# Lymph node metastases near the celiac trunk should be considered separately from other nodal metastases in patients with cancer of the esophagus or gastroesophageal junction after neoadjuvant treatment and surgery

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**Background:** The aim of the present study is to identify the incidence and prognostic significance of lymph node metastases near the celiac trunk in patients who underwent neoadjuvant chemo(radio)therapy followed by esophagectomy.

**Methods:** Between March 1994 and September 2013 a total of 462 consecutive patients with cancer of the esophagus or gastroesophageal junction (GEJ) who underwent potentially curative esophageal resection after neoadjuvant chemotherapy (N=88; 19.0%) or neoadjuvant chemoradiotherapy (CRT) (N=374; 81.0%) were included.

**Results:** Seventy one (15.4%) patients had truncal node metastases in the resection specimen. Metastases to these nodes occurred more frequently in male patients with adenocarcinoma and in tumors at the gastroesophageal junction. A lower response to neoadjuvant treatment, higher ypT and ypN stages and a poorer grade of differentiation were significantly related with truncal node metastases. Patients with tumor positive truncal nodes had a worse median overall survival (17 *vs.* 55 months). In multivariate analysis, truncal node metastases were independently associated with a worse survival. Only 22 (31.0%) of the 71 patients with tumor positive truncal nodes on EUS or CT, but metastases in the pathology specimen were absent.

**Conclusions:** In the present study, it is demonstrated that positive truncal nodes in the resection specimen after neoadjuvant therapy, are associated with advanced tumor stages and are an independent factor for inferior survival.

Keywords: Esophageal carcinoma; neoadjuvant therapy; truncal node metastases

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# Introduction

Cancer of the esophagus and gastroesophageal junction (GEJ) is an aggressive disease and notorious for rapid dissemination (1). The preferred curative strategy for patients with esophageal or GEJ cancer without distant metastases consists of neoadjuvant chemo(radio)therapy followed by esophagectomy (2,3).

In the seventh edition of the American Joint Committee on Cancer (AJCC) esophageal TNM staging system, the number of node metastases plays a pivotal role (4). The N stage is subdivided into N0–N3 based on the number of involved nodes. However, the present staging system does not take into account the location of nodal metastases. In former TNM staging systems, positive lymph nodes near the celiac axis were seen as distant metastatic (M1a) disease (4).

Truncal lymph nodes lie around the celiac artery, which is 1–2 cm long and trifurcates into the left gastric, common hepatic and splenic artery (5). There is considerable controversy surrounding the clinical importance of lymph node metastases near the celiac trunk in patients with cancer of the esophagus or GEJ (5-7). This has several reasons. In both the diagnostic process and the pathologic specimen interpretation, it may be hard to differentiate between celiac nodes, and nodes around the hepatic, splenic and left gastric artery (5) as they are anatomically very close to one another.

Surgeons historically have given patients with small resectable lymph node metastases near the celiac trunk the "benefit of the doubt" and have proceeded with resection (6). Although long-term survival was achieved in a small percentage of patients, these nodes were considered as an indicator of poor prognosis (6). However, the eradication of lymphadenopathy with neoadjuvant therapy is possible and therefore, it has been suggested that these patients were good candidates for neoadjuvant treatment regimens followed by surgery (5).

In the neoadjuvant era, it is unclear what the clinical relevance of these lymph nodes is, whether they can be identified preoperatively and what the prognostic value of these nodes is. Therefore the aim of the present study is to identify the incidence and prognostic significance of celiac trunk metastasis in patients who underwent neoadjuvant chemo(radio) therapy followed by a esophagectomy.

# Methods

# Patient population

Between March 1994 and September 2013 all consecutive

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patients with cancer of the mid-to-lower thoracic esophagus or GEJ who underwent potentially curative esophageal resection after neoadjuvant chemo(radio)therapy were included in the present study. Patients were selected from a prospectively collected and maintained database at the Department of Surgery, Academic Medical Centre, Amsterdam, the Netherlands. Patients with histologically confirmed, potentially curable squamous-cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma of the esophagus or GEJ were eligible for inclusion in the study. The study was approved by the institutional ethics committee of the Academic Medical Centre, Amsterdam, the Netherlands.

