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Clinical Impact of Lymphadenectomy Extent in Resectable Esophageal Cancer

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Abstract Esophageal cancer (EC) frequently presents with advanced stages and is associated with high recurrence rates after esophagectomy. The value of an extended lymph node dissection (ELND) remains unclear in this setting. An EC data set was created from the Surveillance, Epidemiology, and End-Results 1973–2003 database. Relationships between the number of lymph nodes (LNs) examined and overall survival (OS) were analyzed. From a cohort of 40,129 EC patients, 5,620 individuals were selected. The median age was 65 (range: 11–102), and 75% were men. The median tumor size was 5.0 cm (0.1–30). On multivariate analysis, total LN count (or negative LN count, respectively) was an independent prognostic variable, aside from age, race, resection status, radiation, T category, N category (all at $p<0.0001$), and M category ($p=0.0003$). Higher total LN count (>30) and negative LN count (>15) categories were associated with best OS and lowest 90-day mortality ($p<0.0001$). The numeric LN effect on OS was independent from nodal status or histology. Greater total and negative LN counts are associated with longer EC survival. Although the mechanism remains uncertain, it does not appear to be limited to stage migration. ELND during potentially curative esophagectomy for EC can be supported by the data.

Keywords Lymphadenectomy · Resectable esophageal cancer · Lymph nodes · N staging · Survival

Background

Esophageal cancer (EC) continues to represent a significant therapeutic challenge, with an increasing incidence and death rate, and a mere 16% overall survival (OS) rate.[1,2] Despite its potential to induce significant morbidity, esophagectomy can lead to better OS results than any other treatment modality alone, especially when performed in a high volume setting that is linked to a lower postoperative mortality[3] and superior long-term survival.[4] Many high-volume surgical centers preferably perform extended resections, such as en-bloc esophagectomies or two- or three-field dissections, which may contribute to better regional disease control because of removal of metastatic lymph nodes (LNs), and may be linked to better survival.[5–9] However, neither the minimum number of LNs to be removed during curative intent esophagectomy nor the optimum LN count that could be linked to the best survival results have been well established. Recommended minimum LN counts range from 12 for a greater than 90% staging sensitivity[10], over 16 for greatest survival benefit[11], to 18 for optimal staging accuracy.[12] Few clinical studies have comparatively addressed outcomes after various degrees of LN dissections (LND). A randomized controlled trial (RCT) examined upper mediastinal and cervical LND in patients with squamous cell cancer (SCC) of the mid-esophagus; mean LN counts were 82 compared to 43 in the comparison group, and the OS at 5 years was 66% compared to 48%.[13] A RCT comparing transthoracic with

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transhiatal esophagectomy (THE) yielded 31 versus 16 LNs and a 5-year OS of 39% versus 29%.[14] A case-control study of patients with T3N1 EC undergoing en-bloc esophagectomy compared to transhiatal resection resulted in total LN counts of 52 versus 29 and an OS of 32% compared to 9%.[15] Finally, a nonrandomized European study of two-field LND with THE versus THE alone reported 17 and 5 LNs, respectively, with a disease-free survival at 5 years of 41 and 10%.[16] Thus, it appears that in all studies that compare different operative approaches to EC resection that are associated to different LN counts, survival results are superior for patients in whom more extensive LNDs have been performed, as evidenced through higher LN counts.

We have previously investigated the impact of LN counts on survival after operative therapy for various gastrointestinal cancers, including gastric cancer of early and advanced stages,[17,18] extrahepatic cholangiocarcinomas,[19] and pancreatic cancer.[20] In all instances, population data revealed a strong association between increasing total or negative LN counts and better survival. The rationale for this study was to determine possible associations of LN counts and survival after esophagectomy for EC. To address this question, we resorted to US population information from the Surveillance, Epidemiology, and End-Results (SEER) data set published by the National Cancer Institute.

Patients and Methods

An EC data set was created through structured queries to the public version SEER 1973–2003 database, which includes combined records from multiple cancer registries representative of the US population. EC stage information was created according to the sixth edition American Joint Committee on Cancer tumor–node–metastasis (TNM) criteria,[21] with the exception that metastatic involvement of LNs was classified as N1 disease only, as detailed information on extraregional nodal location was lacking. From 40,129 individuals with EC, 5,620 were extracted based on sufficient information regarding disease extent, operative treatment administered, and known survival outcomes. Those patients who received adjuvant radiation treatment were kept within the analysis; information on chemotherapy is not provided in the SEER data. Patients with incomplete resection information, such as "surgery, not otherwise specified," were kept in the analysis, as long as sufficient information was available to document that resection of the primary tumor had taken place, such as through details in the pathologic findings. Several variables were recategorized or computed anew, such as the negative LN count (from total and positive LNs) and the LN ratio (positive to total LNs removed).

