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ORIGINAL ARTICLE

Prognostic significance of cancer within 1 mm of the circumferential resection margin in oesophageal cancer patients following neo-adjuvant chemotherapy[†‡]

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Abstract

OBJECTIVES: The prognostic significance of the circumferential resection margin (CRM) status in oesophageal cancer patients treated with neo-adjuvant chemotherapy and radical resection is controversial. Furthermore, it is currently unclear whether patients with cancer located at the CRM have a prognosis different from that of those with cancer within 1 mm of the CRM. This is the first study aiming to establish the optimal tumour-free distance from the CRM of an oesophagectomy in patients who have undergone neo-adjuvant chemotherapy.

METHODS: The clinicopathological data of 232 oesophageal cancer patients from two UK centres were analysed. The CRM status was classified as Group A (cancer at the CRM), Group B (cancer within 1 mm but not at the CRM) and Group C (no cancer within 1 mm from the CRM). The relationship between the CRM status and patient survival was investigated.

RESULTS: Thirty-eight specimens were classified as Group A, 89 as Group B and 105 as Group C. CRM status was related to the depth of tumour invasion ($P < 0.001$) and lymph node status ($P < 0.001$). The prognoses of the Group A and the Group B patients were similar. Both were poorer than that of the Group C patients ($P = 0.008$). Lymph node status was the only independent prognostic marker in multivariate analysis.

CONCLUSIONS: Oesophageal cancer patients treated with pre-operative chemotherapy with cancer cells at the CRM or within 1 mm of the CRM of the resected specimen have a significantly worse survival than patients with no cancer cells within 1 mm of the margin. However, this study suggests that the overall prognostic significance of the CRM status is limited in this cohort and the post-operative lymph node status is the most important prognostic factor in oesophageal cancer patients treated with neo-adjuvant chemotherapy and surgery.

Keywords: Oesophageal cancer • Circumferential resection margin • Neo-adjuvant chemotherapy • Prognosis

INTRODUCTION

The importance of the histological examination of the circumferential resection margin (CRM) in oesophagectomy specimens was first demonstrated in a relatively small study of patients treated with surgery alone [1]. Since this first report, results regarding the prognostic significance of the CRM status have been controversial. CRM has been identified as a prognostic factor in oesophageal cancer patients treated with surgery alone [2–5], in oesophageal cancer patients treated with chemotherapy [6] or chemoradiotherapy followed by surgery [7] as well as in oesophageal cancer patients receiving a variety of different treatments [8–10]. However, other studies have not confirmed CRM status as an independent prognostic factor [11–13].

The reported frequency of CRM positivity in oesophageal cancer ranged widely from 20 [11] to 67% [14]. This may at least partly be related to the fact that different definitions are used to identify a positive CRM. In the UK, most pathologists will classify a resection margin as positive if viable cancer cells are present within 1 mm of the margin as recommended by the Royal College of Pathologists [15]. On the other hand, in the USA, a

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resection margin will be classified as positive only if cancer cells are present directly at the margin as recommended by the College of American Pathologists [16].

Two recent studies, one in oesophageal cancer patients treated with surgery alone [14] and one in patients treated with variable treatment modalities [17], have reported that patients with cancer present directly at the CRM have a significantly poorer prognosis compared with patients with no cancer cells directly at the CRM. In contrast, a study in patients treated with surgery alone [5] and a study in patients treated with chemoradiation followed by surgery [7] showed that patients with cancer present at the CRM have the same poor prognosis as patients with cancer present within 1 mm of the CRM.

To date, there have been no data published on oesophageal cancer patients treated with chemotherapy followed by radical resection comparing the prognostic value of cancer cells present at the CRM with that of cancer cells present within 1 mm but not at the CRM.

This study aimed to investigate whether patients with cancer at the CRM in the resection specimen after chemotherapy have a poorer prognosis than those with cancer located >1 mm away from the CRM.

MATERIALS AND METHODS

Ethical approval was given to this study by the relevant local research ethics committees.

Patients

In total, 465 patients who had undergone an Ivor-Lewis oesophagectomy with two-field lymphadenectomy were identified in databases from the Leeds Teaching Hospitals NHS Trust and the University Hospital of South Manchester, both in the UK. The following patients were excluded from this study: patients who died within 30 days following surgery, patients who were treated with either surgery alone or neo-adjuvant radiotherapy and patients with morphology other than squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma (Fig. 1). Also excluded were patients who had a complete pathological response (ypT0) as a measurement of tumour cells from the CRM was not possible ($n = 9$).

