

The Prognostic Value of the Number of Harvested Negative Lymph Nodes in Patients Treated by Esophagectomy With or Without Neoadjuvant Chemoradiation

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Abstract. *Background/Aim:* The prognostic value of the number of harvested negative lymph nodes (NLNs) in patients with node-negative esophageal carcinoma treated by esophagectomy with or without neoadjuvant chemoradiation is unclear. *Patients and Methods:* A total of 136 patients who underwent oncological esophagectomy with two-field lymphadenectomy from 1995 to 2014 were analyzed regarding the prognostic impact of NLNs. 86 patients received primary surgery (group 1) and 50 patients had preoperative chemoradiation followed by surgery (group 2). *Results:* The 5-year overall survival (OS) was 61.1%. Median lymph node harvest was significantly higher in group 1 (39 vs. 34 in group 2, $p=0.007$). In group 1, patients with a higher number of negative lymph nodes (>40) had a better OS [57.6% vs. 78.9%, $HR=0.5$ (0.3-0.9), $p=0.026$], whereas there was no significant difference in group 2 using the same cutoff (47.6% vs. 66.7%, $p=0.476$). *Conclusion:* The number of NLNs is an independent prognostic factor for patients with esophageal carcinoma treated by primary esophagectomy, but not in patients after neoadjuvant chemoradiation.

Esophageal carcinoma is a common malignant cancer worldwide. Due to its aggressive tumor biology and late detection the prognosis of esophageal cancer is poor (1). While the only treatment regimen for patients with distant metastasis is palliative, the primary target of non-metastatic patients is R0 resection as it represents the only curative treatment option (2). In recent years, multimodal treatment especially with neoadjuvant chemoradiation (nCRT) has been shown to improve prognosis and is performed in patients with a locally advanced tumor (3).

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The determination of prognostic factors in patients with esophageal carcinoma is essential for predicting the outcome and for identifying appropriate treatment strategies. Several studies have identified prognostic factors in esophageal cancer (4, 5). One of the most important predictors of survival in patients undergoing esophagectomy is the presence of lymph node metastasis underlining the importance of adequate lymphadenectomy as one of the crucial oncological factors, which can be influenced by surgery (6).

However, there is an ongoing controversy among surgeons regarding the optimal extent of lymphadenectomy during esophagectomy (7-11). Potential benefits of extended lymphadenectomy are the more accurate staging of the disease, better locoregional disease control and perhaps even improved long-term survival. Many studies have investigated the total number of resected lymph nodes (TLN) as an index for the extent of lymphadenectomy and most of them could identify TLN as an independent predictor of survival (6, 11-16). However, this parameter includes both the positive and negative lymph nodes, which represent an important independent prognostic factor. Therefore, the number of negative lymph nodes (NLN) could be a better parameter reflecting the extent of lymphadenectomy as it is more independent of tumor stage. All studies investigating the impact of negative lymph nodes on survival in patients with esophageal carcinoma refer to cohorts with primary resection or to mixed cohorts without differentiation between the patients with primary surgery and those with neoadjuvant chemoradiation (17-23). As neoadjuvant chemoradiation includes all regional lymph nodes and may relieve potentially affected lymph nodes, it is unclear whether extended lymphadenectomy after neoadjuvant chemoradiation is still indicated for prognostic and therapeutic reasons. Previous results on survival depending on the TLN in patients treated by neoadjuvant chemoradiation are divergent (24-27).

Data about the impact of the number of negative lymph nodes (NLNs) on survival in patients with esophageal cancer after neoadjuvant chemoradiation are lacking. The aim of the present

study was to examine the impact of the number of NLNs on survival among a cohort of patients with (y)pN0 esophageal cancer undergoing surgical resection with and without neoadjuvant chemoradiation using a single-institution data set.

Patients and Methods

A retrospective review was performed of the data of consecutive patients with esophageal carcinoma who had undergone curative oncological abdomino-right-thoracic esophagectomy at the Department of Surgery of University Hospital Erlangen between January 1995 and December 2014. Patients with postoperative pathological staging of pT4 or pN+ and patients with distant metastasis (M1) were excluded. Patients' clinical and pathological data were obtained from the Erlangen Cancer Registry of the Department of Surgery. The detailed documentation allowed a classification of pathology and staging for all patients according to the seventh edition of the tumor–node–metastasis (TNM) classification system. As a result, some patients with previous “esophageal carcinoma” were now classified as carcinoma of the esophageal gastric junction (CEG). Morbidity was evaluated by Clavien-Dindo classification. Major morbidity was defined as Clavien-Dindo III and IV. This study was approved by the Ethics Committee of FAU Erlangen (337_19 Bc).