OS was the primary outcome component of interest. OS information in the SEER database reflects time from diagnosis to last follow-up (death or last contact) in monthly increments; censoring criteria were generated accordingly. Actuarial survival was analyzed via the Kaplan–Meier method, for the entire cohort, and for node-negative or node-positive groups separately. To eliminate early postoperative mortality and to determine the impact of LN counts on long-term survival, a conditional OS analysis was performed, only including patients who were alive at least 6 months or beyond. Univariate group comparisons utilized the log-rank test. Cox regression was used for multivariate analysis, with a backward elimination model for all covariates; we selected a threshold for keeping a variable in this elimination model at $p=0.05$. All continuous variables were entered into this analysis as continuous data. Variables included into this multivariate calculation were grade (high versus low), T stage category (T1 versus T2 versus T3+T4), total number of LNs examined (and/or number of negative LNs), N stage category (N0 versus N1), and/or number of positive LNs, race, age, gender, tumor size, year of diagnosis, presence of metastases, and tumor location (overlapping, upper, middle, or lower third). A projected 5-year survival analysis was performed based on a linear projection model as described earlier.[17,18] Simple group data comparisons based on parametric statistics were done via *t*-test; for categorical parameters, chi-square testing was used. Significance of differences was assumed at p values of less than 0.05. Calculations were performed using the SAS 8.2 statistical software package (SAS, Cary, NC) or StatView 5.0.1 software for Macintosh computers (SAS Institute).

Results

Patient Demographics

From a cohort of 40,129 patients with an EC diagnosis within SEER, disease extent information was available in 15,417, and sufficient treatment and survival information was available for 12,102 individuals to calculate actuarial OS as postoperative outcome. Completeness of LN staging information could be identified for 5,620 individuals, which were included in the first multivariate analysis. Of these, 3,568 patients had undergone a resection. After exclusion of unspecified categories, 2,597 cases remained, which served as cohort for subsequent analyses relevant to LN count questions. The median age within the cohort was 65 years (range: 11–102), and 75% of patients were men. Ethnic information identified white patients in 82%, black patients in 12%, and other racial groups in 6% of cases. The location of the primary tumor could be classified as upper esophagus for 4%, middle esophagus for 18%, lower

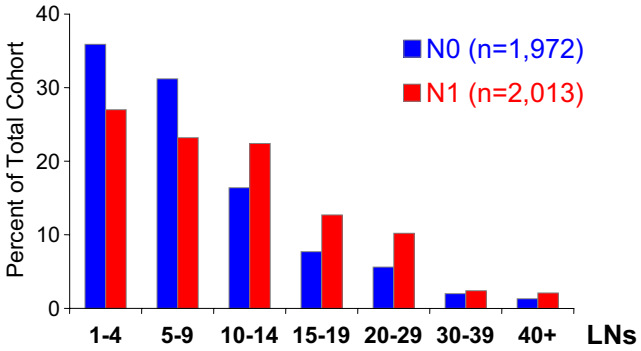

Figure 1 Frequency of categorized number of total lymph nodes examined by N stage category.

esophagus for 71%, and overlapping or unspecified for 7% of patients. The median tumor size was 5.0 cm (range: 0.1–30). Adenocarcinomas encompassed 57% of cases, and squamous cell carcinomas 43%. Of the resected patients with at least one LN examined, the median total LN count was 8 (range: 1–77), the median positive LN count 1 (0–46), and the negative LN count 6 (0–72). Differences were observed in the frequency of categorized number of total LNs examined when separated by N stage category (Fig. 1); patients classified as N0 tended to have fewer LNs identified more frequently than those classified as N1. The median follow-up was 15 months (range: 0–188), with a median follow-up for survivors of 25 months.

Multivariate Survival Analysis

On multivariate analysis, the total LN count was an independent prognostic variable, aside from age, race, resection status, radiation, T category, N category (all at $p<0.0001$), and M category ($p=0.0003$). Parameter estimates and risk ratios for all patients selected on the basis of this Cox proportional hazards model are listed in Table 1. Total LN counts were exchangeable for negative LN counts in this model, at a similar significance level with $p<0.0001$. A second multivariate model based on patients with complete pathologic staging and LN count information yielded the same prognostic variables, in addition to positive LN counts, tumor size, and race (Table 2). Again, negative LN counts were exchangeable with total LN counts. With the second model, grade and tumor location were entered into the model, but the presence of each of these factors forced the resection factor to become nonsignificant above the 0.05 level. It was difficult to interpret this conditional relationship, and so, we chose to report the model in which resection was significant.

Table 1 Parameter Estimates and Risk Ratios for all Patients Selected on the Basis of the Cox Proportional Hazards Model ($n=5,620$)

Factor	*N* (percent)	Median (range)	Hazard ratio	Lower 95% CI	Upper 95% CI	*p* value
Total LN number (*n*, continuous)	N/A	3 (0 to 80)	0.982	0.977	0.988	<0.0001
Age (years, continuous)	N/A	65 (11 to 96)	1.016	1.013	1.019	<0.0001
Resection YN		N/A				<0.0001
No resection	2,133 (38)		Baseline	Baseline	Baseline	
Resection	3,487 (62)		0.785	0.752	0.820	
Radiation YN		N/A				<0.0001
No radiation	2,689 (48)		Baseline	Baseline	Baseline	
Radiation	2,931 (52)		0.854	0.825	0.884	
T Stage		N/A				<0.0001
T1	1,199 (21)		Baseline	Baseline	Baseline	
T2	963 (17)		1.058	0.997	1.122	
T3–T4	3,492 (62)		1.504	1.434	1.577	
N stage		N/A				<0.0001
N0	1,647 (29)		Baseline	Baseline	Baseline	
N1	1,643 (29)		1.383	1.307	1.463	
N unstaged	2,330 (42)		1.032	0.968	1.100	
Metastases		N/A				0.0003
M0	5,246 (93)		Baseline	Baseline	Baseline	
M1	374 (7)		1.134	1.070	1.201	
Race		N/A				<0.0001
White	4,609 (82)		Baseline	Baseline	Baseline	
Black	661 (12)		1.179	1.099	1.264	
Other	350 (6)		0.957	0.879	1.042	

