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Extent of lymphadenectomy and prognosis after esophageal cancer surgery

Running head: Lymphadenectomy and esophageal cancer

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Abstract

Importance: The prognostic role of the extent of lymphadenectomy during surgery for esophageal cancer is uncertain and requires clarification.

Objective: We aimed to clarify whether the number of removed lymph nodes influences mortality following surgery for esophageal cancer.

Design: This was a cohort study of patients who underwent esophagectomy for cancer in 2000-2012 at St Thomas' Hospital London, with follow-up until 2014.

Setting: A high-volume hospital for esophageal cancer surgery, St Thomas' Hospital in London, United Kingdom.

Participants: Consecutive patients with esophageal cancer who underwent surgical resection at the hospital.

Exposures: The main exposure was number of resected lymph nodes. Secondary exposures were number of metastatic lymph nodes and positive-to-negative lymph node ratio.

Main outcome measure: The independent role of the extent of lymphadenectomy in relation to all-cause and disease-specific 5-year mortality was analyzed using Cox proportional hazard regression models, providing hazard ratios (HR) with 95% confidence intervals (CI). The HRs were adjusted for age, pathological T-stage, tumor differentiation, margin status, calendar period of surgery, and response to pre-operative chemotherapy.

Results: Among 606 included patients, the extent of lymphadenectomy did not statistically significantly influence all-cause or disease-specific mortality, independent of the categorization of lymphadenectomy or stratification for T-stage, calendar period, or chemotherapy. Patients in the 4^{th} quartile of number of removed nodes (21-52 nodes) did not demonstrate statistically significantly reduction in all-cause 5-year mortality compared with those in the lowest quartile (0-10 nodes) (HR=0.86, 95% CI 0.63-1.17), particularly not in

the most recent calendar period (HR=0.98, 95% CI 0.57-1.66 years 2007-2012). A greater number of metastatic nodes and a higher positive-to-negative node ratio predicted strongly increased mortality rates, and these associations showed dose-response associations.

Conclusions and Relevance: This cohort study indicates that the extent of lymphadenectomy during surgery for esophageal cancer might not influence the 5-year all-cause or disease-specific survival. These results challenge current clinical guidelines.

Introduction

Esophageal cancer is the 6th most common cause of cancer death globally,[1] and the incidence of esophageal adenocarcinoma is increasing while the prognosis remains poor (<15% 5-year survival).[2] Curatively intended treatment with surgery, typically preceded by oncological therapy,[3] offers a limited (30%) chance of 5-year survival.[4,5] The optimal extent of lymphadenectomy is controversial and requires clarification.[5-9] Esophageal cancer spreads readily in a multidirectional fashion through the extensive submucosal lymphatics that drain the esophagus, and the presence of metastatic lymph nodes are the strongest known prognostic factors.[5] This implies that more extensive lymphadenectomy should improve survival. On the other hand, it is still unclear whether the more extensive removal of regional (metastatic or not) nodes actually contributes to the cure of esophageal cancer patients. There is a possible trade-off between the potential survival benefit with more extensive lymphadenectomy and a decreased postoperative morbidity with less extensive lymphadenectomy.[5-9] Although based on a limited number of studies with methodological concerns with stage migration and confounding, current clinical guidelines recommend 2-field (extensive) lymphadenectomy.[6,7,10] Yet, in routine clinical practice the limited scientific knowledge leaves it up to the discretion of the individual surgeon to decide the preferred extent of lymphadenectomy.[8,9] The present study was prompted by the lack of survival benefit from a more extensive lymphadenectomy in our recent population-based Swedish cohort study.[11] Here, we aimed to test whether the results of that previous study replicated using another design and based on another population. Here we used a prospective and comprehensive clinical data collection from a high-volume surgery center in London with surgeons and pathologist specialized in the field of esophageal cancer.

Methods

Study design

This cohort study included all surgically treated esophageal cancer patients at a high-volume center in London, United Kingdom (St Thomas' Hospital) between 2000 and 2012, with follow-up until January 2014. An earlier version of this cohort has been used in previous publications.[12,13] In brief, all operated patients with esophageal cancer were followed up until death or the end of the study period, whichever occurred first. The main study exposure was the number of removed lymph nodes. Secondary study exposures were the number of metastatic lymph nodes and the ratio of metastatic to total number of lymph nodes. The outcomes were all-cause and disease-specific 5-year mortality. The 5-year cut-off was used since deaths occurring later are usually not due to tumor recurrence.[4] Ethical approval was granted for use of the database.

