Value of Lymphadenectomy in Patients Receiving Neoadjuvant Therapy for Esophageal Adenocarcinoma

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Objective: The aim of this study was to assess the effect on survival of extent of lymphadenectomy during esophagectomy for patients undergoing multimodality (neoadjuvant) therapy for adenocarcinoma of the esophagus and esophagogastric junction using Worldwide Esophageal Cancer Collaboration data.

Summary Background Data: Previous worldwide data demonstrated that optimum lymphadenectomy during esophagectomy alone for esophageal cancer provides accurate staging and maximum survival. However, for patients undergoing neoadjuvant therapy for locally advanced adenocarcinoma, its value is unclear, leading to wide practice variability.

Methods: A total of 3859 patients with adenocarcinoma of the esophagus or esophagogastric junction received neoadjuvant therapy. The endpoint was all-cause mortality, reported as gain or loss of lifetime within 10 years. Lifetime predicted for each regional lymph node resected used quantile survival random forest methodology.

Results: Across all post-neoadjuvant ypTNM cancer categories, some degree of lymphadenectomy was associated with longer lifetime, but in a nonlinear fashion. For patients with ypN0 cancers, there was a modest gain in lifetime up to 25 lymph nodes resected and an incremental loss in lifetime as >25 were resected. For patients with ypN+ cancers, there was a robust gain in lifetime up to 30 lymph nodes resected and then an incremental loss in lifetime.

Conclusions: Worldwide data for adenocarcinoma of the esophagus and esophagogastric junction demonstrate that lymphadenectomy during esophagectomy is a valuable component of neoadjuvant therapy. Survival is maximized when an optimum range of nodes is resected.

Keywords: esophageal adenocarcinoma, lymphadenectomy, neoadjuvant therapy

(*Ann Surg* 2019;xx:xxx–xxx)

Lymphadenectomy has a defined role in managing esophageal and esophagogastric junction cancer in patients undergoing esophagectomy alone.[1] Optimum lymphadenectomy provides accurate staging, maximum survival, and can guide therapy. However, its value and extent during esophagectomy as a component of multimodality (neoadjuvant) therapy in treating esophageal adenocarcinoma is debated.[2,3] Therefore, purposes of this study were to use Worldwide Esophageal Cancer Collaboration (WECC) data[4–9] for neoadjuvant therapy to 1) assess whether lymphadenectomy offers any survival benefit and, if so, to determine optimum lymphadenectomy with respect to survival.

METHODS

Patients and Therapies

At 33 WECC institutions (Appendix 1), 13,365 patients with adenocarcinoma of the esophagus or esophagogastric junction underwent esophagectomy, among whom 4673 had neoadjuvant therapy. Of these, 3859 patients in 22 institutions had data available for the number of lymph nodes resected and whether lymph nodes were (ypN+) or were not (ypN0) positive for cancer (chemotherapy in 868, radiotherapy in 32, both in 2934, and unstated in 25). Patients having both neoadjuvant therapy and post-esophagectomy adjuvant therapy were not included (Tables 1 and 2). Approach to esophagectomy was minimally invasive (total or hybrid) in 678 (19% of 3613 in whom approach was known), hiatal in 642 (18%), thoracotomy in 1852 (51%), thoracoabdominal in 441 (12%), and unstated in 246.

Data

This study used 34 variables from previous analyses of WECC data,[4,5,9] with site and continent excluded to contain dimensionality of data and reduce confounding with treatment [Supplemental Digital Content (SDC) Appendix 1: Variables Used in Random Forest Analysis, http://links.lww.com/SLA/B779]. WECC data were obtained after local ethics board approval of databases, and data-use agreements were executed with Cleveland Clinic. Data were requested in completely deidentified format (Health Insurance Portability and Accountability Act research standards) for a set of required variables with standard definitions. Variables included demographics, comorbidities, cancer characteristics, cancer treatment, and time-related mortality (see SDC Appendix 1, http://links.lww.com/SLA/B779). The Case Cancer Institutional Review Board of Case Western Reserve University and Cleveland Clinic Institutional Review Board approved the entire project and use of these data for research, with patient consent waived.

