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Impact of increasing lymph node yield on staging, morbidity and survival after esophagectomy for esophageal adenocarcinoma

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ABSTRACT

Background: Extended lymphadenectomy during esophagectomy for esophageal cancer may increase survival, but also increase morbidity. This study analyses the influence of lymph node yield after transthoracic esophagectomy for esophageal adenocarcinoma on the number of positive lymph nodes, pathological N-stage, complications and survival.

Materials and methods: Consecutive patients undergoing transthoracic esophagectomy for esophageal adenocarcinoma between 2010 and 2020 were prospectively recorded (follow-up until January 2022). Lymph node yield was analyzed as continuous and dichotomous variable (≤30 vs. ≥31 nodes). The effect of lymph node yield on number of positive lymph nodes, complications, disease-free (DFS) and overall survival (OS) was assessed in multivariable regression analyses.

Results: 585 patients were included. Median lymph node yield increased from 25 (IQR 20–34) in 2010 to 39 (IQR 32–50) in 2020. Higher lymph node yield was associated with more positive lymph nodes (≥31 vs. ≤30 IRR 1.39, 95%CI 1.11–1.75). In 258 (y)pN + patients, the percentage of (y)pN3-stage increased with 14% between patients with ≤30 and ≥ 31 lymph nodes examined (p 0.014). Higher lymph node yield was not associated with more complications. Superior survival was seen in patients with ≥31 vs. ≤30 lymph nodes examined [*DFS*: HR 0.73, 95%CI 0.58–0.93, *OS*: HR 0.71, 95%CI 0.55–0.93)].

Conclusions: A lymph node yield of 31 or higher was associated with upstaging and superior survival after esophagectomy for esophageal adenocarcinoma, without increasing morbidity. Extended lymphadenectomy may therefore be regarded as an important part of the multimodal treatment of esophageal cancer.

1. Introduction

Esophageal cancer is the seventh most commonly occurring cancer worldwide, with over 604.000 new patients in 2020 [1]. The prognosis of esophageal cancer patients is slowly improving from a 5-year survival rate of only 5% in 1970, to 20% today [2]. After curative therapy, consisting of neoadjuvant chemo(radio)therapy and a surgical resection, 5-year survival rate is nowadays approximately 50% [3–5].

An important prognostic factor after esophagectomy is the pathological lymph node status. Lymph node status can be classified as N1, N2 or N3 (when 1–2, 3–6 and ≥7 lymph nodes are involved, respectively) [6,7]. A higher number of positive lymph nodes is associated with an impaired prognosis [8–10].

Although there are guidelines from the East on the extent of lymphadenectomy for squamous cell esophageal carcinoma, the exact extent to which lymph nodes should be dissected for esophageal adenocarcinoma (EAC) remains controversial. Several studies have established a minimum lymph node yield, varying

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from 15 to 30 [10–16]. Besides, the consequences of extended lymphadenectomy on staging, morbidity and survival are reported contradictory in literature [12,17–23]. The objective of this study was to analyze changes in lymph node yield over time in a tertiary referral center, and to investigate the impact of lymph node yield on number of positive lymph nodes, pathological N-stage, postoperative complications and survival in patients following esophagectomy for EAC.

2. Materials and methods

This retrospective study was conducted from a prospectively maintained database at the Amsterdam UMC in the Netherlands.

2.1. Patients

Consecutive patients who underwent transthoracic esophagectomy with gastric conduit reconstruction for EAC between January 2010 and December 2020, were eligible. Patients were excluded if they underwent non-elective or transhiatal resection, resection for other disease than EAC or if reconstruction was not performed by a gastric conduit. Patients were given the opportunity to opt-out if they didn't agree with the usage of their medical data for research. The STROBE guidelines were used to ensure correct reporting of study results [24].

2.2. Treatment

Patients were diagnosed and clinically staged according to the Dutch national guideline [6,7,25]. Neoadjuvant chemoradiotherapy was routinely administered and usually consisted of chemoradiotherapy since the implementation of the CROSS scheme in 2004 (carboplatin AUC and paclitaxel 50 mg/m2 chemotherapy on day 1, 8, 15, 22 and 29 with concurrent 41.4 Gy radiotherapy 23 fractions) [3–5]. Since 2010, ≥80% of all patients in the current center received neoadjuvant chemoradiotherapy [26]. Perioperative chemotherapy was administered in patients with tumors with large gastric involvement.