Surgery

The main surgical approaches were transhiatal or transthoracic (open or minimally invasive) esophagectomy. The preferred esophageal substitute was gastric conduit, anastomosed to the proximal esophagus in the thorax or neck. There were three consultant surgeons conducting the operations during the study period. There was no consensus about the preferred extent of lymphadenectomy.

Histopathology

All resected tumors underwent careful review by a consultant specializing in upper gastrointestinal histopathology. Tumor stage was classified according to the 7th edition of the American Joint Committee on Cancer TNM staging system.[14] Pathologic tumor regression

following pre-operative chemotherapy was assessed according to the Mandard scoring system, ranging from 1 (complete response) to 5 (no response).[15] In this study, the Mandard score was dichotomized, as planned a priori, into a "good" (scores of 1-3) or "poor" (scores of 4-5).

Statistical analysis

Cox proportional hazard modelling was used to analyze associations between the three lymphadenectomy exposure variables (total number of lymph nodes, number of positive lymph nodes and ratio of positive and total number of lymph nodes) and the two mortality outcomes (time to all-cause and disease-specific mortality with 5 years of follow-up). The categorization of total number of removed nodes into decentiles and quartiles was planned before any analyses were initiated. Since there were no dose-response associations between the total number of removed lymph nodes and mortality in the analysis using decentiles, we found it inappropriate to analyze the total number of lymph nodes as an ordinal variable. Thus, we only analyzed the total number of lymph nodes as a categorical variable. The current version of the N-coding system was used to categorize the number of positive lymph nodes (0, 1-2, 3-6, or >6).[16] The ratio of positive and total number of lymph nodes was categorized into four groups (decided before analyses), where the 0 ratio was categorized into one group, and the rest of data split into tertiles. The first group (lowest lymph node harvest, no metastatic nodes and metastatic to non-metastatic ratio of 0) was used as the reference for all lymphadenectomy variables. Hazard ratios (HR) with 95% confidence intervals (CI) were derived from the model. HRs were presented as unadjusted and adjusted for six pre-defined potential confounding factors: 1) age (continuous variable); 2) pathological T-stage (categorized a priori into 2 groups: T0-T2 or T3-T4); 3) tumor grade (3

groups: high-grade dysplasia and well-differentiated, moderately differentiated or poorly differentiated); 4) margin status (2 groups: R0 or R1/R2 [within 1 mm from the circumferential margin]); 5) response to pre-operative chemotherapy (3 groups: not applicable, good response [Mandard score 1–3], or poor response [Mandard score 4–5]); 6) calendar period (2 groups: years 2000-2006 or 2007-2012). Furthermore, we evaluated if the adjusted HRs for the lymphadenectomy variables were modified by T-stage (T0-T2 or T3-T4), calendar period (2000-2006 or 2007-2012) or response to chemotherapy (not applicable, good, or poor) using a product term in the regression models. The HRs and CIs were derived by the hazard ratio statement in the model. Furthermore, nine more variables were created with a combination of each lymphadenectomy exposure and T-stage (T0-T2 or T3-T4), calendar period (2000-2006 or 2007-2012), and response to chemotherapy (not applicable, good, or poor). These stratified analyses were conducted as a potential survival benefit with more extensive node removal might be higher in more advanced tumors,[17] as treatment might change over calendar time and as chemotherapy and the response to it might influence any survival benefits of more extensive lymphadenectomy. To manage partial missing data for Mandard scores (5.3% of the patients had missing data) both complete case analysis and multiple imputation were conducted. The imputation variables were categorized as presented above and included age, pathological T-stage, tumor grade, margin status, response to pre-operative chemotherapy, and all-cause mortality. The number of imputed data sets was 20 and monotone logistic method in PROC MI was used under the assumption that the missing data were missing at random (MAR).[18] PROC MIANALYZE was used to combine the results from the analyses of the 20 datasets. Since the results were similar between the two missing values approaches, we decided to present only HRs and CIs

from the multiple imputation. To avoid influence of collinearity of the exposure variables, these variables were analysed separately without adjusting for any of the other.