Endpoint

The endpoint was all-cause mortality from first management decision, induction therapy in this instance. Median potential follow-up[10] was 7.1 years (25% >11.5 years, 10% >14.9 years) if there were

TABLE 1. Baseline Characteristics of Patients With Adenocarcinoma of the Esophagus

Characteristics	Overall (n = 3859)		ypN0 (n = 2078)		ypN+ (n = 1781)	
	n*	No. (%) or Mean ± SD	n*	No. (%) or Mean ± SD	n*	No. (%) or Mean ± SD
Demographics						
Age (y)	3689	61 ± 9.9	1968	62 ± 9.7	1721	61 ± 10
Female	3859	453 (12)	2078	248 (12)	1781	205 (12)
Body mass index (kg/m^2)	2610	28 ± 5.2	1551	28 ± 5.2	1059	27 ± 5.2
Weight loss (kg)	1341	4.8 ± 8.5	713	4.4 ± 7.0	628	5.3 ± 9.9
Comorbidities						
ECOG performance status	1403		882		521	
0		559 (40)		368 (42)		191 (37)
1		802 (57)		485 (55)		317 (61)
2		34 (2.4)		23 (2.6)		11 (2.1)
3		8 (0.57)		6 (0.70)		2 (0.40)
4		0 (0)		0 (0)		0 (0)
Diabetes mellitus	3643	483 (13)	1974	267 (14)	1669	216 (13)
Insulin-dependent	3501	53 (1.5)	1887	30 (1.6)	1614	23 (1.4)
Non−insulin-dependent	3501	288 (8.2)	1887	150 (7.9)	1614	138 (8.6)
Coronary artery disease	2639	379 (14)	1404	221 (16)	1235	158 (13)
Arrhythmia	1665	27 (1.6)	806	13 (1.6)	859	14 (1.6)
Hypertension	2344	670 (29)	1172	371 (32)	1172	299 (26)
Peripheral arterial disease	2692	72 (2.7)	1410	42 (3.0)	1282	30 (2.3)
Smoker	3011	2034 (68)	1677	1195 (71)	1334	839 (63)
Past	2331	935 (40)	1258	535 (43)	1073	400 (37)
Current	2331	419 (18)	1258	241 (19)	1073	178 (17)
FEV$_1$ (% of predicted)	1946	96 ± 19	1155	95 ± 19	791	97 ± 19
FVC (% of predicted)	1118	100 ± 17	643	99 ± 17	475	101 ± 18
Creatinine (mg/dL)	399	76 ± 21	239	77 ± 21	160	75 ± 22
Bilirubin (mg/dL)	163	10 ± 7.9	84	10 ± 5.6	79	10 ± 9.8

*Patients with data available.

ECOG indicates Eastern Cooperative Oncology Group; FEV$_1$ (%), forced expiratory volume in 1 second (percent of predicted); FVC (%), forced vital capacity (percent of predicted); SD, standard deviation.

no deaths. However, considering deaths in this elderly population with a rapidly lethal cancer, 50% of patients were followed >1.5 years, with 25% followed >3.1 years and 10% >5.4 years.

Data Analysis

Analytic Strategy

Primary objectives of the analyses were to determine if lymphadenectomy during esophagectomy offers a survival benefit and, if so, to identify the number of resected lymph nodes predicted to maximize survival. This was accomplished in 3 steps:

1. Plausible extents of lymphadenectomy: We identified from characteristics of patients and their cancers a plausible extent of lymphadenectomy using quantile random forests regression[11,12] (SDC Appendix 2: Method for Identifying Plausible Extents of Lymphadenectomy, http://links.lww.com/SLA/B779; and SDC Figure 1: Example of how range of plausible lymphadenectomy was determined for 2 patients, http://links.lww.com/SLA/B779). For ypN+ cancers, the minimum plausible number of nodes resected must be 1. We truncated the number of nodes resected at 50 (Fig. 1). Additionally, analyses were restricted to only M0 (non-metastatic) cases, ypN+M0.

2. Survival analysis for each patient: A survival analysis was performed that incorporated interactions of all variables with number of lymph nodes actually resected using an extension of random survival forests[13] (SDC Appendix 3: Method for Survival Analysis Using Random Survival Forests, Virtual Twin, with Interactions[14], http://links.lww.com/SLA/B779). From this analysis, a survival curve for each patient was predicted for actual

number of lymph nodes resected. Then a sequence of survival curves for alternative extents of lymphadenectomy for that patient ("what ifs") was obtained using the same patient and cancer characteristics, but substituting these alternative extents of lymphadenectomy for actual number resected. This generated for each patient a maximum of 51 survival curves, one for each extent of lymphadenectomy for which it was plausible.

3. Optimum lymphadenectomy: Length of life for each "what if" number of resected lymph nodes was estimated by restricted mean survival time ("lifetime"),[15−17] the area beneath a survival curve from beginning of treatment (induction therapy) to a specified time point. For this study, we chose 10 years as that specific time point and calculated for each patient all plausible lifetimes, expressing lifetime in months. We defined optimum lymphadenectomy as the plausible number of lymph nodes resected that yielded maximum lifetime. These lifetime values were summarized separately for patients post-induction therapy who did not ypN0 or did ypN+ have regional lymph nodes positive for cancer.