Treatment. Preoperative staging always included CT-scans of the thorax and abdomen as well as esophago-gastroscopy. Patients with clinical tumor stage of cT1-2 and cN0 received primary surgery, whereas a clinical tumor stage of cT3 or cN+ indicated a neoadjuvant treatment.

Surgery was performed always as Ivor Lewis esophagectomy including a two-field lymphadenectomy (total mediastinal and perigastric lymph nodes).

Neoadjuvant chemoradiation included radiation with a dose of 40-50 Gy in 34% of the patients and a dose of 50-60 Gy in 66% of the patients. Chemotherapeutic regimes included 5-FU + cisplatin (74%), cisplatin + paclitaxel (11%) as well as 5-FU + paclitaxel, carboplatin + paclitaxel and carboplatin mono (each 5%).

Statistics. Data analysis was performed with the SPSS software (SPSS, Inc., Chicago, IL, USA). Comparisons of metric and ordinal data were calculated with the Student *t*-test or Mann Whitney *U*-test. The Chi-square test was used for categorical data. The minimum *p*-value approach was used to determine optimal cutoff of NLNs. Overall survival was calculated for the period between the date of surgery and the date of death or last follow-up. Possible factors related to the overall survival (OAS) of patients were tested using univariate and multivariate analysis. Statistically significant variables ($p \leq 0.05$) were used for multivariate analysis by Cox regression model. Survival curves were plotted using the Kaplan–Meier method and compared with the log-rank test. A *p*-value ≤ 0.05 was considered statistically significant.

Results

Patient demographics. A total of 136 patients were included in this study. Of those, 86 patients were treated by primary surgery (group 1) and 50 patients received preoperative chemoradiation followed by surgery (group 2). Baseline characteristics are shown in Table I. Patients in group 1 were significantly older than those in group 2 (63 vs. 59 years,

$p=0.022$). Gender, preoperative risk factors (smoking, alcohol abuse), tumor location, histological type, pT-category, grading and R classification did not differ among the two groups.

The median numbers of resected and NLNs were 39 (range=9-102) in group 1 and 34 (range=11-55) in group 2, with a significant difference between the two groups ($p=0.007$) (Table I).

Outcome. Two- and 5-year overall survival was 76.5% and 61.1% and tended to be better in group 1 compared to group 2 (83.7% and 67.2% in group 1 versus 64.0 and 53.3% in group 2). Morbidity, major morbidity, in-hospital mortality, 30- and 90-day mortality were 45%, 12%, 9%, 4% and 10%. There were no significant differences between the two groups (Table II).

Most common postoperative complications included respiratory complications (24%) and anastomotic leakage (10%) with no significant difference between the two groups. Anastomotic leakage was treated conservatively in one case (7%), surgically in two cases (14%) and interventionally in eleven cases (79%). Chylus fistula occurred in one patient in group 1 (1%) and in two patients in group 2 (4%).

Cutoff analysis. The *p*-values of the log-rank tests based on the different dichotomized numbers of NLN counts are shown in Table III. Best cutoff in group 1 was at 40 resected and examined negative lymph nodes showing a significant better overall survival of patients with a higher number of lymph node harvest [57.6% (≤ 40 LNs) vs. 78.9% (>40 LNs), $p=0.016$] (Table III).

In group 2 no significant cutoff showing an influence of resected and examined negative lymph nodes on survival could be identified (Table III). For further investigation and comparison to group 1 the same cutoff (≤ 40 LNs vs. >40 LNs) as in group 1 was selected. At this cutoff, the 5-year overall survival in group 2 was 47.6%, when ≤ 40 LNs were resected, compared to 66.7% in patients with higher number of harvested lymph nodes (>40 LNs) ($p=0.476$).

Impact of clinicopathological factors on lymph node harvest and on survival. In group 2, pulmonary complications were more common in patients with lower lymph node harvest (40% vs. 0%, $p=0.004$). Otherwise, patients with a lower and a higher lymph node harvest did not differ in baseline characteristics (Table IV). A higher lymph node harvest was not associated with a higher postoperative complication rate at all (group 1: 45% vs. 42%, $p=0.775$, group 2: 33% vs. 54%, $p=0.174$) or with a higher rate of specific surgical complications like chylus fistula or anastomotic leakage.

Univariate analysis of possible factors influencing the overall survival (OS) in group 1 showed, that NLN count >40 LNs and tumor differentiation $\leq G2$ were significantly associated with a better 5-year overall survival ($p=0.016$ and $p=0.017$, respectively). Multivariate analysis confirmed these

Table I. Baseline patient characteristics.

