Ann Surg Oncol (2020) 27:692–700
https://doi.org/10.1245/s10434-019-07905-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Impact of Lymphadenectomy on Survival After Unimodality Transthoracic Esophagectomy for Adenocarcinoma of Esophagus

A. W. Phillips, MD, MA, FRCSEd (Gen.Surg)[1,2], K. Hardy, BSc[1], M. Navidi, MB, ChB, FRCSEd (Gen.Surg)[1], S. K. Kamarajah, BMedSci, MBChB[1,3], A. Madhavan, MB, ChB, MRCS[1], A. Immanuel, MD, FRCSEd[1], and S. M. Griffin, OBE, MD, PRCSEd[1]

[1]Northern Oesophago-Gastric Cancer Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK; [2]School of Medical Education, Newcastle University, Newcastle upon Tyne, UK; [3]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

ABSTRACT

Background. Debate remains regarding the extent of lymphadenectomy required with esophagectomy. In patients who receive neoadjuvant treatment, this may address lymph node metastases. However, patients with early disease and those with comorbidities may not receive neoadjuvant treatment. The aim of this study is to determine the impact of lymph node yield and location on prognosis in patients undergoing esophagectomy without neoadjuvant treatment.

Patients and Methods. Data from consecutive patients with potentially curable adenocarcinoma of the esophagus or gastroesophageal junction were reviewed. Patients were treated with transthoracic esophagectomy and two-field lymphadenectomy. Outcomes according to lymph node yield were determined. The prognosis of carrying out less radical lymphadenectomy was calculated according to three groups: exclusion of proximal thoracic nodes (group 1), minimal abdominal lymphadenectomy (group 2), and minimal abdominal and thoracic lymphadenectomy (group 3).

Results. 357 patients were included. Median survival was 78 months [confidence interval (CI) 53–103 months]. Absolute lymph node retrieval was not related to survival ($p = 0.920$). An estimated additional 4 (2–6) cancer-related deaths was projected if group 1 nodes were omitted, 15 (11–19) additional deaths if group 2 nodes were omitted, and 4 (2–6) deaths if group 3 nodes were omitted. Minimal lymphadenectomy (groups 1, 2, and 3) was projected to lead to 19 (15–23) additional cancer-related deaths.

Conclusions. Extensive lymphadenectomy allows accurate staging. In patients who do not receive neoadjuvant treatment, it may confer a survival benefit. The number of lymph nodes retrieved may not be a good surrogate for extent of lymphadenectomy, and correlation with location is required.

Prognosis from potentially curable esophageal cancer has improved with the use of neoadjuvant treatment.[1,2] However, early-staged cancers are still treated with unimodality surgery.[3] In addition, patients who are felt to be too high risk to receive neoadjuvant treatment may be offered surgery alone as a curative treatment.

Debate remains regarding the value of radical lymphadenectomy.[4–7] This may be particularly true in those deemed to have an early oncological stage. However, up to 23% of T1b cancers have been shown to have lymph node metastases.[8,9] Extended lymphadenectomy remains advocated by many guidelines,[3,10] but some would stipulate that this has the additional risk of increased surgical morbidity and would not perform such a dissection, particularly in "early" cancers.[11]

It has been previously theorized that greater lymphadenectomy results in removal of potential metastatic cancers and associated lymph nodes, reducing the potential spread of the disease. In addition there is the potential for

© Society of Surgical Oncology 2019

First Received: 16 June 2019;
Published Online: 11 October 2019

A. W. Phillips, MD, MA, FRCSEd (Gen.Surg)
e-mail: awphillips@doctors.net.uk

removal of micrometastases, which may be present in up to 50% of N0 cancers.[12] It remains unclear how these may impact on long-term outcomes.[12–15]

Several studies have sought to establish the importance of lymphadenectomy for survival, usually using lymph node yield as a method of establishing the extent of lymphadenctomy.[4] However, lymph node yield does not necessarily correlate with extent of lymphadenectomy.[16,17]

A previous study from the authors evaluated the impact of extent of lymphadenectomy on survival in patients receiving neoadjuvant chemotherapy in addition to transthoracic esophagectomy and radical en bloc two-field lymphadenectomy.[17] The previous study demonstrated that, whilst absolute lymph node count did not impact on survival, minimal lymphadenectomy could potentially lead to a 23% reduction in survival in node-positive patients. Surgical approach may influence which lymph nodes can be retrieved.[16] A transhiatal approach, whilst allowing abdominal lymph nodes to be removed, may prevent higher mediastinal nodes around the bronchus and trachea from being obtained. It is also possible to perform a less radical resection in the abdomen, which leaves celiac, hepatic, and proximal splenic nodes in situ, and further, some surgeons will choose to carry out a minimal lymphadenectomy in the mediastinum, leaving behind paraaortic and thoracic duct nodes.[18] The implication of leaving lymph nodes with metastatic deposits behind is not conclusive, but it may impact on long-term prognosis.