A total of 232 patients who had received two cycles of 5-fluorouracil (5-FU)/cisplatin chemotherapy according to the OE02 trial regimen [18] followed by surgery were included in this study. Of them, 184 were treated in Leeds between 2001 and 2009 and 48 were treated in Manchester between 1995 and 2008. All resection specimens were dissected by a specialist gastrointestinal pathologist according to the Royal College of Pathologist Minimum Dataset for oesophageal cancer [15].

The following clinicopathological data were used for analyses: age at diagnosis, gender, ypT and ypN categories according to TNM 7th edn. [19], tumour morphology according to WHO classification [20], total number of lymph nodes examined, total number of positive lymph nodes identified and distance of the closest viable cancer cells from the CRM. Follow-up and mortality data were retrieved from Cancer Registry Information Service databases and hospital patient records. The patients were followed up with routine outpatient clinic reviews until the end of the study period or death. Radiological investigations were carried out only on the grounds of clinical suspicion of recurrence.

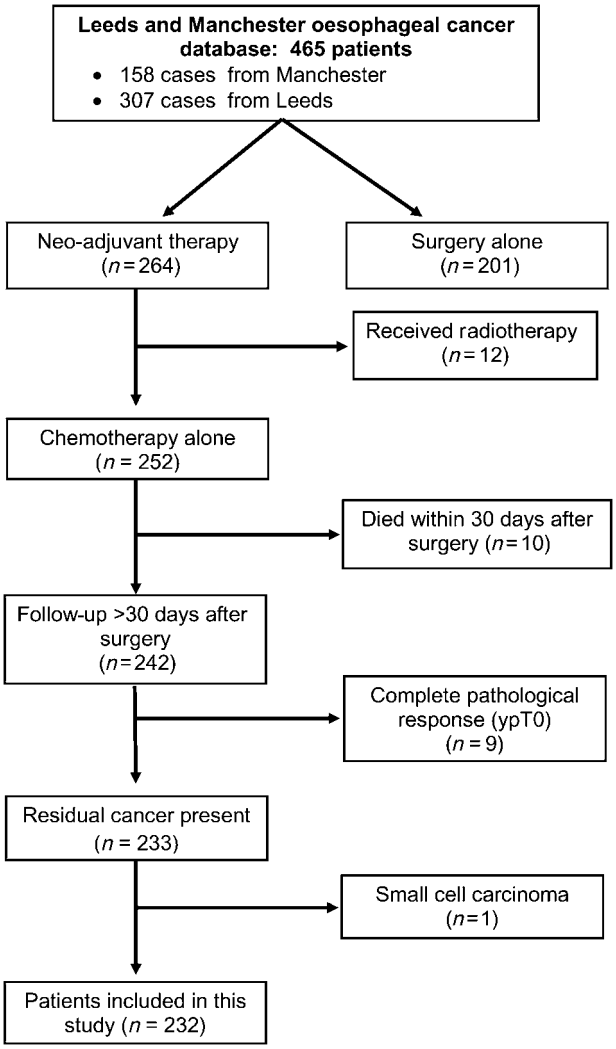

Figure 1: Flow chart of patient selection for the current study with numbers of cases excluded and reasons for exclusion.

CRM status

Specimens were delivered en bloc from the operating theatre to the histopathology laboratories. No lymph node dissections were done before cross-sectioning of the specimen. Specialist gastrointestinal pathologists in Leeds (H.G.) and in Manchester (G.U. and S.P.) reviewed all the histopathology reports. If the distance of cancer cells from the CRM was not provided in the report, the original haematoxylin and eosin stained slides were reviewed and the distance of cancer cells from the CRM was recorded in mm. Direct extension of the primary cancer or cancer cells found within lymph nodes or within vessels in the neighbourhood of the CRM were all classified as 'cancer within x mm of the CRM'.

The CRM status was classified into three groups—Group A: cancer cells at the CRM (equal to a distance of 0 mm from the margin), Group B: cancer cells within 1 mm but not directly at the CRM and Group C: no cancer cells within 1 mm of the CRM.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (Chicago, IL). The Kruskal–Wallis test was used to establish the relationship between CRM status, ypT, ypN and tumour morphology. The relationship between CRM status and cancer-specific survival was determined by the Kaplan–Meier method [21] and differences between groups were tested by the log-rank test. Follow-up was carried out from the day of surgery until patient death or the end of the study period.