	All patients n (%)	Patients with primary surgery n (%)	Patients with neoadjuvant chemoradiation n (%)	p-Value
Number	136	86	50	
Age median [range] (years)	61 [37-81]	63 [37-81]	59 [38-74]	0.022
Gender				
Male	118 (86.8)	74 (86)	44 (88)	
Female	18 (13.2)	12 (14)	6 (12)	0.746
Smoking				
Never	35 (25.7)	19 (22)	16 (32)	
Previously	45 (33.1)	30 (35)	15 (30)	
Yes	35 (25.7)	24 (28)	11 (22)	
Unknown	21 (15.4)	13 (15)	8 (16)	0.598
Alcohol abuse				
Never	60 (44.1)	40 (47)	20 (40)	
Previously	20 (14.7)	12 (14)	8 (16)	
Yes	38 (27.9)	24 (28)	14 (28)	
Unknown	18 (13.2)	10 (12)	8 (16)	0.837
Tumor location				
Mid-thoracic portion	41 (30.1)	22 (26)	19 (38)	
Lower thoracic portion	55 (40.4)	39 (45)	16 (32)	
Overlapping lesion	1 (0.7)	1 (1)	0 (0)	
CEG I	39 (28.7)	24 (28)	15 (30)	0.303
Histological type				
Squamous cell carcinoma	64 (47.1)	40 (47)	24 (48)	
Adenocarcinoma	70 (51.5)	46 (53)	24 (48)	
Adenosquamous carcinoma	1 (0.7)	0 (0)	1 (2)	
Undifferentiated carcinoma	1 (0.7)	0 (0)	1 (2)	0.303
pT category				
ypT0	28 (20.6)		28 (56)	
pT1/ypT1	50 (36.8)/6 (4.4)	50 (58)	6 (12)	
pT2/ypT2	17 (12.5)/6 (4.4)	17 (20)	6 (12)	
pT3/ypT3	19 (14.0)/9 (6.6)	19 (22)	9 (18)	
ypTx	1 (0.7)		1 (2)	-
Grading				
G1/2	56 (41.2)	56 (65)	-	
G3/4	30 (22.1)	30 (35)	-	
Not applicable (nCRT)	50 (36.8)	-	50 (100)	-
Number of regional lymph nodes examined				
Median [range]	37 [9-102]	39 [9-102]	34 [11-55]	0.007
R classification				
R0	135 (99.3)	85 (99)	50 (100)	
R1	1 (0.7)	1 (1)	0 (0)	1.000

CEG I: Carcinoma of the esophagogastric junction type I; nCRT: neoadjuvant chemoradiation. Bold values show significance.

two parameters as independent prognostic factors [HR=0.5 (0.3-0.9), $p=0.026$ and HR=2.0 (1.1-3.6), $p=0.029$; respectively] (Table V). In univariate analysis there were no significant factors affecting survival in group 2 (Table VI). Therefore, a multivariate analysis was omitted in this group.

Discussion

Multimodal therapy especially with neoadjuvant chemoradiation for locoregional advanced disease has improved survival and has

changed treatment strategy for esophageal carcinomas. Patients with esophageal carcinoma either receive neoadjuvant chemoradiation, followed by surgery or primary surgery, eventually followed by adjuvant chemotherapy dependent on the final tumor stage. We investigated the impact of the number of negative lymph nodes (NLNs) on survival among patients with (y)pN0 esophageal cancer undergoing surgical resection with and without neoadjuvant treatment. Our results showed that the number of NLNs is an independent prognostic parameter for patients with node-negative esophageal carcinoma treated by

Table II. Short-term outcome parameters.

	All patients (n=136) n (%)	Patients with primary surgery (n=86) n (%)	Patients with neoadjuvant chemoradiation (n=50) n (%)	p-Value
Morbidity	61 (44.9)	37 (43)	24 (48)	0.574
Clavien-Dindo grade				
I-II	33 (24.3)	19 (22)	14 (28)	
III-IV	16 (11.8)	12 (14)	4 (8)	
V (In-hospital mortality)	12 (8.8)	6 (7)	6 (12)	0.508
30-day mortality	5 (3.7)	3 (3)	2 (4)	1.0
90-day mortality	13 (9.6)	7 (8)	6 (12)	0.460

Table III. Minimum p-Value approach: number of regional lymph nodes examined.