Missing Data

Missing data for covariates were imputed using "on the fly" random forest imputation[18] implemented in the open source randomForestSRC R package under default settings.[13]

RESULTS

Extent of Lymphadenectomy

Number of lymph nodes resected during esophagectomy for adenocarcinoma of the esophagus peaked between 15 and 17. Forty-nine patients had ≥50 nodes resected and 55 had 0 nodes resected.

TABLE 2. Clinical (c) and Post-Neoadjuvant Therapy Pathologic (yp) Cancer Characteristics

Characteristic	Clinical n*	Clinical No. (%)	Pathologic n*	Pathologic No. (%)
T	3605		3610	
T0		9 (0.25)		606 (17)
Tis		5 (0.14)		12 (0.33)
T1		122 (3.4)		555 (15)
T2		682 (19)		706 (20)
T3		2674 (74)		1656 (46)
T4		113 (3.1)		75 (2.1)
TX		254		249
N	3709		3859	
N0		1308 (35)		2078 (54)
N+		2401 (65)		1781 (46)
N1	75	55 (73)	1779	914 (51)
N2	75	18 (24)	1779	534 (30)
N3	75	2 (2.7)	1779	331 (19)
NX		150		2
M	3859		3859	
M0		3664 (95)		3664 (95)
M1		195 (5.1)		195 (5.1)
Grade†	1481		3443	
G1		40 (2.7)		695 (20)
G2		700 (47)		1212 (35)
G3		741 (50)		1536 (45)
G4		0 (0)		0 (0)
GX		2378		416
Location	3646		3646	
Upper		22 (0.6)		22 (0.6)
Middle		121 (3.3)		121 (3.3)
Lower		3503 (96)		3503 (96)
LocationX		213		213
Resection			3859	
R0		—		3404 (88)
R1		—		299 (7.7)
R2		—		156 (4.0)

*Patients with data available.

†G1 indicates well differentiated; G2, moderately well differentiated; G3, poorly differentiated; G4, undifferentiated; GX, unknown.

Among 16 institutions of the 22 that reported on ≥20 patients, the percentage of patients with ≥30 lymph nodes resected varied from 0% to 35%, median 12% (SDC Table 1, showing institutional volume and extent of lymphadenectomy, http://links.lww.com/SLA/B779). Extensive lymphadenectomy of ≥30 nodes varied according to surgical approach to esophagectomy: 4.2% (27/642 patients) during transhiatal esophagectomy, 14% (64/441 patients) during thoracoabdominal esophagectomy, 16% (106/678 patients) during minimally invasive esophagectomy, and 19% (357/1852 patients) during esophagectomy via thoracotomy, with transhiatal esophagectomy being significantly fewer than other approaches [P (Bonferoni adjusted) <0.0001].

Value of Lymphadenectomy

Across all ypT and ypN classifications, there was a predicted survival benefit of at least some degree of lymphadenectomy >0 nodes resected (Fig. 2), although in a nonlinear parabolic fashion (Figs. 3 and 4, and see SDC Fig. 2, http://links.lww.com/SLA/B779, which shows predicted lifetime across all ypT categories and 4 groups of number of lymph nodes resected for ypN0M0 cancers; and SDC Fig. 3, http://links.lww.com/SLA/B779, which shows the same data for ypN+ cancers). Increasing number of lymph nodes resected was associated with a gain in lifetime up to a point, after which a decrease in lifetime was observed for both ypN0 and ypN+ cancers (Fig. 2). Overall survival was 98.2% and 98.1% at 30 days for both ypN0 and ypN+ patient cohorts, respectively, highest for the 55 with no nodes resected (SDC Table 2, http://links.lww.com/SLA/B779, showing 30-day mortality according to extent of lymphadenectomy).