The aim of this study is to evaluate the impact of lymph node yield and also lymph node location in patients treated with unimodality transthoracic esophagectomy and two-field lymphadenectomy for esophageal adenocarcinoma.

PATIENTS AND METHODS

Patient Population

A contemporaneously maintained database containing all patients with cancers of the esophagus, gastroesophageal junction (GEJ), and stomach was reviewed. The data were sorted to leave only patients with adenocarcinoma of the esophagus and GEJ who underwent esophagectomy with two-field lymphadenectomy without undergoing neoadjuvant treatment. Those with unresectable tumors or palliative resections were excluded. Patients who underwent endoscopic mucosal resection (EMR) followed by esophagectomy were included. All patients who fulfilled the inclusion criteria and underwent surgery between January 2000 and November 2017 were included. Ethics approval was gained from Newcastle University (Ref. No. 8169/2018).

Staging and Treatment

Patient initial staging was performed using endoscopy and histological biopsy, endoscopic ultrasound, and thoracoabdominal computed tomography. PET (CT) was not part of routine staging in patients treated earlier in the time period but has become routine for all patients. UICC-TNM 7 was used to stage all patients in the study.[19]

Patients staged clinically with T2 N0 disease or earlier are offered surgery as unimodality treatment as per institution policy. Those with more advanced disease T3+ or N+ are usually offered multimodal treatment. However, patients with advanced disease with comorbidities that preclude neoadjuvant treatment (e.g., poor glomerular filtration rate) may be offered unimodality surgery.

Operative Treatment

Patients who underwent standardized transthoracic esophagectomy with two-field lymphadenectomy for adenocarcinoma as previously described were included.[20] As per local protocol, after surgery, all removed lymph nodes were dissected from the specimen by the operating surgeon and placed into individual histological posts for further analysis.[21] The following lymph nodes were presented separately to the pathologist: subcarinal LN, left and right bronchial LN, right paratracheal LN, paraesophageal LN, paraaortal/thoracic duct LN, left and right paracardial LN, lesser curve LN, left gastric artery LN, common hepatic LN, proximal splenic artery LN, and celiac trunk LN.

Pathology

All pathology reports were carried out by a specialist gastrointestinal pathologist following standardized proforma in line with guidelines produced by the Royal College of Pathologists.[22] The following was reported: tumor type and differentiation, depth of tumor invasion, total lymph node number, lymph node sites, and resection margins.

Follow-Up and Definition of Recurrence

Following their surgery, patients were seen in outpatient clinics at 3–6-month intervals for years 0–2, then at 6- or 12-month intervals for 2–5 years. Following the 5-year point, patients were seen annually, up to 10 years after surgery, when they were then discharged from consultant care if there were no signs of disease recurrence or areas for concern. Disease recurrence was established clinically and confirmed with imaging (CT or endoscopy), with or without histological confirmation.

Lymph Node Groupings

Lymph node analysis was performed in two different ways. One looked at total lymph node number, while the other looked at the location of the lymph nodes removed. For the former, absolute count analysis was performed and yields were grouped into quartiles as previously performed: 0–20, 21–28, 29–36, > 36.[23,24]

As only patients with positive lymph nodes could benefit from extended lymphadenectomy, only they were included, with lymph node-negative patients being excluded from subsequent lymph node analysis.

Extent of lymphadenectomy analysis involved splitting node locations into the following groups, with nodes not normally being removed for given surgical methods being identified:

1. Transhiatal resection: subcarinal, bronchial, and paratracheal nodes would not be resected
2. Minimal abdominal lymphadenectomy: celiac axis, hepatic, and splenic lymph nodes would not be resected
3. Minimal chest lymphadenectomy: paraaortic and thoracic lymph nodes would not be resected

The theoretical estimation of extra cancer-related deaths was based on the hypothesis that those patients with positive nodes in one of the described extended fields, who survived, would not have survived with a less extensive lymphadenectomy since tumor was left in situ.