A Cox's proportional hazard model was used for multivariate analysis. Only variables that were significant in univariate survival analysis were included in multivariate analysis. *P*-values < 0.050 were considered to be significant.

RESULTS

The median age at diagnosis of all the patients was 62 years (range: 35–78 years). The median number of lymph nodes per specimen was 30 (range: 3–82 nodes) and the median number of positive nodes was 2 (range: 0–63 nodes). Table 1 shows the median and the ranges of these variables stratified by morphology. Table 2 shows the median and the ranges of these variables stratified by CRM groups. There was a significant difference between the number of positive nodes in the three CRM groups. However, there were no other significant differences in variables between patients by morphological subtype or CRM groups. The median follow-up of all the patients was 1.5 years (range: 0.1–9.0 years) and the median survival of the patients alive at the end of the study period was 2.5 years (range: 0.2–9.0 years).

Table 1: Patient age, total number of lymph nodes and number of positive distributions

	Total (n = 232)	Adeno[a] (n = 183)	Squam[b] (n = 45)	*P*-value
Age (years)				
Median	62	62	61	0.34
Range	35–78	35–78	41–75	
No. lymph nodes (total)				
Median	30	29	34	0.57
Range	3–82	3–82	3–70	
No. positive lymph nodes				
Median	2	2	1	0.52
Range	0–63	0–63	0–15	

[a]Adenocarcinoma subgroup.
[b]Squamous cell carcinoma subgroup.

CRM status and pathological variables

Thirty-eight (17%) specimens were classified as Group A (cancer cells at CRM), 89 (38%) as Group B (cancer cells within 1 mm but not at CRM) and 105 (45%) as Group C (no cancer cells within 1 mm of CRM). The clinicopathological characteristics of the patients by CRM status group are shown in Tables 2 and 3. A significant relationship was found between CRM status group, depth of tumour invasion (ypT) and lymph node status (ypN). Group A and Group B had more commonly a higher ypT stage and higher ypN stage compared with Group C patients, all $P < 0.001$, Table 3. There was no significant relationship between CRM status group and any other clinicopathological variable.

Subgroup analyses were performed for patients with adenocarcinomas (adeno, $n = 183$) and squamous cell carcinomas (squam, $n = 45$), excluding adenosquamous carcinomas ($n = 4$). The analysis of the adenocarcinoma subgroup showed a significant relationship between CRM status group, depth of tumour invasion (ypT) and lymph node status (ypN), whereas the CRM status group was only significantly related to ypT stage in the squamous cell carcinoma subgroup, all $P < 0.001$.

CRM status and cancer-specific survival

Considering all the patients, there was no difference in cancer-specific survival between Group A (tumour at the margin) and

Table 2: Patient age, total number of lymph nodes and number of positive distributions across CRM groups by morphology

	Group A			Group B				Group C			
n (%)[c]	Adeno 30 (16)	Squam 8 (18)	Total 38	Adeno 65 (36)	Squam 22 (49)	Total 89	*P*-value[a]	Adeno 88 (48)	Squam 15 (33)	Total 105	*P*-value[b]
Age (years)											
Median	63	59	62	63	61	62	0.47	61	61	61	0.54
Range	46–76	41–69	41–76	42–78	41–72	41–78		35–78	41–75	35–78	
No. lymph nodes (total)											
Median	30	33	31	29	31	30	0.64	29	37	31	0.88
Range	9–64	11–45	9–64	3–82	13–70	3–82		3–77	3–68	3–77	
No. positive lymph nodes											
Median	5	7	6	4	2	3	0.98	1	0	1	<0.001
Range	0–63	0–15	0–63	0–28	0–13	0–28		0–16	0–8	0–16	

[a]Kruskal–Wallis test comparing Group A (total) with Group B (total).
[b]Kruskal–Wallis test comparing Groups A (total)+B (total) with Group C (total).
[c]Number and percentage of the total from each morphological subtype found in each CRM group (total adeno = 183 and total squam = 45).
Group A: Tumour cells at the circumferential margin; Group B: Tumour cells within 1 mm but not at the margin and Group C: No tumour cells within 1 mm of the margin.