To validate the results, we performed a sensitivity analysis by calculating propensity scores. Logistic regression with generalized logit function was used with total number of lymph nodes in quartiles and the six covariates in the model. The distribution of propensity score by outcome group was similar. The propensity scores divided into quintiles were then used in the Cox proportional hazard model as a covariate by each pair of the total number of lymph nodes comparison. The data management and statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Patient characteristics

The study included 606 patients, the majority with a diagnosis of adenocarcinoma of the esophagus (83.5%) while fewer patients had squamous cell carcinoma (15.2%) or adeno-squamous carcinoma (1.3%) of the esophagus. Characteristics of these participants, in total and split into quartiles by the extent of lymphadenectomy, are presented in Table 1. Among 323 (53%) patients who died within 5 years of surgery, 235 (39%) died from tumor recurrence. The age distribution was similar between patients in the four lymphadenectomy categories. More advanced T-stages were slightly overrepresented in the higher two quartiles of lymphadenectomy, while well-differentiated tumors and tumors with high-grade dysplasia or complete pathological response were overrepresented in the lower two quartiles of lymphadenectomy. A higher proportion of patients received preoperative chemotherapy during the last calendar period (77% in 2000-2006) compared to the first calendar period (53% in 2007-2012). The lymph node yield was higher during the later calendar period than the earlier period. The median number of removed nodes during the entire study period was 14 (range 0-52). The in-hospital postoperative mortality was 3% (18 patients out of 606).

Lymph node variables and 5-year mortality

There was no dose-response association between lymphadenectomy levels and 5-year mortality when 10 or 4 categories of lymphadenectomy were assessed (Table 2). The crude HRs generally indicated a tendency of increased mortality, while the adjusted HRs generally indicated the opposite. It was mainly the adjustment for T-stage and tumor differentiation that decreased the HRs in the adjusted model (data not shown). However, none of the HRs

was statistically significant (Table 2). The adjusted HR for all-cause 5-year mortality in the highest quartile of lymphadenectomy (21-52 nodes) was 0.86 (95% CI 0.63-1.17) compared to the lowest quartile (0-10 nodes). There were strong dose-response associations between the number of metastatic nodes and mortality as well as the ratio of positive and total number of lymph nodes and mortality (Table 2). There were generally no major differences between all-cause and disease-specific 5-year mortality (Table 2).

Lymph node variables and T-stage specific 5-year mortality

No statistically significant associations were found in the analysis stratified for T-stages (Table 3). However, the HRs for all-cause 5-year mortality were slightly lower with more extensive lymphadenectomy in more advanced tumors (T3-T4) (HR 0.80, 95% CI 0.54-1.19 in the 4^{th} quartile) compared to the less advanced tumors (T0-T2) (HR 0.96, 95% CI 0.58-1.60 in the 4^{th} quartile). The prognostic influence of metastatic nodes and the ratio of positive and total number of lymph nodes were of similar strength in less and more advanced T-stages (Table 3). The HRs of disease-specific mortality did not differ much from those of the all-cause mortality (Table 3).

Lymph node variables and calendar period specific 5-year mortality

In analyses stratified by the calendar periods 2000-2006 and 2007-2012, no statistically significant associations were found between total lymphadenectomy and all-cause or disease-specific 5-year mortality (Table 4). The point HRs of total lymphadenectomy during the earlier period were slightly decreased, while the HRs were close to 1 in the more recent calendar period (Table 4). The HR of all-cause mortality was 0.98 (95% CI 0.57-1.66) in the highest quartile of lymphadenectomy compared to the lowest during the more recent period

(2007-2012). The associations between the number of metastatic nodes and mortality, as well as the ratio of positive and total number of lymph nodes and mortality, were stronger during the later calendar period compared to the earlier, and the disease-specific HRs were higher compared to the all-cause HRs (Table 4). The highest quartiles of metastatic nodes (>6) and lymph node ratio (>0.37) had HRs of 6.00 (95 % CI 2.83-12.7) and 7.12 (95 % CI 3.47-14.6), respectively, compared to the corresponding lowest quartiles (0 and 0).

