Prognostic significance of circumferential resection margin involvement following oesophagectomy for cancer and the predictive role of endoluminal ultrasonography

**TD Reid¹, DSY Chan¹, SA Roberts², TDL Crosby³, GT Williams⁴ and WG Lewis⁵,¹**

¹Department of Surgery, South East Wales Cancer Network, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK; ²Department of Radiology, South East Wales Cancer Network, University Hospital of Wales, Cardiff, UK; ³Department of Oncology, Velindre Hospital, Cardiff, UK; ⁴Department of Pathology, South East Wales Cancer Network, University Hospital of Wales, Heath Park, Cardiff, UK.

**BACKGROUND:** The optimum multimodal treatment for oesophageal cancer, and the prognostic significance of histopathological tumour involvement of the circumferential resection margin (CRM +) are uncertain. The aims of this study were to determine the prognostic significance of CRM + after oesophagectomy and to identify endosonographic (endoluminal ultrasonography (EUS)) features that predict a threatened CRM +.

**METHODS:** Two hundred and sixty-nine consecutive patients underwent potentially curative oesophagectomy (103 surgery alone, 124 neoadjuvant chemotherapy (CS) and 42 chemoradiotherapy (CRTS)). Primary outcome measures were disease-free survival (DFS) and overall survival (OS).

**RESULTS:** CRM + was reported in 98 (38.0%) of all, and in 90 (62.5%) of pT3 patients. Multivariate analysis of pathological factors revealed: lymphovascular invasion (HR 2.087, 95% CI 1.396–3.122, \(P<0.0001\)), CRM + (HR 1.762, 95% CI 1.201–2.586, \(P = 0.004\)) and lymph node metastasis count (HR 1.563, 95% CI 1.018–2.400, \(P = 0.041\)) to be independently and significantly associated with DFS. Lymphovascular invasion (HR 2.160, 95% CI 1.432–3.259, \(P<0.001\)) and CRM + (HR 1.514, 95% CI 1.000–2.292, \(P = 0.050\)) were also independently and significantly associated with OS. Multivariate analysis revealed EUS T stage (T3 or T4, OR 24.313, 95% CI 7.438–79.476, \(P<0.0001\)) and use or not of CRTS (OR 0.116, 95% CI 0.035–0.382, \(P<0.0001\)) were independently and significantly associated with CRM +.

**CONCLUSION:** A positive CRM was a better predictor of DFS and OS than standard pTNM stage.

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Pathological involvement of the circumferential resection margin (CRM +) after rectal cancer surgery is a well-established prognostic indicator (Adam et al, 1994), and patients deemed on radiological criteria to be at risk of a threatened CRM are offered preoperative chemoradiotherapy (Klautke et al, 2005). In contrast, the prognostic significance of CRM + after oesophageal cancer surgery is less certain and the literature polarised. The overall reported incidence of CRM + ranges from 20 to 50% (Sagar et al, 1993; Dexter et al, 2001; Khan et al, 2003; Griffiths et al, 2006; Sujendran et al, 2008; Thompson et al, 2008; Deeter et al, 2009; Saha et al, 2009; Scheepers et al, 2009; Mirnezami et al, 2010; Pultram et al, 2010; Chao et al, 2011; Verhage et al, 2011; Harvin et al, 2012; Rao et al, 2012; Sahi et al, 2012).

Although some report an independent negative association between CRM + and survival (Dexter et al, 2001; Griffiths et al, 2006; Sujendran et al, 2008; Deeter et al, 2009; Saha et al, 2009; Scheepers et al, 2009; Pultram et al, 2010; Verhage et al, 2011), others have not (Khan et al, 2003; Thompson et al, 2008; Mirnezami et al, 2010; Chao et al, 2011; Harvin et al, 2012; Rao et al, 2012; Sahi et al, 2012), and in the most recent UK national oesophagogastric audit was reported to be 29% (NHS Information Centre, 2010).