Table 3: Patient gender, morphology, ypT categories and ypN categories by CRM status group

	Total (n = 232) n (%)	Group A (n = 38) n (%)	Group B (n = 89) n (%)	P-value[a]	Group C (n = 105) n (%)	P-value[b]
Gender						
Male	177 (76)	32 (84)	64 (72)	0.141	81 (77)	0.318
Female	55 (24)	6 (16)	25 (28)		24 (23)	
ypT category						
T1a	7 (3)	0 (0)	0 (0)	0.128	7 (7)	<0.001
T1b	15 (6)	0 (0)	1 (1)		14 (13)	
T2	39 (17)	1 (3)	5 (6)		33 (31)	
T3	162 (70)	33 (86)	79 (89)		50 (48)	
T4	9 (4)	4 (11)	4 (4)		1 (1)	
ypN category						
N0	70 (30)	5 (13)	18 (20)	0.113	47 (45)	<0.001
N1	60 (26)	8 (21)	22 (25)		30 (29)	
N2	49 (21)	8 (21)	23 (26)		18 (17)	
N3	53 (23)	17 (45)	26 (29)		10 (9)	
Morphology						
Adeno[c]	183 (79)	30 (79)	65 (73)	0.451	88 (84)	0.196
Squam[d]	45 (19)	8 (21)	22 (25)		15 (14)	
Adenosq[e]	4 (2)	0 (0)	2 (2)		2 (2)	

[a]Kruskal–Wallis test comparing Group A with Group B.
[b]Kruskal–Wallis test comparing Groups A+B with Group C.
[c]Adenocarcinoma.
[d]Squamous cell carcinoma.
[e]Adenosquamous carcinoma.
Group A: Tumour cells at the circumferential margin; Group B: Tumour cells within 1 mm but not at margin and Group C: No tumour cells within 1mm of resection margin.

Group B (tumour within 1 mm) (P = 0.945). However, patients from both the groups had significantly poorer survival compared with the Group C patients (P = 0.008, Fig. 2). Univariate analysis showed that ypT and ypN were significantly related to patient prognosis, and were therefore included in multivariate analysis as shown in Table 4. Multivariate analysis showed that CRM status was not an independent prognostic factor. Only the lymph node status (ypN category) remained significant on multivariate analysis (P = 0.003).

In the adeno subgroup, Kaplan–Meier survival analysis showed that there is a significant difference in survival between the patients in CRM status Groups A+B compared with Group C (P = 0.01) and no significant difference in survival between the patients in Groups A and B (P = 0.861, Fig. 3A). Multivariate analysis including ypT and ypN in the model showed that CRM status group was not an independent prognostic factor (data not shown).

In the squam subgroup, Kaplan–Meier survival analysis showed that there is no significant difference in survival between the patients in CRM status Groups A+B compared with Group C (P = 0.354) and no significant difference in survival between the patients in Groups A and B (P = 0.643, Fig. 3B).

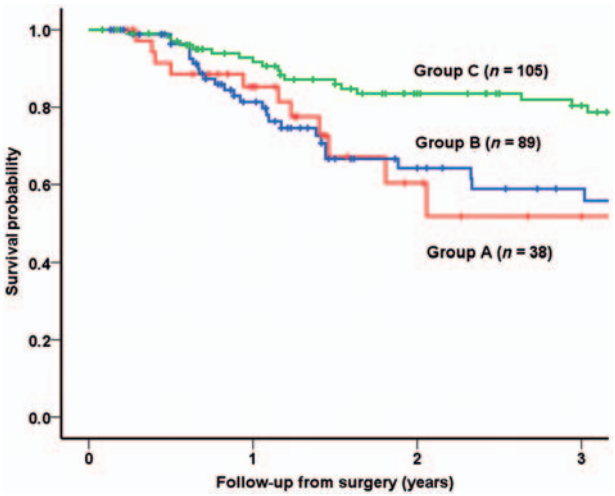

Figure 2: Kaplan–Meier cancer-specific survival plot including all the patients. Kaplan–Meier plot comparing the cancer-specific survival probability of Group A (tumour cells at CRM), Group B (tumour cells within 1 mm but not at CRM) and Group C (no tumour cells within 1 mm). There is a significant difference in survival between the patients in Group C compared with both Group A and Group B (log-rank test P = 0.008; hazard ratio = 0.45; 95% confidence intervals 0.27–0.75). However, no significant difference in cancer-specific survival was demonstrated between Group A and Group B (P = 0.945).