Evaluated cut-off (lymph nodes)	p-Value	Lower number of lymph nodes examined		Higher number of lymph nodes examined	
		n	5-year OAS/SE (%)	n	5-year OAS/SE (%)
Patients with primary surgery (n=86)					
≤35	0.156	32	58.2/8.9	54	72.2/6.1
≤36	0.045	34	54.8/8.7	52	75.0/6.0
≤37	0.161	39	58.1/8.0	47	74.5/6.4
≤38	0.122	43	57.3/7.6	43	76.7/6.4
≤39	0.074	44	56.0/7.6	42	78.6/6.3
≤40	0.016	48	57.6/7.2	38	78.9/6.6
≤41	0.027	51	58.2/7.0	35	80.0/6.8
≤42	0.039	52	59.0/6.9	34	79.4/6.9
≤43	0.042	54	60.5/6.7	32	78.1/7.3
≤44	0.097	56	62.0/6.5	30	76.7/7.7
Patients with neoadjuvant chemoradiation (n=50)					
≤35	0.995	27	51.4/9.7	23	55.8/10.5
≤36	0.946	30	52.5/9.3	20	54.5/11.2
≤37	0.986	32	52.4/9.0	18	55.0/11.9
≤38	0.476	35	47.6/8.6	15	66.7/12.2
≤39	0.476	35	47.6/8.6	15	66.7/12.2
≤40	0.476	35	47.6/8.6	15	66.7/12.2
≤41	0.388	39	47.4/8.2	11	72.7/13.4
≤42	0.388	39	47.4/8.2	11	72.7/13.4
≤43	0.270	40	46.2/8.1	10	80.0/12.6
≤44	0.270	40	46.2/8.1	10	80.0/12.6

primary surgery (best cutoff: ≤40 vs. >40 LNs), but has no significant impact on survival in patients after neoadjuvant chemoradiation.

Thus, our results confirm the positive impact of an extended lymphadenectomy as an important part of primary esophagectomy on survival, which has already been shown in several studies (16-18, 20, 22-24, 26, 27). In contrast, our evaluated cutoff for optimal lymphadenectomy (>40 LNs) is higher than in previous studies. In the literature, the recommended lymph node harvest ranges from >1 to >31 lymph nodes (17-23). Moreover, the total number of resected and examined lymph nodes in our cohort (median 37 LNs)

was higher than that in other studies. This “upward shift” could be due to differences in the surgical technique and/or to a different enthusiasm for lymph nodes search by the pathologist or different pathological examination protocols.

However, the role of lymphadenectomy during esophagectomy in patients with neoadjuvant chemoradiation remains controversial, as nCRT is known to be able to “sterilize” regional nodes (11, 24-36). About 56% of patients with ypT0 and significant less resected lymph nodes after neoadjuvant chemoradiation in our investigation are consistent with reported effects of neoadjuvant chemoradiation, which lead on the one hand to a relevant

Table IV. Baseline characteristics and postoperative outcome parameters stratified to the number of examined regional lymph nodes (ln).

	Patients with primary surgery (n=86)				Patients with neoadjuvant chemoradiation (n=50)			
	n (%) 86	≤40 ln 48	>40 ln 38	p-Value	n (%) 50	≤40 ln 35	>40 ln 15	p-Value
Age (years)								
≤60	36 (42)	19 (40)	17 (45)		29 (58)	19 (54)	10 (67)	
>60	50 (58)	29 (60)	21 (55)	0.630	21 (42)	16 (46)	5 (33)	0.416
Gender								
Male	74 (86)	39 (81)	35 (92)		44 (88)	29 (83)	15 (100)	
Female	12 (14)	9 (19)	3 (8)	0.149	6 (12)	6 (17)	0 (0)	0.160
Tumor location								
Mid-thoracic portion	22 (26)	12 (25)	10 (26)		19 (38)	14 (40)	5 (33)	
Lower thoracic portion	39 (45)	21 (44)	18 (47)		16 (32)	11 (31)	5 (33)	
Overlapping lesion	1 (1)	1 (2)	0 (0)		0 (0)	0 (0)	0 (0)	
CEG I	24 (28)	14 (29)	10 (26)	0.818	15 (30)	10 (29)	5 (33)	0.898
Histological type								
Squamous cell carcinoma	40 (47)	22 (46)	18 (47)		24 (48)	18 (51)	6 (40)	
Adenocarcinoma	46 (53)	26 (54)	20 (53)		24 (48)	16 (46)	8 (53)	
Adenosquamous carcinoma	0 (0)	0 (0)	0 (0)		1 (2)	0 (0)	1 (7)	
Undifferentiated carcinoma	0 (0)	0 (0)	0 (0)	0.887	1 (2)	1 (3)	0 (0)	0.365
pT category*								
ypT0/ypTis/pT1/ypT1	50 (58)	29 (60)	21 (55)		34 (68)	26 (74)	8 (57)	
pT2/ypT2	17 (20)	9 (19)	8 (21)		6 (12)	3 (9)	3 (21)	
pT3/ypT3	19 (22)	10 (21)	9 (24)	0.891	9 (18)	6 (17)	3 (21)	0.392
Grading								
G1/2	56 (65)	29 (60)	27 (71)		-	-	-	
G3/4	30 (35)	19 (40)	11 (29)	0.304	-	-	-	-
Morbidity								
No	49 (57)	28 (58)	21 (55)		26 (52)	16 (46)	10 (67)	
Yes	37 (43)	20 (42)	17 (45)	0.775	24 (48)	19 (54)	5 (33)	0.174
Postoperative complications								
Anastomotic leakage	7 (8)	6 (13)	1 (3)	0.127	7 (14)	6 (17)	1 (7)	0.420
Chylus fistula	1 (1)	1 (2)	0 (0)	1.000	2 (4)	1 (3)	1 (7)	1.000
Pulmonary complications	18 (21)	9 (19)	9 (24)	0.603	15 (30)	14 (40)	0 (0)	0.004
Cardiac complications	4 (5)	3 (6)	1 (3)	0.627	1 (2)	1 (3)	0 (0)	1.000
Psychiatric complications	4 (5)	2 (4)	2 (5)	1.000	0 (0)	0 (0)	0 (0)	-
In-hospital mortality								
Yes	6 (7)	5 (10)	1 (3)		6 (12)	5 (14)	1 (7)	
No	80 (93)	43 (90)	37 (97)	0.222	44 (88)	30 (86)	14 (93)	0.654

