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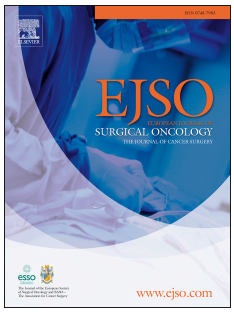

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Prognostic significance of circumferential resection margin involvement in patients receiving potentially curative treatment for oesophageal cancer

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Abstract:

Introduction

The utility of Circumferential Resection Margin (CRM) status in predicting prognosis in oesophageal cancer is controversial, with different definitions used by the College of American Pathologists and the Royal College of Pathologists. We aimed to determine prognostic significance of CRM involvement and evaluate which system is the best predictor of prognosis.

Methods

A cohort of 390 patients who had potentially curative oesophagectomy (-+ neoadjuvant chemotherapy) were analysed. Associations between CRM involvement and patient outcome were assessed for the whole cohort, and for pre-specified subgroups of T3 tumours and those who received neo-adjuvant chemotherapy.

Results

CRM-involvement was associated with higher T and N stage, tumour differentiation, increased tumour length and both lymphovascular and perineural invasion. Overall Survival (OS) and Recurrence Free Survival (RFS) significantly worsened with CRM-involvement ($p=0.001$, $p<0.001$). R1a (< 1mm but no macroscopic involvement) resulted in significantly improved OS ($p=0.037$) and RFS ($P=0.026$) compared to R1b (macroscopic involvement), but did not differ significantly from R0 (≥ 1mm). The association between CRM-involvement and both OS and RFS remained significant regardless of whether neoadjuvant chemotherapy was given. However, CRM-involvement was not a significant prognostic marker in T3 patients ($p=0.148$). Multivariable analysis found N stage, lymphovascular invasion, patient age and neoadjuvant chemotherapy to be significantly predictive of patient outcome. CRM-involvement was not a significant independent prognostic marker.

Conclusions

CRM-involvement was not found to be independently predictive of prognosis, after accounting for other prognostic markers. As such, CRM should not be considered a major prognostic factor in patients with oesophageal cancer. [250]

Keywords: 'Oesophageal cancer', 'Oesophagectomy', 'Circumferential Resection Margin', 'Survival', 'Recurrence'.

Word Count (Main Text):

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Introduction

Oesophageal cancer is the sixth most common cancer in the developed world(1) and incidence continues to rise, due to rising rates of obesity, reflux disease and Barrett's oesophagus(2). Although oesophagectomy is performed with curative intent, disease recurrence is common within two years of surgery(3) and survival rates remain poor (3–5).

Resection margin status is an important prognostic finding and involvement of the proximal and/or distal resection margins is associated with a significantly worse prognosis in terms of recurrence and survival(6). However, the prognostic significance of circumferential resection margin (CRM) involvement in oesophageal cancer remains unclear. Interest in CRM stems from the overwhelming significance of CRM as a negative prognostic marker in rectal cancer studies(7). Numerous studies have investigated CRM in oesophageal cancer but have elicited conflicting results, with some showing it is a significant prognostic factor(8–15) whereas others show that it does not add valuable prognostic information(16,17).

CRM status has been defined differently by the College of American Pathologists (18) and Royal College of Pathologists (19). The College of American Pathologists classifies CRM into clear (R0) and involved (R1) if the tumour lies directly at the margin(18), whereas British Royal College of Pathologists guidelines(19) class tumours within 1mm as involved (R1). In our unit, pathologists have used a hybrid classification system for CRM status. This is defined as R0 if the CRM is uninvolved at ≥1mm, R1a for CRM < 1mm but not grossly involved and R1b if the CRM is directly involved at 0mm. Although some studies(20–26) have attempted to define which classification system is best, this is currently an understudied area, especially in the era of neoadjuvant therapy for oesophageal cancer. It is also unclear whether operative technique, including the use of minimally invasive oesophagectomy affects the rate of CRM involvement.

The aim of this study was to 1) assess the prognostic significance of CRM involvement in a modern cohort of patients, 2) compare and contrast the College of American Pathologists and Royal College of Pathologists definitions and assess our hybrid classification in order to identify an optimal cut-off for CRM involvement and finally 3) consider the effect of neoadjuvant chemotherapy / use of minimally invasive surgery on the significance of CRM as a prognostic marker.

Methods

A retrospective analysis of consecutive patients was performed on a prospectively collected departmental database from January 2006 to July 2016. Patients who underwent a non-curative resection on final pathology due to either proximal or distal resection margin involvement (n=11) or due to unsuspected metastatic disease (n=11) were excluded from the study. The circumferential resection margin status of these excluded patients, were R0 in 8 (36%), R1a in 4 (18%) and R1b in 10 (45%). After these exclusions, a total of n=390 were available for analysis. This dataset included patient demographics, staging investigations, operative details, oncological treatment, histopathology reports and long-term follow-up with recurrence and survival reported. All patients had surgical resection performed at the Queen Elizabeth Hospital, Birmingham. Our standard catchment area included patients from other sites across the West Midlands Region, including Manor Hospital, Walsall; Russells Hall Hospital, Dudley and City Hospitals, West Birmingham. Some patients who were managed at our tertiary centre came from further afield. 'This study did not require ethical approval as it was a retrospective review of database

When follow-up data were missing, clinical records were analysed in the respective hospitals. Inclusion criteria consisted of patients with oesophageal cancer who received oesophagectomy with curative intent. The majority of patients received neoadjuvant chemotherapy as per recent randomized controlled trial evidence(27,28).