Lymph node variables and 5-year mortality following chemotherapy response

The analyses stratified for pre-operative chemotherapy revealed no statistically significant associations between the extent of lymphadenectomy and mortality in any of the stratification categories (Table 5). The HRs of mortality were close to 1 in the non-chemotherapy group (all-cause HR 1.03, 95% CI 0.56-1.90 and disease-specific HR 0.97, 95% CI 0.46-2.06, comparing the highest and lowest quartiles). The HRs of mortality tended to be slightly decreased in both good and poor responders to pre-operative chemotherapy (Table 5). The number of metastatic nodes and the ratio of metastatic to all nodes were both strongly associated with risk of mortality in all three chemotherapy categories, but possibly even more so in the group of poor responders (Table 5).

Lymph node variables and 5-year mortality using other reference categories

The stratified results while using other reference categories are presented in a Supplementary Table. There was no influence of the total number of removed nodes on all-cause or disease-specific mortality, while metastatic nodes and the ratio of metastatic and all nodes were strongly prognostic. An additional analysis of the risk of mortality in patients in quartiles of total lymphadenectomy in each of the four categories of metastatic nodes

revealed no patterns of any decreased mortality with more extensive lymphadenectomy (data not shown).

The propensity score analysis resulted in similar risk estimates as in the Cox regression analysis, and therefore these results are not presented.

Discussion

This study did not provide any support for the notion that the extent of lymphadenectomy during surgery is a prognostic factor in esophageal cancer. Although most point risk estimates were decreased, the HRs were generally close to zero effect, and were particularly so for earlier T-stages, during the more recent calendar period and in patients who did not have pre-operative chemotherapy. A higher number of metastatic nodes and a higher ratio of positive and total number of lymph nodes were, as expected, strong and dose-dependent prognostic factors.

Some methodological issues merit attention before moving on to discuss the findings of the present study. The cohort design is the best available for studies specifically addressing in detail the effects of the number of removed lymph nodes. It is not feasible to randomize patients into numerous categories of lymphadenectomy, and thus an interventional study design is not an option for this purpose. An additional strength is the exclusive inclusion of patients operated on at a high-volume center, avoiding potential bias resulting from differential surgical skills and experience. A potential concern is that the pathological assessment of removed lymph nodes is dependent on the experience and interest of the responsible pathologist, which could introduce exposure misclassification and dilutions of associations. A major strength was therefore that only highly specialized and dedicated upper gastrointestinal pathologists performed these assessments in all patients included in this study. The strong associations between identified metastatic nodes and prognosis confirm the validity of the pathological nodal assessment. The outcome mortality was completely and accurately assessed for all patients since there were no losses to follow-up in this single-center study, where all patients were followed up routinely for at least 5 years

following surgery. Bias from confounding can never be excluded in an observational study, but the ability to adjust the results for all known strong prognostic factors counteracts confounding. Since we could not enlarge this study and had data from our previous study,[11] we did not perform any sample size calculations. Despite the large sample, chance might be a concern since the power to verify weak associations was limited, particularly in the stratified analyses. However, the overall results showed no dose-response associations between total lymphadenectomy and mortality independent of various categorizations and stratifications, and the HRs were generally close to unity, particularly during the more recent calendar period. Finally, the multi-ethnic population of London suggests that the results might be generalizable.

The lack of any clearly decreased mortality with more extensive lymphadenectomy in this study supports the findings of our recent study on this topic.[11] That study included 1,044 patients and from Sweden, and found no decreased mortality following a more extensive lymphadenectomy (HR 1.00, 95% CI 0.99-1.01 when number of removed nodes were analyzed as a continuous variable).[11] These results challenge clinical guidelines recommending 2-field lymphadenectomy. The scientific evidence supporting more extensive lymphadenectomy (2-field or even 3-field lymphadenectomy) is limited and the topic is controversial.[5-9] Our findings are contradictory to those of a study using data from a consortium of institutions, where a greater extent of lymphadenectomy was followed by better survival,[17] and in a meta-analysis comparing 2-field or even 3-field lymphadenectomy that indicated better 5-year survival rates with 3-field dissection.[19] However, these findings were derived from studies that might be hampered by stage migration issues, since a more extensive lymph node yield tends to result in a more accurate assessment of metastatic