All patients underwent either open or minimally invasive transthoracic esophagectomy with gastric conduit reconstruction, either intrathoracic or cervical anastomosis and two-field lymphadenectomy. Two-field lymphadenectomy included stations 4R/L (lower paratracheal), 5 (aortopulmonary window), 7 (subcarinal), 8 M/Lo (middle and lower para esophageal), 9 R/L (pulmonary ligament), 15–20 (diaphragmatic, paracardial, left gastric, common hepatic, splenic and celiac trunk) and lymph nodes along the hepatoduodenal ligament. In case of McKeown esophagectomy, station 8U (upper para esophageal) was additionally resected. When indicated based on preoperative imaging or in case of biopsy-proven lymph node involvement, station 2 R/L (upper paratracheal) was additionally resected.

During the study period, several changes have been made to the surgical management of esophageal cancer patients in this tertiary referral center (Fig. 1). In 2010, a shift from open to minimally invasive McKeown took place, followed by the gradual replacement of minimally invasive McKeown esophagectomy by minimally invasive Ivor Lewis esophagectomy in 2013. Hereafter, McKeown esophagectomy was reserved for proximal or mid-esophageal tumors, and for patients with paratracheal lymph node metastases or radiation fields above the carina. Transhiatal esophagectomy remained reserved for frail patients, unfit to undergo transthoracic surgery. The extent of lymphadenectomy has also expanded over the years. In 2013, standard supracarinal lymphadenectomy was introduced (station 4R and 5). Also in 2013, a minimum lymph node yield of 15 was implemented as quality indicator of upper gastrointestinal surgery in the nationwide Dutch Upper Gastrointestinal Cancer Audit (DUCA), and ex vivo back table dissection of the specimen for lymph nodes was implemented in the context of the TIGER study [27,28]. Lastly in 2014, paratracheal lymphadenectomy was extended to station 4L, and the 'flap and wrap' reconstruction was introduced to protect intrathoracic anastomoses against severe leakage [26].

2.3. Pathology

For histopathologic examination, both the esophageal resection specimens and separately sent lymph node stations were processed by the pathology department. The specimen was embedded in paraffin, fixated in formalin overnight and carefully analyzed for remaining lymph nodes. The separately submitted lymph nodes were embedded in paraffin as well (nodes less than 5 mm completely, larger ones in slices of 3–4 mm thick). With microscopic evaluation, both the lymph nodes on the resection specimen, as well as the separately sent lymph nodes were counted. Initial microscopic evaluation was performed by standard H&E staining, or on indication with additional keratin stains. Subsequently, the total lymph node yield as well as the number of positive lymph nodes and their location was registered in the pathology report.

2.4. Follow up

Patients were followed up until 5 years postoperatively. The first year after surgery, patients were seen every 3 months, the 2nd-4th year after surgery every 6 months, and once yearly until the 5th postoperative year. Radiology imaging and/or endoscopy was performed when indicated based on signs and symptoms. Follow-up data was collected until January 2022.

2.5. Study outcomes

Study outcomes were the median lymph node yield per year, and the association of lymph node yield with positive lymph node yield, pathological N-stage, complications, disease-free (DFS) and overall survival (OS). DFS was defined as the time from surgery to recurrent disease or death (whichever occurred first), or last follow up. OS was defined as the time from surgery to death or last follow up.

2.6. Statistical analysis

For descriptive statistics, variables were compared using independent *T*, Pearson Chi-square or Fisher's Exact tests when appropriate, and outcomes were reported accordingly as either the mean ± standard deviation (SD) or numbers with corresponding percentages. Trends in lymph node yield over time were visualized in a bar chart and presented as median with interquartile range (IQR). Lymph node yield was in all analyses entered both as continuous variable and dichotomous variable (≤30 and ≥ 31 lymph nodes examined). This particular cut-off was considered because 30 is the minimum recommended lymph node yield in previous literature [11,16,27,29]. To investigate the association between lymph node yield and number of positive lymph nodes, a negative binomial regression model was used (results reported as incidence rate ratio (IRR) with 95% confidence interval (CI)). To correct for confounding, cT-stage, cN-stage, neoadjuvant therapy and surgical approach were added to the multivariate model as these factors may influence the (positive) lymph node yield. To study the effect of lymph node yield on the pathological N-stage, Chi2 test was used. To study the effect of lymph node yield on postoperative complications, binary logistic regression was

