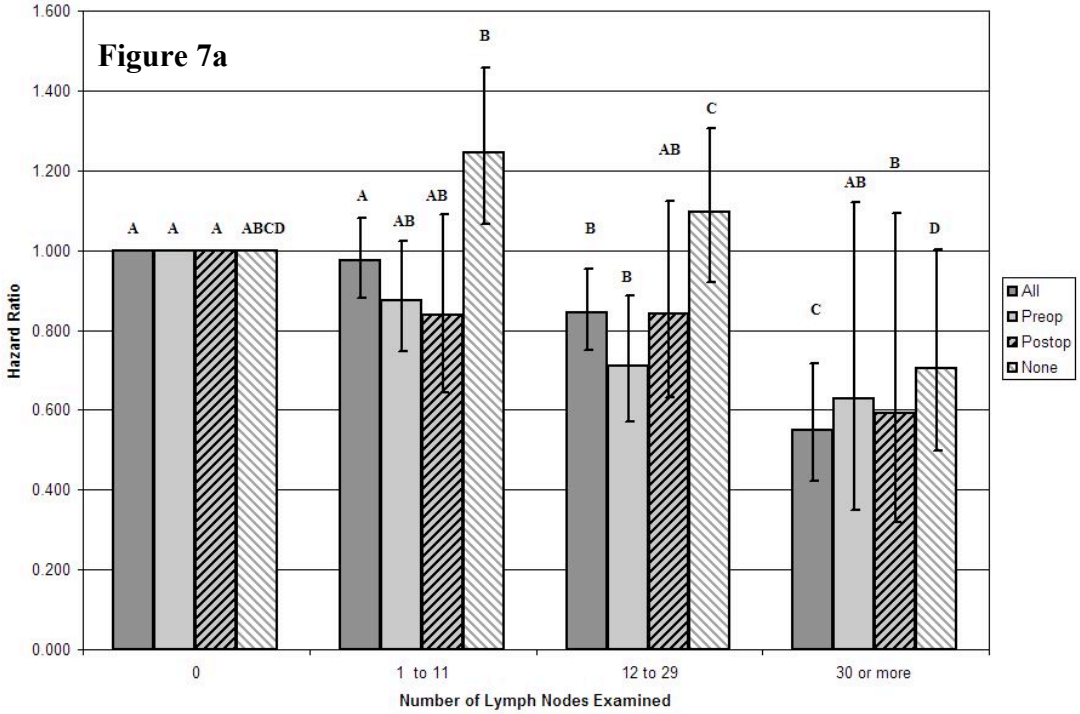


Figure 6: Hazard ratios for all-cause (Figure 6a) and cancer-specific mortality (Figure 6b) stratified by histology and adjusted for the same covariates as the full model.
A,B,C: Hazard ratios that do not share a letter are significantly different ($p < 0.05$); hazard ratios that share a letter are not significantly different.

We found significant heterogeneity across tumor grade strata ($p = 0.002$). Our results were unchanged when we stratified our analysis for modeterately differentiated and poorly differentiated tumors. We were unable to stratify by all tumor grades since few patients with more than 30 lymph nodes examined had well-differentiated (n=12) or undifferentiated tumors (n=7) (data not shown).

Our results confirmed our hypothesis that patients who underwent neoadjuvant radiation therapy had significantly lower ($p < 0.0001$) lymph node yields (median, 5; range, 0 to 71) than patients who did not (median, 7; range 0 to 90). The test for heterogeneity across timing of radiation strata was significant ($p < 0.0001$). After stratifying our results by timing of radiation therapy, we found that patients with 30 or more lymph nodes examined had the lowest mortality rates as compared to the other groups. However, this difference was not significantly different, likely due to a lack of statistical power. Nonetheless, our stratified analysis did not change our overall study findings: (1) there is an association between higher lymph node counts and reduced mortality and (2) patients with a least 30 lymph nodes examined had the lowest mortality rates (Figure 7).