nodes and thus higher tumor stage. Moreover, confounding, e.g. by the known prognostic factor of surgeon volume is a threat to these studies,[20] since more experienced surgeons tend to remove more nodes. In our study, all surgeons had a similarly high annual volume of esophagectomies, which offers good control of that potential confounding factor. Our results are supported by some well-designed studies that found no survival difference between a more extensive lymphadenectomy via transthoracic esophagectomy and a more limited lymphadenectomy by a transhiatal approach; a large Dutch randomized clinical trial,[21,22] our recent cohort study,[13] and a meta-analysis of 52 studies.[23] Moreover, a randomized clinical trial comparing 2-field with 3-field lymphadenectomy found no difference in survival.[24]

Presence of metastatic lymph nodes and a high lymph node ratio strongly predicted survival in this study, which confirms the results of previous studies.[14] These findings highlight the relevance of not only considering the presence or absence of metastatic nodes, but also the number of involved nodes in the prediction of prognosis.[25] Thus, a limited level of lymphadenectomy provides a good basis for prognosis prediction.

The results of this study indicate a need for further research addressing the value of more and less extensive lymphadenectomy, e.g. a multi-site interventional study comparing wide excision of lymph nodes versus standard excision. Yet, it might be justified to compare the results of this study with the developments in lymphadenectomy during surgery for other tumors. In breast cancer, the previously advocated more extensive lymphadenectomy did not improve survival,[26] but increased morbidity.[27] As a result, a less extensive and more tailored approach to lymphadenectomy has been adopted. A similar development has been

seen in the treatment of endometrial cancer.[28,29] Among other gastrointestinal cancers, recent meta-analyses reveal no evident survival benefits with extended lymphadenectomy during surgery for pancreatic, gastric or rectal cancer.[30-33] It is possible that lymphadenectomy does not improve survival in esophageal cancer simply because positive nodes represent a disseminated disease, while non-metastatic nodes do not need to be removed.

In conclusion, this cohort study with adjustment for prognostic factors from a dedicated esophageal cancer center suggests that the extent of lymphadenectomy does not influence survival after surgery for esophageal cancer. These results challenge current guidelines and need confirmation in further research.

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Table 1. Characteristics of 606 patients who underwent esophagectomy for cancer in 2000-2012.

Characteristics	**Categorization**	**Total cohort**	**Total lymph nodes removed in quartiles** [range]			
			I [0-10]	**II** [11-14]	**III** [15-20]	**IV** [21-52]
		N (%)	N (%)	N (%)	N (%)	N (%)
Total		606 (100)	166 (27)	139 (23)	151 (25)	150 (25)
5-year mortality	All-cause	323 (53)	87 (52)	69 (50)	86 (57)	81 (54)
	Disease-specific	235 (39)	67 (40)	52 (37)	59 (39)	57 (38)
Age (years)	Median [range]	64 [29-83]	63 [29-80]	64 [38-83]	64 [34-83]	65 [32-81]
T-stage	T0-T2	311 (51)	90 (54)	77 (55)	72 (48)	72 (48)
	T3-T4	295 (49)	76 (46)	62 (45)	79 (52)	78 (52)
Tumor differentiation	Well*	71 (12)	26 (16)	18 (13)	13 (9)	14 (9)
	Moderate	331 (55)	85 (51)	75 (54)	92 (61)	79 (53)
	Poor	204 (34)	55 (33)	46 (33)	46 (30)	57 (38)
Resection	R0	340 (56)	88 (53)	82 (59)	88 (58)	82 (55)
	R1 or R2†	266 (44)	78 (47)	57 (41)	63 (42)	68 (45)
Mandard score‡	1, 2 or 3	163 (27)	36 (22)	35 (25)	41 (27)	51 (34)
	4 or 5	196 (32)	28 (17)	50 (36)	58 (38)	60 (40)
	NA	215 (35)	84 (51)	50 (36)	45 (30)	36 (24)
	Missing	32 (5)	18 (11)	4 (3)	7 (5)	3 (2)
Calendar period	2000-2006	367 (61)	126 (76)	88 (63)	79 (52)	74 (49)
	2007-2012	239 (39)	40 (24)	51 (37)	72 (48)	76 (51)

* This category includes tumors that are well-differentiated, high-grade dysplasia or complete pathological response to pre-operative chemotherapy.
† Circumferential resection margin <1mm from the tumor.
‡ Grading of response to pre-operative chemotherapy, where scores 1-3 represent good to moderate response, 3-4 represent poor or no response and NA represents the group where no pre-operative chemotherapy was given.