*One patient ypTX. Bold value shows significance.

downstaging of the tumor and on the other hand to a decrease of the number of resected and examined lymph nodes in the specimen (27, 37).

Regarding the influence of the number of removed lymph nodes on survival after nCRT several studies have shown contradictory findings (11, 24-36). A retrospective analysis of 303 patients with esophageal squamous cell carcinoma treated by surgery after nCRT revealed a strong survival benefit after extensive lymph node dissection (33). Moreover, two large cancer registry studies with 18777 patients with esophagectomy after induction therapy and 3149 patients with surgery after radiotherapy concluded that resected lymph node count was an independent prognostic factor in esophageal cancer patients (29, 34). In contrast, there are two post hoc

analyses of randomized trials showing no association between the number of resected lymph nodes and survival after chemoradiation, and questioned the maximization of lymphadenectomy (26, 27). This result was confirmed by some retrospective studies (11, 25, 28, 32, 36). All mentioned studies have investigated the total number of resected lymph nodes and not the number of resected negative lymph nodes as a more independent parameter. We could reveal that a higher harvest of NLNs during esophagectomy after neoadjuvant chemoradiation for lymph node negative esophageal cancer has no significant survival benefit showing no indication of extended lymphadenectomy in these patients.

Most studies investigating the impact of lymphadenectomy on survival did not report morbidity, although an increase of

Table V. Univariate and multivariate analysis of factors related to the overall survival (OAS): patients with node-negative esophageal carcinoma treated by primary surgery without neoadjuvant treatment (n=86).

Patients with primary surgery (n=86)	n	Univariate analysis			Multivariate analysis		
		2-year OAS/SE (%)	5-year OAS/SE (%)	p-Value	Hazard ratio	95%CI	p-Value
All patients	86	83.7/4.0	67.2/5.1				
Age (in years)							
≤60	36	86.1/5.8	74.6/7.3				
>60	50	82.0/5.4	61.9/6.9	0.443			
Gender							
Male	74	85.1/4.1	68.6/5.4				
Female	12	75.0/12.5	58.3/14.2	0.759			
Tumor location							
Mid-thoracic portion	22	77.3/8.9	72.7/9.5				
Lower thoracic portion	39	84.6/5.8	71.4/7.3				
Overlapping lesion	1	100	100				
CEG I	24	87.5/6.8	54.2/10.2	0.747			
Histological type							
Squamous cell carcinoma	40	82.5/6.0	74.8/6.9				
Adenocarcinoma	46	84.8/5.3	60.8/7.2	0.952			
pT category							
pT1	50	86.0/4.9	74.0/6.2				
pT2	17	70.6/11.1	64.2/11.8				
pT3	19	89.5/7.0	52.6/11.5	0.860			
Number of examined lymph nodes							
≤40 ln	48	83.3/5.4	57.6/7.2		1.0		
>40 ln	38	84.2/5.9	78.9/6.6	0.016	0.5	0.3-0.9	0.026
Grading							
G1/2	56	87.5/4.4	76.8/5.6		1.0		
G3/4	30	76.7/7.7	48.8/9.3	0.017	2.0	1.1-3.6	0.029
Morbidity							
No	49	91.8/3.9	68.9/6.7				
Yes	37	73.0/7.3	64.9/7.8	0.267			

Bold values show significance.

morbidity is the main risk of extended lymphadenectomy. Wu *et al.* have shown a significant higher postoperative complication rate in patients with more than 19 resected lymph nodes during primary esophagectomy (22). In our study, extended lymphadenectomy was not associated with a higher rate of morbidity or mortality.