Sagar et al (1993) first reported an association between CRM + and local recurrence after oesophagectomy, and several studies have since examined the influence of CRM + on survival (Dexter et al, 2001; Khan et al, 2003; Griffiths et al, 2006; Sujendran et al, 2008; Thompson et al, 2008; Deeter et al, 2009; Saha et al, 2009; Scheepers et al, 2009; Mirnezami et al, 2010; Pultram et al, 2010; Chao et al, 2011; Verhage et al, 2011; Harvin et al, 2012; Rao et al, 2012; Sahi et al, 2012). Most UK oesophageal cancer patients present with locoregional advanced disease, and the aim of neoadjuvant therapy is to increase the probability of potentially curative (R0) resection. Following the publication of MRC OE02, contemporary optimum treatment in the United Kingdom has been considered to be neoadjuvant chemotherapy (CS) followed by surgery (Medical Research Council Oesophageal Cancer Working Group, 2002), but less than 30% of patients are suitable (NHS Information Centre, 2010), and for those that are, 5-year survival remains poor at just 23% (Allum et al, 2009). Neoadjuvant chemoradiotherapy has been reported to downstage tumours in over 90% of patients (Reynolds et al, 2007), facilitating R0 resection, but has fallen out of favour in
Consecutive patients treated for oesophageal cancer between 1 January 1998 and 29 February 2012, by the regional SE Wales upper GI cancer network, were studied. Patients were excluded if they had been treated for high-grade dysplasia in the absence of invasive malignancy, if open and close surgery had been performed (aborted resection), if there was pathological involvement of the longitudinal resection margins, or if pathological tumour nodes metastasis stage information was missing. Patients were also excluded if they underwent salvage surgery following definitive chemoradiotherapy. No patients had synchronous or metachronous ENT carcinomas. After exclusions, 269 patients underwent potentially curative oesophagectomy, and form the basis of this study (Figure 1). Clinical, radiological and pathological information was collected on a prospectively maintained database. Preoperative staging was in accordance with the UICC Tumour Nodes Metastasis 6th Edition, and involved computed tomography and EUS in all patients, and also laparoscopy if appropriate. More recently, CT-PET has been utilised for patients with early-stage tumours of the lower third of the oesophagus, with poorer performance status, in whom it was considered that a thoracotomy may carry an unacceptable risk of respiratory complications. All surgery was performed by specialist upper GI surgeons. Oesophageal resection was defined as potentially curative when all visible tumour had been removed in continuity, with poorer performance status, in whom it was considered that a thoracotomy may carry an unacceptable risk of respiratory complications. All surgery was performed by specialist upper GI surgeons. Oesophageal resection was defined as potentially curative when all visible tumour had been removed and both proximal and distal resection margins were free from tumour on histological examination. Operative mortality was defined as death occurring within 30 days of surgery. No patients in this study received adjuvant therapy.

**Materials and Methods**

The aims of this study were three-fold: to identify the relative prognostic significance of CRM+ after potentially curative oesophagectomy; to assess the predictive value of EUS in determining whether the CRM is likely to be threatened; and to examine the relative influence of specific neoadjuvant modalities on CRM+ status.

**Circumferential margin assessment**

Pathological involvement of the CRM+ was defined according to the Royal College of Pathologists, as the presence of tumour within 1 mm of the circumferential margin (Mapstone, 2007). Reporting of CRM status was based on best practice at the time, guided by the first (Mapstone, 1998), and second (Mapstone, 2007) editions of the Royal College of Pathologists’ Dataset for the histopathological reporting of oesophageal carcinoma.

**Follow-up and disease recurrence**

Patients were reviewed every 3 months for the first year and then 6 monthly thereafter. Where disease recurrence was suspected it was confirmed with investigations, usually CT or endoscopy. The time of recurrence was taken as the date of the confirmatory investigation. Death certification was obtained from the Office for National Statistics.