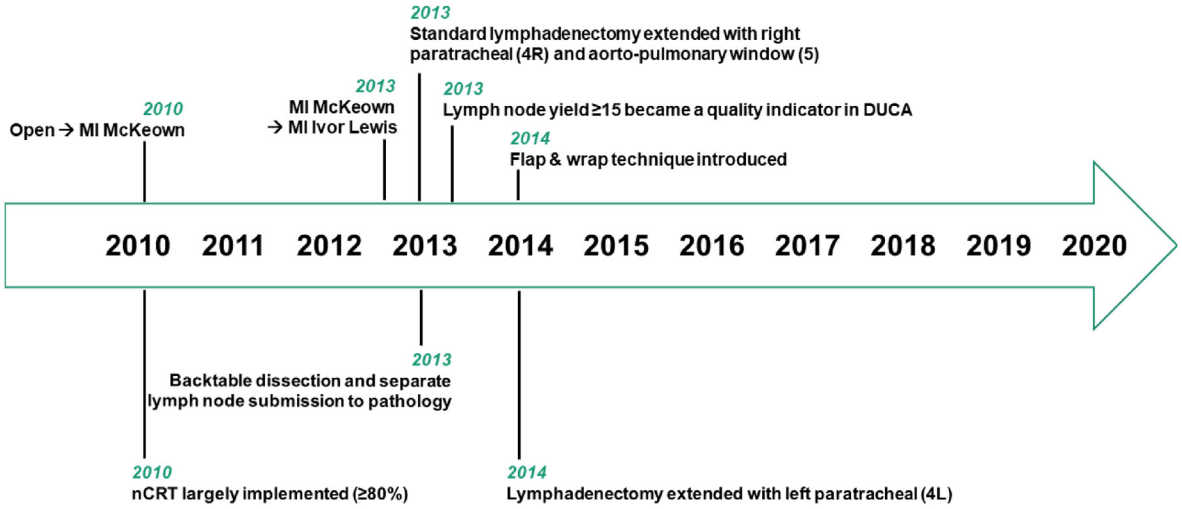

Fig. 1. Changes in the extent of lymphadenectomy visualized in time.
Abbreviations: MI = Minimally Invasive, nCRT = Neoadjuvant ChemoRadioTherapy, DUCA = Dutch Upper Gastrointestinal Cancer Audit.

performed (corrected for ASA score, BMI, cT-stage, cN-stage, neoadjuvant therapy and surgical approach as these factors may impact lymph node yield or the occurrence of complications; results reported as odds ratios (OR) with 95%CI). The influence of lymph node yield on survival was assessed with Kaplan-Meier curves, log-rank test and multivariable Cox regression analyses, corrected for cT-stage, cN-stage, neoadjuvant therapy, surgical approach and operation year (2010–2012/2013-2020), and reported as 3-year survival probabilities and hazard ratios (HR) with 95%CI. Missing data was 1.5% and handled with complete case analysis [30]. A p-value <0.05 was considered to be statistically significant. Data were analyzed using IBM SPSS Statistics Version 28.0.

3. Results

Between 2010 and 2020, 935 patients underwent esophagectomy for cancer. After applying the in- and exclusion criteria, 350 patients were excluded (supplementary A). Table 1 outlines the baseline characteristics of all 585 included patients. Their mean age at surgery was 63.5 ± 9.4 years. The majority of patients was male (85.3%) and most tumors were located in the distal esophagus (79.3%).

The median lymph node yield in the entire study period was 32 (IQR 24–40). Median lymph node yield increased from 25 lymph nodes (IQR 20–34) in 2010 to 39 lymph nodes (IQR 32–50) in 2020. Fig. 2 visualizes the median lymph node yield over the years in a bar chart.

3.1. Positive lymph nodes

In multivariable analyses with lymph node yield as continuous variable, patients with a higher lymph node yield were more likely to have positive lymph nodes identified at pathological examination. For every extra lymph node examined, the risk of having positive lymph nodes increased by 1.019 times (IRR 1.019, 95%CI 1.01–1.03, p < 0.001) (Table 2).

When categorizing lymph node yield, 26 patients (4.4%) had <15 lymph nodes examined, 251 patients (42.9%) had 15-30 lymph nodes examined and 308 patients (52.6%) had 31 or more lymph nodes examined. Because only 4% of the study population had <15 lymph nodes examined, and because this is well-consensus for inadequate lymph node yield in esophageal cancer (a minimum lymph node yield of 15 nodes is one of the DUCA quality indicators), these patients were excluded from further categorized analyses.