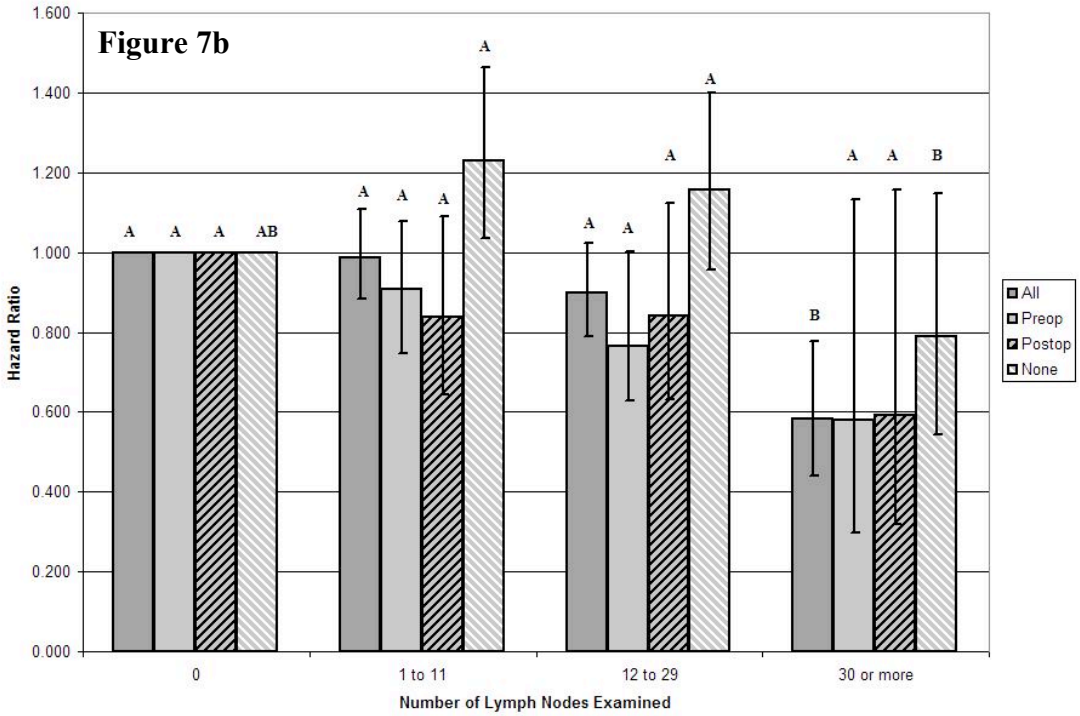


Figure 7: Hazard ratios for all-cause (Figure 7a) and cancer-specific mortality (Figure 7b) stratified by timing of radiation therapy and adjusted for the same covariates as the full model. ***A,B,C:*** Hazard ratios that do not share a letter are significantly different ($p < 0.05$); hazard ratios that share a letter are not significantly different.

Lymph Node Counts and Nodal Staging

We plotted the probability of finding at least 1 positive lymph node by the number of lymph nodes examined, and used LOWESS smoothing to eliminate the noise in the data (Figure 8). The slope of the curve was largest (indicative of the greatest impact on finding lymph node metastasis) when at least 3 lymph nodes were examined, as compared with examination of less than 3 lymph nodes (adjusted odds ratio [OR] 2.97; 95% confidence interval [CI]: 2.32 to 3.79). The probability of finding a positive node reaches an asymptote near 15 lymph nodes examined, which suggests that higher lymph node yields do not improve the accuracy of nodal staging (Figure 8). Indeed, patients who had 12 to 29 lymph nodes examined were significantly more likely to have lymph node metastasis detected than patients with 11 or fewer lymph nodes examined (OR 1.69; 95% CI: 1.44 to 1.98). There was no significant difference in the odds of detecting lymph node metastasis between patients who had 30 or more lymph nodes examined and patients who had 12 to 29 lymph nodes examined (OR 0.93, 95% CI: 0.63 to 1.37).

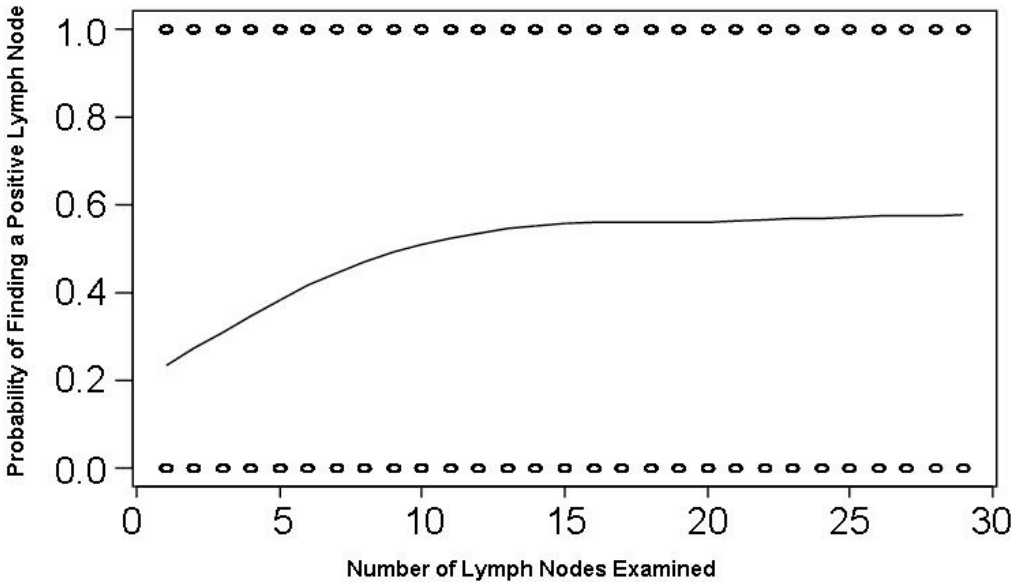


Figure 8: Locally weighted least squares (LOWESS) smooth of the percentage of patients with at least one positive lymph node as function of the number of lymph nodes examined.