# Pretreatment staging

Initial staging consisted of endoscopy with biopsy, endoscopic ultrasonography (EUS), external ultrasonography of the neck and a thoracoabdominal CT scan. A PET (CT) scan was not part of the standard initial staging, but was performed in some cases as part of a research protocol, by the referring physicians and in more recent years, after neoadjuvant CRT.

### Pretreatment staging of truncal nodes

The diagnostic criteria for malignant lymph node involvement were size 1 cm or larger; round shape; homogeneous hypoechoic pattern; and sharp and distinct borders. Suspected lymph nodes in the region of the celiac trunk were defined as such when they were located within 2 cm of the celiac trunk on EUS or (PET-) CT. These nodes were not considered a contraindication for resection when patients were otherwise resectable. Patients with distant metastases did not undergo curative treatment and were not included in this study.

### Neoadjuvant therapy

Neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy was indicated in patients deemed fit for surgery with histologically proven, locally advanced, resectable esophageal malignancy without distant metastases (cT1N+M0 or cT2-4aN0-3M0).Two neoadjuvant CRT regimens were employed in the present study. Most patients received 23 fractions of 1.8 Gy (41.4 Gy) externalbeam radiotherapy combined with weekly administered carboplatin (AUC2) and paclitaxel (50 mg/m<sup>2</sup>). Additionally,

as part of a phase II clinical trial, a small proportion of patients received panitumumab (human monoclonal antibody to the epidermal growth factor receptor), at a dose of 6 mg/kg in addition to the standard neoadjuvant CRT (ClinicalTrials.gov Identifier: NCT01077999). Also, some patients were treated with CRT combined with deep loco-regional hyperthermia as part of a clinical trial (8). Radiation fields included the primary tumor plus a margin of at least 3 cm in caudal direction, plus all clinically suspect lymph nodes. Whether the truncal lymph nodes were included in the radiation fields was not recorded.

Neoadjuvant chemotherapy [EOX (epirubicin, oxaliplatin, capecitabine) or ECC (epirubicin, cisplatin, capecitabine)] was administered when the tumor bulk was located in the gastric cardia with involvement of the lower-thoracic esophagus (4).

Patients were restaged after neoadjuvant chemo(radio) therapy with CT, PET or PET-CT. Patients who developed distant metastases during neoadjuvant treatment were not operated. Also, patients with unresectable tumors during exploratory surgery or macroscopically incomplete resections (R2) and patients who died in hospital after surgery, were not included in the present study.

# Surgery

Esophagectomy was performed by means of an open or minimally invasive transthoracic or transhiatal approach, as previously described by our institute (9-11). Surgery was performed within 6–10 weeks after completion of neoadjuvant chemo(radio)therapy.

#### Pathology

Pathologic findings were described in a standardized format by an experienced gastro-intestinal pathologist. In the absence of macroscopic tumor, any abnormal-appearing tissue was paraffin-embedded in total in order to make an adequate assessment for the presence of residual tumor and the effects of therapy. When no tumor cells were seen in the proximal, distal and circumferential resection margins, the resection was classified as R0. To grade the response to neoadjuvant CRT, the degree of histomorphologic regression was classified using the Mandard score (12). Pathologic complete response was defined as absence of viable tumor in the surgical resection specimen (both the esophagus and resected lymph nodes).

The origin of the left gastric artery and the subcarinal

nodes were marked in the resection specimen by the surgeon. Separate lymph nodes (e.g., paratracheal) were marked by location and analyzed separately. Larger lymph nodes were cut in two and routine H&E staining was performed using a standardized protocol.

#### Definition of positive nodes near the celiac trunk

Lymph nodes near the origin of the left gastric artery were always removed as part of an esophagectomy. The origin of the left gastric artery was routinely marked by the surgeon. Nodes within 1 cm of this location in the specimen were considered truncal nodes in the present study. Furthermore, separate positive lymph nodes found at the hepatic artery and splenic artery were also classified as truncal nodes.