**Statistical analysis**

Grouped data were expressed as median (range) and non-parametric methods used for comparison. Comparison of categorical variables was performed with the \( \chi^2 \) test, and comparison of continuous variables with the Mann–Whitney \( U \)-test. Median follow-up was calculated using the reverse Kaplan–Meier method. Overall survival was calculated in months from the date of diagnosis. Disease-free survival was also calculated in months from the date of diagnosis, with either the confirmation of disease recurrence or death constituting the end point. Cumulative survival was calculated according to the life-table method of Kaplan and Meier, and differences between groups were analysed with the log-rank test. Univariate and multivariate survival analyses were performed using Cox regression. Univariate and multivariate analyses of pre-treatment factors influencing CRM status were performed using binary logistic regression. Statistical tests were two-sided and the level of significance taken as 0.05.
RESULTS
The clinical and radiological details of the patients related to neoadjuvant treatment type are shown in Table 1, and pathological details in Table 2. There were progressive increases in the radiological T and N stages of the patients treated between the surgery alone, CS and neoadjuvant chemoradiotherapy groups. A complete pathological response occurred in more than one-third of patients who received chemoradiotherapy, but was a relatively rare event in those treated with chemotherapy. For all patients the median lymph node harvest was 12 (0–41), and the median number of lymph node metastases was 1 (0–18). CRM status was reported in 258 (96.0%) patients, of which 98 (38.0%) were CRM +.

Follow-up
Follow-up until 5 years or death was available for 226 (84.0%) patients. The median follow-up was 88 months (range 4–157).

Survival related to CRM status for all patients
A negative CRM (CRM –) was associated with significantly better DFS (median: 63 vs 19 months, 2 year: 67.1 vs 36.7%, \( P < 0.0001 \)) and overall survival (OS; median: 66 vs 26 months, 2 year: 70.8 vs 55.5%, \( P < 0.0001 \)). Figure 2 demonstrates DFS related to CRM status for all patients and Figure 3 for patients with pT3 stage. In this pT3 subgroup CRM – was associated with significantly better DFS (median: 30 vs 20 months, 2 year: 60.3 vs 39.3%, \( P = 0.019 \)) and OS (median: 36 vs 28 months, 2 year: 66.1 vs 59.9%, \( P = 0.032 \)) when compared with CRM +.

Table 1 Details of the patients

| S | CS | CRTS | P-value |
|---|---|---|-------|
| Number | 103 | 124 | 42 | \( <0.0001 \)* |
| CPR | NA | 3 (2.5) | 15 (35.7) | \( <0.0001 \)* |

Table 2 Pathological details of the patients

| S | CS | CRTS | P-value |
|---|---|---|-------|
| Number | 103 | 124 | 42 | \( <0.0001 \)* |

Abbreviations: CPR = complete pathological response to neoadjuvant therapy; CRTS = circumferential resection margin; CS = neoadjuvant chemotherapy; LAN = lymph node; LCSM = lymph node metastasis count; LV = lymphovascular; M = male; S = surgery alone; SCC = squamous cell carcinoma. Stage figures are numbers (%). Length and thickness parameters are median cm (range). *Mann–Whitney U-test. Italic values indicate \( P < 0.0001 \).

Figure 2 Disease-free survival related to CRM status for all patients.

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Clinical Studies

Survival related to CRM status stratified by treatment type
For patients treated with surgery alone, CRM – was associated with significantly better DFS (median: 74 vs 19 months, 2 year: 70.4 vs 41.5%, P < 0.0001) and OS (median: 77 vs 25, 2 year: 73.7 vs 58.8%, P = 0.001). For patients treated with CS, CRM – was associated with significantly better DFS (median: 30 vs 18 months, 2 year: 63.3 vs 35.5%, P = 0.001) and OS (median: 43 vs 26, 2 year: 68.2 vs 53.1%, P = 0.004). For patients treated with neoadjuvant chemoradiotherapy, CRM – was associated with trends towards better DFS (median: 49 vs 23 months, 2 year: 66.7 vs 20.0%, P = 0.345) and OS (median: 64 vs 26 months, 2 year: 69.4 vs 60.0%, P = 0.363), although the number of patients treated in this way was small (n = 42).