Our study’s strengths are the examination of only negative lymph nodes, as it is more independent of tumor stage compared to the total amount of resected lymph nodes, and the detailed report of morbidity and mortality, the main risk of extended lymphadenectomy. However, this study has some limitations. First, the small sample size limited the statistical power and the retrospective design of our study may have incurred some bias. Second, there is a relevant heterogeneity in our cohort regarding tumor location and histological type as well as neoadjuvant treatment including chemotherapeutic regimens. Third, data were collected over a long timeframe, which could have affected the results due to changes in therapeutic strategies.

Conclusion

Extended lymph node resection during oncological esophagectomy was associated with better survival in patients with primary surgery without increasing morbidity. In contrast, patients with neoadjuvant chemoradiation followed by surgery have no significant survival benefit from extended lymph node resection. The evidence regarding extended lymphadenectomy after neoadjuvant chemoradiation remains insufficient and has to be investigated in further studies.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

Authors’ Contributions

MB collected, analyzed and interpreted the data, conducted the literature search and wrote the paper. SM and GW analyzed and

Table VI. Univariate analysis of factors related to the overall survival (OAS): patients with node-negative esophageal carcinoma treated by surgery with neoadjuvant chemoradiation (n=50).

	n	2-year OAS/SE (%)	5-year OAS/SE (%)	p-Value
All patients	50	64.0/6.8	53.3/7.2	
Age (in years)				
≤60	29	62.1/9.0	51.7/9.3	0.654
>60	21	66.7/10.3	55.7/11.2	
Gender				
Male	44	59.1/7.4	52.0/7.6	0.568
Female	6	100	60.0/21.9	
Tumor location				
Mid-thoracic portion	19	68.4/10.7	68.4/10.7	0.149
Lower thoracic portion	16	68.8/11.6	56.3/12.4	
CEG I	15	53.3/12.9	27.4/12.7	
Histological type				
Squamous cell carcinoma	24	66.7/9.6	62.5/9.9	0.182
Adenocarcinoma	24	66.7/9.6	46.7/10.8	
Other	2	0	0	
ypT category				
ypT0/ypTis	28	67.9/8.8	60.3/9.3	0.141
ypT1	6	50.0/20.4	33.3/19.2	
ypT2	6	83.3/15.2	62.5/21.3	
ypT3	9	44.4/16.6	33.3/15.7	
Number of examined lymph nodes				
≤40 ln	35	62.9/8.2	47.6/8.6	0.476
>40 ln	15	54.2/10.2	66.7/12.2	
Morbidity				
No	26	73.1/8.7	65.2/9.4	0.082
Yes	24	56.0/9.9	41.7/10.1	

interpreted the data and wrote the paper. All Authors read and approved the final manuscript and were involved in a way justifying authorship.

References

- Chen MF, Yang YH, Lai CH, Chen PC and Chen WC: Outcome of patients with esophageal cancer: a nationwide analysis. *Ann Surg Oncol* 20(9): 3023-3030, 2013. PMID: 23525703. DOI: 10.1245/s10434-013-2935-4
- Lordick F, Mariette C, Haustermans K, Obermannová R and Arnold D; ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27(suppl 5): v50-v57, 2016. PMID: 27664261.
- van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Slangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW and van der Gaast A; CROSS Group: Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 366: 2074-2084, 2012. PMID: 22646630. DOI: 10.1056/NEJMoa1112088.
- Lin CS, Chang SC, Wei YH, Chou TY, Wu YC, Lin HC, Wang LS and Hsu WH: Prognostic variables in thoracic esophageal squamous cell carcinoma. *Ann Thorac Surg* 87: 1056-1065, 2009. PMID: 19324127. DOI: 10.1016/j.athoracsur.2008.11.051
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A: American Joint Committee on Cancer (AJCC) cancer staging manual. 7th ed. Chicago, IL: Springer, pp. 67-72, 2010.
- Mariette C, Piessen G, Briez N and Triboulet JP: The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg* 247: 365-371, 2008. PMID: 18216546. DOI: 10.1097/SLA.0b013e31815aaadf
- Jamieson GG, Lamb PJ and Thompson SK: The role of lymphadenectomy in esophageal cancer. *Ann Surg* 250: 206-209, 2009. PMID: 19638911. DOI: 10.1097/SLA.0b013e3181b16cd1
- Lerut T, Naftoux P, Moons J, Coosemans W, Decker G, De Leyn P, Van Raemdonck D and Ectors N: Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper half esophageal carcinoma. *Ann Surg* 240: 962-972, 2004. PMID: 15570202.
- Herrera LJ: Extent of lymphadenectomy in esophageal cancer: how many lymph nodes is enough? *Ann Surg Oncol* 17: 676-678, 2010. PMID: 19953331. DOI: 10.1245/s10434-009-0824-7
- Mariette C and Piessen G: Oesophageal cancer: how radical should surgery be? *Eur J Surg Oncol* 38: 210-213, 2012. PMID: 22236956. DOI: 10.1016/j.ejso.2011.12.022
- Lagergren J, Mattsson F, Zylstra J, Chang F, Gossage J, Mason R, Lagergren P and Davies A: Extent of lymphadenectomy and prognosis after esophageal cancer surgery. *JAMA Surg* 151(1): 32-39, 2016. PMID: 26331431. DOI: 10.1001/jamasurg.2015.2611.
- Altorki N, Zhou XK, Stiles B, Port JL, Paul S, Lee PC and Mazumdar M: Total number of resected lymph nodes predicts survival in esophageal cancer. *Ann Surg* 248: 221-226, 2008. PMID: 18650631. DOI: 10.1097/SLA.0b013e31817bbe59
- Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, Hölscher A, Lerut T, Law S, Rice TW, Ruol A, van Lanschot JJ, Wong J and DeMeester TR: The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. *Ann Surg* 248: 549-556, 2008. PMID: 18936567. DOI: 10.1097/SLA.0b013e318188c474
- Greenstein AJ, Little VR, Swanson SJ, Divino CM, Packer S and Wisnivesky JP: Prognostic significance of the number of lymph node metastases in esophageal cancer. *J Am Coll Surg* 206: 239-246, 2008. PMID: 18222375. DOI: 10.1016/j.jamcollsurg.2007.09.003
- Hu Y, Hu C, Zhang H, Ping Y and Chen LQ: How does the number of resected lymph nodes influence TNM staging and prognosis for esophageal carcinoma? *Ann Surg Oncol* 17: 784-790, 2010. PMID: 19953333. DOI: 10.1245/s10434-009-0818-5
- Rizk NP, Ishwaran H, Rice TW, Chen LQ, Schipper PH, Kesler KA, Law S, Lerut TE, Reed CE, Salo JA, Scott WJ, Hofstetter WL, Watson TJ, Allen MS, Rusch VW and Blackstone EH: Optimum lymphadenectomy for esophageal cancer. *Ann Surg* 251: 46-50, 2010. PMID: 20032718. DOI: 10.1097/SLA.0b013e3181b2f6ee
- Greenstein AJ, Little VR, Swanson SJ, Divino CM, Packer S and Wisnivesky JP: Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. *Cancer* 112: 1239-1246, 2008. PMID: 18224663. DOI: 10.1002/cncr.23309