The risk of having positive lymph nodes increased by 1.389 times (IRR 1.389, 95%CI 1.11–1.75) by having a lymph node yield of ≥31 instead of ≤30, p 0.005 (Table 3). In patients with positive lymph nodes at pathological examination (n = 244), the pathological N-stage increases with increasing lymph node yield (p 0.014). When ≤30 lymph nodes were examined, 11% of patients had pN3-stage vs. 25% of patients with ≥31 lymph nodes examined (Table 4).

3.2. Complications

Among all 559 patients, 333 patients (59.6%) had one or more complications during admission or within 30 days after discharge. Pneumonia, pneumothorax, cardiac, urologic and thromboembolic complications, recurrent nerve injury and chyle leakage were equally common within the two groups. The incidence of pulmonary and gastrointestinal complications in general, and anastomotic leakage was higher in patients with ≤30 lymph nodes examined than in patients with ≥31 lymph nodes examined (supplementary B). Patients with a higher lymph node yield were not more likely to have postoperative complications, neither with lymph node yield as continuous variable (OR 1.01, 95%CI 0.99–1.02, p 0.475), nor as dichotomous variable (≥31 vs. ≤30: OR 0.859, 95% CI 0.60–1.24, p 0.412) (supplementary C).

3.3. Survival

3-year DFS rate for patients with ≤30 lymph nodes examined was 41.4%; this was 49.5% for patients with ≥31 lymph nodes examined (p 0.034) (Fig. 3A). Median DFS was 24 months (95%CI 17.44–29.7) for patients with a lymph node yield of ≤30 vs. 36 months (95%CI 21.66–49.80) for patients with a lymph node yield of 31 or more, p 0.034. In multivariable analysis, superior DFS was seen in patients with ≥31 lymph nodes examined compared to patients with ≤30 lymph nodes examined [HR 0.73, 95%CI 0.58–0.93, p 0.010]).

3-year OS was 49.7% for patients with ≤30 lymph nodes examined and 61.5% for patients with 31 or more lymph nodes examined (p 0.011) (Fig. 3B). Median OS was 36 months (95%CI

Table 1
Characteristics of 585 included patients, stratified by lymph node yield.

	All patients n = 585 n (%)	Lymph node yield <15 n = 26 n (%)	Lymph node yield 15–30 n = 251 n (%)	Lymph node yield ≥31 n = 308 n (%)	p-value
Age in years, mean ± SD	63.5 ± 9.4	64.8 ± 9.7	62.5 ± 9.5	64.2 ± 9.2	**0.254**
Sex					
Female	86 (14.7)	7 (26.9)	41 (16.3)	38 (12.3)	0.087
Male	449 (85.3)	19 (73.1)	210 (83.7)	270 (87.7)	
ASA score					
I	157 (26.8)	8 (30.8)	86 (34.4)	63 (20.5)	**0.004**
II	315 (53.8)	15 (57.7)	116 (46.2)	184 (59.7)	
III	113 (19.3)	3 (11.5)	49 (19.5)	61 (19.8)	
Clinical T-stage					
cT1	38 (6.7)	1 (4.0)	13 (5.2)	24 (8.1)	**0.008**
cT2	112 (19.6)	5 (20.0)	55 (22.2)	52 (17.5)	
cT3	410 (71.9)	16 (64.0)	174 (70.2)	220 (74.1)	
cT4	10 (1.8)	3 (12.0)	6 (2.4)	1 (0.3)	
Clinical N-stage					
cN0	194 (33.6)	5 (20.0)	83 (33.3)	106 (35.0)	0.066
cN1	263 (45.6)	15 (60.0)	126 (50.6)	122 (40.3)	
cN2	111 (19.2)	5 (20.0)	36 (14.5)	70 (23.1)	
cN3	9 (1.6)	0 (0.0)	4 (1.6)	5 (1.7)	
Localization					
Mid	15 (2.6)	1 (3.8)	8 (3.2)	6 (1.9)	0.670
Distal	464 (79.3)	21 (80.8)	201 (80.1)	242 (78.6)	
Gastroesophageal Junction	106 (18.1)	4 (15.4)	42 (16.7)	60 (19.5)	
Neoadjuvant treatment					
None	38 (6.5)	1 (3.8)	9 (3.6)	28 (9.1)	**0.028**
Chemotherapy	28 (4.8)	0 (0.0)	9 (3.6)	19 (6.2)	
Chemoradiotherapy	519 (88.7)	25 (96.2)	233 (92.8)	261 (84.7)	
Approach					
Open	72 (12.3)	8 (30.8)	44 (17.5)	20 (6.5)	**<0.001**
Minimally Invasive	513 (87.7)	18 (69.2)	207 (82.5)	288 (93.5)	
Anastomosis					
Cervical	192 (32.8)	19 (73.1)	106 (42.2)	67 (21.8)	**<0.001**
Intrathoracic	393 (67.2)	7 (26.9)	145 (57.8)	241 (78.2)	
Pathological (y)pT-stage					
(y)pT0	113 (19.3)	6 (23.1)	34 (13.5)	73 (23.7)	**<0.001**
(y)pT1	115 (19.7)	1 (3.8)	53 (21.1)	61 (19.8)	
(y)pT2	85 (14.5)	3 (11.5)	36 (14.3)	46 (14.9)	
(y)pT3	245 (41.9)	11 (42.3)	108 (43.0)	126 (40.9)	
(y)pT4	5 (0.9)	0 (0.0)	5 (2.0)	0 (0.0)	
(y)pTx	22 (3.8)	5 (19.2)	15 (6.0)	2 (0.6)	
Pathological (y)pN-stage					
(y)pN0	327 (55.9)	12 (46.2)	141 (56.2)	174 (56.5)	**0.023**
(y)pN1	130 (22.2)	7 (26.9)	64 (25.5)	59 (19.2)	
(y)pN2	83 (14.2)	7 (26.9)	34 (13.5)	42 (13.6)	
(y)pN3	45 (7.7)	0 (0.0)	12 (4.8)	33 (10.7)	