# Follow-up

During the first 5 years after surgery all patients were seen at the outpatient clinic at three to four month intervals during the first 2 years and every 6 months during the next 3 years. After 5 years, follow-up data was obtained by telephone from the patient or the patient's family practitioner. Recurrent disease was diagnosed on clinical grounds. When recurrence was suspected, additional investigations were performed.

# **Statistics**

Statistical calculations were performed by SPSS software, version 20.0 (SPSS, Chicago, IL, USA). Differences between groups were tested by the Mann-Whitney U-test for continuous data. To compare categorical data, the Chisquare or Fisher exact test was used. Multivariate Cox regression analysis was carried out to identify independent prognostic factors. All factors from the univariate analysis with a P value less than 0.05 were entered in this multivariate analysis. P values less than 0.05 (two-sided) were considered statistically significant.

# **Results**

Between March 1994 and September 2013, 503 patients with cancer of the mid-to-lower thoracic esophagus or GEJ underwent esophageal resection after neoadjuvant chemo(radio)therapy. In 6 (1.2%) patients metastases detected during surgical exploration lead to a palliative resection. Fourteen (2.8%) patients underwent a salvage

**Table 1** Pretreatment clinicopathologic characteristics of 462patients with cancer of the esophagus or gastroesophageal junctionwho underwent neoadjuvant chemo (radiation) therapy followed bysurgery

Patient characteristic	N (%) or mean (range)
Age* (year)	62.67 (29.80–83.49)
Male	345 (74.7)
Histology	
Adenocarcinoma	317 (68.6)
Squamous cell carcinoma	140 (30.3)
Other	5 (1.1)
Tumor location	
Mid thoracic esophagus	87 (18.8)
Lower thoracic esophagus	283 (61.3)
Gastroesophageal junction	92 (19.9)
Neoadjuvant treatment	
Chemotherapy	88 (19.0)
Chemoradiotherapy	374 (81.0)
Operative approach	
Open transhiatal esophagectomy	125 (27.1)
Open transthoracic esophagectomy	174 (37.7)
Minimally invasive transhiatal esophagectomy	10 (2.2)
Minimally invasive transthoracic esophagectomy	153 (33.1)
Pretreatment clinical T-stage	
cT1	7 (1.5)
cT2	72 (15.6)
cT3	359 (77.7)
cT4	3 (0.6)
сТх	21 (4.6)
Pretreatment clinical N-stage	
cN0	100 (21.6)
cN1	206 (44.6)
cN2	123 (26.6)
cN3	12 (2.6)
cNx	21 (4.5)
Pretreatment suspicion of celiac node metastases	
No	403 (87.2)
Yes	59 (12.8)

\*, values depicted are mean (range).

resection (long course CRT, or residual disease after definitive CRT). Both groups were excluded. Twenty-one (4.2%) died due to postoperative complications. These patients were excluded.

Of the 462 included patients 345 were male (74.7%). The tumor was located in the mid-thoracic esophagus in 87 (18.8%), in the lower thoracic esophagus in 283 (61.3%) and at the GEJ/cardia in 92 patients (19.9%). The majority (68.6%) had an adenocarcinoma, with the following clinical staging (*Table 1*).

Eighty-eight patients (19.0%) underwent preoperative chemotherapy and 374 (81.0%) underwent neoadjuvant CRT (*Table S1*). Different types (open and minimal invasive) of transthoracic and transhiatal surgery were performed in the inclusion period (*Table 1*). A total of 439 (95.0%) patients underwent a radical (R0) resection; microscopic tumor was left behind (R1 resection) in the other 23 patients (5.0%) (*Table 2*).

#### Positive nodes near the celiac trunk

According to the marked pathology specimen, in 71 (15.4%) patients metastases were localized in the truncal nodes. Metastases in truncal nodes occurred significantly more frequent in male patients with adenocarcinoma and in patients with tumors located at the GEJ (*Table 3*). Pretreatment stage was significantly more advanced for both tumor depth (cT stage) and number of suspected lymph nodes (cN stage).

Postoperative characteristics of aggressive disease (*Table 3*) were significantly related with celiac node metastases (worse Mandard score, higher ypT and ypN stage and a poor differentiation).