Statistical Analysis

Statistical calculations were carried out using SPSS software version 22. Chi squared or Fisher exact test was used for comparing categorical data. Mann–Whitney *U* test was used to compare continuous variables. Kaplan–Meier analysis and life tables were used for calculation of 5-year survival rates. Survival calculations for each of the extent of lymphadenectomy groups were based on looking at the survival in each of the groups amongst patients who were node positive in that group and assuming these patients would have not survived 5 years had those nodes been left in place. Multivariable Cox regression analysis was carried out to identify independent prognostic factors. All factors with p value < 0.20 on univariate analysis were entered into this multivariate analysis. p values < 0.05 (two sided) were considered to be statistically significant.

RESULTS

Between January 2000 and November 2017, 357 patients underwent treatment for esophageal or GEJ adenocarcinoma with primary transthoracic esophagectomy. Twelve patients (3.4%) died in hospital.

Within this cohort, 289 (81%) patients were male and the median age was 65 (34–83) years. Approximately 45% (162) of patients had a T3 tumor or positive nodes on preoperative staging who would ordinarily have been considered for neoadjuvant treatment but were not offered this due to concerns it may significantly decondition them and prevent a subsequent operation, 195 (55%) patients being stage T2 N0 or earlier. The tumor was deemed esophageal in 199 (56%) of patients and at the GEJ (Siewert type 1 or 2) in 158 (44%) of patients (Table 1).

A greater proportion of patients with GEJ cancer were found to be node positive (44%) than in those with esophageal cancer (32%) ($p = 0.03$).

On pathological examination 349 (97.8%) had a clear (R0) (proximal and distal) resection margin. Circumferential is not routinely reported as it cannot be assessed due to the immediate postoperative dissection by the surgeon. The median number of nodes retrieved was 29 (2–66), with only 23 (6.4%) of patients having fewer than 15 nodes identified, and 277 (62.5%) patients having no evidence of lymph no metastases (N0). There was N1 (1–2 positive lymph nodes) disease in 108 (30.3%) patients, N2 (3–6 lymph nodes) disease in 16 (4.5%) patients, and N3 (7 nodes or more) in 10 (2.8%) patients.

A total of 215 patients were staged at T2 or earlier, of whom only 9 (4%) were found to a have more advanced pathological T stage. In addition, 221 patients were staged as N0/Nx, of whom 40 (18%) were actually node positive.

Analysis of patient outcomes according to lymph node quartiles (2–20, 21–28, 29–36, 37 nodes or more) revealed no significant correlation between the number of nodes and preoperative factors such as age, sex clinical "T" stage, and clinical "N" stage. Similarly, there was no relation between lymph node quartile and postoperative (pathological) factors such as tumor location, pT stage, pN stage, and radicality of the resection.

Outcomes

Overall cancer-related survival was 78 months (CI 53–103 months). Patients who would be regarded as having "early" staged disease (T2 N0 or better) had significantly better survival outcomes ($p < 0.001$) than those with locally advanced disease (Fig. 1).

There was no relation between survival and the number of resected nodes (Fig. 2) ($p = 0.920$). Whilst univariable analysis suggested tumor location and completeness of resection (R0/R1) were prognostic indicators of survival, only pathological "T" stage ($p = 0.003$) and "N" stage (Fig. 3) ($p < 0.001$) were significantly related to median survival on multivariable analysis (Table 2).

Only two patients from the cohort were given adjuvant chemotherapy as part of their treatment.

TABLE 1 Clinical and pathological characteristics and posttreatment pathological results of patients with adenocarcinoma of the esophagus or gastroesophageal junction who underwent transthoracic esophagectomy with two-field lymphadenectomy