- 18 Baba Y, Watanabe M, Shigaki H, Iwagami S, Ishimoto T, Iwatsuki M and Baba H: Negative lymph-node count is associated with survival in patients with resected esophageal squamous cell carcinoma. *Surgery* 153: 234-241, 2013. PMID: 22980434. DOI: 10.1016/j.surg.2012.08.001
- 19 Hsu PK, Huang CS, Wang BY, Wu YC, Chou TY and Hsu WH: The prognostic value of the number of negative lymph nodes in esophageal cancer patients after transthoracic resection. *Ann Thorac Surg* 96(3): 995-1001, 2013. PMID: 23866797. DOI: 10.1016/j.athoracsur.2013.04.098
- 20 Liu Q, Tan Z, Lin P, Long H, Zhang L, Rong T, Meng Y and Ma G: Impact of the number of resected lymph nodes on postoperative survival of patients with node-negative oesophageal squamous cell carcinoma. *Eur J Cardiothorac Surg* 44(4): 631-636, 2013. PMID: 23477926. DOI: 10.1093/ejcts/ezt097
- 21 Ma M, Tang P, Jiang H, Gong L, Duan X, Shang X and Yu Z: Number of negative lymph nodes as a prognostic factor in esophageal squamous cell carcinoma. *Asia Pac J Clin Oncol* 13(5): e278-e283, 2017. PMID: 27488406. DOI: 10.1111/ajco.12567
- 22 Wu H, Liu C, Xu M, Guo M, Xu S and Xie M: Prognostic value of the number of negative lymph nodes in esophageal carcinoma without lymphatic metastasis. *Thorac Cancer* 9(9): 1129-1135, 2018. PMID: 29952086. DOI: 10.1111/1759-7714.12796
- 23 Zhu Z, Chen H, Yu W, Fu X, Xiang J, Li H, Zhang Y, Sun M, Wei Q, Zhao W and Zhao K: Number of negative lymph nodes is associated with survival in thoracic esophageal squamous cell carcinoma patients undergoing three-field lymphadenectomy. *Ann Surg Oncol* 21(9): 2857-2863, 2014. PMID: 24740827. DOI: 10.1245/s10434-014-3665-y
- 24 Ho HJ, Chen HS, Hung WH, Hsu PK, Wu SC, Chen HC and Wang BY: Survival impact of total resected lymph nodes in esophageal cancer patients with and without neoadjuvant chemoradiation. *Ann Surg Oncol* 25(13): 3820-3832, 2018. PMID: 30284131. DOI: 10.1245/s10434-018-6785-y
- 25 Guo JC, Lin CC, Huang TC, Huang PM, Kuo HY, Chang CH, Wang CC, Cheng JC, Yeh KH, Hsu CH and Lee JM: Number of resected lymph nodes and survival of patients with locally advanced esophageal squamous cell carcinoma receiving preoperative chemoradiotherapy. *Anticancer Res* 38: 1569-1577, 2018. PMID: 29491087.
- 26 Koen Talsma A, Shapiro J, Looman CW, van Hagen P, Steyerberg EW, van der Gaast A, van Berge Henegouwen MI, Wijnhoven BP, van Lanschot JJ; CROSS Study Group, Hulshof MC, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG and Tilanus HW: Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy. *Ann Surg* 260: 786-793, 2014. PMID: 25379850. DOI: 10.1097/SLA.0000000000000965
- 27 Robb WB, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, Boige V, Pezet D, Le Brun-Ly V, Bosset JF, Mabrut JY, Triboulet JP, Bedenne L, Seitz JF and Mariette C; Fédération Française de Cancérologie Digestive, Société Française de Radiothérapie Oncologique, Union des Centres de Lutte Contre le Cancer, Groupe Coopérateur Multidisciplinaire en Oncologie, French EsoGAstic Tumour working group, Fédération de Recherche En Chirurgie: Impact of neoadjuvant chemoradiation on lymph node status in esophageal cancer. *Ann Surg* 261: 902908, 2015. PMID: 25361220. DOI: 10.1097/SLA.0000000000000991