Abbreviations: ASA = American Society Anesthesiology, SD = Standard Deviation.

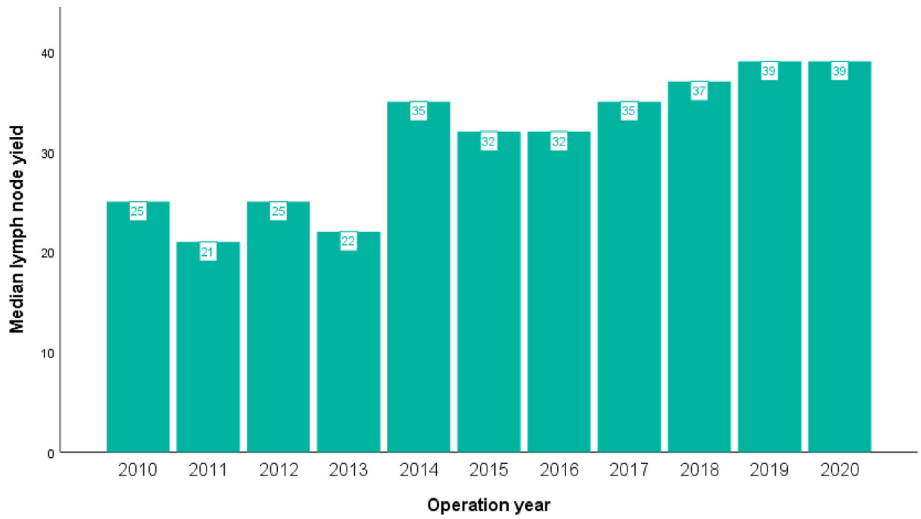

Fig. 2. Median lymph node yield over the years.

Table 2
Influence of lymph node yield as continuous variable on the number of positive lymph nodes.

