Original article

Lymph node regression and survival following neoadjuvant chemotherapy in oesophageal adenocarcinoma

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Background: The aim was to define the pathological response in lymph nodes following neoadjuvant chemotherapy for oesophageal adenocarcinoma and to quantify any associated survival benefit.

Methods: Lymph nodes retrieved at oesophagectomy were examined retrospectively by two pathologists for evidence of a response to chemotherapy. Patients were classified as lymph node-negative (either negative nodes with no evidence of previous tumour involvement or negative with evidence of complete regression) or positive (allocated a lymph node regression score based on the proportion of fibrosis to residual tumour). Lymph node responders (score 1, complete response; 2, less than 10 per cent remaining tumour; 3, 10–50 per cent remaining tumour) and non-responders (score 4, more than 50 per cent viable tumour; 5, no response) were compared in survival analyses using Kaplan–Meier and Cox regression analysis.

Results: Among 377 patients, 256 had neoadjuvant chemotherapy. Overall, 68 of 256 patients (26·6 per cent) had a lymph node response and 115 (44·9 per cent) did not. The remaining 73 patients (28·5 per cent) had negative lymph nodes with no evidence of regression. Some patients had a lymph node response in the absence of a response in the primary tumour (27 of 99, 27 per cent). Lymph node responders had a significant survival benefit ($P < 0·001$), even when stratified by patients with or without a response in the primary tumour. On multivariable analysis, lymph node responders had decreased overall (hazard ratio 0·53, 95 per cent c.i. 0·36 to 0·78) and disease-specific (HR 0·42, 0·27 to 0·66) mortality, and experienced reduced local and systemic recurrence.

Conclusion: Lymph node regression is a strong prognostic factor and may be more important than response in the primary tumour.

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Introduction

Neoadjuvant chemotherapy and chemoradiotherapy are both established treatment modalities that have demonstrated a survival benefit in the management of operable oesophageal adenocarcinoma in RCTs[1–3]. The rationale for neoadjuvant treatment is downstaging of the primary tumour, improved rates of surgical margin clearance and the treatment of occult micrometastatic disease that may be present in a high proportion of these patients[4,5]. The Mandard tumour regression grade is used widely in the assessment of response to neoadjuvant chemotherapy in oesophageal cancer[6]. Although originally devised for use after neoadjuvant chemoradiotherapy, the scoring system, based on the degree of fibrosis in proportion to residual viable tumour, has been shown to have prognostic value in patients treated with chemotherapy alone[7,8].

There is emerging evidence of a discrepancy, in some patients, in the response of the primary tumour compared with that in the lymph nodes, based on radiological staging[9]. Clinical data suggest that tumour downstaging, particularly nodal response, after neoadjuvant therapy results in improved survival and a reduction in both local and systemic recurrence[10,11]. However there is a lack of evidence documenting pathological lymph node response to neoadjuvant treatment. Therefore, the lymph nodes of patients undergoing oesophagectomy in a single unit were analysed with the intention of correlating lymph node response to neoadjuvant chemotherapy with clinical outcomes.

Methods

This was a clinical cohort study conducted in the Guy's and St Thomas' Oesophago-Gastric Centre, a tertiary referral centre for upper gastrointestinal cancer surgery, in London, UK. Patients with histopathological oesophageal cancer specimens available for analysis were identified from a prospectively maintained database. The database has been described in earlier publications[10]. Patients who had surgery between 2003 and 2015 were included in the study. Only patients who had oesophagectomy for adenocarcinoma of the oesophagus or oesophagogastric junction (Siewert type 1 or 2) were included. Ethical approval was obtained to assess chemotherapy response in oesophageal cancer (15/EE/0228) and for use of the clinical database (12/NW/0511). The primary aim of the study was to assess the effects of pathological lymph node regression on survival. Secondary aims included the assessment of recurrence, and the relationship between response in the primary tumour and that in the lymph nodes.

Clinical management

All patients were discussed in a specialist upper gastrointestinal multidisciplinary team meeting. Each patient considered for therapy with curative intent underwent a standard protocol of investigation that included endoscopy, CT, endoscopic ultrasonography and fluorodeoxyglucose PET. Patients staged clinically as T2 (or greater) and/or N1 (or greater) were considered for neoadjuvant treatment depending on medical co-morbidities and physical fitness assessment.

Chemotherapy practice in the UK evolved during the study interval with the successful completion of large multicentre RCTs[1,2,12]. All patients were managed by regimens that reflected these trial protocols, including two to four cycles of neoadjuvant treatment with cisplatin and 5-fluorouracil (CF), epirubicin, cisplatin and 5-fluorouracil (ECF) or epirubicin, cisplatin and capecitabine (ECX). Following neoadjuvant chemotherapy, patients were restaged by CT of the thorax, abdomen and pelvis.