N/A Not applicable

Table 2 Parameter Estimates and Risk Ratios for all Staged Patients Selected on the Basis of the Cox Proportional Hazards Model (n=2,597)

Factor	*N* (percent)	Median (range)	Hazard ratio	Lower 95% CI	Upper 95% CI	*p* value
Total LN count (*n*, continuous)	N/A	8 (1 to 74)	0.966	0.959	0.973	<0.0001
Positive LN count (*n*, continuous)	N/A	1 (0 to 28)	1.073	1.055	1.091	<0.0001
Tumor size (mm, continuous)	N/A	40 (1 to 300)	1.004	1.002	1.006	<0.0001
Age (years, continuous)	N/A	64 (11 to 90)	1.018	1.013	1.023	<0.0001
Resection Y/N		N/A				0.0341
No resection	210 (8)		Baseline	Baseline	Baseline	
Resection	2,387 (92)		0.917	0.847	0.992	
Radiation Y/N		N/A				<0.0001
No radiation	1,615 (62)		Baseline	Baseline	Baseline	
Radiation	982 (38)		0.850	0.806	0.897	
T stage		N/A				<0.0001
T1	517 (20)		Baseline	Baseline	Baseline	
T2	519 (20)		1.130	1.035	1.234	
T3–T4	1,561 (60)		1.441	1.333	1.557	
N stage		N/A				<0.0001
N0	1,254 (48)		Baseline	Baseline	Baseline	
N1	1,343 (52)		1.279	1.205	1.358	
Metastases		N/A				0.0117
M0	2,468 (95)		Baseline	Baseline	Baseline	
M1	129 (5)		1.144	1.034	1.265	
Race		N/A				0.0293
White	2,227 (86)		Baseline	Baseline	Baseline	
Black	208 (8)		1.171	1.034	1.326	
Other	162 (6)		0.921	0.803	1.056	

N/A Not applicable

Univariate Survival Analysis of Lymph Node Count Impact

Higher total LN counts (up to >30) and negative LN counts (up to >15) categories were associated with the best OS ($p<0.0001$) and the lowest 30- and 90-day mortality ($p<0.0001$). The numeric total LN count effect on OS is depicted in Fig. 2. It was observed for both N0 and N1 stage subgroups, but appeared to be linked to greater OS differences for N0 EC in comparison to N1 EC (Fig. 3). A similar effect of better OS outcomes with higher total LN counts was observed for both squamous cell and adenocarcinoma EC histologies (data not shown). Negative LN counts demonstrated a strong association with OS as well. The actuarial OS for patients with EC dependent on various negative LN count categories is displayed in Fig. 4. This negative LN count impact persisted when the cohort was split by nodal status and appeared to present in a similar magnitude of OS differences (Fig. 5). Median survival and long-term OS (in percent) are listed in Table 3.

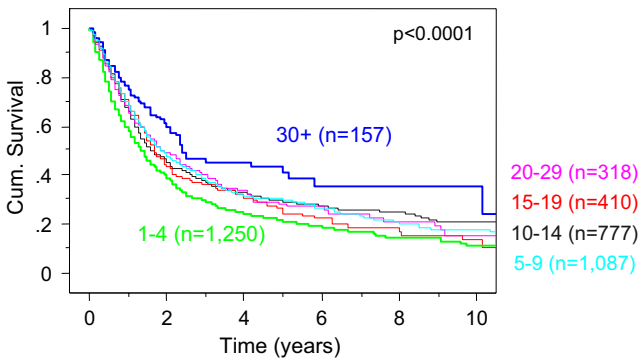

Figure 2 Actuarial overall survival curve for patients with esophageal cancer by various total lymph node count categories.

A cutpoint analysis intended to detect the total LN number related to the greatest OS differences. As tabulated in the same table, the highest chi-square statistic representing greatest group differences was observed at low LN counts: one for the overall cohort and five for N0 and N1 resected patients. However, significant differences were still encountered for cutpoints above 30 total LNs, always in favor of the group with higher total LN counts. The highest significant cutpoints were at 45 for N0 and at 35 for N1 disease stages.