Univariate and multivariate survival analyses
A univariate analysis of clinical and pathological factors influencing both disease-free and OS is shown in Table 3. The same six factors were identified as significant for both the measures of survival, and were entered into multivariate analyses, with individual models for disease-free and OS (Table 4). Additional multivariate analyses were performed with stratification by treatment type for patients treated with surgery and CS (Table 4). The relatively small number of patients treated with neoadjuvant chemoradiotherapy precluded meaningful multivariate analysis of this subgroup. For all patients lymphovascular invasion and CRM + were independently and significantly associated with both measures of survival. In addition, for all patients the pathological lymph node metastasis count was independently and significantly associated with DFS, but did not reach statistical significance for OS (P = 0.051).

Cancer recurrence related to CRM status
The assessment of oesophageal cancer recurrence excluded patients who died in hospital (in-hospital mortality) and those in whom CRM status was not reported. CRM + was associated with a significantly higher incidence of cancer recurrence than CRM – (67 of 94 vs 63 of 152, 71.3 vs 41.4%, P < 0.0001).

Univariate and multivariate survival analyses
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Univariate analyses of factors influencing survival
Table 3

| Factor                  | Disease-free survival | Overall survival |
|-------------------------|-----------------------|------------------|
| Age (years)             | HR 0.995–1.028        | 0.181            |
| Gender                  | 1.283                 | 0.213            |
| Year of treatment       |                       |                  |
| 1998–99                 | Reference group       |                  |
| 2000–01                 | 1.701                 | 0.224            |
| 2002–03                 | 2.205                 | 0.059            |
| 2004–05                 | 1.977                 | 0.099            |
| 2006–07                 | 2.097                 | 0.078            |
| 2008–09                 | 1.593                 | 0.313            |
| 2010–11                 | 1.278                 | 0.123            |
| Path cell type          | 0.785                 | 0.233            |
| Path cell type          | 0.810                 | 0.463            |
| Treatment type          |                       |                  |
| T1                      | 1.194                 | 0.312            |
| T2                      | 0.980                 | 0.931            |
| T3                      | 0.990                 | 0.931            |
| T4                      | 0.990                 | 0.931            |
| pT stage                |                       |                  |
| Tumor grade             |                       |                  |
| Well                    | Reference group       |                  |
| Poor                    | 4.157                 | 0.001            |
| CRM                    | 2.263                 | <0.0001          |
| LV invasion             | 2.861                 | <0.0001          |
| LNMC                    | 1.131                 | <0.0001          |

Abbreviations: 95% CI = 95% confidence interval; CPR = complete pathological response; CRM = circumferential resection margin; CS = neoadjuvant chemoradiotherapy; OS = overall survival; DFS = disease-free survival; HR = hazard ratio; LNMC = lymph node metastasis count; LV = lymphovascular; neo = neoadjuvant; path = pathological; S = surgery alone.

CRM status related to EUS-defined T stage
The overall rates of CRM + related to EUS-defined T stage were T1 (0), T2 (7 of 46, 15.2%), T3 (81 of 165, 49.1%), T4 (6 of 16, 37.5%). For patients treated with surgery alone these CRM + rates were T1 (0), T2 (2 of 33, 6.1%), T3 (28 of 39, 71.8%) and T4 (4 of 11, 36.4%). For patients treated with CS, the equivalent rates were T1 (0), T2 (5 of 33, 15.2%), T3 (28 of 39, 71.8%) and T4 (1 of 7, 14.3%). The reduced CRM + rate for EUS T3 tumours following neoadjuvant chemoradiotherapy (12.1%), compared with surgery alone (71.8%), and CS (52.7%) was highly statistically significant (P < 0.0001).

CRM status related to pathological T stage
The overall rates of CRM + related to pT stage were T1 (0), T2 (4 of 44, 9.1%), T3 (90 of 144, 62.5%), T4 (4 of 5, 80%). The rates of CRM + in the 144 patients with pT3 tumours related to neoadjuvant treatment type were: surgery (28 of 44, 63.6%), CS (58 of 86, 67.4%) and neoadjuvant chemoradiotherapy (4 of 14, 28.6%, P = 0.020).
### Influence of EUS derived factors on CRM involvement

The results of univariate and multivariate binary logistic regression analysis of the association between various EUS derived factors and subsequent CRM involvement are presented in Table 5. Neoadjuvant treatment type was also included in this analysis, because of the significant influence on CRM outlined above. Other baseline patient factors including age, gender and pathological cell type were analysed and found to have no association with CRM involvement on univariate analysis. All factors significant on univariate analysis were entered into the multivariate model. The results of univariate and multivariate binary logistic regression analysis of the association between various EUS derived factors and subsequent CRM involvement are presented in Table 5.