Lymphadenectomy in ypN0M0 Cancers

For patients with ypN0 cancers, there was a predicted gain up to 20 months in potential lifetime associated with up to 25 lymph nodes resected. This is illustrated in Figure 3 and SDC Figure 2, http://links.lww.com/SLA/B779, panels M-P, from which Figure 3 was extracted, for ypT0, ypT1, ypT2, and ypT3/4 patients who actually had between 18 and 25 regional lymph nodes resected.
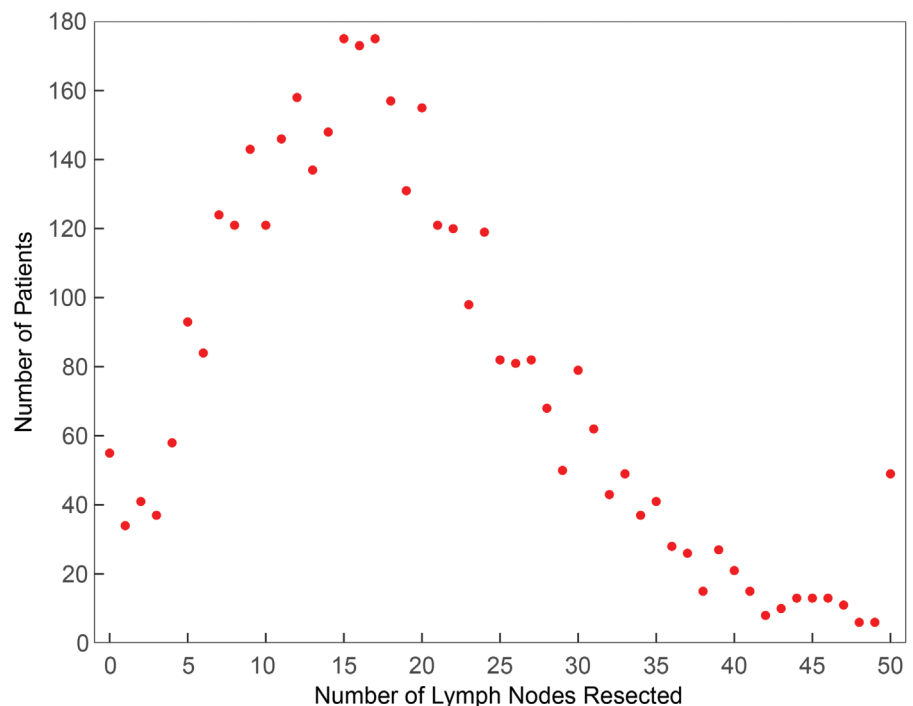
FIGURE 1. Extent of lymphadenectomy. Each dot depicts number of patients with that number of lymph nodes resected. Last dot represents ≥50 nodes resected. Of the 3859 patients, 55 (1.4%) had 0 nodes resected; 735 (19%) had 1 to 9; 1521 (39%) had 10 to 19; 976 (25%) had 20 to 29; 523 (14%) had 30 to 49; and 49 (1.3%) had ≥50.
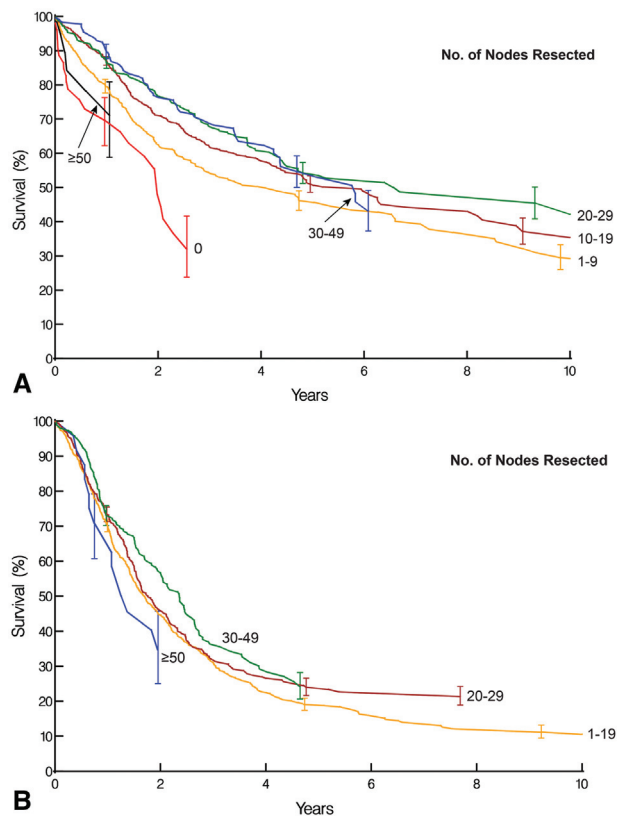
FIGURE 2. Non–risk-adjusted survival stratified by number of lymph nodes resected. Symbols represent deaths and vertical lines asymmetric confidence intervals equivalent to ±1 standard error. A, ypN0M0 cancers with survival stratified by 0, 1 to 9, 10 to 19, 20 to 29, 30 to 49, and ≥50 nodes resected. These curves show the value of >0 nodes resected, increasing survival until 20 to 29 are resected, and decreasing survival for more extensive lymphadenectomy. B, ypN+MO cancers with survival stratified by 1 to 19, 20 to 29, 30 to 49, and ≥50 nodes resected. Survival is lowest when 1 to 19 nodes are resected, somewhat higher when 20 to 29 nodes are resected, but somewhat lower when more nodes are resected.