- 28 Hanna JM, Erhunmwunsee L, Berry M, D'Amico T and Onaitis M: The prognostic importance of the number of dissected lymph nodes after induction chemoradiotherapy for esophageal cancer. *Ann Thorac Surg* 99: 265-269, 2015. PMID: 25440285. DOI: 10.1016/j.athoracsur.2014.08.073
- 29 Samson P, Puri V, Broderick S, Patterson GA, Meyers B and Crabtree T: Extent of lymphadenectomy is associated with improved overall survival after esophagectomy with or without induction therapy. *Ann Thorac Surg* 103: 406-415, 2017. PMID: 28024648. DOI: 10.1016/j.athoracsur.2016.08.010
- 30 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW and van der Gaast A; CROSS Group: Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 366: 2074-2084, 2012. PMID: 22646630. DOI: 10.1056/NEJMoa1112088
- 31 Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, Boige V, Pezet D, Robb WB, Le Brun-Ly V, Bosset JF, Mabrut JY, Triboulet JP, Bedenne L and Seitz JF: Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of a randomized controlled phase III trial FFCO 9901. *J Clin Oncol* 32: 2416-2422, 2014. PMID: 24982463. DOI: 10.1200/JCO.2013.53.6532
- 32 Shridhar R, Hoffe SE, Almanna K, Weber JM, Chuong MD, Karl RC and Meredith K: Lymph node harvest in esophageal cancer after neoadjuvant chemoradiotherapy. *Ann Surg Oncol* 20: 3038-3043, 2013. PMID: 23625142. DOI: 10.1245/s10434-013-2988-4
- 33 Chao YK, Liu HP, Hsieh MJ, Wu YC, Liu YH, Yeh CH, Chang HK and Tseng CK: Lymph node dissection after chemoradiation in esophageal cancer: a subgroup analysis of patients with and without pathological response. *Ann Surg Oncol* 19: 3500-2505, 2012. PMID: 22622470. DOI: 10.1245/s10434-012-2402-7
- 34 Wu SG, Zhang ZQ, Liu WM, He ZY, Li FY, Lin HX, Sun JY, Lin H and Li Q: Impact of the number of resected lymph nodes on survival after preoperative radiotherapy for esophageal cancer. *Oncotarget* 7: 22497-22507, 2016. PMID: 26992210. DOI: 10.18632/oncotarget.8113
- 35 van der Schaaf M, Johar A, Wijnhoven B, Lagergren P and Lagergren J: Extent of lymph node removal during esophageal cancer surgery and survival. *J Natl Cancer Inst*, 2015. PMID: 25748792. DOI: 10.1093/jnci/djv043
- 36 Phillips AW, Lagarde SM, Navidi M, Disep B and Griffin SM: Impact of extent of lymphadenectomy on survival, post neoadjuvant chemotherapy and transthoracic esophagectomy. *Ann Surg* 265: 750-756, 2017. PMID: 27467444. DOI: 10.1097/SLA.0000000000001737
- 37 Issaka A, Ermerak NO, Bilgi Z, Kara VH, Celikel CA and Batirel HF: Preoperative chemoradiation therapy decreases the number of lymph nodes resected during esophagectomy. *World J Surg* 39: 721-726, 2015. PMID: 25344144. DOI: 10.1007/s00268-014-2847-x

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