### Operative morbidity and mortality

The overall rates of operative morbidity after surgery alone, CS and neoadjuvant chemoradiotherapy were 46 (44.7%), 53 (42.7%) and 21 (50.0%), respectively ($P = 0.747$). Thirty day (operative) mortality rates were 3 (4.9%), 1 (0.8%) and 5 (11.9%), respectively ($P = 0.006$). Ninety-day mortality rates were 7 (6.8%), 1 (0.8%) and 5 (11.9%), respectively ($P = 0.007$). The in-hospital mortality rates were 7 (6.8%), 1 (0.8%) and 5 (11.9%), respectively ($P = 0.007$).

### DISCUSSION

This study represents the third largest report of the prognostic significance of CRM involvement following oesophagectomy, and the only one to address the potential value of EUS in predicting a threatened CRM. The principal findings were that a positive CRM was independently and significantly associated with disease-free and OS, for tumours of all pT stages, as well as pT3 stage. The co-finding of lymphovascular invasion and lymph node metastasis count as important independent prognostic factors is in keeping with the literature (Von Rahden et al., 2005; Mariette et al., 2008) and lends further credibility to this series. Several EUS factors were associated with a CRM +, but endosonographic T stage was the strongest, with almost half of all patients with EUS T3 tumours proving subsequently to have a positive CRM. A positive CRM was significantly less common after neoadjuvant chemoradiotherapy than CS for patients diagnosed with endosonographic T3 tumours. The literature related to oesophageal CRM status is heterogeneous and conclusions inconsistent. Reports vary regarding study design, the use of neoadjuvant therapy, surgical technique, pathological processing and definition of CRM +. Eight studies report a negative survival association with CRM + on multivariate analysis, whereas seven others, including the two largest, failed to demonstrate an independent survival association with CRM status. Khan et al. (2003) report no association with survival, despite having the largest sample size, but their 329 patients were treated between 1987 and 1996, and none received neoadjuvant treatment, yet their reported CRM + rate was the lowest at 20%, which questions the accuracy of the histological assessment. More recently Mirnezami et al. (2010) reported a series of 314 patients which identified CRM status as associated with survival on univariate analysis, but not multivariate analysis. However, this report included patients with positive longitudinal resection margins, a possible additional confounding factor.

The study has several potential weaknesses. The reporting of histological factors was undertaken by three separate pathology departments within the cancer network, and there could therefore be discrepancies in the reporting of CRM, particularly considering the difficulties related to this. However, the rates of CRM involvement lie within the range reported in published series, and it therefore seems unlikely that CRM involvement was

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**Table 4** Multivariate analyses of factors influencing survival

| Disease-free survival | Hazard ratio | 95% CI | P-value |
|-----------------------|-------------|-------|---------|
| All patients          |             |       |         |
| Lymphovascular invasion | 2.087       | 1.396–3.122 | <0.0001 | 0.013 |
| CRM involvement      | 1.762       | 1.201–2.586 | 0.004  | 0.041 |
| LNMC                  | 1.563       | 1.018–2.400 | 0.041  |       |
| Surgery alone         |             |       |         |
| Lymphovascular invasion | 2.360       | 1.135–4.910 | 0.022  |       |
| pT stage              |             |       |         |
| T1                    | Reference group |       |       |       |
| T2                    | 4.316       | 1.356–13.734 | 0.013 |       |
| T3                    | 3.887       | 1.374–11.001 | 0.011 |       |
| Neoadjuvant chemotherapy |             |       |         |
| Lymphovascular invasion | 2.338       | 1.408–3.884 | 0.001  |       |
| LNMC                  | 2.323       | 1.282–4.209 | 0.005  |       |
| CRM involvement      | 1.892       | 1.123–3.189 | 0.017  |       |
| Overall survival      |             |       |         |
| All patients          |             |       |         |
| Lymphovascular invasion | 2.160       | 1.432–3.259 | <0.0001|       |
| CRM involvement      | 1.514       | 1.000–2.292 | 0.050  |       |
| LNMC                  | 1.054       | 1.000–1.112 | 0.051  |       |
| Surgery alone         |             |       |         |
| Lymphovascular invasion | 2.204       | 1.061–4.581 | 0.034  |       |
| pT stage              |             |       |         |
| T1                    | Reference group |       |       |       |
| T2                    | 4.263       | 1.336–13.603 | 0.014 |       |
| T3                    | 3.763       | 1.327–10.676 | 0.013 |       |
| Neoadjuvant chemotherapy |             |       |         |
| Lymphovascular invasion | 2.244       | 1.303–3.863 | 0.004  |       |
| LNMC                  | 1.073       | 1.016–1.132 | 0.011  |       |