DISCUSSION

CRM status has been recognized as an important prognostic factor for patients with rectal cancer [22] and pancreatic cancer [23]. In rectal cancer, a 1 mm cut-off has been used to define a positive CRM [24]. Initial studies in oesophageal cancer patients treated with surgery alone adopted this 1 mm cut-off and showed through univariate [1] and multivariate analyses that the presence of cancer cells within 1 mm of the CRM is related to patient survival [2]. A number of subsequent studies confirmed this finding in univariate analysis [3, 5, 7, 10] and multivariate analysis [4, 6, 8, 9], whereas others showed that CRM status is not an independent prognostic factor [12, 13] or not related to prognosis at all [11].

Table 4: Cox univariate and multivariate survival analyses, using cancer-specific mortality

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.01	0.97–1.03	0.744	–	–	–
Gender	1.47	0.78–2.75	0.232	–	–	–
Morphology	0.48	0.23–1.01	0.053	–	–	–
ypT	1.94	1.27–2.98	0.002	1.49	0.96–2.32	0.078
ypN	1.99	1.57–2.54	<0.001	1.53	1.45–2.05	0.004
CRM Status Group						
Group A vs. C	2.20	1.06–4.54	0.034	0.745	0.33–1.70	0.484
Group B vs. C	2.23	1.30–3.85	0.004	1.30	0.73–2.34	0.375
Number of lymph nodes	0.99	0.97–1.01	0.205	–	–	–
Number of positive nodes	1.10	1.07–1.12	<0.001	1.06	1.02–1.10	0.004

HR: hazard ratio; CI: confidence interval.

The ongoing controversy over the prognostic value of the CRM in oesophageal cancer patients may be related to the fact that the investigated patient cohorts received different treatment regimens. Furthermore, while most authors have used the presence of cancer cells within 1 mm as the primary definition of a positive CRM [1–3, 8, 11], some have used cancer cells at the margin to define a positive CRM status [14, 17] resulting in a wide range of reported CRM positivity rates from 20 [11] to 67% [14].

This study was the first to compare the prognostic value of cancer cells at the CRM with that of cancer cells within 1 mm but not at the CRM in a large cohort of oesophageal cancer patients who were all treated with 5-FU/cisplatin chemotherapy followed by surgery in two independent UK cancer hospitals. In total, 54% of specimens were classified as CRM positive (tumour cells within 1 mm of the CRM) in this study, which is comparable to CRM positivity rates reported previously [1, 2, 5, 7, 12].

In this study, patients treated with neo-adjuvant chemotherapy and no viable cancer cells within 1 mm of the CRM had a significantly better survival than those in whom cancer was found within 1 mm of the CRM. There was no difference in the survival probability of the patients with cancer at the margin compared with those with cancer within 1 mm of the CRM. These results are in agreement with previous reports from patients treated with surgery alone [5] or with neo-adjuvant chemoradiation [7]. Thus, our results do not support the recently advocated view that the American College of Pathologists (CAP) CRM definition [16] (i.e. cancer cells at the margin) is more accurate for patient risk stratification [14, 17].

The same results were obtained when the analyses were restricted to patients with adenocarcinomas ($n = 183$; 79%). The fact that CRM groups had no significant relationship to survival in patients with squamous cell carcinomas is likely to be due to the small number of patients in this subgroup ($n = 45$).

In our patient cohort, the prognostic value of the CRM status was no longer apparent in multivariate analysis where only lymph node status (ypN) remained an independent prognostic factor. Our results are in contrast to a number of CRM studies [2, 4, 6, 8, 9, 14, 17], including the only other study in patients treated with pre-operative chemotherapy [6]. However, the current study cohort included more than double the number of patients taken from two independent cancer centres and included squamous cell carcinomas as well as adenocarcinomas. This may explain the differences in results.

The current study has some limitations. This was a retrospective analysis using data from two different centres; however, as the disease stage, cancer mortality and survival did not differ between the two centres (data not shown) the data sets from the two hospitals were suitable to be combined. Although the study had a relatively short follow-up period, the median follow-up time of the study was similar to those of previous CRM studies [5, 6, 17]. Owing to the retrospective nature of this study, the pattern of tumour recurrence was not available and we were therefore unable to investigate the relationship between CRM group and site of recurrence. For multivariate survival analysis, the tumour regression grade following neo-adjuvant chemotherapy might have been of interest. As the data collection was done over a long period, there was uncertainty whether a consistent tumour regression grading system was applied throughout, and hence tumour regression grade was not included in the final analysis.