Pathological analysis

All patients who underwent surgical resection had final tumour histology available (ypTNM) after a thorough review by a member of a team of dedicated upper gastrointestinal pathologists. Pathological assessment was according to the seventh edition of the TNM staging system[13]. A positive circumferential resection margin was defined by the presence of tumour at or within 1 mm of the radial margin, according to the Royal College of Pathologists criteria[14].

Oesophagectomy resection slides were recalled from the St Thomas' Hospital slide archive for eligible adenocarcinoma cases from the clinical database. After removing those for which the slide set was incomplete there were 377 left for further analysis. Pathological primary tumour regression was graded using a categorical scale between 1 (complete pathological response) and 5 (no response), as described originally by Mandard and colleagues[6].

Lymph nodes were processed according to Royal College of Pathologists guidelines[14]. This involved embedding the lymph node whole if it was smaller than 5 mm; larger lymph nodes were sliced into 3-mm sections, all of which were embedded. One section from each block was analysed. No immunohistochemistry was employed. All lymph node slides for each specimen were reviewed by a senior trainee histopathologist, with initial supervision for 30 cases. All slides showing any evidence of lymph node response were reviewed by both histopathologists.

Evidence of a lymph node response comprised substantial areas of fibrosis within the nodal parenchyma, mucin pools or necrotic foci. A lymph node regression score was created according to the proportion of fibrosis and residual tumour within the lymph node: score 1, complete response; score 2, less than 10 per cent remaining tumour; score 3, 10–50 per cent remaining tumour; score 4, more than 50 per cent viable tumour; and score 5, no evidence of response (*Fig. 1*). Negative lymph nodes with no evidence of regression or previous tumour involvement were also recorded (negative LNs group).