	N	
Number of patients	357	
Age*	65 (34–83) years	
Male	289 (81%)	
Tumor location		
Esophagus	199 (56%)	Node positive: 64 (32%)
GEJ	158 (44%)	Node positive: 69 (44%)
Degree of differentiation		
Well differentiated	43 (12%)	
Moderately differentiated	138 (39%)	
Poorly differentiated	120 (34%)	
Unknown	56 (16%)	
Pretreatment clinical T-stage (cT)#/posttreatment PT stage		
cTx/pT0 (HGD)	65 (18.2%)	29 (8.1%)
cT1/pT1	87 (24.3%)	175 (49%)
cT2/pT2	62 (17.4%)	26 (7.3%)
cT3/pT3	135 (37.8%)	120 (33.6%)
cT4/pT4	7 (2.0%)	7 (2.0%)
Pretreatment clinical *N*-stage (cN)#/posttreatment pN-stage		
cNx	4 (1.1%)	–
cN0/pN0	218 (61.1%)	224 (62.7%)
cN1/pN1	119 (33.3%)	47 (13.2%)
cN2/pN2	15 (4.2%)	52 (14.6%)
cN3/pN3	1 (0.3%)	34 (9.5%)
Radicality proximal and distal resection margin		
R0	349 (97.8%)	
R1	8 (2.2%)	
Perineural invasion	120 (33.6%)	
Venous invasion	96 (26.9%)	
Lymphatic invasion	132 (37.0%)	
Extracapsular spread present	44 (24%)	
Not present	138 (76%)	
Unknown	175	
Number of resected nodes*	29 (2–66)	
Number of positive nodes*	0 (0–24)	

R0 microscopically radical resection, *R1* microscopically tumor left behind, *GEJ* gastroesophageal junction

*Median (range)

#Measured with endosonography or esophagogastroscopy

Impact of Limited Lymphadenectomies

Table 3 provides the characteristics of each of the following subgroups of patients used to determine the theoretical impact of more limited lymphadenectomies.

Group 1: Transhiatal Resection with Complete Abdominal Lymphadenectomy A total of 29 patients with positive lymph nodes had involvement of nodes that would not be expected to be resected through a transhiatal esophagectomy (subcarinal, bronchial, and paratracheal lymph nodes). Estimated cancer-specific 5-year survival rates were 14.5% (standard error 7.4%) in this group when the nodes are resected. Omitting this field in the present study would have led to a theoretical extra estimated 4 (2–6) cancer-related deaths in this group of patients.

Group 2: Limited Abdominal Lymphadenectomy In 79 patients, celiac axis, hepatic, and splenic artery lymph nodes were positive. If a minimal abdominal lymphadenectomy had been performed, these nodes may not be removed. Metastatic proximal nodes were found in

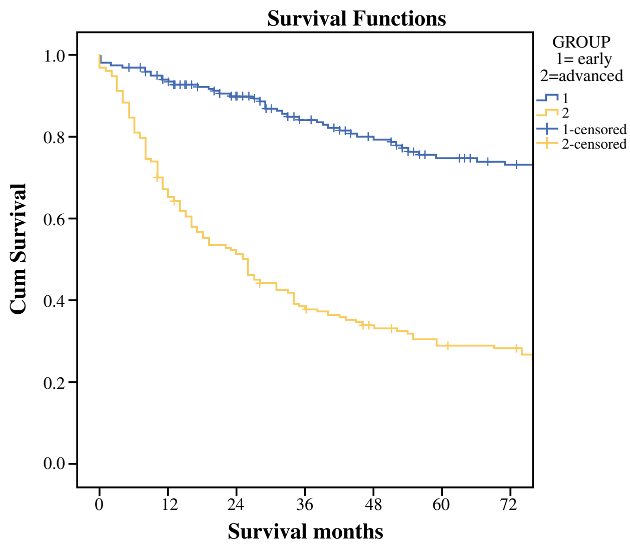

FIG. 1 Survival curves comparing early-stage (T2 N0) versus locally advanced cancer ($p < 0.001$)

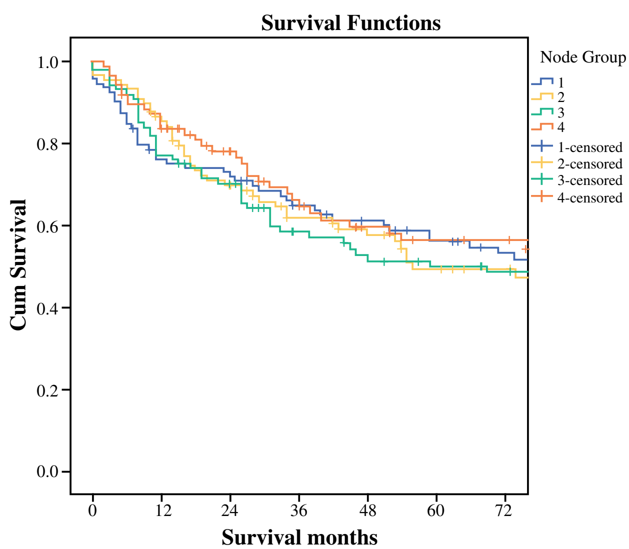

FIG. 2 Survival by interquartile range of lymph node yield: 0–20 (group 1), 21–28 (group 2), 29–36 (group 3), and 37–66 (group 4) ($p = 0.920$ log rank)

18 (22.7%). Estimated cancer-specific 5-year survival rates were 19.3% (standard error 4.6%) when they were removed. Omitting this field in the present study would have consequently led to a theoretical extra estimated 15 (12–19) cancer-related deaths in this group of patients.