Abbreviations: 95% CI = 95% confidence interval; CRM = circumferential resection margin; LNMC = lymph node metastasis count.

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**Table 5** Analysis of pre-treatment factors associated with circumferential margin involvement

| Factor            | Odds ratio | 95% CI | P-value |
|-------------------|------------|-------|---------|
| Univariate analysis |             |       |         |
| EUS T stage       |             |       |         |
| T1/T2             | Reference group |       |       |       |
| T3/T4             | 8.726       | 3.798–20.050 | <0.0001|       |
| EUS N stage       |             |       |         |
| NO                | Reference group |       |       |       |
| N1                | 1.781       | 1.060–2.992 | 0.029 |       |
| EUS tumour length | 1.173       | 1.056–1.303 | 0.003 |       |
| EUS disease length| 1.087       | 1.013–1.167 | 0.020 |       |
| EUS tumour thickness| 1.795       | 0.974–3.309 | 0.061 |       |
| EUS LNMC           | 1.156       | 1.033–1.294 | 0.012 |       |
| Neox Tx           | Reference group |       |       |       |
| CS                | 2.468       | 1.410–4.322 | 0.002 |       |
| CRTS              | 0.310       | 0.111–0.869 | 0.026 |       |
| Multivariate analysis |             |       |         |
| EUS T stage       |             |       |         |
| T1/T2             | Reference group |       |       |       |
| T3/T4             | 24.313      | 7.438–79.476 | <0.0001|       |
| Neox Tx           | Reference group |       |       |       |
| S                 | Reference group |       |       |       |
| CS                | 0.641       | 0.289–1.420 | 0.273 |       |
| CRTS              | 0.116       | 0.035–0.382 | <0.0001|       |

Abbreviations: 95% CI = 95% confidence interval; CRM = circumferential resection margin; CRTS = neoadjuvant chemoradiotherapy; CS = neoadjuvant chemotherapy; EUS = endoluminal ultrasonography; LNMC = lymph node metastasis count; neoTx = neoadjuvant treatment type; S = surgery alone.
substantially under reported. Moreover, the pathologists involved with the reporting of CRM status were effectively ‘blind’ to a degree, as they were unaware at the time that these data would be analysed in a future retrospective study. Although the numbers in this study are relatively large, they are not large enough and subsequently underpowered for subgroup analyses. This prevented exclusive analysis of patients with endosonographic T3 tumours, to establish the relative influence of the radiological factors other than EUS T stage, that may be predictive of CRM involvement. The comparison of different neoadjuvant modalities is also open to bias, as these treatments were allocated on a non-randomised, per patient basis, and according to MDT practice at the time.