Early Postoperative Deaths Based on Lymph Node Numbers

To separate esophagectomy-related (early) mortality from long-term survival in the analysis of LN count associations, we analyzed early mortality associations and conditional long-term OS separately. Death within 30 days occurred to 3% of N0 and 5% of N1 patients ($p=0.0004$). Similarly,

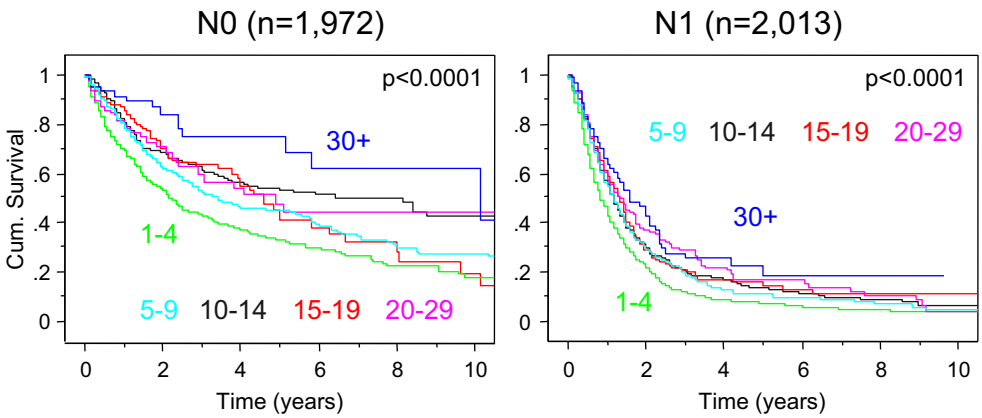

Figure 3 Actuarial overall survival curve for patients with esophageal cancer by various total lymph node count categories and separated by N category.

mortality at 30 days after resection was 5%, but 14% without resection ($p<0.0001$); the corresponding 90-day mortality was 13% versus 30% ($p<0.0001$). Significant relationships between mortality and LN counts existed for total LN counts, LN ratio, and negative LN counts, always with the lowest mortality rate for the higher LN count categories. Figure 6 depicts such mortality within 90 days by total LN count categories, LN ratio categories, and negative LN count categories. A long-term survival impact of LN counts was examined after excluding all deaths within 6 months after diagnosis. Figure 7 depicts actuarial conditional OS curves for patients with EC by various total LN count categories. Survival differences are less obvious, but still evident especially at LN counts of >30.

Projected Numeric Lymph Node Impact on Overall Survival

Plots of actuarial OS at 5 years and at 10 years were generated for various total LN count categories (Fig. 8). The highest OS results were invariably observed at the highest LN count categories for the overall patient cohort as well as for adenocarcinoma and squamous cell carcinoma histologies. Based on a resulting linear regression model, the projected numeric total LN impact on 5-year OS was calculated for the entire cohort and separately by histologic type (Table 4). The results show a relative increase in OS at 5 years for every ten LNs identified of between 4 and 5%.

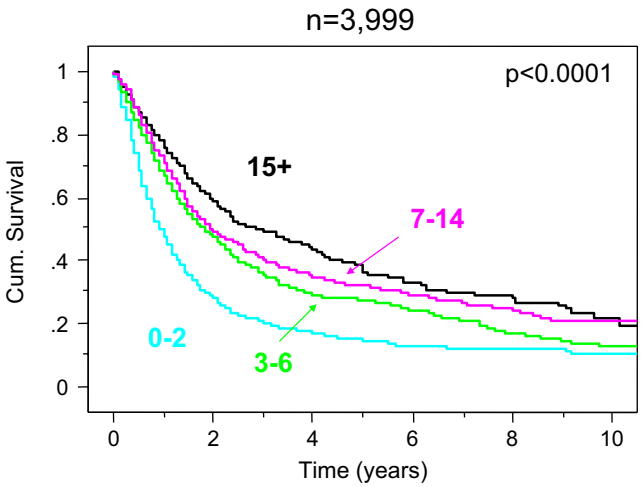

Figure 4 Actuarial overall survival curve for patients with esophageal cancer by various negative lymph node count categories.

Implications of Lymph Node Ratio

The ratio of metastatic to total LNs (LN ratio), a previously reported prognostic parameter for EC survival, showed a strong association with OS results. When divided into quintiles, the lowest LN ratio (0.01 to 0.19) associated with the best survival (median=1.75 years) and the highest LN ratio (0.8 and greater) with the worst OS (median=0.67 years; $p<0.0001$) in nodal positive patients. To examine the implications of total LN counts on LN ratio, we assessed median OS relationships with various LN ratio categories, again excluding 0 (i.e., N0 patients). Separation between OS outcomes of different LN ratio categories was greatly enhanced in settings of higher total LN counts, as displayed in Fig. 9.

Discussion

The results show a strong association between postoperative LN counts and survival after esophagectomy for EC. Invariably, higher total LN counts or negative LN counts are linked to better OS, which is observed in both N0 and N1 stage groups, as well as in both main histologic types of EC. These findings are perhaps even more profound, as they are derived from population data, with an anticipated mix between providing hospitals and surgeons regarding esophagectomy volume. Best survival after esophagectomy is usually obtained in high-volume settings, where more extensive resections including extended LNDs are the norm.[5–7] Our findings would therefore generally corrobo-