During the time frame of the study, oesophagectomy procedures were performed by specialist Upper Gastrointestinal Consultant Surgeons (total n=10) who used similar techniques. Oesophagectomies were classified as: (1) open 2 or 3 stage procedures involving open abdominal incisions with open right thoracotomy; (2) laparoscopic abdominal gastric mobilization with an open right thoracotomy (hybrid oesophagectomy) plus or minus cervical incision; or (3) minimally invasive oesophaghectomy (MIO) with laparoscopic and thoracoscopic oesophageal mobilization with either intra-thoracic or cervical anastomosis. The decision regarding operative method was at the discretion of the Consultant Surgeon

involved. Operative methods evolved over the time period of the study. The first laparoscopic gastric mobilization was performed in the unit in 2006 and fully minimally invasive procedures were introduced in 2008.

Histopathological assessment

After receipt of the oesophagogastrectomy specimen in the laboratory, the CRM was inked and allowed to dry. Subsequently, the specimens were opened longitudinally from proximal to distal, extending this incision distally along the greater curve of the stomach. The resections were pinned on corkboard then left to fix in formalin for at least twenty four hours. The macroscopic features were then recorded, including tumour dimensions measured to the closest 1mm. The tumours were thinly (3-5mm) sliced transversely from 2cm above to 2cm below, with areas showing tumour closest to the inked circumferential margin sampled for microscopy (Figure 1). Involvement of a surgical resection margin was classified as R0 if the CRM was uninvolved (≥1mm), R1a if the CRM involved < 1mm but was not grossly involved, or R1b if the CRM was directly involved (0mm)(18,19). At least four blocks of tumour were examined histologically as were all resection margins, representative areas of oesophagus and stomach, any additional macroscopic abnormalities and all lymph nodes identified.

The Siewert classification system was used to classify junctional tumours(29). The 7th edition of the TNM system was used(30). Mandard grading was used to classify response to chemotherapy(31).

Statistical Methods

Initially, a range of patient, disease and treatment related factors were compared between the three CRM groups based on the hybrid classification. Where a significant difference was detected, post-hoc pairwise comparisons were performed between R1a and the other two groups. Continuous variables were assessed for normality, prior to analysis. Those that were found to be normally distributed were

reported as mean ± standard deviation (SD), with one-way ANOVA used to compare across groups, followed by Dunnett's post-hoc tests. Non-normal and ordinal variables were reported as medians and interquartile ranges (IQRs), with comparisons across groups performed using Kruskal-Wallis tests followed by pairwise Dunn's tests. Nominal variables were compared using Fisher's exact test, followed by Bonferroni-corrected pairwise Fisher's exact tests, where significance was observed. In cases where Fisher's exact test was incalculable, due to a large number of groups, the Chi^2 test was used instead. Survival outcomes were assessed using Kaplan-Meier curves, with univariable Cox regression models used to produce hazard ratios (HRs) and 95% confidence intervals (95% CIs). Follow up was started at the point of surgery, with all subsequent deaths (including inpatient mortality) treated as outcomes.

CRM was then dichotomised based on the American College of Pathologists and Royal College of Pathologists guidelines(18,19). Univariable Cox regression models were produced for each definition of CRM for both the cohort as a whole, and within pre-defined patient subgroups. Multivariable Cox regression models were then produced, to consider the association between CRM and patient outcomes, after accounting for other potentially confounding factors. A backwards stepwise approach was used to select independent predictors of patient outcome. The CRM variables were then individually added to the resulting model.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY). Missing data were excluded on a per-analysis basis, and $p<0.05$ was deemed to be indicative of statistical significance throughout.

Results

Study Group

A total of 390 patients who underwent oesophagectomy with curative intent for oesophageal cancer were included in this study. The mean age of the cohort was 67.3 ± 9.2 years (range 23-89 years), and 79% (N=308) were male. The majority of patients had adenocarcinoma (n=308, 79%), and tumours were principally located in the lower 1/3 of the oesophagus or Siewert type 1 (n=283, 73%) . Surgery was generally by hybrid (n=164, 42%), open (n=93, 24%) or minimally invasive (n=86, 22%) oesophagectomy, and the majority of patients received neoadjuvant chemotherapy (n=298, 77%). Post-operative mortality rates were 3.9% and 6.9% at 30 and 90 days, respectively.

CRM Involvement in relation to other histopathological factors and patient outcomes

In our cohort, 66% of patients had an R status of R0, with the remainder divided between R1a (18%) and R1b (16%). CRM involvement was only identified in patients with T3 or T4 staging. Associations between resection margins and a range of factors are reported in Tables 1a and 1b. Higher R status was found to be associated with significantly poorer differentiation ($p<0.001$), higher T stage ($p<0.001$) and N- stage ($p<0.001$), and higher rates of peri-neural ($p<0.001$) and lymphovascular invasion ($p<0.001$). In addition, those with higher R status had significantly greater numbers of lymph nodes ($p=0.016$), of which more were positive ($p<0.001$). Higher Rstatus also associated with greater tumour length ($p=0.014$) and reduced responsiveness to chemotherapy, as assessed by Mandard grading ($p<0.001$). There were no significant associations between R status and either the surgical approach ($p=0.531$) or the use of neoadjuvant chemotherapy ($p=0.105$).

