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Multivariate analysis of clinical, operative and pathologic features of esophageal cancer: who needs adjuvant therapy?

K. Zafirellis, K. Dolan, A. Fountolakis, S. P. L. Dexter, I. G. Martin, H. M. Sue-Ling

Division of Surgery, The General Infirmary at Leeds, Leeds, UK

SUMMARY. **The failure of adjuvant therapy to significantly improve the prognosis of patients undergoing esophago-gastrectomy for cancer may be because of poor patient selection. We sought prognostic factors that would identify those patients who could benefit from adjuvant therapy. Data on 15 possible prognostic factors were prospectively collected on 225 patients undergoing esophago-gastrectomy at a single institution, and univariate and multivariate analyzes performed. T, N, M and overall UICC stage, differentiation, involvement of the circumferential resection margin and number of metastatic of lymph nodes were identified as significant prognostic factors by univariate analysis. Multivariate analysis revealed that the completeness of resection (R-category), ratio of metastatic to total nodes resected and the presence of vascular invasion were independently significant prognostic factors. Following R0 or R1 resection, patients with a metastatic to total lymph node ratio > 0.2 and/or the presence of vascular invasion have a poor prognosis, and the effects of adjuvant therapy in these patients should be studied.**

INTRODUCTION

Over the last 25 years, the incidence of esophageal cancer has risen dramatically,[1,2] whereas the 5-year survival has remained worryingly poor at less than 10%.[3,4] The poor prognosis is generally ascribed to the advanced stage of the disease at presentation and, indeed, approximately half of all patients with esophageal cancer present with disease that is too advanced to contemplate surgery.[5,6] Although surgery remains the gold standard treatment,[7,8] meta-analysis has revealed that patients with operable disease have a median 5-year survival of 20% following esophago-gastrectomy.[9]

Neo-adjuvant therapy has been used in an attempt to improve the prognosis of operable esophageal cancer, but randomized controlled trials have generally failed to show any survival advantage for preoperative radiotherapy,[10] chemotherapy,[11] or chemoradiotherapy.[12] These trials have randomized patients with esophageal cancer deemed operable by radiologic TNM staging[13] of the cancer. Similarly, postoperative adjuvant radiotherapy[14] or chemotherapy[15] have not influenced survival in randomized controlled trials. To our knowledge, postoperative chemoradiotherapy in esophageal cancer has yet to be studied in a randomized trial. Failure to show a survival advantage for neo-adjuvant or adjuvant therapy may be due to the inclusion of patients who would have been successfully treated by surgery alone. Preoperative staging will continue to rely on radiologic imaging, but more informative prognostic factors based on operative and pathologic features could identify those patients who would benefit most from adjuvant therapy. Indeed a non-randomized retrospective review of patients undergoing esophago-gastrectomy for cancer found that postoperative chemoradiotherapy improved the survival of patients with metastatic lymph node disease.[16] Multivariate analyzes have predictably identified depth of invasion[8,17] and nodal disease[8,18] as independent prognostic factors, whereas other studies describe involvement of the circumferential resection margin,[19] radicality of resection,[20] and need for blood transfusion[21,22] as prognostically significant.

To identify prognostic factors that may help determine the need for adjuvant therapy, a comprehensive analysis of clinical, operative and pathologic features of patients with esophageal cancer

Address correspondence to: Dr Kevin Dolan, Division of Surgery, Room 42 L Floor, Royal Brisbane Hospital, Herston Road, Herston, Queensland 4029, Australia. Tel: (+61) 7 3636 1621; Fax: (+61) 7 3636 1314; E-mail: medkd@leeds.ac.uk

undergoing esophago-gastrectomy over the last decade at The General Infirmary at Leeds was performed.

MATERIALS AND METHODS

Between January 1990 and December 2000, 225 patients with esophageal carcinoma underwent esophago-gastrectomy at The General Infirmary at Leeds. Overall in-hospital mortality was 12.9%, and these 29 patients were excluded from our analysis of prognostic factors. Two patients received preoperative radiotherapy, 15 received preoperative chemotherapy and 23 received preoperative chemoradiotherapy, and again these patients were excluded from our analysis as neo-adjuvant therapy may have affected the pathologic factors studied. This left 156 patients discharged from hospital following esophago-gastrectomy for cancer to be analyzed.

Data was prospectively collected on 15 possible prognostic factors. Clinical factors included age and sex, and operative factors were 'type of operation' and 'type of resection' (R-category). Pathologic factors were: cancer subtype, subsite, differentiation, T, N, M and overall UICC stage, number of metastatic nodes, ratio of metastatic nodes to total number of nodes resected, involvement of the circumferential resection margin (defined as cancer within 1 mm of the resection margin) and the presence of vascular invasion (defined as the presence of cancer cells within an endothelial vascular space).