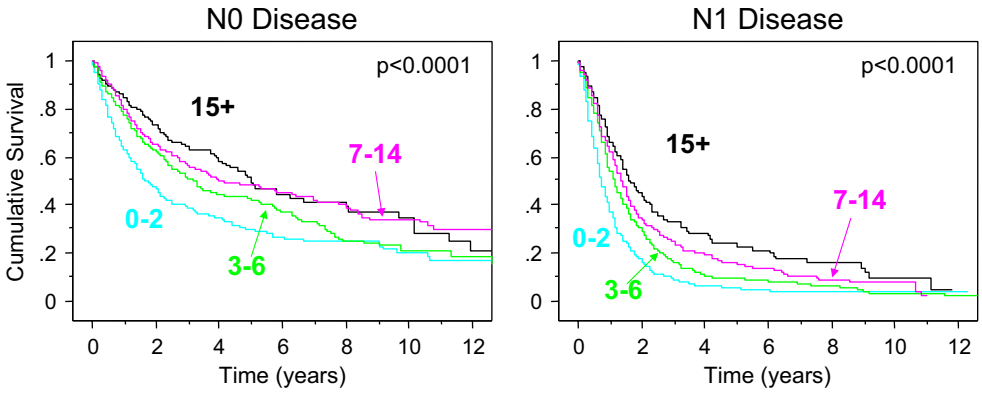

Figure 5 Actuarial overall survival curve for patients with esophageal cancer by various negative lymph node count categories and separated by N category.

rate those reports of others in which resection techniques linked to larger LN counts are associated with better OS results.[13–16] From available reports, it remains unclear which EC patients might benefit most from more extensive dissections with greater LN counts. Accordingly, among subsets that have been reported to benefit are patients with N0 SCC,[22] N0 adenocarcinoma,[23] T3N1 adenocarcinomas when less than nine LNs are involved,[15] early SCCs where distant LN spread is more common that in early adenocarcinoma,[24] or in those midthoracic lesions for which cervical and/or abdominal LND is included.[6,25–27] Although, in our results, the total LN count impact was more obvious in N0 than N1 disease, the observed benefits of greater LN counts are not restricted to any specific patient subsets and have thus to be explained as a more general phenomenon.

Whereas a therapeutic benefit of removing more LNs with potential metastatic disease is assumed to partake in this phenomenon, it cannot be proven from the available

Table 3 Overall Survival by Total LN Count, by Nodal Staging Category

LN Count	Number	Median OS (years)	3-year OS (%)	5-year OS (%)	Log-rank χ square statistic
All patients (n=12,102)					
0 nodes	8,113	0.66	14	9	*930.9*
1 node	370	1.08	24	18	907.2
2–4 nodes	777	1.58	34	25	701.1
5–9 nodes	1,184	1.75	36	28	368.1
10–14 nodes	774	1.67	37	29	184.6
15–19 nodes	408	1.67	36	24	113.8
20–29 nodes	318	1.83	40	28	55.0
30+ nodes	158	2.42	45	41	20.9
N0 patients, at least 1 LN examined (n=1,972)					
1 node	220	1.75	38	28	32.2
2–4 nodes	487	2.42	46	35	*49.5*
5–9 nodes	615	3.42	52	45	38.0
10–14 nodes	324	8.17	62	53	13.4
15–19 nodes	152	4.58	63	41	12.4
20–29 nodes	110	4.92	60	48	11.8
30+ nodes	64	10.17	75	75	5.4
N1 patients, at least 1 LN examined (n=2,013)					
1 node	150	0.67	6	4	34.0
2–4 nodes	290	0.91	14	9	*36.3*
5–9 nodes	569	1.17	18	10	21.9
10–14 nodes	450	1.17	20	13	16.5
15–19 nodes	256	1.33	21	15	13.5
20–29 nodes	206	1.33	29	17	7.0
30+ nodes	92	1.58	26	19	2.9

Cutpoint analysis for detecting the total lymph node number related to greatest overall survival differences
The log-rank χ square statistic corresponds to the maximum within the range for that group versus the minimum within the next group of total LN counts. For example, "5–9 LNs log-rank χ square statistic" compares the K–M curve between 0–9 LNs examined (or 1–9 LNs examined for N0 and N1) versus 10+LNs examined. The italicized value corresponds to the cutpoint with the largest χ^2 statistic, i.e., the greatest detectable survival differences within the entire cohort. The χ^2 statistic in the 30+ rows reflect 39 or fewer LNs versus 40 or more LNs. A χ^2 statistic of more than 4 is accompanied by a p value of less than 0.05.

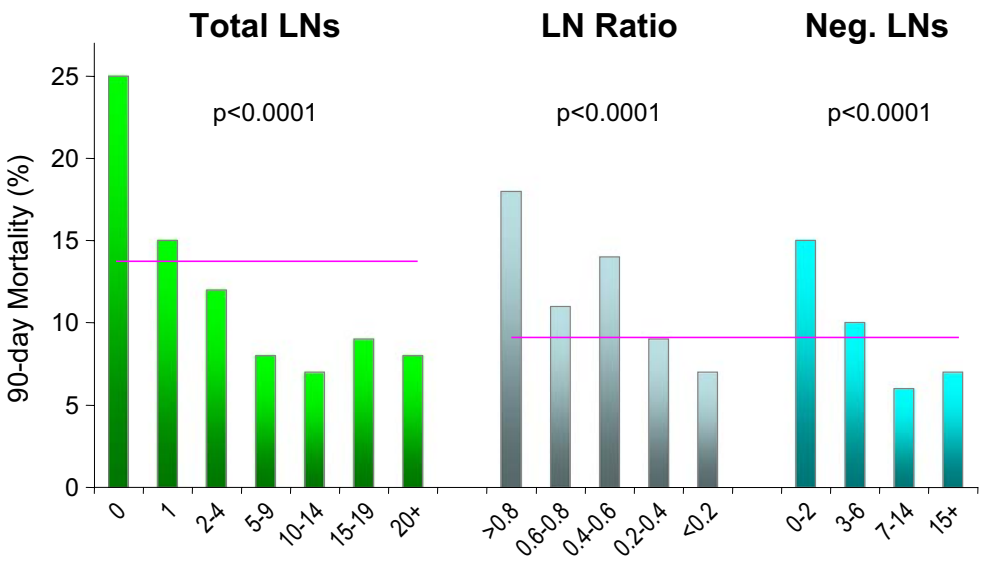

Figure 6 Mortality within 90 days by total LN count categories, LN ratio categories and negative LN count categories. The *horizontal bars* mark the average 90-day mortality for that patient cohort.