However, with a potentially larger number of nodes resected, particularly >30, potential lifetime for these "what if" scenarios decreased up to 30 months (see SDC Fig. 2, http://links.lww.com/SLA/B779, which illustrates this pattern of loss of lifetime).

This pattern was least pronounced among patients with ypT0N0 cancers (complete response) across all ranges of actual lymph nodes resected (see SDC Figure 2, http://links.lww.com/SLA/B779, panels A, E, I, M, and Q, which demonstrate this). For patients with residual advanced adenocarcinoma (ypT3/4), the relationship was similarly blunted (see SDC Figure 2, http://links.lww.com/SLA/B779, panels D, H, L, P and T, which illustrate this). The peaking parabolic pattern was most pronounced among ypT1N0 and ypT2N0 cancers.

Lymphadenectomy in ypN+M0 Cancers

For patients with ypN+ cancers, there was a substantial predicted gain in lifetime associated with about 30 lymph nodes resected, often 20 more months. This is illustrated in Figure 4 and

SDC Figure 3, http://links.lww.com/SLA/B779, panels Q-T, from which Figure 4 was extracted for ypT0, ypT1, ypT2, and ypT3/4 patients who actually had 22 to 29 lymph nodes resected. However, with a potentially larger number of nodes resected beyond 30 (see SDC Fig. 3, http://links.lww.com/SLA/B779, panels Q-T, which illustrate this pattern), potential lifetime for these "what if" cancers decreased.

The decrement in lifetime was blunted in patients with ypT0N+ cancers but robust in higher T categories (see SDC Fig. 3, http://links.lww.com/SLA/B779, panels A, E, I, M, and Q and panels D, H, L, P, and T). The pattern of incremental increase in lifetime up to a point, followed by a decrement, held true for patients with 1 to 2 positive lymph nodes as well as for those with ≥3 positive nodes (see SDC Fig. 3, http://links.lww.com/SLA/B779, green and red dashed lines), although lifetime was substantially shortened when ≥3 nodes were positive.

DISCUSSION

Principal Findings

Based on worldwide data for adenocarcinoma of the esophagus and esophagogastric junction across all post-induction (ypTNM) cancer categories, some degree of lymphadenectomy was found to be associated with longer lifetime, but in a nonlinear parabolic fashion. Increasing number of lymph nodes resected was associated with a gain in lifetime up to a point, after which there was progressive loss in lifetime for both ypTN0 and ypTN+ cancers. For patients with ypN0 cancers, an incremental potential gain in lifetime was predicted for up to 25 lymph nodes resected, and an incremental decrease when a more extensive lymphadenectomy was performed, most pronounced in ypT1−2. For patients with ypN+ cancers, a similar gain in lifetime was predicted for up to about 30 nodes resected, followed by an incremental decrease in lifetime. Given the low perioperative mortality, these findings are not explained by early adverse events. Nor was this finding owing to results at a small number of institutions, as most institutions performed extensive lymphadenectomy in a reasonable number of patients.

Value of Lymphadenectomy in Neoadjuvant Therapy

The role of lymphadenectomy in treatment-naïve patients undergoing esophagectomy alone is not in debate, but the role of lymphadenectomy after induction therapy is largely unknown, with a paucity of data that is contradictory. Using the National Cancer Database (NCDB), Samson et al[2] evaluated 18,777 patients undergoing esophagectomy and found that lymphadenectomy was limited (<15 lymph nodes resected) in almost 63% of patients having lymphadenectomy. Among those undergoing esophagectomy after induction therapy, patients who had ≥15 lymph nodes resected had a survival benefit compared with those who had fewer nodes resected. In the same year, Giugliano et al[3] noted that among 174 patients at their institution undergoing esophagectomy after induction chemoradiotherapy, resection of <15 lymph nodes did not affect survival. Both studies used specific lymph node resection cutoff values (greater or less than 15 lymph nodes), with some analyses assessing the hazard ratio in 5-lymph-node increments.