The unit policy is for life-long follow-up, with clinic visits every 3 months for the first year, every 6 months for the next 4 years and annually thereafter. Thorough physical examination and routine bloods were performed at each clinic visit. Further investigations such as CT and or endoscopy were performed if recurrence was suspected.

Survival was measured from the date of diagnosis to the date of death or until February 2001, the end of the study period. The cause of death was identified from hospital case-notes or from the Yorkshire Cancer Registry, with deaths from causes other than esophageal cancer regarded as censored at the time of death. All surviving patients were reviewed in clinic or by telephone during February 2001. Survival was analyzed by Kaplan–Meier and log rank test.[23] Those factors found to significantly influence prognosis by univariate analysis were included in the multivariate analysis using the Cox proportional hazards model.[24] Statistical analysis was performed using SPSS 10.0 for Windows (SPSS, USA).

RESULTS

The median age of 156 patients undergoing esophago-gastrectomy for esophageal cancer was 65 years (range 29–87 years) and 111 (71.2%) were men (Table 1); 125 (80.1%) patients had adenocarcinoma of the esophagus, 127 (81.4%) underwent Ivor–Lewis esophago-gastrectomy, 18 underwent thoracoscopically assisted Ivor–Lewis esophago-gastrectomy, six underwent McKeown esophago-gastrectomy and a single patient had esophago-gastrectomy via a left

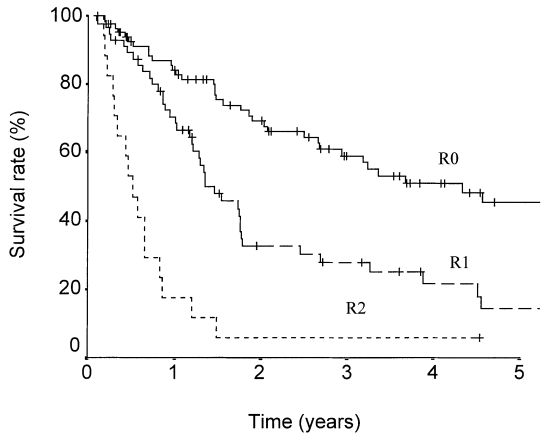
Table 1. Univariate analysis of prognostic factors in patients with esophageal cancer undergoing resection ($n = 156$)

Variable	No. of patients (%)	MST (months)	5-Year survival rate (%)	*P*-value*
Overall	156	22.3	29.2	
Age (years)				
≤ 70	105 (67.3)	22.3	31.0	NS
> 70	51 (32.7)	21.4	23.7	
Sex				
Male	111 (71.2)	21.0	25.9	NS
Female	45 (28.8)	38.8	38.5	
Tumor location				
Middle	32 (20.5)	21.4	26.0	NS
Lower	124 (79.5)	22.3	29.9	
Histology				
Adenocarcinoma	125 (80.1)	22.8	27.1	NS
Squamous	31 (19.9)	21.2	37.5	
Tumor differentiation				
Well	21 (13.5)	54.1	40.6	
Moderate	64 (41.0)	32.2	35.3	0.03
Poor	71 (45.5)	17.4	20.6	
Vascular invasion				
Present	30 (19.2)	11.3	9.0	< 0.0001
Absent	126 (80.8)	35.2	33.9	
Type of resection				
R0	82 (52.6)	51.9	45.3	
R1	57 (36.5)	17.5	14.4	< 0.0001
R2	17 (10.9)	6.2	–	
pT stage				
pT1	26 (16.7)	NR	74.2	
pT2	20 (12.8)	40.2	30.5	< 0.0001
pT3	104 (66.7)	20.9	24.1	
pT4	6 (3.8)	4.0	0	
pN stage				
pN0	57 (36.5)	NR	56.6	< 0.0001
pN1	99 (63.5)	17.6	14.5	
pM stage				
pM0	134 (85.9)	31.9	34.6	< 0.0001
pM1	22 (14.1)	6.2	0	
UICC stage				
I	22 (14.1)	NR	71.6	
II	51 (32.7)	51.9	44.6	< 0.0001
III	61 (39.1)	20.9	16.4	
IV	22 (14.1)	6.2	0	
CRM status				
Negative	90 (57.7)	40.2	42.1	< 0.0001
Positive	66 (42.3)	15.6	12.3	
No. of involved lymph nodes				
≤ 3	107 (68.6)	51.9	41.6	< 0.0001
> 3	49 (31.4)	11.4	3.5	
Lymph node ratio				
≤ 0.2	92 (59.0)	NR	51.5	< 0.0001
> 0.2	64 (41.0)	12.2	2.2	

*Log rank test.
CRM, circumferential resection margin; MST, median survival time; NR, not reached; NS, not significant.