information. The numeric total LN effect in N1 patients, the benefit of negative LN counts in patients with more than 1 positive LN, and the conditional survival benefits of LN counts beyond 6 months, all usually within a range of 10 to 20% when comparing lowest and highest LN count groups, let us suspect some therapeutic effect because of better regional disease control. Multiple studies have described a high rate of immunohistochemically identified micrometastases to regional LNs, with generally negative prognostic implications, even when standard histopathologic examination would not reveal evidence for LN involvement.[28–30] Removing more of these LNs at risk may reasonably reduce avenues for subsequent oncologic progression.

There are, however, numerous caveats that need to be respected in the interpretation of our results. The large SEER population database has not been established to analyze specific surgical technical questions, and therefore, significant limitations in information accompany this analysis. Firstly, patients with sufficient information are highly selected from within the database, and coding errors or potential omissions cannot be ruled out. The selection process is necessitated in part by identifying patients who underwent surgical therapy, but also because of lack of complete data among surgically treated individuals. Naturally, this selection could introduce bias, if cases with complete data differ from others by treatment or other survival hazards; however, such potential bias cannot be controlled for in the context of numeric LN analyses. Furthermore, we lack data on LN location, the exact operative technique for local and regional dissections, any margin status, any chemotherapy given, or any response to preoperative chemoradiation. Other parameters that have been linked to post-esophagectomy survival are equally unknown, such as the institutional volume, surgeon volume, the patient's performance or nutritional status, and the quality of macroscopic and histopathologic examination, all of which could possibly influence the LN status entered into the database. Is the total LN count or the

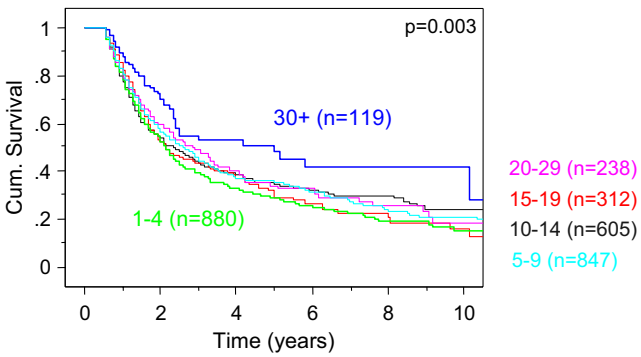

Figure 7 Actuarial conditional overall survival curves for patients with esophageal cancer by various total lymph node count categories. Included are only individuals alive at least 6 months from diagnosis.

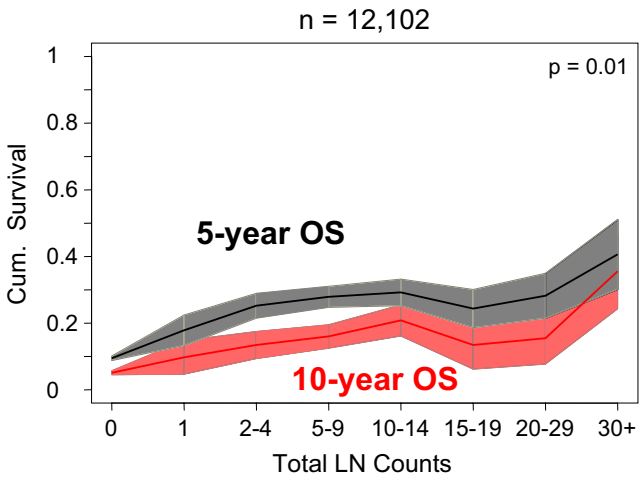

Figure 8 Plots of actuarial overall survival at 5 and 10 years by total lymph node count categories. The *shaded areas* represent the 95% confidence intervals.

Table 4 Projected Numeric Total Lymph Node Impact on 5-Year Overall Survival, by Histologic Type

Stage subgroup	Patients (*n*)	Baseline 5-year survival (based on 0 LNs examined for all groups; %)	For every ten extra LNs examined, survival improved by (%)	*p* value
All patients	12,102	18	5.0	0.0115
N0 subgroup, 1+ LNs examined	1,972	32	10.0	0.0075
N1 subgroup, 1+ LNs examined	2,013	8	3.0	0.006
Adenocarcinomas	5,695	21	3.2	0.1123
Squamous cell carcinomas	5,740	11	10.7	0.0007

The baseline 5-year survival in this linear projection model is based on the *y*-intercept and thus represents a hypothetical survival number for the groups shown. Accordingly, if a squamous cell carcinoma patient had only seven LNs examined, his expected 5-year overall survival would be 11%+7×1.07=18.5%. If an adenocarcinoma patient had 27 LNs dissected, his expected 5-year overall survival would be 21%+27×0.32=29.6%.