The median survival in patients with postoperative positive truncal nodes was 17 months (95% confidence interval, 11 to 24 months) in comparison to 55 months, (95% confidence interval, 37 to 72 months) for patients without truncal metastasis In *Figure 1*, the patients without truncal node metastases are divided into four groups: ypN0 (n=263, median survival 82 months), ypN1 (n=76, median survival 35 months), ypN2 (n=41, median survival 21 months) and ypN3 (n=11, median survival 11 months).

In multivariate analysis ypN stage, ypT stage, pathological response as well as positive truncal nodes were independently associated with survival (*Table 4*).

# Preoperative suspected nodes near the celiac trunk

In 59 (12.8%) patients there was suspicion on metastases

**Table 2** Post-surgery clinicopathologic characteristics of 462patients with cancer of the esophagus or gastroesophageal junctionwho underwent neoadjuvant chemo (radiation) therapy followed bysurgery

Pathological characteristic	N (%) or mean (SD)
Pathologic response primary tumor <sup>#</sup>	
TRG 1	95 (20.6)
TRG 2	67 (14.5)
TRG 3	132 (28.6)
TRG 4	57 (12.3)
TRG 5	37 (8.0)
Missing	74 (16.0)
Radicality	
R0	439 (95.0)
R1	23 (5.0)
Number of resected lymph nodes*	21.91 (10.47)
Number of tumor positive lymph nodes*	1.63 (3.44)
Post treatment T-stage	
урТ0	95 (20.6)
ypT1	63 (13.6)
ypT2	71 (15.4)
урТ3	232 (50.2)
ypT4	1 (0.2)
Post treatment N-stage	
ypN0	263 (56.9)
ypN1	108 (23.4)
ypN2	64 (13.9)
ypN3	27 (5.8)
Post treatment celiac node metastases	
No	391 (84.6)
Yes	71 (15.4)

<sup>#</sup>, TRG is only given for patients treated with neoadjuvant chemoradiation therapy. \*, values depicted are mean (SD). TRG, tumor regression grade according to Mandard; R0, microscopically radical resection; R1, microscopically tumor left behind.

localized in truncal nodes based on EUS and (PET-) CT findings before the start of neoadjuvant therapy. Although there was a significant increase in the chance of having truncal node metastases when pretreatment evaluation showed suspicious truncal nodes, only 22 (31.0%) of 71 patients with positive truncal nodes were identified preoperatively with EUS or (PET-)CT. Interestingly, in 37 patients (62.7%) suspicious truncal nodes were identified preoperatively and may have been included in the radiation fields, but in the pathology specimen truncal node metastases were not found. These 37 patients without truncal node metastases in the resection specimen had a median overall survival of 40 months (95% confidence interval, 7 to 73 months) (*Figure 2*). Patients with truncal node metastasis had significantly (P=0.021) more often hematogenous dissemination but not peritoneal/pleural and locoregional lymphatic metastases.

# Discussion

Lymphatic dissemination remains the most important predictor for survival in patients with cancer of the esophagus or GEJ. In the present study it has been demonstrated that not only the number of involved nodes but also the presence of positive truncal nodes in the surgical specimen after neoadjuvant treatment harbors important prognostic information. Thus, celiac nodal involvement is a strong predictor for widespread microscopic disease that may become evident later. The TNM-staging system, based on depth of tumor invasion, number of positive lymph nodes and distant metastases (4,13-15), is the most frequently used system to predict prognosis. This staging system is based on patients treated with primary surgery. However, this staging system is also applied to patients who are treated with neoadjuvant therapy and have complete, partial or no response to chemo(radiation) therapy in their primary tumor and lymph nodes. The present study shows that patients with positive truncal nodes after chemo(radiation) therapy have a dismal prognosis. In former TNM staging systems, positive lymph nodes near the celiac axis were categorized as M1a disease. Using this previous TNM staging system Schomas et al. assessed the impact of truncal node metastases in 310 patients who underwent esophagectomy between 1976 and 1999 for carcinoma of the distal esophagus or gastro-esophageal junction (16). The 52 patients (17%) with celiac node involvement had a significantly worse survival compared to pN0 patients, but no significant difference in survival was found in the comparison with pN+ patients without truncal node metastases. The authors concluded that the number of positive nodes, not their location, correlated best with survival (16). Studies like this led to the mentioned adaption