Post-hoc pairwise analyses found that, where differences were detected across the resection margin groups, this was largely a result of variations between R1a and R0, rather than between R1a and R1b. For example, the rates of peri-neural invasion were 42% in R1a and 49% in R1b, compared to 20% in R0. The only instance in which significant differences between R1a and R1b were observed was for tumour type (p=0.027), where R1b patients were less likely to have squamous cell carcinoma (SCC) than those in the R1a group (11% vs. 28%).

Survival analysis found both overall (p=0.001, Figure 2a) and recurrence-free (p<0.001, Figure 2b) survival to differ significantly across the three CRM categories. Median overall survival was found to be similar for the R0 and R1a groups (25 vs. 27 months, p=0.334), but to be significantly shorter in the R1b group (15 months, p=0.037). A similar trend was observed for recurrence-free survival (Table 2).

Survival analyses: College of American Pathologists vs. Royal College of Pathologists guidelines

CRM was then reclassified based on the two guidelines, with Royal College of Pathologists treating the R1a group as having involved CRM (R1), whilst College of American Pathologists treated these patients as being non-involved (R0). As a result, according to the Royal College of Pathologists guidelines, 34% of the cohort had an involved CRM whereas, according to College of American Pathologists guidelines, only 16% had an involved CRM. Univariable survival analyses using these guidelines found that patients in the R1 groups of both the College of American Pathologists and Royal College of Pathologists guidelines had significantly shorter survival than R0 patients. However, the difference between the groups was marginally larger for College of American Pathologists than for Royal College of Pathologists (HR: 1.80 vs. 1.48, Figure 2c and 2d). The same trend was observed for recurrence-free survival (HR: 1.92 vs. 1.62).

Subgroup analyses

This analysis was then repeated within selected patient subgroups (Table 3). This found that the greatest difference in survival between R1 and R0 patients was in those where chemotherapy was not used (N=91), with HRs of 2.32 (p=0.012) and 2.02 (p=0.022) for R1 vs. R0 in the College of American Pathologists and Royal College of Pathologists guidelines, respectively. Neither of the guidelines performed well for the subgroup of patients with N0 stage (n=153), with HRs of 1.39 (p=0.417) for College of American Pathologists and 0.94 (p=0.843) for Royal College of Pathologists. Similar findings were observed for the subgroup of T3 stage patients (N=260), with HRs for 1.38 (p=0.097) for College of American Pathologists and 1.10 (p=0.545) for Royal College of Pathologists. Consistent results were observed for recurrence-free survival.

Multivariable analyses

Multivariable analyses were then performed, to consider the effect of CRM after accounting for potentially confounding factors. This analysis found overall patient survival to be significantly shorter with increasing N-stage, lymphovascular invasion, and in those that did not receive neoadjuvant chemotherapy (Table 4 and Figure 3a-c). A significant association with age was also detected, with survival found to be longest in the most elderly group (Figure 3d). After accounting for these factors, no significant difference in patient survival was detected between patients with CRM of R1 vs. R0 by either the College of American Pathologists (HR: 1.21, 95% CI: 0.81 – 1.81, p=0.353) or Royal College of Pathologists (HR: 1.02, 95% CI: 0.73 – 1.44, p=0.907) guidelines. Multivariable analysis of recurrence-free survival returned similar results (Table 4).

Discussion:

These results demonstrate that CRM involvement is significantly associated with higher T and N staging, poor tumour differentiation, presence of perineural and lymphovascular invasion and longer tumour length. There are also differences in patient demographics, disease and treatment factors between patients dependant on CRM status: predominantly in R0 vs. R1a, but less so between R1a vs. R1b. Despite this, univariable analysis found survival to be similar in R0 vs. R1a, but significantly worse in R1b vs. R1a. As a result, the College of American Pathologists guideline is more strongly associated with survival in univariable analysis, as this combines the groups with the most similar outcomes together (i.e.R0 and R1a). Multivariable analysis found that, after accounting for other confounding factors such as lymphovascular invasion and N-stage, neither of the CRM classifications were independent predictors of either overall or recurrence-free survival.

We were unable to demonstrate the prognostic significance of CRM involvement using multivariable analysis, which has been shown in historical studies(8,10–14,23). Heterogeneity exists between these studies and our report because of differing methodologies and variability in confounding factors, which include study population size, length of follow-up, methodology (retrospective or prospective in nature), the proportion receiving neoadjuvant chemotherapy and operative techniques employed. Interestingly, studies with the largest datasets (314 and 329 patients) and longest duration of follow-up with also concluded that CRM was not associated with prognosis on multivariable analysis (20). Nevertheless, despite their larger datasets, neither of these studies included patients with preoperative chemotherapy. Likewise, a ten year follow-up study by Theologou et al (32) (n=199), who restaged patients according the 7th edition TNM and who received neoadjuvant chemotherapy, showed no prognostic significance on multivariable analysis. We therefore demonstrate CRM to be a non-significant prognostic marker on multivariable analysis in the largest prospectively-collected dataset, the majority of whom received neoadjuvant chemotherapy and who were staged with the 7th edition TNM. This suggests that CRM involvement should not be considered as a

major prognostic marker in patients who undergo oesophagectomy. As it is not a significant independent predictor of outcome, there could be an argument to avoid the routine reporting the CRM status. However, it is recommended that it continue to be assessed to help in quality assurance and surgical audit, provided the treating teams understand it does not appear to be a strong prognostic factor.