Group 3: Limited Intrathoracic Lymphadenectomy In 24 patients, lymph nodes in the "circumferential" plane (para aortic and thoracic duct nodes) were involved. These nodes would have remained in situ if a minimal lymphadenectomy was performed. Estimated cancer-specific 5-year survival rates were 16.3% (standard error

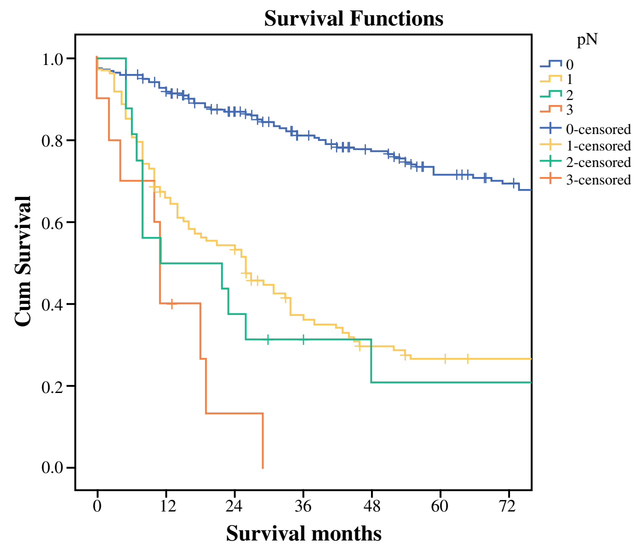

FIG. 3 Survival according to pathological N stage

4.2%) when they were removed Omitting this field in the present study would have consequently led to a theoretical extra estimated 4 (2–6) cancer-related deaths in this group of patients.

Impact of Limited Transhiatal Resection (Group 1 and Group 2 and Group 3 combined) If a limited transhiatal resection had been performed routinely, all the above-mentioned nodal stations would have been left in situ. This would have affected 95 (71.4%) of the patients who had positive nodes. The estimated cancer-specific 5-year survival rates are 20.4% (standard error 4.4%) for these patients when they are removed. Omission of these nodal groups by performing a limited trans-hiatal resection would have consequently led to a predicted 19 (15–23) extra cancer-related deaths in this group of patients.

DISCUSSION

This study seeks to evaluate the impact of extent of lymphadenectomy in patients treated primarily with esophagectomy for adenocarcinoma of the esophagus and gastroesophageal junction. The median lymph node yield is high,[4] and nodal stations routinely retrieved represent those that would be expected to be retrieved from a two-field lymphadenectomy. This allows the importance of yield to be evaluated, as well as permitting analysis of the impact of lesser lymphadenectomies. The premise for the study is that leaving positive lymph nodes behind will lead[14,25] to disease recurrence. Whilst this is a theoretical study, and it may be argued that there is no evidence that leaving positive nodes behind leads to recurrence, there is increasing evidence that extensive lymphadenectomy confers a survival advantage,

TABLE 2 Uni- and multivariable analysis of prognostic factors for disease-free survival in patients with cancer of the esophagus or gastroesophageal junction who underwent transthoracic esophagectomy without neoadjuvant chemotherapy

	Median survival (95% confidence interval)	*p* value univariable[†]	*p* value multivariable
Sex			
Male	71 (42.4–99.5)	0.392	0.276
Female	94.0 (51.4–136.6)		
Nodal quartiles			
2–20 nodes	91.0 (33.3–148.6)		0.920
21–28 nodes	56 (20.7–91.3)		
29–36 nodes	69.0 (1.2–136.9)		
> 36 nodes	90.0 (37.1–142.9)		
Tumor location			
Esophagus	117 (62.3–171.7)	0.011	0.283
GEJ	52 (28.3–75.6)		
Completeness of resection			
R0	87 (54.6–119.4)	< **0.001**	**0.002**
R1	6 (4.5–7.5)		
Posttreatment T-stage (pT)			
pT0	174.0	< **0.001**	**0.003**
pT1	184.0 (126.7–241.3)		
pT2	59.0 (49.4–69.6)		
pT3	23.0 (16.0–30.0)		
pT4	5.0 (3.7–6.2)		
Posttreatment N-stage (pN)			
pN0	174 (132.3–215.6)	< **0.001**	< **0.001**
pN1	26 (17.1–34.9)		
pN2	11 (0–38.4)		
pN3	11 (9.5–12.5)		