Independent variable	Coefficients	p-value	IRR (95%CI)
Univariable analysis			
Intercept	−0.226	0.153	0.797(0.585–1.087)
Lymph node yield	0.023	**<0.001**	1.024(1.015–1.032)
Multivariable analysis[a]			
Intercept	−1.433	**<0.001**	0.239(0.118–0.481)
Lymph node yield	0.019	**<0.001**	1.019(1.011–1.028)
cT-stage			
cT1 (reference)			
cT2	0.126	0.790	1.134(0.451–2.852)
cT3	1.206	**0.008**	3.340(1.374–8.119)
cT4	1.086	0.081	2.908(0.875–9.664)
cN-stage			
cN0 (reference)			
cN1	0.351	**0.011**	1.421(1.086–1.860)
cN2	0.819	**<0.001**	2.268(1.656–3.107)
cN3	0.839	**0.033**	2.313(1.068–5.008)
Neoadjuvant therapy			
No (reference)			
Yes	−0.121	0.787	0.886(0.369–2.130)
Surgical approach			
Open (reference)			
Minimally invasive	0.114	0.517	1.121(0.794–1.582)

Abbreviations: CI = Confidence Interval, IRR = Incidence Rate Ratio.
[a] = corrected for cT-stage, cN-stage, neoadjuvant therapy and surgical approach.

Table 3
Influence of lymph node yield as categorical variable on the number of positive lymph nodes.

Independent variable	Coefficients	p-value	IRR(95%CI)
Univariable analysis			
Intercept	0.366	**<0.001**	1.441(1.225–1.695)
Lymph node yield			
≤30 (reference)			
≥31	0.404	**<0.001**	1.498(1.211–1.854)
Multivariable analysis[a]			
Intercept	−1.146	**0.001**	0.318(0.161–0.745)
Lymph node yield			
≤30 (reference)			
≥31	0.329	**0.005**	1.389(1.106–1.745)
cT-stage			
cT1 (reference)			
cT2	0.212	0.654	1.236(0.489–3.128)
cT3	1.289	**0.005**	3.629(1.485–8.866)
cT4	0.900	0.181	2.460(0.658–9.203)
cN-stage			
cN0 (reference)			
cN1	0.411	**0.003**	1.508(1.148–1.980)
cN2	0.870	**<0.001**	2.386(1.738–3.277)
cN3	0.910	**0.021**	2.484(1.149–5.370)
Neoadjuvant therapy			
No (reference)			
Yes	−0.199	0.657	0.820(0.341–1.969)
Surgical approach			
Open (reference)			
Minimally invasive	0.272	0.143	1.312(0.913–1.887)

Abbreviations: CI = Confidence Interval, IRR = Incidence Rate Ratio.
[a] = corrected for cT-stage, cN-stage, neoadjuvant therapy and surgical approach.

26.61–45.06) for patients with a lymph node yield of ≤30 vs. 58 months (95%CI 50.10–62.90) for patients with a lymph node yield of 31 or more, p 0.011. In multivariable analysis, superior OS was seen in patients with ≥31 lymph nodes examined compared to patients with ≤30 lymph nodes examined [HR 0.71, 95%CI 0.55–0.93, p 0.011].

Table 4
Pathological N-stages for different lymph node yields.

	pN1		pN2		pN3	
	N	%	N	%	N	%
≤30	64	58.2	34	30.9	12	10.9
≥31	59	44.0	42	31.3	33	24.6
All patients	*123*	*50.4*	*76*	*31.1*	*45*	*18.4*