Furthermore, superiority between Royal College of Pathologists or College of American Pathologists definitions has not yet been established and has been explored to a limited degree in the existing literature with conflicting results. Of the two systematic reviews performed in patients with oesophageal cancer(33–35) and the one systematic review performed specifically in patients with squamous cell carcinoma (36), results were mixed. Wu et al.(33) suggested superiority of the College of American Pathologists definition whereas Chan et al.(34) and Ahmad et al.(35) suggested superiority of the Royal College of Pathologists criteria. On consideration of the individual studies, those that designated Royal College of Pathologists as superior tended to have retrospective follow-up, small-medium sized cohort (n=98-226) and patients who received neoadjuvant chemotherapy(20–22) whereas those in support of College of American Pathologists excluded patients who received neoadjuvant chemotherapy(23,24). We report neither Royal College of Pathologists nor College of American Pathologists to be discriminative as their predictive accuracy for survival outcomes was low in both classification systems. This finding is supported other studies (25)(26), although our study population is more generalizable and representative than these previous studies.

We chose to include all T stages in our overall analysis to increase the generalizability of our work. Some studies have limited their analysis to T3 tumours only. The rationale for this is that CRM involvement should not occur in T1/T2 disease unless the surgical field is violated. Patients with T4 tumours are less likely to have clear CRM; however, as a lot of these are due to direct invasion of the diaphragmatic crura, it is possible to achieve R0 clearance with wide diaphragmatic margins.

Lymph node involvement is a well-established marker of prognosis in oesophageal cancer(37), but the importance of CRM involvement in relation to N stage is disputed. Griffiths et al.(8) showed that CRM was a more significant prognostic marker if patients had a low lymph node burden, suggesting lymph node status was a more important factor in long-term survival(38). Yet, Saha et al.(10) found that both CRM involvement and lymph node involvement were independent prognostic factors. In addition, they reported that survival of node negative patients could be compromised with CRM involvement. We have failed to confirm this on our subgroup analysis. Our study shows that N stage categorisation of the 7th edition of the TNM offers a superior prognostic marker compared to CRM involvement. Our multivariable analyses also revealed the independent prognostic importance of lymphovascular invasion. This is in accordance with other studies which have reported the prognostic significance of lymphovascular(4,15,39) and perineural invasion(4) on multivariable analyses.

The chemotherapy regimens implemented in our study were typically MAGIC(27) and OE02(28). The MAGIC(27) trial did not compare outcomes by CRM status, however did report a significant decrease in median oesophageal diameter in the neoadjuvant chemotherapy treated group. The OE02 trial(28) reported increased incidence of unresectable tumours and macroscopically incomplete resections in the surgery only group. Neither trial specifically assessed the effect of CRM. The fact that neoadjuvant chemotherapy use was an independent predictor of survival in our study underpins its value in the modern management of oesophageal cancer.

There has been recent interest in assessing chemoradiotherapy as neoadjuvant therapy prior to oesophagectomy and some studies have shown a survival advantage from this treatment (40,41). Intuitively, this could be related to sterilisation of the CRM. To back up this hypothesis, in Chan et al's meta-analysis of rates of CRM involvement in six studies of patients with neoadjuvant chemotherapy and four studies with neoadjuvant chemoradiotherapy, reduced rates of CRM involvement were found in those treated with chemoradiotherapy (42). In the group treated with neoadjuvant chemotherapy, the rate of CRM involvement was 15.8% (72 of

457) and 34.3% (361 of 1053) according to College of American Pathologists and Royal College of Pathologists criteria, respectively. However, in patients treated with neoadjuvant chemoradiotherapy, CRM involvement was 11.2% (50 of 446) and 31.9% (259 of 812) according to College of American Pathologists and Royal College of Pathologists criteria, respectively. In the CROSS randomised trial, overall R0 resection margins were achieved in 92% of patients in the chemoradiotherapy group compared with only 69% in the surgery group (P<0.001). This was largely due to rates of complete pathological response rates of 29% in the chemoradiotherapy group where a significant survival advantage was observed (40). As no specific information was given regarding the CRM status in the CROSS study it difficult to interpret in light of our results. It is likely that proximal and distal margin involvement overrides the prognostic implications of CRM involvement and that is why we excluded these patients from our study.

The impact of surgical approach on CRM involvement has been assessed in some other studies. One study compared Minimally Invasive Oesophagectomy, Conventional Open and Hybrid oesophgectomy and showed that neither CRM involvement nor survival differed with surgical procedure(43). Another demonstrated significant differences in CRM involvement between open and laparascopic transhiatal oesophagectomies(12). A Scottish audit(44) reported increased CRM involvement in transhiatal oesophagectomy compared to the Ivor Lewis procedure, although the radicality of resection in this paper has been questioned. In addition, Haverkamp et al. identified increased CRM involvement in patients treated with extended total gastrectomy as opposed to oesophagectomy for junctional adenocarcinoma(45).