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 Table 3 Clinicopathologic characteristics of patients with cancer of the esophagus or gastroesophageal junction who underwent neoadjuvant chemo(radiation)therapy followed by surgery. Patients are divided by the presence of truncal node metastases in the resection specimen

Patient characteristic	Truncal node metastases, N=71 (15.4%)	No truncal node metastases, N=391 (84.6%)	P value
Age* (year)	62.81 (9.06)	62.64 (9.50)	0.860
Male	60 (84.5%)	285 (72.9%)	0.038
Neoadjuvant treatment			0.142
Chemotherapy	18 (25.4%)	70 (17.9%)	
Chemoradiotherapy	53 (74.6%)	321 (82.1%)	
Adenocarcinoma	58 (81.7%)	259 (66.2%)	0.030
Tumor location			
Mid thoracic esophagus	6 (8.5%)	81 (20.7%)	0.001
Lower thoracic esophagus	41 (57.7%)	242 (61.9%)	
Gastroesophageal junction	24 (33.8%)	68 (17.4%)	
Pretreatment clinical T-stage			
cT1 or cT2	5 (7.0%)	74 (18.9%)	0.015
cT3 or cT4	62 (87.3%)	300 (76.7%)	
сТх	4 (5.6%)	17 (4.3%)	
Pretreatment clinical N-stage			
cN0	8 (11.3%)	92 (23.5%)	0.010
cN1	32 (45.1%)	174 (44.5%)	
cN2	22 (31.0%)	101 (25.8%)	
cN3	5 (7.0%)	7 (1.8%)	
cNx	4 (5.6%)	17 (4.3%)	
Pretreatment suspicion of celiac node metastase	S		
Yes	22 (31.0%)	37 (9.5%)	<0.001
Pathologic response primary tumor#			
TRG 1	5 (7.0%)	90 (23.0%)	<0.001
TRG 2	4 (5.6%)	63 (16.1%)	
TRG 3	26 (36.6%)	106 (27.1%)	
TRG 4	11 (15.5%)	46 (11.8%)	
TRG 5	9 (12.7%)	28 (7.2%)	
Missing	16 (22.5%)	58 (14.8%)	
Radicality (R0)	66 (93.0%)	374 (95.7%)	0.144
Number of resected lymph nodes*	22.01 (10.54)	21.89 (10.47)	0.999
Number of tumor positive lymph nodes*	5.51 (6.22)	0.93 (1.95)	<0.001

Table 3 (continued)

Patient characteristic	Truncal node metastases, N=71 (15.4%)	No truncal node metastases, N=391 (84.6%)	P value
Post treatment T-stage			
урТО	5 (7.0%)	90 (23.0%)	<0.001
ypT1	3 (4.2%)	60 (15.3%)	
урТ2	11 (15.5%)	60 (15.3%)	
урТЗ	52 (73.2%)	180 (46%)	
урТ4	0	1 (0.3%)	
Post treatment N-stage			
ypN0	-	263 (67.3%)	<0.001
ypN1	32 (45.1%)	76 (19.4%)	
ypN2	23 (32.4%)	41 (10.5%)	
ypN3	16 (22.5%)	11 (2.8%)	

Table 3 (continued)

Statistically significant P values are in italic. \*, values depicted are mean (SD). <sup>#</sup>, TRG is only given for patients treated with neoadjuvant chemoradiation therapy. TRG, tumor regression grade according to Mandard; R0, microscopically radical resection.



**Figure 1** Overall survival of patients with cancer of the esophagus or gastro-esophageal junction who underwent neoadjuvant chemo(radio) therapy followed by surgery. Patients are divided between those with and without postoperative truncal nodes metastases. The patients without truncal node metastases are subdivided based on the postoperative nodal stage (ypN).

in the latest TNM staging system in which the number of involved lymph nodes is the sole determining factor of the nodal status (4). However, the present study suggests that the presence of positive truncal nodes has important prognostic implications. It should be documented in the standard pathology report. The prognostic value of these nodes should be confirmed in larger multi-center series, but the inclusion of truncal nodes should be considered as a subcategory in future TNM staging systems.