negative LN count not just a result of more extensive regional dissection, but perhaps a surrogate for a healthier patient, or a better patient selection reflective of a high-volume, higher quality healthcare setting where better survival can be expected without actual better oncologic control of the underlying cancer? The SEER data alone do not allow controlling for volume–outcome relationships. However, high esophagectomy volume institutions frequently subscribe to standardized, wider regional dissection extents, and much of the undisputable volume–survival relationship may in fact already result from a greater lymphadenectomy extent alone.[4] It is thus plausible that a large component of the LN count effects observed in the population data represents the spectrum from low-volume institutions in low LN count categories to high LN counts obtained in many high-volume settings. Obviously, LN numbers do not always equate to the true lymphadenectomy extent, but they certainly are the best surrogate available. Nevertheless, all these questions have to be considered carefully before possibly any practical implications of the results can be claimed.

Total and negative LN counts appear to be rather important for survival prediction of EC, and this information extends beyond predictive information from the TNM staging criteria. Limitations of the TNM staging system have been highlighted by others, but outside the number of positive LNs, LN counts have not been suggested as clinical staging criteria.[31,32] The LN ratio does obviously reflect total LN counts aside from positive LN number. The LN ratio has been reported as prognostic variable in EC,[5,32,33] including in one study based on the SEER data for EC between 1988 and 1997.[34] We did not intend to merely duplicate this earlier effort with our analysis, but had a specific practical interest to define an optimal LN number to be removed at the time of esophagectomy, which would preferably represent a valid numeric target even for N0 disease, which the LN ratio is not. A definable number of LNs known preoperatively as target, to be removed by the surgeon and to be identified by the pathologist, would likely serve as a standard goal of EC care, irrespective of ultimate nodal involvement, in a system where standards throughout the population appear rather variable. Undoubtedly, wider LND influences the quality of staging,[12,35] and the LN count impact on OS in N0 disease will reflect a mechanism of stage migration to a large extent. This is certainly corroborated by our findings of nodal stage assignment linked to different LN count profiles, and the largest cutoff point differences in low LN count ranges. Irrespective of the contributing mechanism being a result of better staging and/or better disease control, total LN counts of 30 or higher would appear to represent this preoperative target that can be linked to optimal survival results in our analysis. It should be noted, however, that the recommended total LN count of 30 is merely reflective of a desirable practical target; the observed numeric LN count impact is not an all-or-nothing phenomenon, but a gradual effect of a continuous biologic variable, i.e., the involved LN count. Complex biologic tumor and patient heterogeneity would suggest that the risk for residual positive LNs is not eliminated at a certain total or negative LN count, but rather likely to decrease gradually with increasing counts.

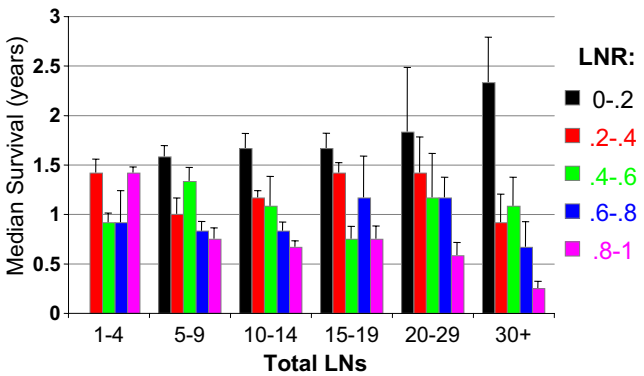

Figure 9 Median actuarial overall survival by various lymph node ratio and total LN count categories. The *bars* represent the standard error. *LNR* lymph node ratio. Only N+ patients are included.

Evidence for a continued numeric LN effect at higher LN count ranges and for nodal positive patients, is perhaps the strongest argument in favor of a true lymphadenectomy–survival relationship that can be extracted from the available data. In addition, these population-derived observations corroborate the findings of the few available RCTs mentioned earlier.[13,14,16]

Our results suggest that larger total LN counts are linked to better outcomes, with an optimal number of 30 or greater. This putative dissection goal is derived from standard LN evaluation techniques and may indeed change with qualitative analysis of LN involvement, such as through the sentinel LN technique.[36] Other factors that may influence a wider LND goal in the future may be the development of specific and reliable staging criteria for early stage disease or major responses to preoperative chemoradiation,[37] which could render the need for LN removal superfluous. For now, however, we interpret the findings as supportive for a more extended LN retrieval at the time of esophagectomy and recommend to obtain 30 or more LNs to expect an optimized quality of numeric EC staging, an optimal ability for survival prediction, and an optimized regional disease control with its potential for improved EC survival.

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DISCUSSION

Jeffrey H. Peters, M.D. (Rochester, NY): A wise man, his name is Tom DeMeester, once told me that medicine is a field that is forced to be practiced before it can be proven or completely understood. This aphorism could not be more true than in the debate about lymphadenectomy and cancer. We could spend the rest of the week trying to answer the question of its benefit.

That said, the 20-something years now of my career and data such as this convince me, that given solid tumors of the GI tract, this author is correct: There is a benefit to lymphadenectomy in esophageal cancer, probably in gastric cancer, and probably also in colon cancer. Proving it is of course the challenge, a big challenge. This is a well-written manuscript by the way, which critiques itself very nicely. I come away with the thought that this is not sloppy science, but rather well thought through data.