Our study has a range of strengths and limitations. Although it was retrospective, it was largely an analysis of high quality prospectively collected data from a specialist high volume unit. Inherent with other similar studies in this area it suffers from heterogeneous features, such as the changes in type of neoadjuvant chemotherapy used, operative procedures performed and the consultant surgical team. However,

CRM status did not appear to be related to type of oesophagectomy or the use of neoadjuvant chemotherapy. We also acknowledge some missing data, including rates of perineural and lymphovascular invasion, as these have recently been shown to be relevant.

In conclusion, analysis of our large cohort did not find CRM involvement to be an independent prognostic marker of patient survival. Rates of CRM involvement were not found to differ significantly with the surgical procedure performed and, importantly, Minimally Invasive Oesophagectomy did not appear to compromise the CRM. Lymph node involvement and lymphovascular invasion provide superior prognostic information in patients with oesophageal cancer. Neither the College of American Pathologists nor the Royal College of Pathologists definitions of involvement were found to be significantly discriminatory after accounting for these factors.

Tables legends

Table 1a – Comparison of demographics and tumour factors between resection margin groups

Bold p-values are significant at p<0.05

Key:

[a]Data reported as mean±SD, with overall p-value from one-way ANOVA, and pairwise comparisons from Dunnett's tests.

[b]Data reported as N (%), with overall p-value from Fisher's exact test, and pairwise comparisons from Bonferroni-corrected Fisher's exact tests.

[c]Data reported as N (%), with overall p-value from Chi-square tests.

[d]Data reported as N (%), with overall p-value from Kruskal-Wallis tests (treating the factor as ordinal), and pairwise comparisons from Dunn's tests.

[e]Data reported as median (IQR), with overall p-value from Kruskal-Wallis tests, and pairwise comparisons from Dunn's tests.

Adeno – Adenocarcinoma
SCC - Squamous Cell Carcinoma
GOJ - Gastro-oesophageal junction (Siewert type)
v7 - 7th Edition TNM

Table 1b – Comparison of tumour and treatment factors between resection margin groups

**In patients that received chemotherapy*

Bold p-values are significant at p<0.05

Key:

[a]Data reported as mean±SD, with overall p-value from one-way ANOVA, and pairwise comparisons from Dunnett's tests.

[b]Data reported as N (%), with overall p-value from Fisher's exact test, and pairwise comparisons from Bonferroni-corrected Fisher's exact tests.

[c]Data reported as N (%), with overall p-value from Chi-square tests.

[d]Data reported as N (%), with overall p-value from Kruskal-Wallis tests (treating the factor as ordinal), and pairwise comparisons from Dunn's tests.

[e]Data reported as median (IQR), with overall p-value from Kruskal-Wallis tests, and pairwise comparisons from Dunn's tests.

Hybrid - laparoscopic gastric mobilisation and open right thoracotomy
MIO - Fully Minimally Invasive Oesophagectomy

Table 2 – Univariable survival analysis by resection margin for the whole cohort

Hazard ratios and p-values are from univariable Cox regression models, and median survival times are Kaplan-Meier estimates

Bold p-values are significant at p<0.05.

CAP - College of American Pathologists definition with CRM involvement defined as at the margin only(22)
RCPath - Royal College of Pathologists definition with CRM involvement defined as within 1mm of the margin(23)

Table 3 – Subgroup analyses

Hazard ratios and p-values are from univariable Cox regression models, and are for R1, relative to R0.
Bold p-values are significant at p<0.05

CAP - College of American Pathologists definition with CRM involvement defined as at the margin only(22)
RCPath - Royal College of Pathologists definition with CRM involvement defined as within 1mm of the margin(23)

Table 4 – Multivariable analysis of overall survival and recurrence free survival

Results are from multivariable Cox regression models. All factors in Table 1a/b were initially considered for inclusion in backwards stepwise models to identify significant independent predictors of outcome. Significant factors were then included in models alongside the resection margin. The final models are based on N=256, after excluding cases with missing data.
Bold p-values are significant at p<0.05

Figure Legends

Figure 1

Microscopy images of various CRM status in lower oesophageal adenocarinoma. An R0 margin is shown with > 1mm distance from the tumour and the inked CRM (Figure 1a). Tumour within 1mm of the inked CRM (R1a) (Figure 1b). Tumour directly involving the inked CRM (R1b) (Figure 1c)

Figure 2

Kaplan-Meier survival curves for CRM. Overall survival (Figure 2a) and recurrence free survival (Figure 2b) for resection margin status (R0, R1a, R1b), with p-values representing comparisons across the three groups.
Overall survival by the American College of Pathologists (CAP) definition of CRM status (Figure 2c) and by the Royal College of Pathologists definition of CRM status (Figure 2d)

Figure 3

Kaplan-Meier survival curves for overall survival in N Stage (Figure 3a), Lymphovascular Invasion (Figure 3b), Neoadjuvant Chemotherapy (Figure 3c) and patient age (Figure 3d).

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Mar;61(2):69–90.