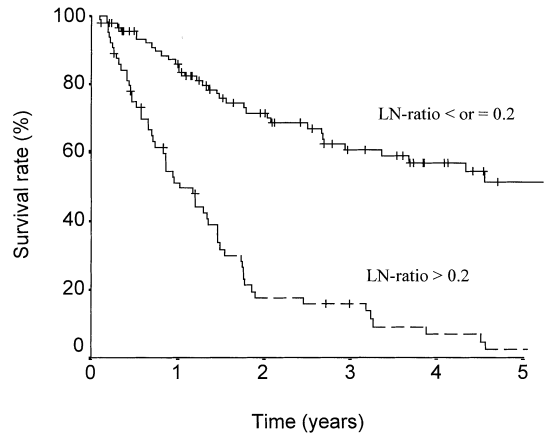
thoracoabdominal incision. R0 resection was achieved in 82 (52.6%) cases. The median number of harvested lymph nodes was 13 (range 6–56).

In February 2001, 61 (39.1%) patients were alive with no evidence of disease, a single patient was alive with disease and 93 (59.6%) patients had died, only three from causes not related to esophageal cancer. The 1-, 3- and 5-year survivals were 72%, 41% and 29%, respectively, with a median survival of 22 months. Univariate analysis revealed that age, sex, cancer subtype and subsite did not affect prognosis (Table 1). The type of operation did not affect prognosis, although this is not surprising as the vast majority of patients underwent Ivor–Lewis esophago-gastrectomy. Ten factors evaluated in the univariate analysis had a significant effect on survival: T, N, M and overall UICC stage, differentiation,



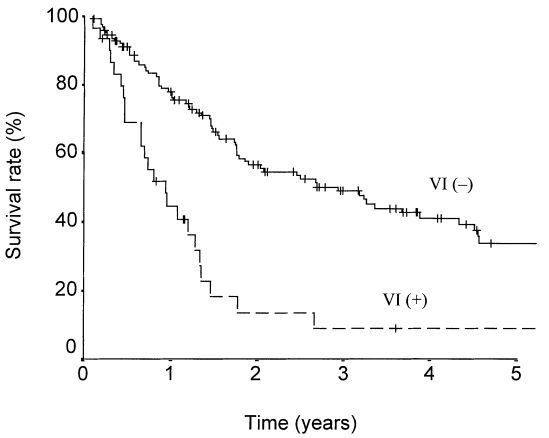
No. at risk						
R0	82	61	45	30	21	14
R1	57	37	14	11	6	4
R2	17	3	1	1	1	0

Fig. 1 Survival curves according to type of resection (R-category) ($P < 0.0001$, log rank).



No. at risk						
< or = 0.2	92	71	50	35	25	17
> 0.2	64	30	10	7	3	1

Fig. 2 Survival curves according to lymph node ratio ($P < 0.0001$, log rank).



No. at risk						
VI (–)	126	89	57	40	27	17
VI (+)	30	12	3	2	1	1

Fig. 3 Survival curves according to vascular invasion (VI) ($P < 0.0001$, log rank).

Table 2. Multivariate analysis of prognostic factors in patients with esophageal cancer undergoing resection ($n = 156$)

Variables	Regression coefficient	SE	Relative risk	95% CI	*P*-value
R-category					
R0	0	–	1	–	–
R1	0.39	0.25	1.49	0.91–2.42	< 0.001
R2	1.36	0.34	3.91	1.98–7.69	< 0.0001
Lymph node ratio					
≤ 0.2	0	–	1	–	–
> 0.2	1.25	0.24	3.49	2.18–5.61	< 0.001
Vascular invasion					
Absent	0	–	1	–	–
Present	0.77	0.26	2.15	1.29–3.58	0.003

Reference categories are indicated by relative risk = 1, and *P*-values refer to comparisons with reference categories.

R-category, involvement of the circumferential resection margin, number of positive lymph nodes (≤ 3 vs. > 3), ratio of metastatic to total nodes (≤ 0.2 vs. > 0.2) and vascular invasion.

Only factors significant on univariate analysis were subjected to multivariate analysis, which revealed that R-category ($P < 0.001$, Fig. 1), lymph node ratio ($P < 0.001$, Fig. 2) and vascular invasion ($P = 0.022$, Fig. 3) were independently significant prognostic factors for patients undergoing esophago-gastrectomy for esophageal cancer (Table 2). R-category had the most significant impact on survival (relative risk 4.63), followed by lymph node ratio (relative risk 2.38), and the presence of vascular invasion (relative risk 1.74).