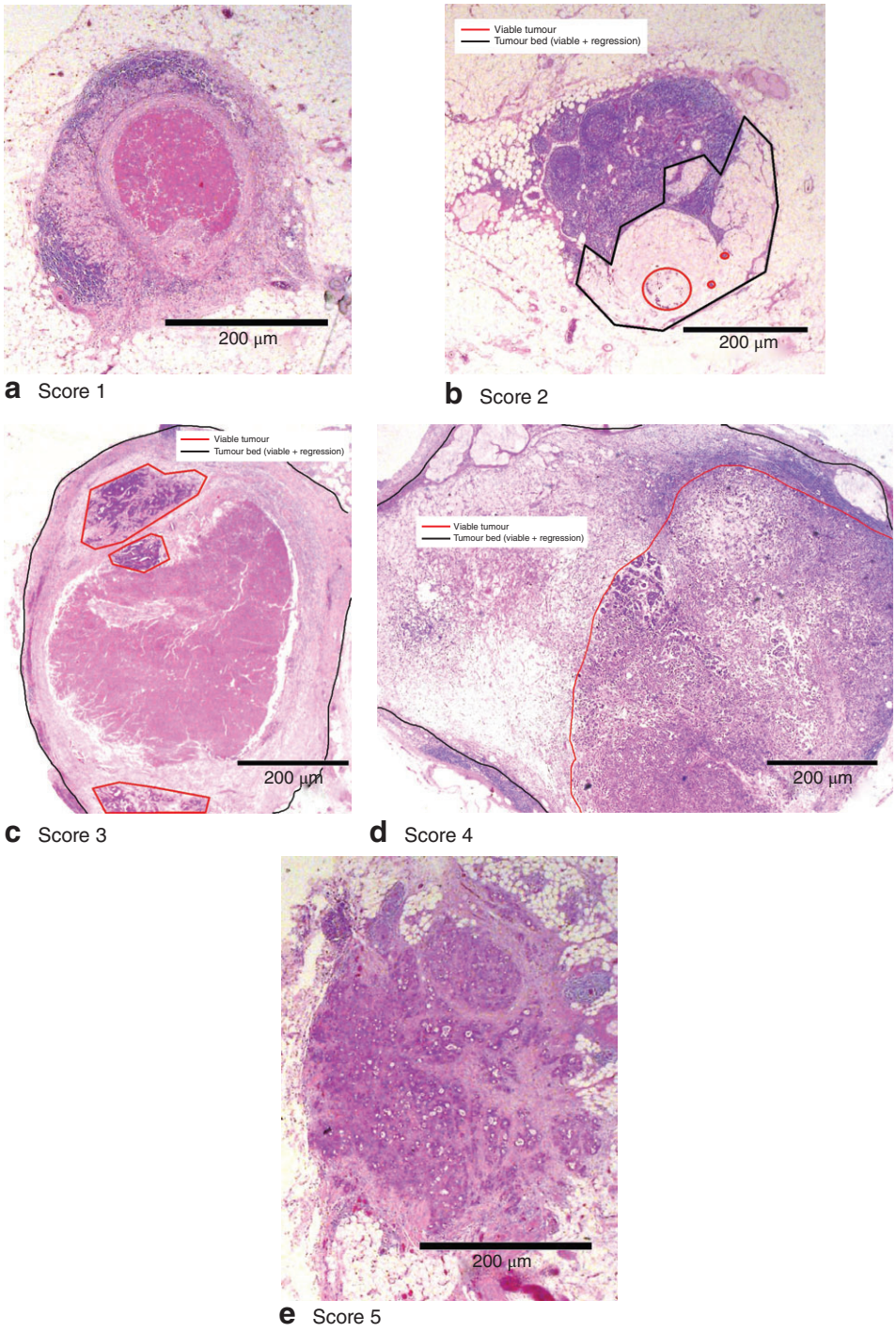

Fig. 1 Histological images of haematoxylin and eosin-stained lymph nodes representative of each lymph node regression score. **a** Score 1: a lymph node with tumour bed composed of central necrosis and a periphery of foamy macrophages; there is no residual viable tumour. **b** Score 2: a lymph node with a tumour bed of mostly acellular mucin pools with scattered small groups of viable tumour cells comprising less than 10 per cent of the total tumour bed area. **c** Score 3: a lymph node that is largely replaced by tumour bed with predominant fibrosis and necrosis; there is viable tumour making up 10–50 per cent of the tumour bed area. **d** Score 4: a lymph node with a large tumour bed area composed of mucin with more than 50 per cent viable tumour, but still with recognizable regression. **e** Score 5: a lymph node completely replaced by metastatic tumour showing no clear signs of regression

Table 1 Demographics, staging and recurrence according to lymph node response after neoadjuvant chemotherapy and surgery in patients with oesophageal adenocarcinoma

	LN-NR ($n = 115$)	LN-R ($n = 68$)	Negative LNs ($n = 73$)	P†
Age (years)*	62·7 (40–78)	63·5 (41–79)	61·4 (32–77)	< 0·001‡
Sex				0·310
F	19 (16·5)	7 (10)	7 (10)	
M	96 (83·5)	61 (90)	66 (90)	
Tumour grade				0·322§
Well differentiated	1 (0·9)	1 (1)	1 (1)	
Moderately differentiated	49 (42·6)	38 (56)	43 (59)	
Poorly differentiated	65 (56·5)	29 (43)	29 (40)	
Pathological stage (ypTNM)				< 0·001
ypT0 N0	0 (0)	3 (4)	8 (11)	
ypT1–2 N0	0 (0)	7 (10)	37 (51)	
ypT1–2 N1–3	38 (33·0)	19 (28)	0 (0)	
ypT3–4 N0	0 (0)	9 (13)	28 (38)	
ypT3–4 N1–3	77 (67·0)	30 (44)	0 (0)	
Resection margin status				0·001
R0	55 (47·8)	41 (60)	53 (73)	
R1	60 (52·2)	27 (40)	20 (27)	
Lymphovascular invasion				< 0·001
No	31 (27·0)	40 (59)	48 (66)	
Yes	84 (73·0)	28 (41)	25 (34)	
Mandard score				< 0·001§
1	0 (0)	3 (4)	8 (11)	
2	1 (0·9)	8 (12)	3 (4)	
3	28 (24·3)	26 (38)	32 (44)	
4	61 (53·0)	25 (37)	20 (27)	
5	11 (9·6)	2 (3)	4 (5)	
Not available	14 (12·2)	4 (6)	6 (8)	
Tumour recurrence				< 0·001
No	29 (25·2)	40 (59)	50 (68)	
Yes	86 (74·8)	28 (41)	23 (32)	
Recurrence pattern				
Local	20 (17·4)	5 (7)	9 (12)	0·002
Distant	37 (32·2)	14 (21)	7 (10)	< 0·001
Local and distant	29 (25·2)	9 (13)	7 (10)	0·010
No recurrence	29 (25·2)	40 (59)	50 (68)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). LN-NR, lymph node non-responders; LN-R, lymph node responders; LN, lymph node. †χ^2 test, except ‡Student's t test and §Fisher's exact test.

Statistical analysis

Survival analysis was performed using the Kaplan–Meier method and the log rank test; $P < 0·050$ indicated statistical significance. Survival was calculated from the date of surgery. Fisher's and χ^2 tests were used to assess categorical variables, whereas Student's t test and the Mann–Whitney U test were used for analysis of continuous variables.