Bold values indicate statistically significant

TABLE 3 Postsurgery pathologic characteristics of patients with adenocarcinoma of the esophagus or gastroesophageal junction who underwent transthoracic esophagectomy with two-field lymphadenectomy; 133 patients have positive lymph nodes. Patients divided into groups based on theoretical less extensive lymphadenectomy (NB patients may fall in multiple groups)

	Group 1	Group 2	Group 3
Number of patients	29 (21.8%)	79 (59.4%)	24 (18%)
R1 resection	2	6	0
Location GEJ	10	46	9
Poor differentiation	13	47	5
Median N0 of positive nodes*	4 (1–19)	2 (2–8)	6 (1–24)
Posttreatment T-stage (pT)			
pT0	0	0	0
pT1	4	6	3
pT2	4	5	0
pT3	19	66	20
pT4	2	2	1
Posttreatment N-stage (pN)			
pN1	25	57	18
pN2	1	12	2
pN3	3	10	4
5-year cancer-specific survival (SE)	14.5% (7.4%)	19.3% (4.4%)	16.3% (4.2%)

and it could be inferred that this is because leaving positive nodes behind is more likely to lead to recurrence. The results indicated that close to 20% of patients staged as being node negative may have nodal metastases. Thus, lymphadenectomy is particularly pertinent in this cohort where preoperative chemotherapy is not employed.

As with a previous study from this institution which included patients who had received neoadjuvant treatment, absolute lymph node yield did not appear to confer an advantage on survival. However, the extent of lymphadenectomy ensuring more proximal mediastinal nodes and abdominal clearance does make a difference.[17]

The results demonstrated that a limited lymphadenectomy that has been advocated by some, and which neglected routine removal of lymph node stations in groups 1–3, would lead to 19 additional cancer-related deaths. This equates to curative resection in 56 patients rather than the 75, which equates to a 25% reduction. This is similar to the results found in patients who received neoadjuvant chemotherapy. Those most likely to benefit from this lymphadenectomy are patients staged as "N" positive. Notably, in this series, 25 (12.8%) patients of the 195 who were staged T2 N0 or earlier were found to have positive nodes.

Extended nodal resection would also have the impact of potentially removing micrometastases. These have been found in up to 50% of N0 patients.[12] The clinical significance of micrometastases remains unclear, although some have suggested that they are responsible for recurrence in node negative patients, and there has been an association with poorer prognosis when present.[12,13] However, others have stated that these deposits have no prognostic significance.[14,15]

A number of authors have suggested that the number of lymph nodes that should be removed is related to either lymph node involvement or "T" stage. Omloo advocated that an extended lymphadenectomy was beneficial in patients with fewer than 8 lymph nodes involved,[26] and Rizk proposed that higher "T" stage demands increased lymphadenectomy and those with T3/4 disease should have 31–42 nodes removed.[3] More recently a metaanalysis by Visser et al. found that increased lymph node yield provided a survival benefit in patients who received neoadjuvant chemotherapy followed by esophagectomy.[4] Whilst guidelines suggest a minimum of 15–23 nodes to ensure optimal staging, only two studies within the metaanalysis had a median yield greater than 23 and only eight greater than 15 nodes.

Patients who do not receive neoadjuvant chemotherapy broadly fall into two categories. Those staged with early disease, where it is felt it is not merited, and those with locally advanced disease who are not deemed fit enough to tolerate chemotherapy. In this study, 195 patients (55%) were clinically staged at T2 N0 or earlier and therefore not considered for neoadjuvant chemotherapy in line with local guidelines. Within this cohort, 24 patients were found to be node positive in this group and only 2 were greater than T2. Within these node-positive patients, overall survival was 65%. It is likely that extensive lymphadenectomy contributed to survival in these patients. The second group of patients are those deemed not fit enough for neoadjuvant chemotherapy, largely due to having preoperative renal function that would not support this or concerns that neoadjuvant treatment would decondition the patient such that they may not receive an operation. The survival benefit for a more extensive lymphadenectomy has been debated particularly since neoadjuvant treatment has become the standard of care for locally advanced disease. The argument for these patients is that neoadjuvant chemotherapy will serve to treat lymph node metastases. Despite this, the metaanalysis by Visser indicated that increased yield does have a positive impact on survival in patients who receive neoadjuvant treatment, and a previous study by the authors implied that *extent* as determined by the location of the lymphadenectomy was important in a cohort with a high median yield of lymph nodes.[4,17]