Table 2. All-cause and disease-specific 5-year mortality after esophageal cancer surgery in relation to lymph node variables, presented as hazard ratios (HR) with 95% confidence intervals (CI).

Exposure	Patients	5-year all-cause mortality		5-year disease-specific mortality	
	N (%)	Crude HR (95% CI)	Adjusted* HR (95% CI)	Crude HR (95% CI)	Adjusted* HR (95% CI)
Number of nodes (decentiles)					
0-6	76 (13)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
7-9	64 (11)	1.14 (0.71-1.82)	0.71 (0.44-1.16)	1.10 (0.65-1.87)	0.71 (0.41-1.23)
10-11	55 (9)	1.28 (0.80-2.05)	0.81 (0.49-1.32)	0.98 (0.56-1.73)	0.66 (0.37-1.19)
12-13	76 (13)	1.21 (0.77-1.89)	0.85 (0.54-1.35)	1.23 (0.75-2.02)	0.91 (0.55-1.53)
14-14	34 (6)	0.86 (0.46-1.58)	0.82 (0.44-1.52)	0.76 (0.37-1.55)	0.79 (0.38-1.64)
15-16	62 (10)	1.43 (0.91-2.25)	1.03 (0.65-1.64)	1.39 (0.84-2.31)	1.06 (0.63-1.79)
17-19	69 (11)	1.10 (0.70-1.74)	0.66 (0.41-1.06)	0.86 (0.50-1.49)	0.55 (0.31-0.97)
20-22	49 (8)	1.58 (0.98-2.57)	0.87 (0.52-1.43)	1.18 (0.66-2.11)	0.66 (0.36-1.22)
23-28	68 (11)	1.09 (0.69-1.73)	0.64 (0.39-1.04)	0.84 (0.49-1.46)	0.53 (0.30-0.95)
29-52	53 (9)	1.18 (0.72-1.92)	0.72 (0.43-1.20)	1.19 (0.69-2.04)	0.80 (0.45-1.41)
Number of nodes (quartiles)					
0-10	166 (27)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
11-14	139 (23)	0.98 (0.72-1.35)	0.93 (0.67-1.30)	0.96 (0.67-1.39)	0.94 (0.65-1.38)
15-20	151 (25)	1.16 (0.86-1.56)	0.93 (0.68-1.26)	1.03 (0.73-1.47)	0.85 (0.59-1.22)
21-52	150 (25)	1.07 (0.79-1.44)	0.86 (0.63-1.17)	0.97 (0.68-1.39)	0.83 (0.57-1.20)
Number of metastatic nodes					
0	274 (45)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1-2	136 (22)	2.75 (2.02-3.75)	2.04 (1.49-2.80)	3.34 (2.30-4.85)	2.45 (1.67-3.59)
3-6	116 (19)	4.90 (3.61-6.64)	2.82 (2.03-3.92)	5.99 (4.15-8.65)	3.32 (2.24-4.94)
>6	80 (13)	6.58 (4.74-9.14)	3.48 (2.43-4.98)	8.04 (5.42-11.9)	3.84 (2.50-5.91)
Ratio of metastatic to all nodes					
0	274 (45)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
0.02-0.14	111 (18)	2.56 (1.84-3.56)	1.84 (1.31-2.59)	3.01 (2.02-4.48)	2.23 (1.48-3.36)
0.15-0.37	111 (18)	3.98 (2.91-5.44)	2.46 (1.77-3.44)	4.81 (3.30-7.02)	2.79 (1.87-4.18)
>0.37	110 (18)	7.10 (5.25-9.61)	4.12 (2.95-5.77)	8.97 (6.24-12.9)	4.64 (3.11-6.95)

* Adjusted for age, pathological T-stage, tumor differentiation, margin status, response to pre-operative chemotherapy and calendar period.