Discussion:

Using a large United States population-based cancer registry, we demonstrated that the number of pathologically examined lymph nodes removed at the time of esophagectomy has a significant impact on all-cause and cancer-specific mortality. We were not able to ascertain a threshold of mortality benefit - survival continues to improve as more lymph nodes are examined, independent of patient characteristics, tumor characteristics, and use of neoadjuvant radiation therapy. Though the inclusion criteria and methodologies are different, our results corroborate other recently published single-institution, international, and population-based studies that have examined the association between lymph node counts and survival in esophageal cancer patients [16-20].

Bollscheweiller et al. performed a single-institution retrospective review of 213 esophageal cancer patients who underwent surgical resection with curative intent (predominately by en bloc esophagectomy and 2-field lymphadenectomy) and determined that at least 16 lymph nodes should be examined [17]. As compared with patients who had 16 to 30 lymph nodes examined, they did not find an improvement in survival if more than 30 lymph nodes were examined; however, only 7 patients with more than 30 lymph nodes examined had 4 or more years of follow-up.

Altorki et al. reviewed their experience of 264 patients who underwent esophagectomy without neoadjuvant therapy [16]. Patients were divided into quartiles based on the number of lymph nodes examined. They found that higher lymph node counts were associated with improved survival. Similar to our results, they found that patients with more than 26 lymph nodes examined (without an upper limit of survival benefit) had the most favorable survival rates. Unlike our results, however, their results

differed based on lymph node status. In patients with N0 disease, survival was maximized when 26 lymph nodes were examined. Patients with N1 disease, however, required examination of more than 40 lymph nodes to achieve a significant improvement in survival as compared with patients who had 16 or fewer lymph nodes examined. After stratifying by lymph node positivity, we did not find a difference in the number of lymph nodes that should be examined; survival was maximized when more than 30 nodes were examined, regardless of lymph node status. Differences in our patient population, sample size, inclusion criteria (we did not exclude patients underwent neoadjuvant radiation therapy), variables included in our multivariate survival model, and methodology may explain this discrepancy between their results and ours. In particular, they created lymph node groups by arbitrarily dividing patients into quartiles; we created lymph node groups based on a recursive portioning analysis. As such, our lymph node groups are different.

The results of a retrospective, international, multi-institutional study of 2,303 patients who underwent an R0 resection for esophageal cancer were recently published by Peyre et al. [19]. Similar to other studies, they excluded patients who underwent neoadjuvant or adjuvant therapy. They dichotomized patients into lymph node groups using every threshold of 1 to 60 lymph nodes examined (i.e., ≤ 1 vs. >1, ≤ 2 vs. >2, etc.) and found that the chi-square for the lymph node variable in their Cox proportional hazards regression model was maximized (suggestive of the greatest effect) when 23 to 29 lymph nodes were examined. Similar to our results, however, they did not identify a threshold lymph node count above which there was no incremental improvement in survival; survival continued to improve as more lymph nodes were examined.

Recently, Greenstein et al. utilized the SEER database (1988 to 2003) to assess the association between negative lymph node counts and survival in patients with node-negative (AJCC stage I and IIa) esophageal carcinoma who did not undergo neoadjuvant radiation therapy. Unlike our study, they found heterogeneity across pT stage strata. For patients with pT1 disease, they determined that a higher lymph node yield (more than 18 lymph nodes) was necessary to maximize survival. However, for patients with pT2 or pT3 disease, examination of 11 to 17 lymph nodes provided the same survival advantage as examination of more than 18 lymph nodes [18]. Differences in methodology may explain this discrepancy. They focused on number of *negative* lymph nodes examined; we focused on *total* lymph node counts. They restricted their analysis to patients with localized disease; we included patients with localized *and* regional disease. They excluded patients who underwent neoadjuvant therapy; we did not. In addition to adenocarcinomas and squamous cell carcinomas, they also included other histologies (small cell carcinomas, lymphomas, melanomas, and sarcomas). We chose to exclude these tumors since they likely have different biological behavior than adenocarcinomas and squamous cell carcinomas of the esophagus.