Along this line, an analysis of patients in the CROSS trial found no prognostic effect of extent of lymphadenectomy after induction therapy.[19] This finding may be due to the relatively small number of patients (159 vs 3859) compared with our study. More plausible, based on the parabolic relationship of risk-adjusted survival to extent of lymphadenectomy we have found, is that the assumed linear relationship of survival to number of nodes resected in that analysis was incorrect (model misspecification). It is known
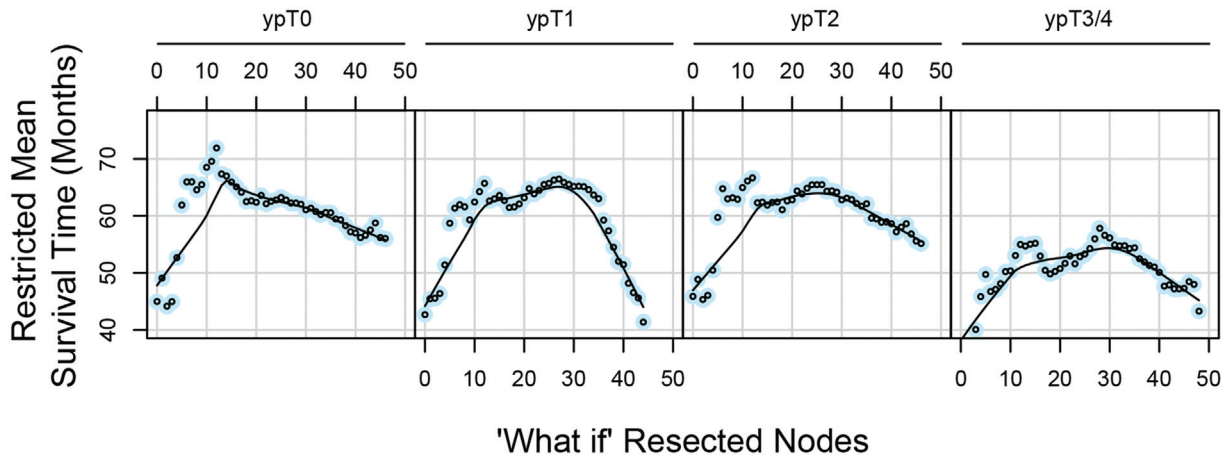
FIGURE 3. Restricted mean survival time in months for patients with ypN0M0 cancers who had 18 to 25 regional lymph nodes resected. Along the horizontal axis is potential ''what if'' number of resected nodes, and panels represent ypT categories with ypT3 and ypT4 combined. Each dot represents a minimum of 10 patients. Patients with ypT3 and ypT4 cancers have been combined. These curves are panels I–L of Supplemental Digital Content Figure 2, http://links.lww.com/SLA/B779.

that a parabolic relationship, particularly a symmetrical one, will show no linear effect. In contrast to this method, we examined the effect of number of lymph nodes resected as a discrete whole-number variable using nonparametric machine learning without any assumption of the shape of the relationship, examining the effect on survival of each number of nodes resected based on both the actual number of nodes resected and on counterfactual ''what if'' scenarios for number of nodes resected in an ''individual treatment effect'' causal inference framework. With this we were able to quantify the survival benefit of lymphadenectomy and describe the shape of the relationship of survival to extent of lymphadenectomy. Use of nonparametric machine learning for the present analysis, and those leading to the staging recommendations for both the 7th and 8th editions of the AJCC/UICC cancer staging manuals, was in recognition of nonlinear relationships of survival to TNM and nonanatomic cancer

characteristics along with strong interactions that are difficult to tease out with traditional statistical methods.[20–22]

Optimum Lymphadenectomy During Neoadjuvant Therapy

We also report both an incremental survival benefit of more resected nodes and a survival decrement when lymphadenectomy is too extensive. This finding was generally pervasive across all ypT stages and among groups with a variable actual number of lymph nodes resected.