In conclusion, our study has demonstrated that oesophageal cancer patients treated with neo-adjuvent chemotherapy with cancer cells at the CRM or within 1 mm of the CRM of the resected specimen have a significantly worse survival than patients with no cancer cells within 1 mm of the margin. This study therefore supports the use of the 'cancer within 1 mm of the CRM' rule e.g. the Royal College of Pathologists definition [15], to define a positive CRM.

CRM status was not an independent prognostic factor in our series and our results suggest that post-operative lymph node status remains the most important independent factor in determining prognosis in oesophageal cancer patients treated with neo-adjuvant chemotherapy. Our study seems to indicate that a more radical lymph node dissection may be more important than a negative CRM in order to improve outcome for patients with oesophageal cancer treated with neo-adjuvant chemotherapy. However, there is currently still controversy whether a better outcome can be achieved with a three-field or a two-field lymphadenectomy resection [25].

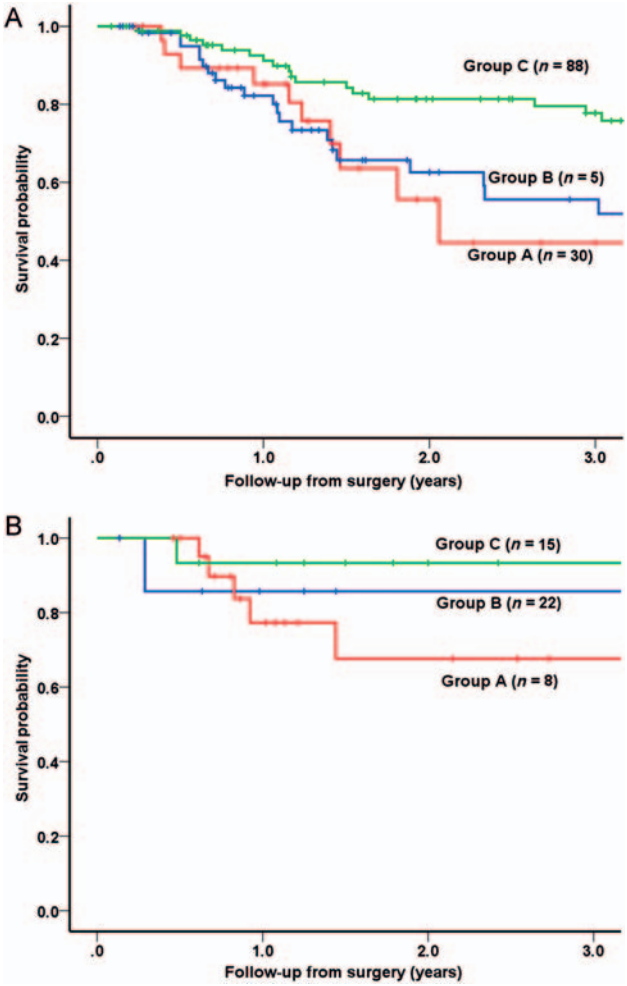

Figure 3: Kaplan–Meier cancer-specific survival plot by morphological subtype comparing the cancer-specific survival probability of Group A (tumour cells at CRM), Group B (tumour cells within 1 mm but not at CRM) and Group C (no tumour cells within 1 mm). (**A**) Kaplan–Meier plot for patients with adenocarcinoma ($n = 183$). There is a significant difference in survival between the patients in Group C compared with both Group A and Group B (log-rank test $P = 0.01$; hazard ratio = 0.61; 95% confidence intervals 0.43–0.87). However, no significant difference in cancer-specific survival was demonstrated between Group A and Group B ($P = 0.861$). (**B**) Kaplan–Meier plot for patients with squamous cell carcinoma ($n = 45$). There is no significant difference in survival between the patients in Group C compared with both Group A and Group B (log-rank test $P = 0.354$; hazard ratio = 0.617; 95% confidence intervals 0.22 –1.74). No significant difference in cancer-specific survival was demonstrated between Group A and Group B ($P = 0.643$).

Conflict of interest: none declared.

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