In contrast to many of these previous studies [16, 18, 19], we chose to include patients who underwent neoadjuvant radiation therapy because it is becoming the standard of care for locally advanced esophageal carcinoma [2]. Therefore, our results may be more generalizable to today's esophageal cancer patient. We found that the esophageal specimens from patients who complete neoadjuvant radiation therapy have significantly fewer lymph nodes than patients who did not, which is not surprising since radiation therapy may cause lymphocyte depletion and stromal fibrosis resulting in significantly

smaller (or even ablated) lymph nodes [30]. Nonetheless, lymph node counts are still important in patients who undergo preoperative radiation therapy; radiation therapy should not be an excuse for not finding lymph nodes in an esophagectomy specimen.

Though our results indicate that a large number of lymph nodes should be examined to maximize overall and cancer-specific survival, it does not provide insight into the debates regarding the optimal esophagectomy approach (i.e., transhiatal, transthoracic, and 3-field) or the optimal extent of lymphadenectomy (i.e., 2-field vs. 3-field). Our results simply indicate that 30 or more lymph nodes should be examined (regardless of the operative technique).

Though it is clear that lymph node counts are associated with survival, the underlying mechanisms behind this association are poorly understood. There are a number of possibilities. One such mechanism is improved local tumor control - clearing more lymph nodes (to assure removal of occult or overt metastasis) may reduce local recurrence rates and improve survival. Indeed, recurrent disease is almost uniformly fatal [7]. Unfortunately, SEER does not collect recurrence data, preventing us from further analyzing this potential association.

More accurate cancer staging is another potential mechanism. By removing more lymph nodes, the risk of failing to detect lymph node metastasis (which may prevent patients from receiving optimal adjuvant therapy) is lessened. However, we demonstrated that the number of lymph nodes needed to optimize cancer-specific mortality (30 or more lymph nodes) is not the same as the number need to maximize the likelihood of detecting lymph node metastasis (about 15 lymph nodes). Our findings are similar to a recursive partitioning analysis of data from 336 patients who underwent

esophagectomy at the Memorial Sloan-Kettering Cancer Center; examination of 18 lymph nodes was recommended to optimize the accuracy of cancer staging [21]. This discordance between the number of lymph nodes that should be examined to optimize survival and the number needed to optimize cancer staging has been replicated in the colorectal cancer literature. In a study using the SEER-Medicare database, Wong et al. demonstrated that removing 12 lymph nodes (the standard of care for colorectal cancer to optimize survival [31]) did not increase the accuracy of colorectal cancer staging [32].

The discordance between the number of lymph nodes needed to optimize survival and the number needed to accurately stage patients suggests that there are common factors that impact both esophageal and colorectal cancer patients (and likely patients with other malignancies as well) that confound the association between lymph node counts and survival. Such factors include: (1) surgeon factors (training, esophagectomy volume, and oncologic quality of the esophagectomy and lymphadenectomy), (2) pathologist factors (skill and diligence looking for lymph nodes), (3) hospital factors (esophagectomy volume, teaching status, and global quality of patient-care), (4) patient factors (ability to mount an immune response to cancer thereby making it easier to find lymph nodes), or (5) other (unrecognized) factors.

There are a number of limitations of our study, some of which are inherent limitations of SEER data. In particular, the SEER cancer registries do not collect information on several factors which are associated with survival, such as performance status [33], co-morbidities [34], use of chemotherapy [35], completeness of resection [36], margin length [37] , time to local recurrence [36], weight loss (more than 10%) [38], and surgeon and hospital esophagectomy volume [39, 40]. Therefore, we could not adjust for these covariates

in our model. In addition, SEER does not mandate endoscopic verification of tumor location. As a result, there is a potential for misclassification. However, when we stratified patients into broader tumor location groups (cervical, thoracoabdominal and overlapping), our results were unchanged, indicating that misclassification of tumor location was not a significant source of error.

Finally, we restricted our analysis to only include adenocarcinomas and squamous cell carcinomas to reduce the confounding influence of the varying biological behaviors of other tumor histologies. As a result, our results may not be generalizable to other esophageal cancer histologies.

We believe our use of a large population-based cancer registry, inclusion of patients representative to today's esophageal cancer patients (i.e., those that undergo neoadjuvant therapy), and demonstration of consistent results across a variety of strata adds to the growing body of evidence in the literature regarding the association between lymph node counts and survival. Additional studies are needed to ascertain the underlying mechanisms behind lymph node counts and survival.

Conclusion:

Though the underlying mechanisms have yet to be elucidated, the number of lymph nodes examined in an esophagectomy specimen from patients with esophageal carcinoma is a significant independent determinant of all-cause and cancer-specific mortality, even among patients who complete neoadjuvant radiation therapy. Therefore, lymph node counts after esophageal resection should be a central feature of surgical quality assessment.

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