Table 3. T-stage stratified mortality after esophageal cancer surgery in relation to lymph node variables, presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI)*.

Exposure	Number of patients		5-year all-cause mortality		5-year disease-specific mortality	
	T-stage		T-stage		T-stage	
	T0-T2	T3-T4	T0-T2	T3-T4	T0-T2	T3-T4
	N (%)	N (%)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Number of nodes (quartiles)						
0-10	90 (29)	76 (26)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
11-14	77 (25)	62 (21)	0.59 (0.33-1.04)	1.22 (0.82-1.82)	0.59 (0.29-1.19)	1.18 (0.75-1.85)
15-20	72 (23)	79 (27)	1.06 (0.64-1.76)	0.87 (0.59-1.28)	1.12 (0.60-2.10)	0.75 (0.48-1.18)
21-52	72 (23)	78 (26)	0.96 (0.58-1.60)	0.80 (0.54-1.19)	0.92 (0.48-1.76)	0.78 (0.50-1.23)
Number of metastatic nodes						
0	192 (62)	82 (28)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1-2	69 (22)	67 (23)	1.69 (1.07-2.68)	2.41 (1.55-3.74)	1.91 (1.07-3.41)	2.95 (1.76-4.96)
3-6	35 (11)	81 (27)	2.86 (1.70-4.79)	2.97 (1.93-4.55)	3.25 (1.69-6.24)	3.59 (2.16-5.96)
>6	15 (5)	65 (22)	3.15 (1.61-6.17)	3.77 (2.42-5.86)	3.46 (1.50-7.96)	4.22 (2.50-7.13)
Ratio of metastatic to all nodes						
0	192 (62)	82 (28)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
0.02-0.14	60 (19)	51 (17)	1.55 (0.95-2.53)	2.15 (1.34-3.45)	2.02 (1.11-3.66)	2.43 (1.38-4.29)
0.15-0.37	41 (13)	70 (24)	2.84 (1.72-4.68)	2.39 (1.53-3.71)	2.54 (1.30-4.94)	3.02 (1.80-5.07)
>0.37	18 (6)	92 (31)	3.43 (1.87-6.31)	4.43 (2.92-6.74)	3.94 (1.89-8.21)	5.07 (3.08-8.35)

* Adjusted for age, pathological T-stage, tumor differentiation, margin status, response to pre-operative chemotherapy and calendar period.

Table 4. Calendar period stratified mortality after esophageal cancer surgery in 2000-2006 and 2007-2012 in relation to lymph node variables, presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI)*.

Exposures	Number of patients		5-year all-cause mortality		5-year disease-specific mortality	
	Calendar period		Calendar period		Calendar period	
	2000-2006	2007-2012	2000-2006	2007-2012	2000-2006	2007-2012
	N (%)	N (%)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Number of nodes (quartiles)						
0-10	126 (34)	40 (17)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
11-14	88 (24)	51 (21)	0.80 (0.54-1.19)	1.32 (0.74-2.35)	0.87 (0.56-1.35)	1.22 (0.58-2.59)
15-20	79 (22)	72 (30)	0.88 (0.59-1.29)	1.09 (0.64-1.87)	0.77 (0.49-1.21)	1.07 (0.54-2.13)
21-52	74 (20)	76 (32)	0.83 (0.56-1.24)	0.98 (0.57-1.66)	0.81 (0.52-1.28)	0.93 (0.47-1.84)
Number of metastatic nodes						
0	173 (47)	101 (42)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1-2	89 (24)	47 (20)	2.10 (1.43-3.07)	1.96 (1.12-3.41)	2.56 (1.65-3.99)	2.19 (1.03-4.65)
3-6	59 (16)	57 (24)	2.48 (1.64-3.75)	3.37 (2.02-5.62)	3.07 (1.92-4.93)	3.83 (1.92-7.66)
>6	46 (13)	34 (14)	2.76 (1.77-4.30)	5.10 (2.91-8.96)	3.15 (1.90-5.22)	6.00 (2.83-12.7)
Ratio of metastatic to all nodes						
0	173 (47)	101 (42)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
0.02-0.14	64 (17)	47 (20)	1.97 (1.30-3.00)	1.78 (1.01-3.13)	2.41 (1.49-3.90)	2.03 (0.95-4.37)
0.15-0.37	59 (16)	52 (22)	1.94 (1.27-2.97)	3.50 (2.07-5.90)	2.46 (1.52-3.97)	3.66 (1.79-7.47)
>0.37	71 (19)	39 (16)	3.45 (2.32-5.13)	5.85 (3.40-10.1)	3.93 (2.49-6.22)	7.12 (3.47-14.6)