Fewer lymph nodes are resected during esophagectomy in patients who have undergone induction therapy compared with those who undergo esophagectomy alone.[3] Speculatively, this may be due to fibrosis of lymph nodes from induction therapy, specifically radiotherapy.[3,23] These studies have been used to
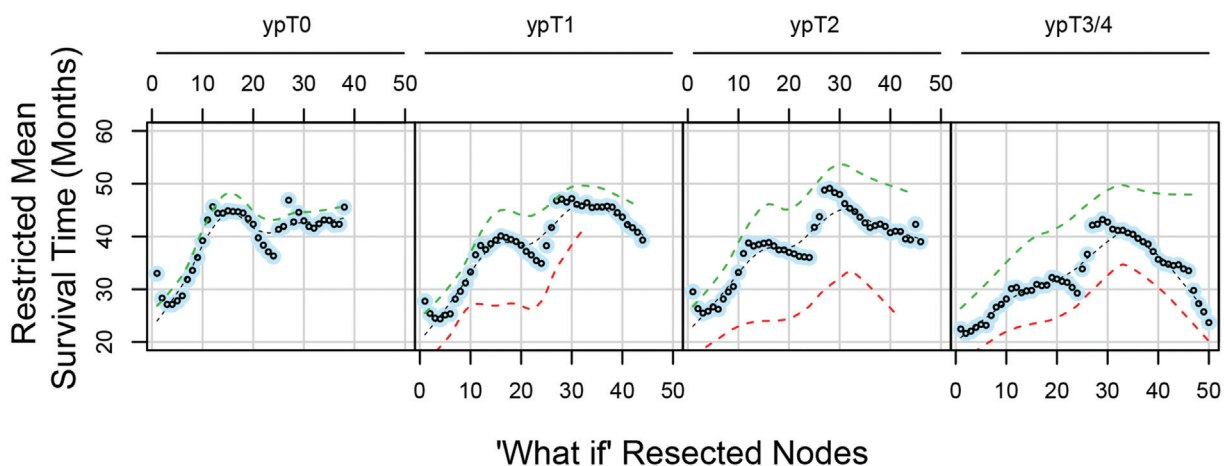
FIGURE 4. Restricted mean survival time (RMST) in months for patients with ypN+ cancers who had 22 to 29 regional lymph nodes actually resected. Along the horizontal axis is potential ''what if'' number of lymph nodes, and panels represent ypT categories, with ypT3 and ypT4 combined. Each dot represents a minimum of 10 patients. Black dashed line is a loess fit to data, green dashed lines show RMST loess fits for patients with 1 or 2 positive lymph nodes, and red dashed lines show loess fits for patients with ≥3 positive nodes. These curves are panels M-P in Supplemental Digital Content Figure 3, http://links.lww.com/SLA/B779.

justify lymph node counts as low as a median of 8 nodes resected. Our data suggest that when few lymph nodes are resected, there is a survival decrement, albeit not as great as lymphadenectomy at the opposite extreme.

Rizk et al[1] defined specific optimum lymph node counts per pT stage for esophagectomy alone in treatment-naïve patients. Our study shows that after induction therapy, such granularity by ypT stage is not needed. Specifically, that study recommended resecting 29 to 50 lymph nodes to maximize survival of patients with pT3/4 cancers. The present study shows that after induction therapy, there is a decrement, not a maximization, of survival with that great an extent of lymphadenectomy.

There is a stark contrast between the benefit of lymphadenectomy in treatment-naive (esophagectomy-only) patients and that in those who have undergone induction therapy. In patients experiencing a complete response (ypT0N0M0), extent of lymphadenectomy seems to have a limited correlation with survival. However, when residual disease is present (particularly ypN+), there is a benefit of more extensive lymphadenectomy up to a point. The decrement in survival with more extensive lymphadenectomy beyond about 30 nodes is a novel finding. The mechanism for the decrement is unclear. One can speculate that extensive lymphadenectomy occurs during radical resection, which might have increased morbidity; the WECC database lacks granularity to further examine this possibility. However, 30-day mortality was <2% in both N0 and N+ groups, and much of this mortality occurred in patients recorded as having no nodes resected. When zero lymph nodes were resected, one could speculate that the reasons may have been related to intraoperative complications or to findings that led to a palliative esophagectomy where oncological principles could not be followed.

Limitations

Data used in this analysis reflected real-world therapy for adenocarcinoma of the esophagus or esophagogastric junction from every inhabited continent[4]; however, such a multicontinent, multinational, multi-institutional database is limited by lack of protocol standardization among institutions regarding extent of lymphadenectomy and pathologic review of the resection specimen. The method for counting lymph nodes resected may be institution-specific, and some pathology laboratories may not have been as fastidious as others, thereby providing an artificially low count. The measure of optimum lymphadenectomy was risk-adjusted all-cause mortality. Despite the high lethality of esophageal cancer, all-cause mortality likely included a few noncancer deaths. Nevertheless, it is a reliable endpoint, and when adjusted for comorbidities as in this study, may be more reliable than disease-specific survival[24,25]; it is also the basis for most cancer staging.[26,27] We did not have morbidity information according to extent of lymphadenectomy, although 30-day mortality was low overall.[4] Although the analyses performed in this study were within a machine-learning causal framework, the findings still represent correlations, not a causal relationship. We have no plausible biologic explanation for the nonlinear parabolic relationship identified.

Finally, a limitation of a study in which lymph node counts are recommended is that such information is available only after the fact. Intraoperatively, it is not possible to specifically count lymph nodes and stop at a certain point. The recommendations are meant to provide quality metrics for surgeons, pathologists, and programs to set benchmarks and to monitor frequency of outliers.