DISCUSSION

It is not surprising that univariate analysis identified T, N, M and overall UICC stage as highly significant predictors of survival following esophago-gastrec-

tomy for esophageal cancer. Similarly, it is to be expected that poorly differentiated cancers had a worse prognosis than well differentiated cancers. Prognosis was not significantly affected by histologic subtype, although a larger study has recently suggested that adenocarcinomas of the esophagus have a better prognosis than squamous cell cancers.[8] Subsite did not influence prognosis, however, in our study all cancers were present in the middle or lower third of the esophagus, and previous analyzes have suggested that cancers of the upper third of the esophagus have a worse prognosis than cancers of the lower two-thirds.[2,25] Age and sex of the patient did not influence prognosis significantly and the 5-year survival was almost identical for patients younger than 70 years and patients older than 70 years, although the in-hospital mortality was slightly higher in those older than 70 years. The authors agree that age should not be a barrier to esophago-gastrectomy, as previously reported.[26]

Only three out of 15 factors were found to be independently significant on multivariate analysis, namely the completeness of resection (R-category), the ratio of metastatic to total number of lymph nodes and the presence of vascular invasion. R-category has been reported as a strong predictor of prognosis in other studies of esophageal cancer.[27,28] Patients with involvement of the circumferential resection margin by cancer had a significantly poorer prognosis than those with circumferential margins free of cancer, but this was not a significant independent prognostic factor on univariate analysis. The importance of circumferential margin involvement has previously been reported.[19,29]

The importance of metastatic nodal disease was demonstrated in our analysis using the 5-year survival of node-negative patients being four times greater than that of patients with metastatic nodes. The prognostic significance of the presence of metastatic disease in lymph nodes is well known.[8,28,30] It would seem logical that quantitation of metastatic nodal disease would improve prognostic deliberation. A single author has attempted to estimate the volume of cancer within lymph nodes by measurement of the area of cancer within the thickest part of the node.[31] However, the accuracy of this estimation is questionable and indeed this estimation was of less prognostic value than the N stage. Other authors have attempted to quantify nodal disease by the number of metastatic nodes resected. Univariate analyzes have identified a poorer prognosis in patients with more than two,[25] three,[32] four,[33,34] and seven[35] metastatic nodes. However, the number of metastatic nodes detected depends partly on the radicality of resection, and a more accurate method of quantifying nodal disease may be the ratio of metastatic nodes to the total number of nodes resected. Indeed in our study the number of metastatic nodes was of prognostic value in univariate analysis but lost its significance in multivariate analysis, whereas the ratio of metastatic to total number of nodes resected was prognostically significant in both univariate and multivariate analyzes. The significance of metastatic lymph node ratio has been described in adenocarcinoma of the esophagus in Western patients (ratio of 0.3),[28] squamous cell carcinoma in Western patients (ratio of 0.2),[36] and squamous cell carcinoma in Japanese patients (ratio of 0.1).[37] The differences in the ratios for each of these studies may reflect the difference in nodal yield from a two-field esophago-gastrectomy for adenocarcinoma and a three-field esophago-gastrectomy for squamous cell carcinoma, and the difference in extent of nodal dissection between Western and Japanese surgeons and/or pathologists. Our study included both adenocarcinoma and squamous cell carcinoma of the esophagus and a ratio of 0.2 was used as this represented the median of the three previous studies. It is of note that in all four studies lymph node ratio was of greater prognostic significance than N stage.

The final factor identified by multivariate analysis as an independent prognostic factor was the presence of vascular invasion, as described in two other analyzes.[18,38] The majority but not all patients with evidence of vascular invasion eventually developed visceral metastases, identifying this as a potential determining factor for the use of adjuvant therapy.

A plethora of molecular markers have been analyzed as possible prognostic factors in patients with esophageal cancer including expression of proliferating cell nuclear antigen (PCNA), epidermoid growth factor receptor (EGFR), cyclin D1, p53, and p21. To date, none of these markers has been of clinical value.[39,40]

The most significant prognostic factors in patients with esophageal cancer undergoing esophago-gastrectomy are the completeness of resection (R-category), ratio of metastatic nodes to total nodes resected, and the presence of vascular invasion. Patients undergoing R0 or R1 resections with either a lymph node ratio greater than 0.2 and/or the presence of vascular invasion have a poor prognosis following esophago-gastrectomy, and the effects of adjuvant therapy in these patients needs to be studied.

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