For the purposes of survival analysis, patients exhibiting a mixed pattern of lymph node regression were categorized according to the best score recorded. Lymph node responders (LN-R group) were patients with a best lymph node regression score of 1–3, and non-responders (LN-NR group) had a score of 4–5. This was based on prestudy survival analysis of a cohort of 845 patients that demonstrated significantly improved survival in patients with a Mandard score of 3 compared with a score of 4. It was acknowledged that other studies[7,8,15] had suggested prognostic regression groupings of 1–2 *versus* 3–5 and so both categorizations were analysed.

Cox proportional hazard models were used to calculate hazard ratios (HRs) with 95 per cent confidence intervals for the association between lymph node response (study exposure) and the two main study outcomes, overall and disease-free survival. Crude (model 1) and adjusted (model 2) analyses were performed. The prognostic markers adjusted for in the multivariable model included patient age (continuous variable), pathological tumour stage (grouped into ypT0 N0, T1–2 N0, T1–2 N1–3, T3–4 N0 or T3–4 N1–3), tumour grade (well, moderately or poorly differentiated), lymphovascular invasion (yes or no), resection margin status (R0 or R1) and Mandard tumour regression score in the primary tumour (Mandard 1–3, 4–5 or not available). The assumption of proportionality of hazards was tested with

Table 2 Distribution of lymph node regression by number of patients and number of lymph nodes in relation to best regression score per patient

Best lymph node regression score per patient	Lymph node regression score										All negative	
	1		2		3		4		5			
	Patients	LNs	Patients	LNs	Patients	LNs	Patients	LNs	Patients	LNs	Patients	LNs
1	45	117	9	10	5	12	5	5	20	69	44	623
2	0	0	13	18	5	7	2	4	9	55	12	170
3	0	0	0	0	10	12	6	11	9	49	10	90
4	0	0	0	0	0	0	5	5	5	44	5	42
5	0	0	0	0	0	0	0	0	110	605	109	1216
Negative LNs	0	0	0	0	0	0	0	0	0	0	73	1090
Total	45	117	22	28	20	31	18	25	153	822	253	3231

LN, lymph node.

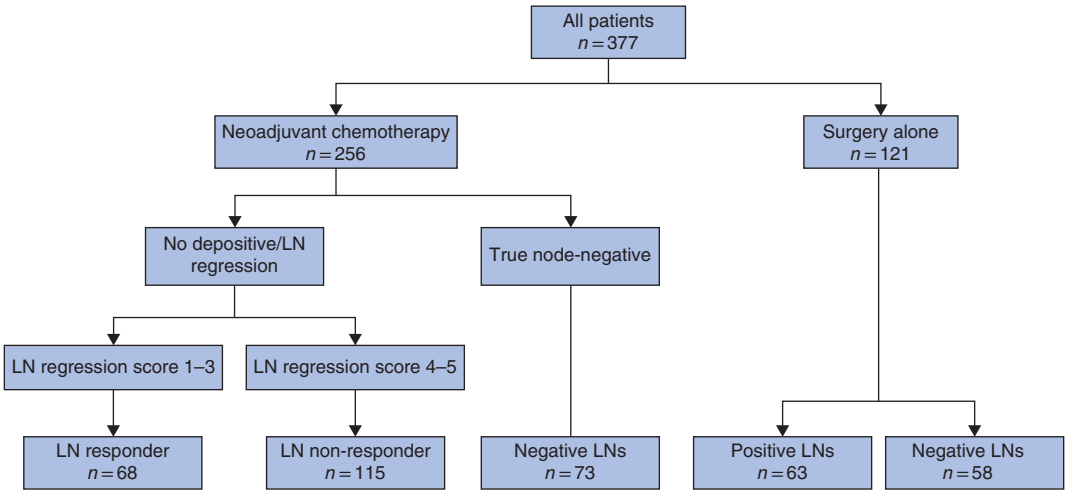

Fig. 2 Flow chart summarizing study patients according to lymph node (LN) status

Schoenfield residuals, and was met for all co-variables. Data management and analyses were undertaken using SAS® version 9.4 software (SAS Institute, Cary, North Carolina, USA).

Results

Patient demographics, staging data and recurrence outcomes are shown in *Table 1*. Among 377 patients identified from the database with pathological slides available, 256 had neoadjuvant chemotherapy. The median age was 62 years with a male preponderance (223 men, 87·1 per cent).

Pathological analysis

The median lymph node yield was 18 (range 5–47). A total of 5990 lymph nodes were examined. Evidence of regression was sought in 4254 of these nodes, which were from patients who received neoadjuvant chemotherapy. Among these, 3231 lymph nodes were negative with no signs of regression. The distribution of lymph node regression scores in patients who had chemotherapy is shown in *Table 2*.