Recommendations

National Comprehensive Cancer Network guidelines suggest 15 lymph nodes as a number to optimize survival, and our data would suggest a higher number, up to 25 to 30 lymph nodes (https://www.nccn.org/professionals/physician_gls/default.aspx#site).

Knowing the value of the adequacy of lymph node counts allows one to set programmatic benchmarks for these counts and increase the fastidiousness of both surgeon and pathologist. At Cleveland Clinic, we addressed the issue of adequacy of lymphadenectomy by deliberately sampling various lymph node stations, sending these as separate specimens for pathologic analysis. During discussions of the pathology of the cancer in tumor board meetings, number of lymph nodes resected is reported.

CONCLUSIONS

Lymphadenectomy should be performed in all esophageal resections after induction therapy because there is a survival benefit in doing so. Based on analysis of worldwide data, for the purpose of maximizing survival, we recommend the minimum bar for lymphadenectomy be raised from the commonly accepted 15 lymph nodes to a number closer to 25 to 30 nodes.

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Appendix 1. Worldwide Esophageal Cancer Collaboration: Participating Institutions and Investigators

Institution	Location	Investigators
Beijing Cancer Hospital, Peking University	Beijing, China	Ken N. Chen
Cleveland Clinic	Cleveland, OH	Thomas W. Rice Eugene H. Blackstone
Case Western Reserve University	Cleveland, OH	Carolyn Apperson-Hansen
Erasmus Medical Center	Rotterdam, The Netherlands	Bas P.L. Wijnhoven Jan van Lanschot Sjoerd Lagarde
Fourth Hospital of Hebei Medical University	Shijiazhuang, Hebei; China	Jun-Feng Liu
Fox Chase Cancer Center	Philadelphia, PA	Walter J. Scott Donna Edmondson
Groote Schuur Hospital, University of Cape Town	Cape Town, South Africa	Riette Burger
Guy's & St. Thomas' Hospitals	London, UK	Andrew R. Davies Janine Zylstra
Helsinki University Hospital	Helsinki, Finland	Jari V. Räsänen Jarmo A. Salo Yvonne Sundstrom
Hospital Universitario del Mar	Barcelona, Spain	Manuel Pera
Hôpital Nord	Marseille, France	Xavier B. D'Journo
Indiana University Medical Center	Indianapolis, IN	Kenneth A. Kesler
University of Texas MD Anderson Hospital	Houston, TX	Wayne L. Hofstetter Arlene Correa Stephen G. Swisher
Mayo Clinic	Rochester, MN	Mark S. Allen
Medical University of South Carolina	Charleston, SC	Chad E. Denlinger
Memorial Sloan-Kettering Cancer Center	New York, NY	Valerie W. Rusch
University of Queensland, Princess Alexandra Hospital	Brisbane, Australia	B. Mark Smithers David Gotley Andrew Barbour Iain Thomson
University of Newcastle upon Tyne	Newcastle upon Tyne, UK	S. Michael Griffin Jon Shenfine
Oregon Health & Science University	Portland, OR	Paul H. Schipper John G. Hunter
Royal Marsden NHS Foundation Trust	London, UK	William H. Allum
Shanghai Chest Hospital	Shanghai, China	Wentao (Vincent) Fang
Toronto General Hospital	Toronto, ON; Canada	Gail E. Darling
University Zeikenhuizen Leuven	Leuven, Belgium	Tony E.M.R. Lerut Phillipe R. Nafteux
University Medical Center Utrecht	Utrech, The Netherlands	Richard van Hillegersberg
University of Alabama at Birmingham	Birmingham, AL	Robert J. Cerfolio
Hospital de Clinicas, University of Buenos Aires	Buenos Aires, Argentina	Luis Durand Roberto De Antón
The University of Chicago, Department of Surgery	Chicago, IL	Mark K. Ferguson
University of Hong Kong Medical Center, Queen Mary Hospital	Hong Kong, China	Simon Law
University of Michigan	Ann Arbor, MI	Mark B. Orringer Becky L. Marshall
University of Montreal	Montreal, Quebec; Canada	André Duranceau Susan Howson
University of Pittsburgh Medical Center	Pittsburgh, PA	James D. Luketich Arjun Pennathur Kathy Lovas
University of Rochester	Rochester, NY	Thomas J. Watson
University of São Paulo	São Paulo, Brazil	Ivan Cecconello
West China Hospital of Sichuan University	Chengdu, Sichuan; China	Long-Qi Chen