2. Devesa SS, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer. 1998 Nov 15;83(10):2049–53.

3. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D, ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2016 Sep;27(suppl 5):v50–7.

4. Lagarde SM, Phillips AW, Navidi M, Disep B, Immanuel A, Griffin SM. The presence of lymphovascular and perineural infiltration after neoadjuvant therapy and oesophagectomy identifies patients at high risk for recurrence. Br J Cancer. 2015 Nov 17;113(10):1427–33.

5. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, et al. EUROCARE-3: survival of cancer patients diagnosed 1990-94--results and commentary. Ann Oncol Off J Eur Soc Med Oncol. 2003;14 Suppl 5:v61–118.

6. Mulligan ED, Dunne B, Griffin M, Keeling N, Reynolds J V. Margin involvement and outcome in oesophageal carcinoma: a 10-year experience in a specialist unit. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2004 Apr;30(3):313–7.

7. Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg. 2002 Mar;89(3):327–34.

8. Griffiths EA, Brummell Z, Gorthi G, Pritchard SA, Welch IM. The prognostic value of circumferential resection margin involvement in oesophageal malignancy. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2006 May;32(4):413–9.

9. Dexter SP, Sue-Ling H, McMahon MJ, Quirke P, Mapstone N, Martin IG. Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer. Gut. 2001 May;48(5):667–70.

10. Saha AK, Sutton C, Rotimi O, Dexter S, Sue-Ling H, Sarela AI. Neoadjuvant Chemotherapy and Surgery for Esophageal Adenocarcinoma: Prognostic Value of Circumferential Resection Margin and Stratification of N1 Category. Ann Surg Oncol. 2009 May 28;16(5):1364–70.

11. Sujendran V, Wheeler J, Baron R, Warren BF, Maynard N. Effect of neoadjuvant chemotherapy on circumferential margin positivity and its impact on prognosis

in patients with resectable oesophageal cancer. Br J Surg. 2007 Oct 18;95(2):191–4.

12. Scheepers JJG, van der Peet DL, Veenhof AAFA, Cuesta MA. Influence of circumferential resection margin on prognosis in distal esophageal and gastroesophageal cancer approached through the transhiatal route. Dis Esophagus. 2009 Feb;22(1):42–8.

13. Sagar PM, Johnston D, McMahon MJ, Dixon MF, Quirke P. Significance of circumferential resection margin involvement after oesophagectomy for cancer. Br J Surg. 1993 Nov;80(11):1386–8.

14. Zafirellis K, Dolan K, Fountoulakis A, Dexter SPL, Martin IG, Sue-Ling HM, et al. Multivariate analysis of clinical, operative and pathologic features of esophageal cancer: who needs adjuvant therapy? Dis Esophagus Off J Int Soc Dis Esophagus. 2002;15(2):155–9.

15. Mirnezami R, Rohatgi A, Sutcliffe RP, Hamouda A, Chandrakumaran K, Botha A, et al. Multivariate analysis of clinicopathological factors influencing survival following esophagectomy for cancer. Int J Surg. 2010;8(1):58–63.

16. Khan OA, Fitzgerald JJ, Soomro I, Beggs FD, Morgan WE, Duffy JP. Prognostic significance of circumferential resection margin involvement following oesophagectomy for cancer. Br J Cancer. 2003 May 19;88(10):1549–52.

17. Ghadban T, Reeh M, Koenig AM, Nentwich MF, Bellon E, Izbicki JR, et al. Prognostic Significant or Not? The Positive Circumferential Resection Margin in Esophageal Cancer: Impact on Local Recurrence and Overall Survival in Patients Without Neoadjuvant Treatment. Ann Surg. 2016 Sep 9;1.

18. College of American Pathologists. Surgical Pathology Cancer Case Summary (Checklist): Esophagus. Northfield; 2005.

19. Mapstone N. Minimum dataset for Oesophageal Carcinoma Histopathology Reports (1st edn.). London; 1998.

20. Rao VSR, Yeung MMY, Cooke J, Salim E, Jain PK. Comparison of circumferential resection margin clearance criteria with survival after surgery for cancer of esophagus. J Surg Oncol. 2012 Jun 15;105(8):745–9.

21. Pultrum BB, Honing J, Smit JK, van Dullemen HM, van Dam GM, Groen H, et al. A critical appraisal of circumferential resection margins in esophageal carcinoma. Ann Surg Oncol. 2010 Mar 19;17(3):812–20.

22. O'Neill JR, Stephens NA, Save V, Kamel HM, Phillips HA, Driscoll PJ, et al. Defining a positive circumferential resection margin in oesophageal cancer and its implications for adjuvant treatment. Br J Surg. 2013 Jul;100(8):1055–63.

23. Deeter M, Dorer R, Kuppusamy MK, Koehler RP, Low DE. Assessment of criteria and clinical significance of circumferential resection margins in esophageal cancer. Arch Surg Chic Ill 1960. 2009 Jul 20;144(7):618–24.

24. Verhage RJJ, Zandvoort HJA, ten Kate FJW, van Hillegersberg R. How to define a positive circumferential resection margin in T3 adenocarcinoma of the esophagus. Am J Surg Pathol. 2011 Jun;35(6):919–26.