With these caveats in mind, let me then ask you a couple of questions. In yours, as well as similar published data, a dose response is often observed. Why? This study and others like it in the colon and the stomach clearly show a dose response. I would expect that there would be a threshold response, not a dose response. One would suspect that there would be a point, at 20 nodes or 30 nodes or 40 nodes or 50 nodes that you would not find any more benefit, and that is not what we see here.

Secondly, you mentioned it a little bit, but I wonder if you could pinpoint the few key rebuttals to the criticism that this does not prove anything, and that such data is simply an epiphenomenon. I am convinced that it does prove that there is a benefit here somewhere, even though some of the benefit may be due to stage migration or other factors. What are the key rebuttals of that criticism?

And finally, it strikes me that there may be a very real correlation between the number of lymph nodes removed and high volume, high quality multi-specialty centers. Do you have the center data and can you refute this potential confounding factor.

Again, there is beginning to be a preponderance of similar data that I believe is swinging the pendulum back, in tumors of the GI tract, toward the recognition that lymphadenectomy is indeed of benefit. We are a long way from proving it, but at some point each of us must decide how you are going to practice.

Very good paper, I enjoyed it very much. Thank you for the opportunity to discuss it.

Roderich E. Schwarz, M.D. (Dallas, TX): Thank you very much, Dr. Peters. It is nice to be supported by a grateful review, and I appreciate it. In fact, the rationale, in part, was brought forth by an excellent symposium that you had put on at the American College meeting that discussed the same question, and it was an attempt to provide at least more data than are currently available in the literature, and because you mentioned the wise man, a wise answer to complex part of statements would be not to answer too much in detail.

Why is there no cutoff? I think it is, in part, statistical and it is, in part, that we truly have a mixture of different phenomena at play. Therefore, it is not a simple oncologic phenomenon or therapeutic phenomenon. We do not have a natural distribution or bell-shaped distribution of lymph node counts in here. Therefore, a lot of what we see is a continuous variable that increases possible effects as the counts go up, and really, there is no single cutoff, primarily for statistical reasons. If one does a cutoff analysis, which we have attempted in the manuscript, you see that the

higher you go with the cutoff, you continue to see significant differences up to counts between 35 and 40. Therefore, I think it is, in part, a biologic phenomenon, it is, in part, by how the data were accumulated, and that the majority of data are actually in the very low lymph node number counts.

A key rebuttal is difficult because we have really only an ability to speculate on mechanism. We just have no insight, because certainly taking information from this database, which lacks a lot of detailed information such as you mentioned on volume of the institution or maybe even individual surgeon's volume, et cetera, leaves that open to criticism. I think the key is that we see an effect that is measurable and statistically significant in nodal positive disease. That does not rule out the presence of stage migration, but it is much less of a mechanism in stage migration than if you just look at nodal negative disease, and that is perhaps the key response for rebuttal to that part of the criticism.

And your final point to the institutional volume, I think it is very important. Of course, certain high volume institutions, such as your former institution, are included in the database. Therefore, it may be that all the patients in the total 30+ total lymph node category are in fact your former patients from USC, and that could well be, but that does not exclude that there is an oncologic benefit to a certain defined subset of patients who have primarily limited disease in the regional distribution and are at low risk ultimately for systemic disease. That is perhaps the best answer I can come up with on that point.

John G. Hunter, M.D. (Portland, OR): I too enjoyed your paper and I think I learned quite a bit from it. I do not fundamentally disagree with Jeff, but I do have a little sort of bone to pick on the final conclusion, which was that harvesting more than 30 lymph nodes confers survival benefit. In your several graphs of LN harvest and survival, there was little difference between 5 and 29 negative lymph nodes and then it jumped up in the 1930s. My interpretation is that there are just a few expert centers harvesting >30 nodes/specimen, and this is only a surrogate for the quality and care in those centers and does not have anything to do with the lymph node resection rate. I noticed USC is one of these centers.

Therefore, the question I have then is: How many centers are represented in that "over 29 lymph node" category and how much confidence do you have that the improved survival of these patients reflects lymph node harvest rather than the other factors that accrue around a "center of excellence"?

Dr. Schwarz: Thank you very much. Those are excellent points. We do not have the ability from this data set to deduce the actual institution at which the operation or the treatment took place. Patients are categorized by their residence more than anything else. Therefore, this is difficult to analyze. I do not have a good answer to your question.

The recommendation to shoot for a target number of 30 or more is somewhat imprecise. I agree with you. It would be much easier to look at the negative lymph node counts and come up with at least a number of 15 or more, because there the separations between the curves are more obvious. The problem is that I think for the variability in the standards of care for this disease in the population, it is good to have a preoperative target that the surgeon knows about and that the pathologist in fact knows about, hence, that can only be set by the total lymph node count. Therefore, if I try to get 30 lymph nodes during my esophagectomy and if my pathologist is being told by me, I want 30 lymph nodes, your likelihood to achieve 15 or more negative lymph nodes gets much higher. Therefore, I think it is a bit more practical recommendation. But you are absolutely right, the data would be in stronger support for negative lymph nodes that show a bit more obvious progression as the counts increase.