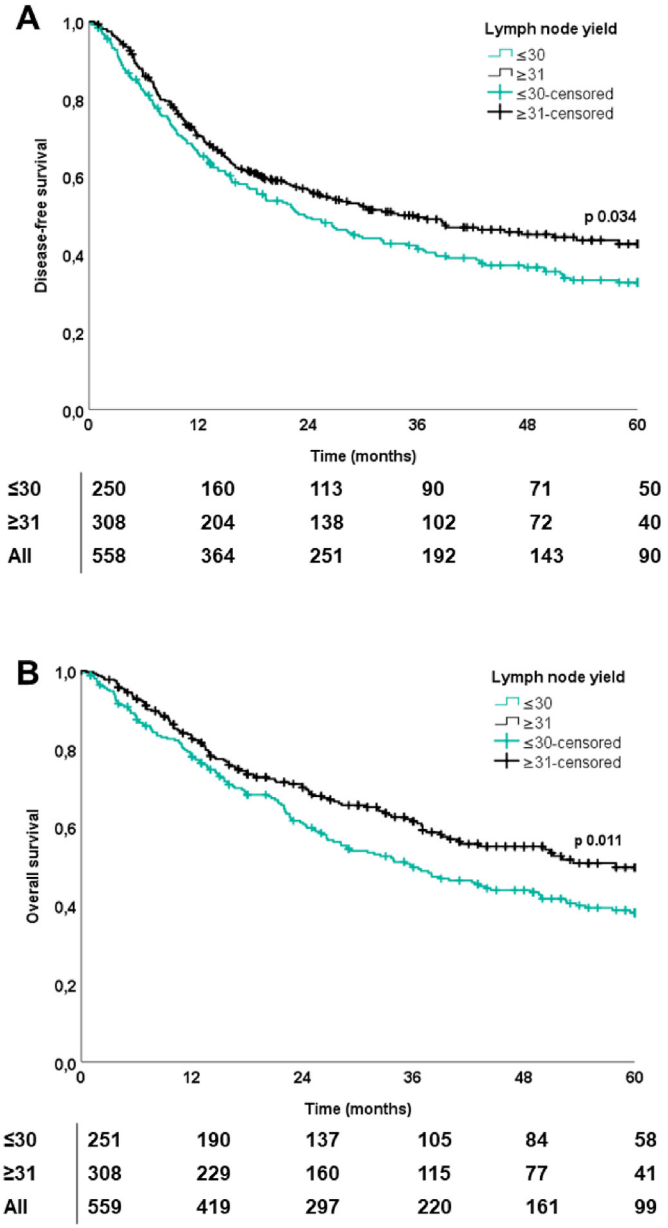

Fig. 3. Impact of lymph node yield on survival in 559 esophageal adenocarcinoma patients treated with esophagectomy in the period 2010–2018.

4. Discussion

This study analyzed trends in lymph node yield after esophagectomy for EAC in a tertiary referral center over time, and investigated the impact of lymph node yield on the number of positive lymph nodes, pathological N-stage, complications and

survival. Lymph node yield has increased significantly during the study period. A higher lymph node yield was associated with a higher number of positive lymph nodes, and the disease of patients with a lymph node yield of ≥31 was 14% more often classified as pN3-stage compared to the disease of patients with a lymph node yield of ≤30. A lymph node yield of ≥31 was associated with superior survival, without leading to higher complication rates.

The median lymph node yield increased with 14 lymph nodes (56%) between 2010 and 2020. The changes in the technique of lymphadenectomy and the start of standard dissection of supracarinal lymph nodes, have almost certainly made a major contribution to this. Another contributing factor is undoubtedly the method of lymph node submission to pathology. Previously, specimens were submitted to the pathologist en-bloc, with lymph nodes still attached. Ex vivo dissection of the lymph nodes by the surgeon helps the pathologist in identifying lymph node tissue and determining its location. A previous study showed that ex vivo lymphadenectomy increases lymph node yield in gastric cancer surgery, and the current study suggests that this is also the case in esophageal cancer surgery [31,32]. Furthermore, the implementation of the DUCA quality parameter of resecting a minimum of 15 lymph nodes has probably led to higher awareness by both surgeons and pathologists for the importance of dissection, identification and pathological evaluation of lymph nodes [27]. All of the above shows that the increasing focus on adequate lymphadenectomy and pathological examination of lymph nodes resulted in a higher lymph node yield after esophageal cancer surgery.

The added value of a high lymph node yield has been a topic of discussion amongst esophageal cancer surgeons for several years. The lymphatic distribution pattern of esophageal cancer is unpredictable due to the very complex lymphatic system surrounding the esophagus, and seems to depend on multiple factors such as tumor location, histology, invasion depth and neoadjuvant treatment. Most efficiently is probably a lymphadenectomy strategy for each individual patient, which this is currently being established in the prospective observational multicenter TIGER study [28]. The TIGER study aims to identify the lymph node stations that should be resected in relation to patient, tumor and treatment characteristics. As long as the evidence is not conclusive, we need to provide adequate lymphadenectomy in all patients to ensure optimal pathological staging, especially since clinical staging has been proven to be unreliable and often not in accordance with pathological staging [33]. We hypothesized that the more lymph nodes are dissected, the lower the possibility of missing positive lymph nodes and therewith an underestimation of pathological stage and incorrect prognostication. In this study, a higher lymph node yield was associated with a higher opportunity to identify positive lymph nodes, which is consistent with findings in previous literature [19,34,35]. Another aspect emphasizing the importance of optimal pathological staging is evident from the adjuvant treatment options for esophageal cancer patients with residual pathological disease (at least ypT1 or ypN1). Recently, adjuvant nivolumab was found to double disease-free survival and reduce the risk of recurrence or death with 31%, in patients with pathological lymph node positive disease [36]. The indication for adjuvant nivolumab for patients with residual pathological disease could possibly be withheld if patients are operated by esophagectomy with limited lymphadenectomy, reducing the chance of tumor positive lymph nodes in the resection specimen.