The lymph node regression score was 1 in 117 lymph nodes (45 patients), 2 in 28 nodes (22 patients), 3 in 31 nodes (20 patients), 4 in 25 nodes (18 patients) and 5 in 882 nodes (153 patients). Based on the best lymph node regression score for each patient, 68 patients (26·6 per cent) were lymph node responders and 115 (44·9 per cent) were lymph node non-responders. The remaining 73 patients had negative lymph nodes with no evidence of regression (*Fig. 2*).

Of 66 patients with a Mandard score of 1–3 in the primary tumour, 37 (56 per cent) were also lymph node responders, whereas 29 (44 per cent) were lymph node

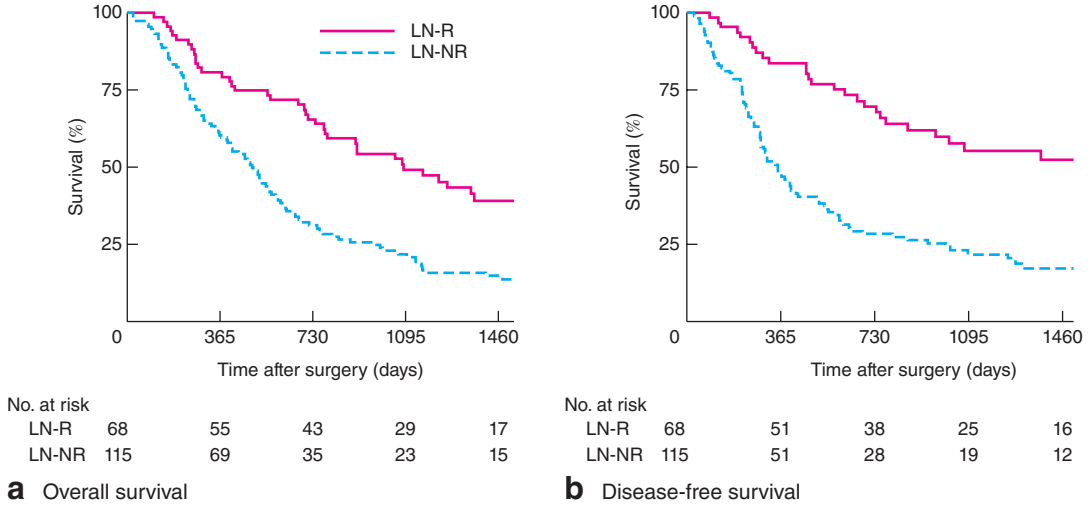

Fig. 3 Kaplan–Meier analysis of **a** overall and **b** disease-free survival in lymph node responders (LN-R) *versus* non-responders (LN-NR). **a** $P < 0{\cdot}001$, **b** $P < 0{\cdot}001$ (log rank test)

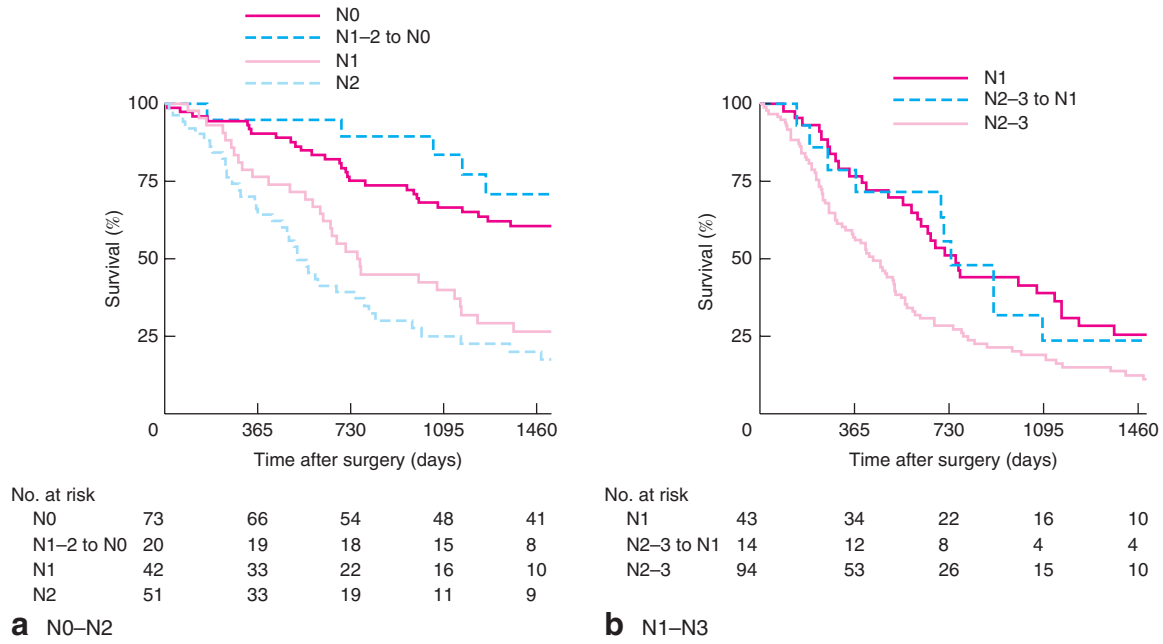

Fig. 4 Kaplan–Meier analysis of overall survival according to node status: **a** N0–N2, including patients downstaged from N1–2 to N0, and **b** N1–N3, including patients downstaged from N2–3 to N1. **a** $P < 0{\cdot}001$, **b** $P = 0{\cdot}015$ (log rank test)