In contrast the study has several strengths, as it represents real life stage-directed practice in a regional upper GI cancer network multidisciplinary team serving a population of 1.4 million over a 14-year period. All treatment was provided by an MDT experienced in the management of oesophageal cancer, whose results have been well audited (Morgan et al, 2007). The EUS component of this study represents particularly original work, and constitutes the only report comparing EUS factors with CRM status, relating this to the effects of neoadjuvant treatment. The radiological expertise involved in the EUS examinations has been well documented and the follow-up data are particularly robust with dates of death obtained from the Office for National Statistics. The role of imaging in predicting oesophageal CRM status is at an embryonic stage of development when compared with rectal CRM status, where MRI offers greater accuracy than EUS in determining a threatened CRM (Lahaye et al, 2005). Early reports suggest potential for MRI to enhance oesophageal cancer staging protocols (Riddell et al, 2006), but at present the thin-walled oesophagus, the proximity of adjacent other mediastinal structures, in particular the heart (necessitating cardiac gating), poses specific and considerable challenges. It is likely that EUS will remain the mainstay of locoregional staging for oesophageal cancer for some time, and therefore any potential role for EUS in predicting CRM involvement deserves further research.

From a histopathology perspective the assessment of the oesophageal CRM is controversial. Although debate continues as to the significance of CRM, pathological lymph node stage is an established prognostic factor. It has been suggested that accurate assessment of both lymph node stage and CRM status are incompatible, and compromise is required (Mapstone, 2007). In particular, the dissection of lymph nodes from the resected specimen by some surgeons renders meaningful assessment of the CRM impossible (Mapstone, 2007). The precise criteria used to define CRM+ is another area of controversy. Whereas in the United Kingdom this is defined as the presence of tumour within 1 mm of the CRM by the Royal College of Pathologists (RCP) (Mapstone, 1998), in the United States the College of American Pathologists (CAP) use a definition of the presence of tumour at the margin itself (Washington et al, 2009). Comparative studies have identified differences in the relative prognostic value of CRM status, depending on the definition used, with support for both the RCP (Pullrum et al, 2010; Rao et al, 2012; Salih et al, 2012) and the CAP (Deeter et al, 2009; Verhage et al, 2011; Harvin et al, 2012) definitions.

Most patients in the United Kingdom present with T3 disease, for which neoadjuvant chemotherapy followed by surgery is the current standard of care. On the basis of these results, patients treated this way have a 52.7% chance of a circumferentially incomplete (R1) resection. These results also suggest the possibility of significantly improved odds (87.3%) of a circumferentially complete (R0) resection when treated with neoadjuvant chemoradiotherapy, an option already considered to be the neoadjuvant modality of choice in the United States (Hingorani et al, 2011). The recent Dutch CROSS randomised trial reported an R0 resection rate of 92% associated with neoadjuvant chemoradiotherapy, significantly higher than the 69% achieved with surgery alone (van Hagen et al, 2012). Moreover, neoadjuvant chemoradiotherapy resulted in a complete pathological response in 29% of patients and was associated with a two-fold increase in median survival from 24.0 to 49.4 months, when compared with oesophagectomy alone (van Hagen et al, 2012). The issue of an involved CRM therefore forms an integral part of the much wider argument relating to the most appropriate neoadjuvant therapy regimes for patients with operable yet locally advanced oesophageal cancer. CS and chemoradiotherapy have both demonstrated clear survival advantages over surgery alone in meta-analyses (Urschel and Vasan 2003; Sjoquist et al, 2011), yet there is little high-quality data comparing these two neoadjuvant modalities to each other. Only two randomised trials have addressed this question (Stahl et al, 2009; Burmeister et al, 2011). Meta-analysis of both showed an insignificant trend towards improved survival with chemoradiotherapy (Sjoquist et al, 2011). There was no association between the type of neoadjuvant treatment and the risk of post-operative mortality, but both trials closed early and were consequently underpowered.

CONCLUSION

Involvement of the oesophageal CRM is an independently significant predictor of poorer disease-free and OS. Assuming appropriate radical surgery has been performed, an involved CRM can be considered more a marker of locoregionally advanced disease, than suboptimal surgery. There is a clear and pressing need for an adequately powered randomised trial of neoadjuvant chemoradiotherapy vs chemotherapy in operable oesophageal cancer, and indeed this has recently been proposed in the United Kingdom (Hingorani et al, 2011). The findings of this study further support this proposition and suggest that patients with endosonographic T3 tumours should be targeted.

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