25. Hulshoff JB, Faiz Z, Karrenbeld A, Kats-Ugurlu G, Burgerhof JGM, Smit JK, et al. Prognostic Value of the Circumferential Resection Margin in Esophageal Cancer Patients After Neoadjuvant Chemoradiotherapy. Ann Surg Oncol. 2015 Dec 28;22(S3):1301–9.

26. Harvin JA, Lahat G, Correa AM, Lee J, Maru D, Ajani J, et al. Neoadjuvant chemoradiotherapy followed by surgery for esophageal adenocarcinoma: significance of microscopically positive circumferential radial margins. J Thorac Cardiovasc Surg. 2012 Feb;143(2):412–20.

27. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med. 2006 Jul 6;355(1):11–20.

28. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-Term Results of a Randomized Trial of Surgery With or Without Preoperative Chemotherapy in Esophageal Cancer. J Clin Oncol. 2009 Oct 20;27(30):5062–7.

29. Siewert JR SH. Carcinoma of the cardia: carcinoma of the gastroesophageal junction—classification, pathology and extent of resection. Esophagus. 1996;9:173–82.

30. Rusch VW, Rice TW, Crowley J, Blackstone EH, Rami-Porta R, Goldstraw P. The seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Staging Manuals: The new era of data-driven revisions. J Thorac Cardiovasc Surg. 2010 Apr;139(4):819–21.

31. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994 Jun 1;73(11):2680–6.

32. Theologou T, Diab M, Kyaw PA, Gosney JR, McShane J, Howes N, et al. The impact of positive circumferential margin on survival following oesophagectomy using the new 7th TNM classification. Eur J Cardiothorac Surg. 2013 Nov 1;44(5):855–9.

33. Wu J, Chen Q-X, Teng L, Krasna MJ. Prognostic significance of positive circumferential resection margin in esophageal cancer: a systematic review and meta-analysis. Ann Thorac Surg. 2014 Feb;97(2):446–53.

34. Chan DSY, Reid TD, Howell I, Lewis WG. Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. Br J Surg. 2013 Mar;100(4):456–64.

35. Ahmad J, Loughrey MB, Donnelly D, Ranaghan L, Shah R, Napolitano G, et al. Prognostic value of added stratification of circumferential resection margin status in oesophageal carcinoma. Histopathology. 2013 Apr;62(5):752–63.

36. Lee GD, Lee SE, Kim K-M, Kim Y-H, Ahn JH, Jung S, et al. New 3-Tiered Circumferential Resection Margin Criteria in Esophageal Squamous Cell Carcinoma. Ann Surg. 2015 Dec;262(6):965–71.

37. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Ann Surg. 2008 Feb;247(2):365–71.

38. Salih T, Jose P, Mehta SP, Mirza A, Udall G, Pritchard SA, et al. Prognostic significance of cancer within 1 mm of the circumferential resection margin in oesophageal cancer patients following neo-adjuvant chemotherapy. Eur J Cardiothorac Surg. 2013 Mar 1;43(3):562–7.

39. von Rahden BHA, Stein HJ, Feith M, Becker K, Siewert JR. Lymphatic vessel invasion as a prognostic factor in patients with primary resected adenocarcinomas of the esophagogastric junction. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Feb 1;23(4):874–9.

40. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, Henegouwen MI van B, Wijnhoven BPL, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. N Engl J Med. 2012 May 31;366(22):2074–84.

41. Pasquali S, Yim G, Vohra RS, Mocellin S, Nyanhongo D, Marriott P, et al. Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. Ann Surg. 2017;265(3):481–91.

42. Chan DSY, Reid TD, Howell I, Lewis WG. Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. Br J Surg. 2013 Mar;100(4):456–64.

43. Khan M, Muzaffar A, Syed AA, Khatak S, Khan AR, Ashraf MI. Changes in oncological outcomes: comparison of the conventional and minimally invasive esophagectomy, a single institution experience. Updat Surg. 2016 Dec 15;68(4):343–9.

44. Gilbert F, Park K TA. Scottish Audit of Gastric and Oesophageal. Cancer Report 1997–2000. Edinburgh; 2002.

45. Haverkamp L, Ruurda JP, van Leeuwen MS, Siersema PD, van Hillegersberg R. Systematic review of the surgical strategies of adenocarcinomas of the gastroesophageal junction. Surg Oncol. 2014 Dec;23(4):222–8.

Table 1a – Comparison of demographics and tumour factors between resection margin groups