non-responders. Interestingly, 27 of 99 patients (27 per cent) with a Mandard score of 4–5 in the primary tumour exhibited a lymph node response. Overall 72 of 165 patients (43·6 per cent) had no response in either the primary tumour or lymph nodes.

Of 121 patients who did not have chemotherapy, only three patients had lymph nodes that were falsely reported as showing evidence of response to treatment. It was not possible retrospectively to identify other potential sources of fibrosis in the lymph nodes of these patients.

Interobserver variability among the two pathologists was minimal (less than 1 per cent overall). There were no discrepancies in the reporting of fibrosis and more than 95 per cent concordance in the individual categorization of lymph node response.

Table 3 Results of Cox proportional hazards analysis to determine the influence of lymph node response on death and recurrence in patients with oesophageal adenocarcinoma

	Event rate	Hazard ratio	
		Unadjusted	Multivariable*
Death			
LN-NR	101 of 115	1·00 (reference)	1·00 (reference)
LN-R	44 of 68	0·45 (0·31, 0·64)	0·53 (0·36, 0·78)
Negative LNs	36 of 73	0·24 (0·16, 0·36)	0·42 (0·27, 0·66)
Recurrence			
LN-NR	87 of 115	1·00 (reference)	1·00 (Reference)
LN-R	29 of 68	0·35 (0·23, 0·54)	0·42 (0·27, 0·66)
Negative LNs	23 of 73	0·20 (0·13, 0·32)	0·39 (0·22, 0·66)

Values in parentheses are 95 per cent confidence intervals. LN-NR, lymph node non-responders; LN-R, lymph node responders; LN, lymph node. *Adjusted for age at operation (continuous), sex, tumour grade (well–moderately *versus* poorly differentiated), stage (ypT0 N0, T1–2 N0, T1–2 N1–3, T3–4 N0, T3–4 N1–3), margin status (R0 *versus* R1), lymphovascular invasion (yes *versus* no), chemotherapy response (Mandard 4–5 *versus* Mandard 1–3 *versus* not available).

Table 4 Results of multivariable Cox proportional hazards analysis to identify risk factors for death and recurrence in patients with oesophageal adenocarcinoma

	Hazard ratio	
	Death	Recurrence
Age at operation (years)	1·02 (1·00, 1·04)	1·01 (0·99, 1·03)
Sex		
F	1·00 (reference)	1·00 (reference)
M	1·07 (0·68, 1·68)	1·18 (0·70, 1·97)
Tumour grade		
Well–moderately differentiated	1·00 (reference)	1·00 (reference)
Poorly differentiated	1·25 (0·92, 1·70)	1·04 (0·73, 1·49)
Tumour stage		
T0–2 N0	1·00 (reference)	1·00 (reference)
T1–2 N1–3	3·74 (1·61, 8·70)	4·28 (1·48, 12·37)
T3–4 N0	1·16 (0·60, 2·24)	1·87 (0·82, 4·25)
T3–4 N1–3	7·27 (3·13, 16·89)	9·69 (3·38, 27·78)
Margin status		
R0	1·00 (reference)	1·00 (reference)
R1 (< 1 mm)	1·22 (0·87, 1·71)	1·15 (0·78, 1·70)
Lymphovascular invasion		
No	1·00 (reference)	1·00 (reference)
Yes	1·57 (1·11, 2·21)	1·44 (0·96, 2·14)
Primary tumour response		
Mandard 4–5	1·00 (reference)	1·00 (reference)
Mandard 1–3	0·74 (0·52, 1·06)	0·74 (0·50, 1·12)
Not available	1·18 (0·71, 1·99)	1·33 (0·75, 2·36)
Lymph node response		
LN-NR	1·00 (reference)	1·00 (reference)
LN-R	0·54 (0·37, 0·81)	0·43 (0·27, 0·69)
Negative LNs	0·36 (0·22, 0·59)	0·31 (0·17, 0·57)

Values in parentheses are 95 per cent confidence intervals. LN-NR, lymph node non-responders; LN-R, lymph node responders; LN, lymph node.