Surgical technique and oncological clearance are likely to contribute to overall outcomes and are certainly known to improve staging, with the 7th TNM and more recent 8th TNM staging system advising lymphadenectomy both to aid staging and to provide better oncological outcomes.[27] As with the previous study by the authors, there was no true "low-yield" group, with only 23 patients (6%) having fewer than 15 nodes obtained. This may be a contributing factor to why actual lymph node yield was not found to contribute towards outcomes. The numbers within the groups in this study are low. Larger-scale trials are required to determine the full impact of extent of lymphadenectomy, and this is a question the TIGER study will seek to help answer.[28] One reason for not performing a more extensive dissection is the association with greater morbidity. However, whilst overall complication rates have been reported at over 50% in the literature,[29,30] mortality has fallen and now approaches 3%. The increasing use of minimally invasive and robotic techniques may reduce morbidity;[31–33] however, it is vital that oncological principles are not compromised with their use.

The results of this study assume that disease recurrence will occur if positive lymph nodes are left behind. This is particularly important to note in a cohort that did not receive neoadjuvant chemotherapy, particularly when the role of adjuvant chemotherapy has not been established. Within this cohort, a standardized surgical technique was employed. Further, lymph node stations were dissected by the operating surgeon, which ensures accuracy for histological analysis and permits pattern of spread to be determined.[21]

The present study demonstrates that extent of lymphadenectomy may be implicated in survival in patients diagnosed with adenocarcinoma of the esophagus who do not receive neoadjuvant treatment. Given that a significant proportion of patients with early-stage disease may still have local lymph node metastases, and that a proportion of patients with more advanced disease may not be suitable for neoadjuvant treatment, radical lymphadenectomy remains an important component of an esophagectomy.

ACKNOWLEDGEMENTS The authors thank Helen Jaretkze NOGU data manager for assistance in the manuscript preparation.

DISCLOSURES The authors declare that no support or grants were received for this work and no conflict of interest.