It has been often suggested that the increased surgical trauma of an extended lymph node dissection results in more complications [21–23]. In the present study, extended lymphadenectomy did not result in increased morbidity. The incidence of several specific complications even decreased with increasing lymph node yield, which is probably due to the implementation of minimally invasive Ivor Lewis esophagectomy in the more recent years of this study, with accompanying increasing lymph node yield. The fact that a higher lymph node yield did not result in more complications, shows that extended lymphadenectomy can be performed safely in expert centers.

Besides the prognostic value of a high lymph node yield in terms of more reliable staging, the therapeutic value of removing more lymph nodes is also frequently debated. Especially results of studies investigating lymph node yield and survival in patients treated with neoadjuvant chemo(radio)therapy are conflicting [18,37]. One study concluded that a threshold of 52 lymph nodes was requisite to achieve improved DFS in patients treated with neoadjuvant therapy [38].

The current study found a 3-year OS benefit of almost 12% when comparing a lymph node yield of ≤30 with ≥31 when carefully regarding important confounders. This difference in survival is substantial, and also larger than survival differences reported in previous oncological trials comparing multimodal therapy with surgery alone, e.g., the adenocarcinoma subpopulation of the CROSS trial, comparing neoadjuvant chemoradiotherapy vs. surgery alone for esophageal cancer [3,4]. This underlines that the quality of lymphadenectomy in esophageal adenocarcinoma might be as important as any additional oncological therapy. The improved survival of patients with a lymph node yield of ≥31 found in the current study, should however be interpreted with some caution, as there might be several explanations for this. Primarily, it is presumable a result of improved cancer control by adequate removal of the lymphatics draining the esophageal tumor. This oncological safety reduces the possibility of leaving potential pathological tissue behind and therewith the possibility of (early) recurrent disease. Secondarily, the improvement in high lymph node yield patients' prognosis could be partly explained by time lead bias. In the past few years, synchronous with the increasing lymph node yield, several other improvements have been accomplished in the management of esophageal cancer patients (e.g. the introduction of minimally invasive Ivor Lewis esophagectomy and better complication management). These factors have also significantly improved esophageal cancer patients' outcomes. However, it is unlikely that this largely explains the survival benefit of a high lymph node yield because we corrected survival analyses for, amongst others, neoadjuvant therapy, surgical approach and operation year.

This study has some limitations. The specific locations of examined lymph nodes were not available for analysis. As a consequence, it is unknown whether the same lymph nodes were staged as positive in the cN and (y)pN staging, nor could we separately analyze the influence of dissection of specific lymph node stations or thoracic versus abdominal lymph node yield on survival. Another limitation is that the final lymph node yield does not directly correspond with the extent of lymphadenectomy, as lymph node yield is not only affected by the surgeon, but also by the use of neoadjuvant therapy and the identification methodology by the pathologist.

In this study we used the pathological lymph node yield to quantify the extent of lymphadenectomy, however, this is in fact a proxy of the surgical radicality. In essence, the value of cancer surgery is merely what is left behind in the patient instead of what is resected. Future research should aim to provide an intraoperative metric by capturing photos/videos during surgery, and to use these photo and video assessments to determine the quality of esophageal cancer surgery.

In conclusion, a vast increase in lymph node yield after esophagectomy for EAC is demonstrated between 2010 and 2020 in this tertiary referral center. A lymph node yield of ≥31 led to higher pathological N-stages and superior survival, without leading to

higher complication rates. Extended lymphadenectomy in esophagectomy is therefore a valuable adjunct to multimodal treatment, and should be standard of care in esophageal cancer surgery, irrespectively of choice of neoadjuvant therapy.

Disclosures

None of the authors declared to have competing interests. M.I.v.B.H. is consultant for Mylan, Johnson & Johnson, Alesi Surgical, BBraun and Medtronic, and received research grants from Stryker. None of these companies were involved in the design, conduct, nor analysis of this study. The remaining authors have nothing to declare.

CRediT authorship contribution statement

Sofie P.G. Henckens: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Eliza R.C. Hagens:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Mark I. van Berge Henegouwen:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. **Sybren L. Meijer:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Wietse J. Eshuis:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. **Suzanne S. Gisbertz:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.07.012.

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