Survival

The overall 1- and 5-year survival rates for the study cohort were 82·2 and 44·3 per cent respectively. Kaplan–Meier survival curves for LN-R *versus* LN-NR groups demonstrated a survival benefit for patients exhibiting a lymph node response in terms of both overall and disease-free survival ($P < 0·001$) (*Fig. 3*). Patients whose disease was downstaged owing to lymph node regression had improved survival compared with those whose tumours were not downstaged. This meant that survival of a patient with disease downstaged from N1–N2 to N0 was comparable to (or better than) that of a patient with N0 disease at the outset and significantly better than that of a patient whose disease remained N1 ($P < 0·001$) (*Fig. 4a*). This pattern was also seen in patients whose tumours were downstaged from N2–3 to N1 ($P = 0·015$) (*Fig. 4b*). The survival benefit for lymph node response was evident even when stratified by response to chemotherapy in the primary tumour (Mandard 1–3, $P = 0·020$; Mandard 4–5, $P = 0·046$) (*Fig. S1*, supporting information).

Multivariable analysis demonstrated lymph node response to be associated with decreased overall mortality (LN-R: HR 0·53, 95 per cent c.i. 0·36 to 0·78) and disease-specific mortality (LN-R: HR 0·42, 0·27 to 0·66) even when adjusted for regression in the primary tumour (*Table 3*). This improvement remained in the alternative categorization of lymph node regression score as 1–2 *versus* 3–5 (overall mortality: HR 0·49, 0·32 to 0·74; disease-specific mortality: HR 0·44, 0·27 to 0·72). Conversely, the significant independent prognostic effect of tumour regression in the primary tumour disappeared when adjusted for lymph node response (Mandard 1–3: adjusted HR 0·74, 0·52 to 1·06) (*Table 4*).

In further comparison of the relative importance of primary tumour and lymph node regression, R^2 analysis demonstrated an additional 2 per cent variability of death when the primary tumour response was incorporated into the basic model ($R^2 = 0·29$ *versus* 0·27), whereas an additional 6 per cent variability was explained when lymph node response was included instead of primary tumour response ($R^2 = 0·33$). This was similar to the final model which included both primary and lymph node response ($R^2 = 0·34$), indicating that better performance of the model was largely explained by the addition of lymph node response. Combining primary tumour and lymph node response categories demonstrated the survival benefit of a response in both the primary tumour and lymph nodes (HR 0·47, 0·27 to 0·82) as well as response in the lymph nodes even in the absence of primary tumour response (HR 0·59, 0·35 to 0·99). Primary tumour response was

prognostic in lymph node-negative patients (HR 0·30, 0·15 to 0·57) (*Table S1*, supporting information).

Tumour stage, particularly N status, remained an important prognostic factor (T1–2 N1–3: HR 3·74, 1·61 to 8·70; T3–4 N1–3: HR 7·27, 3·13 to 16·89) as did lymphovascular invasion (HR 1·57, 1·11 to 2·21). Patient age (HR 1·02, 1·00 to 1·04), poor differentiation (HR 1·25, 0·92 to 1·70) and positive resection margins (R1: HR 1·22, 0·87 to 1·71) were all associated with a higher risk of death without reaching independent statistical significance (*Table 4*). The patterns for disease-specific mortality closely mirrored those for overall mortality.

Patients who had a lymph node response experienced a reduction in both local tumour recurrence (14 of 68 (21 per cent) in LN-R group *versus* 49 of 115 (42·6 per cent) in LN-NR group; $P = 0·004$) and systemic tumour recurrence (23 of 68 (34 per cent) *versus* 66 of 115 (57·4 per cent) respectively; $P = 0·002$).

A *post hoc* power calculation showed that the analysis had more than 80 per cent power to detect an HR of 0·5 in comparisons of overall and recurrence-free survival between categories of lymph node regression scores.

Discussion

This study represents a large series examining the significance of lymph node regression in patients with oesophageal adenocarcinoma treated with neoadjuvant chemotherapy. A statistically significant survival advantage was demonstrated in patients exhibiting a lymph node response that was independent of other known prognostic variables, including the pathological response in the primary tumour. Lymph node responders had reduced rates of both local and systemic tumour recurrence.

Among strengths of the study is the fact that two pathologists independently reviewed the histological slides with high concordance and good quality control metrics. It is acknowledged that the sampling of lymph node slides for evidence of regression may have missed the presence of fibrosis in some instances, despite the use of recognized guidelines for sample processing. Although this would not have affected the survival comparisons of lymph node responders and non-responders, quantifying the accuracy of lymph node sampling is an important area for future work. The large number of patients allowed for the adjustment of relevant prognostic confounders in survival analyses. Nonetheless it remains impossible in studies of this kind to completely eliminate bias due to unmeasured confounding. A further limitation is the single-centre recruitment of patients and, as a result, external validation of the findings of this study is under way. A larger sample of patients will also help to establish the optimal categorization of lymph node response; using lymph node regression scores in a similar way to Mandard scoring in the primary tumour is only one such option. Although there was some evolution in chemotherapy regimens over time, reflecting real-time clinical practice, a recent randomized trial[16] showed no difference in overall survival between these combinations of agents.