REFERENCES

1. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20. https://doi.org/10.1056/NEJMoa055531.
2. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062–7.
3. Rizk NP, Ishwaran H, Rice TW, Chen L-Q, Schipper PH, Kesler KA, et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg. 2010;251(1):46–50.
4. Visser E, Markar SR, Ruurda JP, Hanna GB, van Hillegersberg R. Prognostic value of lymph node yield on overall survival in esophageal cancer patients. Ann Surg. 2018;1.
5. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. Ann Surg. 2011;254(6):894–906.
6. Kutup A, Nentwich MF, Bollschweiler E, Bogoevski D, Izbicki JR, Hölscher AH. What should be the gold standard for the surgical component in the treatment of locally advanced esophageal cancer: transthoracic versus transhiatal esophagectomy. Ann Surg. 2014;260(6):1016–22.
7. Davies AR, Sandhu H, Pillai A, Sinha P, Mattsson F, Forshaw MJ, et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. Br J Surg. 2014;101(5):511–7.
8. Duan X-F, Tang P, Shang X-B, Jiang H-J, Yu Z-T. The prevalence of lymph node metastasis for pathological T1 esophageal cancer: a retrospective study of 143 cases. Surg Oncol. 2018;27(1):1–6.
9. Newton AD, Predina JD, Xia L, Roses RE, Karakousis GC, Dempsey DT, et al. Surgical management of early-stage esophageal adenocarcinoma based on lymph node metastasis risk. Ann Surg Oncol. 2018;25(1):318–25.
10. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449–72.
11. Darling G. The role of lymphadenectomy in esophageal cancer. J Surg Oncol. 2009;99(4):189–93.
12. Hosch S, Kraus J, Scheunemann P, Izbicki JR, Schneider C, Schumacher U, et al. Malignant potential and cytogenetic characteristics of occult disseminated tumor cells in esophageal cancer. Cancer Res. 2000;60(24):6836–40.
13. Izbicki JR, Hosch SB, Pichlmeier U, Rehders A, Busch C, Niendorf A, et al. Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with completely resected esophageal cancer. N Engl J Med. 1997;337(17):1188–94.
14. Glickman JN, Torres C, Wang HH, Turner JR, Shahsafaei A, Richards WG, et al. The prognostic significance of lymph node micrometastasis in patients with esophageal carcinoma. Cancer. 1999;85(4):769–78.
15. Vazquez-Sequeiros E, Wang L, Burgart L, Harmsen W, Zinsmeister A, Allen M, et al. Occult lymph node metastases as a predictor of tumor relapse in patients with node-negative esophageal carcinoma. Gastroenterology. 2002;122(7):1815–21.
16. Talsma AK, Xinxue CJO, Pieter L, Wijnhoven BPL, Ong C-AJ, Liu X, et al. Location of lymph node involvement in patients with esophageal adenocarcinoma predicts survival. World J Surg. 2014;38(1):106–13.
17. Phillips AW, Lagarde SM, Navidi M, Disep B, Griffin SM. Impact of extent of lymphadenectomy on survival, post neoadjuvant chemotherapy and transthoracic esophagectomy. Ann Surg. 2017;265(4):750–6.
18. McK Manson J, Beasley WD. A personal perspective on controversies in the surgical management of oesophageal cancer. Ann R Coll Surg Engl. 2014;96(8):575–8.
19. Sobin LH. TNM classification of malignant tumours. 7th ed. New York: Wiley; 2009.
20. Phillips AW, Dent B, Navidi M, Immanuel A, Griffin SM. Trainee involvement in Ivor Lewis esophagectomy does not negatively impact outcomes. Ann Surg. 2018;267(1):94–8.
21. Lagarde SM, Phillips AW, Navidi M, Disep B, Griffin SM. Clinical outcomes and benefits for staging of surgical lymph node mapping after esophagectomy. Dis Esophagus. 2017;30(12):1–7.
22. Mapstone N. Dataset for the histopahtological reporting of oesophageal carcinoma. 2nd ed. 2007.
23. Schaaf MVD, Johar A, Wijnhoven B, Lagergren P, Lagergren J, van der Schaaf M, et al. Extent of lymph node removal during esophageal cancer surgery and survival. JNCI J Natl Cancer Inst. 2015; 107(5):djv043–djv043.
24. Lagergren J, Mattsson F, Zylstra J, Chang F, Gossage J, Mason R, et al. Extent of lymphadenectomy and prognosis after esophageal cancer surgery. JAMA Surg. 2015;1–8.
25. Veloski J, Boex JR, Grasberger MJ, Evans A, Wolfson DB. Systematic review of the literature on assessment, feedback and physicians' clinical performance: BEME Guide No. 7. Med Teach. 2006;28(2):117–28.
26. Omloo JMT, Lagarde SM, Hulscher JBF, Reitsma JB, Fockens P, van Dekken H, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus. Ann Surg. 2007;246(6):992–1001.
27. Rice TW, Gress DM, Patil DT, Hofstetter WL, Kelsen DP, Blackstone EH. Cancer of the esophagus and esophagogastric junction-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(4): 304–17. https://doi.org/10.3322/caac.21399.
28. Hagens ERC, van Berge Henegouwen MI, van Sandick JW, Cuesta MA, van der Peet DL, Heisterkamp J, et al. Distribution of lymph node metastases in esophageal carcinoma [TIGER study]:

study protocol of a multinational observational study. BMC Cancer. 2019;19(1):662.
29. Sinclair RCF, Phillips AW, Navidi M, Griffin SM, Snowden CP. Pre-operative variables including fitness associated with complications after oesophagectomy. Anaesthesia. 2017;72(12):1501–7.
30. Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, et al. Benchmarking complications associated with esophagectomy. Ann Surg. 2019;269(2):291–8.
31. Mariette C, Markar SR, Dabakuyo-Yonli TS, Meunier B, Pezet D, Collet D, et al. Hybrid minimally invasive esophagectomy for esophageal cancer. N Engl J Med. 2019;380(2):152–62.
32. Navidi M, Phillips AW. Hybrid minimally invasive esophagectomy for esophageal cancer. N Engl J Med. 2019;380(17):e28.
33. Tapias LF, Mathisen DJ, Wright CD, Wain JC, Gaissert HA, Muniappan A, et al. Outcomes with open and minimally invasive ivor lewis esophagectomy after neoadjuvant therapy. Ann Thorac Surg. 2016;101(3):1097–103.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.