In almost 63% of patients with suspicious truncal nodes

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Figure 2 Overall survival of 59 patients with cancer of the esophagus or gastro-esophageal junction with suspicion of positive truncal nodes on EUS or CT who underwent neoadjuvant chemo(radio)therapy followed by surgery. Patients are divided between those with pathology proven truncal node metastases and patients without truncal node metastases.

before neoadjuvant therapy, truncal node metastases were not present in the resection specimen, and in one third of patients not even a single node was positive. These results suggest that the eradication of lymphadenopathy (also of truncal nodes) with neoadjuvant therapy is possible and predicts good survival. However, as described before (17), it is also possible that pre-treatment screening is not very specific for assessing truncal nodes. Suspicious pretreatment node metastases were not proven with EUS-FNA in the present study, since positivity of truncal nodes was not a contraindication for surgery. Based on the study by Grotenhuis et al., the accuracy of CT imaging alone in detecting truncal node metastases is merely 70% (17). Furthermore, it should be realized that techniques for disease staging improved considerably during the time span of the study. The length of this study period [1994-2013] has also caused a certain heterogeneity in terms of treatment characteristics. A variation of both chemotherapy and CRT regimes was used. Despite these differences the type of neoadjuvant therapy was not significantly associated with overall survival on univariate analysis. This

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finding is consistent with that of previous trials comparing perioperative chemotherapy and preoperative CRT for esophageal carcinoma where no significant differences were demonstrated in terms of lymph node yield or survival (18). The operative approach (transhiatal versus transthoracic) did not seem to influence overall survival in our univariate analysis and based on recent literature we have no reason to expect that the switch towards minimally invasive surgery has had an effect on lymph node yield or survival (11,19). Another limitation is the lack of information on whether the truncal lymph nodes were within the radiation field. The question whether positivity of truncal lymph nodes was a failure of the pretreatment or just not treated (outside radiation field) cannot be answered. Consequently the question whether inclusion of positive truncal lymph nodes in the radiation field could have influenced the survival cannot be answered. Nevertheless, the low rate of positive truncal lymph nodes in the surgical specimen in patients with suspect truncal nodes at pre-staging does suggest an effect of preoperative treatment. Therefore, patients should not be declined neoadjuvant therapy followed by surgery based on pre-treatment characteristics of suspicious truncal nodes (20). Another limitation of the present study, and actually previous studies as well (5), is the difficulty to distinguish—both preoperatively and in the resection specimen-nodes along the left gastric artery from nodes near the celiac axis itself. Distance to the celiac trunk is hard to measure and it is not clear yet within which distance to the celiac trunk a node should be considered as a truncal node (5). Furthermore, in the present study also lymph nodes near the hepatic artery and splenic artery were considered as positive truncal nodes. However, these nodes were not separately marked. Assessing the nodal stations separately, might improve the adequacy of staging. For adenocarcinoma there are only few studies that describe the exact localization of mediastinal and abdominal lymph node metastases (21-23). Castoro et al. describe the localization of lymph node metastases in relation to neoadjuvant therapy and found no difference in celiac axis positive nodes between patients treated with surgery alone, neoadjuvant chemotherapy or neoadjuvant CRT (21).

The dismal prognosis of patients with positive truncal nodes in the surgical resection specimen warrants further prospective studies. Future trials assessing the accuracy of EUS and EUS-guided FNA and PET-CT scanning before and after neoadjuvant therapy and the influence of radiation fields are needed. There may even be place for diagnostic laparoscopy to sample truncal nodes in selected patients

Table 4 Prognostic factors for overall survival in patients with cancer of the esophagus or gastroesophageal junction who underwent neoadjuvant chemo (radiation) therapy followed by surgery