A previous study[17] evaluated lymph node regression following neoadjuvant chemoradiotherapy in a mixed cohort of 403 patients with oesophageal adenocarcinoma and squamous cell carcinoma. A significant survival benefit was demonstrated for patients exhibiting signs of lymph node response to treatment, a finding supported by the present results. Another study[18] evaluated lymph node regression after chemotherapy or chemoradiotherapy in 90 patients with oesophageal adenocarcinoma, where patients with negative nodes but evidence of previous cancer involvement had a worse prognosis than node-negative patients with no evidence of response. This contrasts with the present findings, but may reflect a more heterogeneous population and the use of different treatment modalities. A further study[19] used pathological response following chemoradiotherapy to construct a retrospective pretreatment TNM stage, and compared this with both clinical and final pathological stage.

A number of studies[11,20–22] have correlated regression in the primary tumour with reduced lymph node involvement, but these have relied on preoperative imaging to define lymph node downstaging, which may be challenging. Others[10] have found tumour stage after chemotherapy to be more prognostic than that at initial presentation owing to this downstaging effect and, presumably, the effective treatment of micrometastatic disease. A recent large multicentre study[23] showed a survival benefit for responders to chemotherapy (defined as Mandard 1 or 2 in the primary tumour), but an additional benefit for lymph node downstaging (defined by a change in prechemotherapy radiological lymph node status compared with final pathology), even in patients classified as non-responders in the primary tumour (Mandard 3–5). The identification of lymph node response as an important prognostic factor and the idea that response is not necessarily homogeneous between the primary tumour and lymph nodes is in keeping with the results of the present study. Although the role of imaging in the evaluation of lymph node downstaging following chemotherapy is undoubtedly important, there are no widely accepted definitions of what would constitute an anatomical or physiological response in lymph nodes. In addition,

assessment of response may be even more difficult following neoadjuvant chemoradiotherapy because of the local inflammatory reaction[24–27]. Although lymph node downstaging should logically correspond to improved outcomes, it would seem pointless to pursue surrogate radiological markers for this downstaging effect if no meaningful survival benefit could be demonstrated on pathological analysis. The results of the present study demonstrate the positive effect of pathological lymph node regression in oesophageal cancer.

An interesting finding was that the survival benefit for lymph node response was independent of regression in the primary tumour. Conversely, the primary tumour response (Mandard score) was not statistically significant on survival analysis once adjusted for lymph node regression. This, and the fact that improvements in model performance owed largely to the inclusion of lymph node response, imply that the latter may be more important when it comes to predicting prognosis. Contemporaneous studies[8,28,29] have produced conflicting results regarding whether regression in the primary tumour remains prognostic over and above tumour stage. One explanation for this may be that historical regression scores, such as Mandard, which focused on the primary tumour, were unable to identify the group of true responders to chemotherapy. This is supported by the present data, which indicated that some patients have a different response in the primary tumour compared with the lymph nodes. Over one-quarter of patients with a poor response to chemotherapy in the primary tumour had a significant lymph node response. This may have implications for decision-making and needs to be considered when assessing prognosis before selecting patients for surgery, and also when considering adjuvant chemotherapy as part of a perioperative treatment strategy. The selection of patients for more individualized treatment could be further improved with refinements in the definition of chemotherapy responders. This may avoid the unnecessary treatment of non-responders with adjuvant chemotherapy that may cause significant morbidity for no survival benefit[28,30]. The present results suggest that the categories for defining a response should be regression scores of 1–3 (fibrosis over 50 per cent in either the primary tumour or lymph node), although this should be examined in more detail in a large validation cohort.

One topical discussion point is that of tumour regression after neoadjuvant chemotherapy as opposed to chemoradiotherapy. This remains difficult to compare owing to the effects of radiotherapy on the primary tumour bed which may enhance the locoregional response, but in some regimens compromises the dose of systemic chemotherapy[3]. Whether this may have an adverse effect by undertreating the micrometastatic disease that frequently occurs in this patient group remains unclear[31,32]. However, it would appear that responders to neoadjuvant chemotherapy are true systemic responders and it is therefore not surprising that these patients exhibit greater systemic as well as locoregional control. Whether this is because the biology of tumour regression in the lymph nodes more closely resembles that seen in micrometastatic disease following chemotherapy remains a plausible, but as yet unproven, hypothesis.

Collaborators

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.