* Adjusted for age, pathological T-stage, tumor differentiation, margin status, response to pre-operative chemotherapy and calendar period.

Table 5. Mortality following stratification for chemotherapy response in patients undergoing esophageal cancer surgery in relation to lymph node variables, presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI)[1].

Exposures	Number of patients			5-year all-cause mortality			5-year disease-specific mortality		
	Chemotherapy response			Chemotherapy response			Chemotherapy response		
	Not applicable[2]	Good[3]	Poor[4]	Not applicable[2]	Good[3]	Poor[4]	Not applicable[2]	Good[3]	Poor[4]
	N (%)	N (%)	N (%)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Number of nodes									
0-10	84 (39)	45 (25)	37 (17)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
11-14	50 (23)	37 (21)	52 (24)	1.11 (0.64-1.95)	0.76 (0.37-1.57)	0.89 (0.52-1.50)	1.06 (0.54-2.06)	0.87 (0.41-1.87)	0.92 (0.49-1.71)
15-20	45 (21)	44 (25)	62 (29)	0.86 (0.48-1.54)	1.13 (0.60-2.14)	0.85 (0.51-1.40)	0.95 (0.49-1.85)	0.65 (0.28-1.50)	0.87 (0.48-1.58)
21-52	36 (17)	52 (29)	62 (29)	1.03 (0.56-1.90)	0.91 (0.50-1.67)	0.75 (0.45-1.24)	0.97 (0.46-2.06)	0.77 (0.38-1.54)	0.79 (0.44-1.44)
Number of metastatic nodes									
0	132 (61)	92 (52)	50 (23)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1-2	34 (16)	49 (28)	53 (25)	1.02 (0.53-1.96)	2.64 (1.52-4.57)	2.48 (1.42-4.33)	1.69 (0.82-3.49)	2.93 (1.51-5.69)	2.59 (1.33-5.04)
3-6	33 (15)	26 (15)	57 (27)	3.22 (1.90-5.46)	4.30 (2.30-8.06)	2.30 (1.33-3.98)	3.99 (2.07-7.71)	4.87 (2.28-10.4)	2.55 (1.33-4.88)
>6	16 (7)	11 (6)	53 (25)	2.52 (1.28-4.96)	2.33 (0.96-5.68)	4.16 (2.40-7.20)	3.11 (1.37-7.05)	2.37 (0.80-7.06)	4.19 (2.19-8.04)
Ratio of metastatic to all nodes									
0	132 (61)	92 (52)	50 (23)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
0.02-0.14	24 (11)	42 (24)	45 (21)	0.89 (0.41-1.93)	2.49 (1.40-4.44)	2.10 (1.17-3.74)	1.57 (0.68-3.63)	2.77 (1.37-5.59)	2.20 (1.10-4.42)
0.15-0.37	32 (15)	26 (15)	53 (25)	2.41 (1.37-4.24)	4.17 (2.23-7.80)	2.14 (1.23-3.73)	2.96 (1.49-5.91)	4.78 (2.25-10.1)	2.23 (1.16-4.29)
>0.37	27 (13)	18 (10)	65 (31)	3.44 (1.96-6.04)	2.97 (1.44-6.10)	5.01 (2.92-8.57)	4.26 (2.15-8.44)	3.07 (1.29-7.28)	5.22 (2.76-9.87)

[1] Adjusted for age, pathological T-stage, tumor grade, margin status, response to pre-operative chemotherapy and calendar period; [2]No chemotherapy given; [3] Mandard score 1-3; [4] Mandard score 4-5.