Prognostic factor	Median survival in months (95% Cl)	Univariate <sup>†</sup> (P value)	Multivariate*: HR (95% Cl); P value
Age (years)			
<65	51.84 (32.14–71.54)	0.239	
≥65	33.18 (23.97–42.40)		
Gender			
Male	41.40 (31.25–51.54)	0.124	
Female	72.64 (6.74–138.54)		
Histology			
Adenocarcinoma	43.63 (32.30–54.96)	0.692	
Squamous cell carcinoma	50.50 (25.86–75.14)		
Tumor location			
Mid thoracic esophagus	36.53 (18.88–54.18)	0.925	
Lower thoracic esophagus	48.85 (33.41–64.30)		
Gastroesophageal junction	43.63 (15.34–71.92)		
Neoadjuvant treatment			
Chemotherapy	41.66 (22.53–60.78)	0.882	
Chemoradiotherapy	44.03 (31.10–56.95)		
Operative approach			
Transhiatal esophagectomy	41.37 (24.29–58.50)	0.747	
Transthoracic esophagectomy	45.77 (33.39–58.14)		
Post treatment T-stage			
ypT0–ypT1	162.83 (37.78–287.88)	<0.001	0.062 (0.008–0.489); 0.008
урТ2–урТ4	33.02 (24.46–41.58)		
Post treatment N-stage			
ypN0	82.14 (34.58–129.70)	<0.001	0.209 (0.124–0.354); <0.001
ypN1	27.30 (18.63–35.97)		
ypN2	21.06 (14.79–27.33)		
ypN3	9.13 (3.88–14.38)		
Pathologic response primary tumor#			
TRG 1	162.83 (35.93–289.72)	<0.001	0.052 (0.007–0.418); 0.005
TRG >1	37.62 (28.72–46.52)		
Post treatment celiac node metastases			
No	54.74 (37.48–71.99)	<0.001	1.502 (1.038–2.175); <i>0.031</i>
Yes	17.15 (10.74–23.56)		
Radicality			
R0	44.03 (30.17–57.88)	0.021	1.302 (0.760–2.229); 0.336
R1	24.54 (6.97–42.12)		

Statistically significant P values are in italic.<sup>†</sup>, Log rank test; \*, multivariate Cox-regression analysis; <sup>#</sup>, TRG is only given for patients treated with neoadjuvant chemoradiation therapy. TRG, tumor regression grade according to Mandard; R0, microscopically radical resection; R1, microscopically tumor left behind; HR, hazard ratio; CI, confidence interval.

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after neoadjuvant therapy.

In our study it is shown that although patients with positive truncal nodes have a poor prognosis, their survival is still superior compared to patients treated with palliative chemotherapy for distant metastatic disease (24-27) and superior to patients treated with definitive CRT who developed celiac node failures (28). This observation suggests that the presence of truncal node metastases, both before and after neoadjuvant treatment, should not be an absolute contraindication for esophagectomy. However, when truncal node metastases are confirmed after neoadjuvant therapy, their impact on prognosis should be an explicit part of patient counselling.

At his moment there is no evidence to support the use of additional postoperative (chemo)therapy in patients with truncal node metastases, but the presence of these metastases should be a stratification factor in the upcoming trials on adjuvant therapy for esophageal cancer.

In summary, positive truncal nodes found in the resection specimen after neoadjuvant therapy identify a subgroup of patients with a dismal prognosis. It reflects a particularly aggressive disease behavior and should therefore be considered specifically during both preoperative and postoperative decision making.

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# Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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# Supplementary

Table S1 Preoperative treatment regimens of 462 patients with cancer of the esophagus or gastroesophageal junction who underwent neoadjuvant therapy followed by surgery

Neoadjuvant regimen	N (%)
Chemotherapy	88 (19.0)
Epirubicin, oxaliplatin and capecitabine (EOX)	16 (3.5)
Epirubicin, cisplatin and capecitabine (ECC)	4 (0.9)
Cisplatin and etoposide	59 (12.8)
Cisplatin and etoposide and hyperthermia	7 (1.5)
Chemotherapy (other schemes)	2 (0.4)
Chemoradiotherapy	374 (81.0)
Radiotherapy combined with carboplatin and paclitaxel	302 (65.4)
Radiotherapy combined with carboplatin, paclitaxel and panitumumab	37 (8.0)
Radiotherapy combined with carboplatin and paclitaxel and hyperthermia	31 (6.7)
Chemoradiotherapy (other schemes)	4 (0.9)