	N	Resection Margin R0 (N=257)	R1a (N=71)	R1b (N=62)	p-Values Overall	R1a vs. R0	R1a vs. R1b
Age (Years) [a]	390	67.0±9.5	68.3±9.1	67.4±7.9	0.594	-	-
Gender [b]	390				0.611	-	-
Male		201 (78%)	55 (77%)	52 (84%)			
Female		56 (22%)	16 (23%)	10 (16%)			
Tumour Type [b]	390				**0.040**	0.053	**0.027**
Adeno		207 (81%)	47 (66%)	54 (87%)			
SCC		43 (17%)	20 (28%)	7 (11%)			
Other		7 (3%)	4 (6%)	1 (2%)			
Site of Lesion [c]	385				0.185	-	-
Upper		0 (0%)	1 (1%)	1 (2%)			
Mid		17 (7%)	8 (11%)	3 (5%)			
Lower/GOJ1		180 (71%)	55 (77%)	48 (77%)			
GOJ2		45 (18%)	6 (8%)	9 (15%)			
GOJ3		10 (4%)	1 (1%)	1 (2%)			
Differentiation [d]	387				**<0.001**	**<0.001**	0.904
Poor		79 (31%)	37 (53%)	39 (64%)			
Mod		142 (55%)	32 (46%)	18 (30%)			
Well		35 (14%)	1 (1%)	4 (7%)			
T-Stage [d]	390				**<0.001**	**<0.001**	0.334
T0		15 (6%)	0 (0%)	0 (0%)			
T1		56 (22%)	0 (0%)	0 (0%)			
T2		42 (16%)	0 (0%)	0 (0%)			
T3		139 (54%)	70 (99%)	51 (82%)			
T4		5 (2%)	1 (1%)	11 (18%)			
N-Stage (v7) [d]	390				**<0.001**	**<0.001**	0.377
N0		128 (50%)	13 (18%)	12 (19%)			
N1		68 (26%)	27 (38%)	12 (19%)			
N2		38 (15%)	17 (24%)	16 (26%)			
N3		23 (9%)	14 (20%)	22 (35%)			

Bold p-values are significant at p<0.05

Key:

[a]Data reported as mean±SD, with overall p-value from one-way ANOVA, and pairwise comparisons from Dunnett's tests.

[b]Data reported as N (%), with overall p-value from Fisher's exact test, and pairwise comparisons from Bonferroni-corrected Fisher's exact tests.

[c]Data reported as N (%), with overall p-value from Chi-square tests.

[d]Data reported as N (%), with overall p-value from Kruskal-Wallis tests (treating the factor as ordinal), and pairwise comparisons from Dunn's tests.

[e]Data reported as median (IQR), with overall p-value from Kruskal-Wallis tests, and pairwise comparisons from Dunn's tests.

Adeno – Adenocarcinoma
SCC - Squamous Cell Carcinoma
GOJ - Gastro-oesophageal junction (Siewert type)
v7 - 7th Edition TNM

Table 1b – Comparison of tumour and treatment factors between resection margin groups

	N	Resection Margin R0 (N=257)	R1a (N=71)	R1b (N=62)	p-Values Overall	R1a vs. R0	R1a vs. R1b
Peri-Neural Invasion [b]	302				**<0.001**	**0.002**	1.000
No		154 (80%)	34 (58%)	26 (51%)			
Yes		38 (20%)	25 (42%)	25 (49%)			
Lymphovascular Invasion [b]	257				**<0.001**	**<0.001**	1.000
No		116 (68%)	13 (30%)	14 (32%)			
Yes		54 (32%)	30 (70%)	30 (68%)			
Lymph nodes – Total [a]	390	29.4±11.7	33.8±11.4	29.6±11.6	**0.016**	**0.009**	0.065
Lymph nodes - Involved [e]	390	1 (0 - 2)	2 (1 - 5)	4 (1 - 9)	**<0.001**	**<0.001**	0.277
Lymph nodes - Ratio [e]	390	0.02 (0.00 - 0.09)	0.06 (0.02 - 0.17)	0.13 (0.05 - 0.32)	**<0.001**	**<0.001**	0.333
Tumour Length [e]	359	30 (20 - 45)	37 (25 - 50)	40 (29 - 50)	**0.014**	**0.044**	1.000
Operation Type [b]	390				0.531	-	-
Hybrid		106 (41%)	35 (49%)	23 (37%)			
MIO		57 (22%)	14 (20%)	15 (24%)			
Open		58 (23%)	16 (23%)	19 (31%)			
Other		36 (14%)	6 (8%)	5 (8%)			
Neoadjuvant Chemotherapy [b]	389				0.105	-	-
No		61 (24%)	11 (15%)	19 (31%)			
Yes		196 (76%)	60 (85%)	42 (69%)			
Chemo Cycles Planned [e] *	286	3 (2 - 3)	2 (2 - 3)	3 (2 - 3)	0.317	-	-
Chemo Cycles Received [e] *	273	2 (2 - 3)	2 (2 - 3)	3 (2 - 3)	0.278	-	-
Mandard Score [d] *	251				**<0.001**	**<0.001**	1.000
Mandard 1 (Complete)		16 (10%)	0 (0%)	0 (0%)			
Mandard 2		25 (15%)	0 (0%)	2 (6%)			
Mandard 3		34 (21%)	9 (18%)	8 (23%)			
Mandard 4		57 (35%)	21 (41%)	10 (29%)			
Mandard 5 (None)		33 (20%)	21 (41%)	15 (43%)			

**In patients that received chemotherapy*
Bold p-values are significant at p<0.05

Key:

[a]Data reported as mean±SD, with overall p-value from one-way ANOVA, and pairwise comparisons from Dunnett's tests.
[b]Data reported as N (%), with overall p-value from Fisher's exact test, and pairwise comparisons from Bonferroni-corrected Fisher's exact tests.
[c]Data reported as N (%), with overall p-value from Chi-square tests.
[d]Data reported as N (%), with overall p-value from Kruskal-Wallis tests (treating the factor as ordinal), and pairwise comparisons from Dunn's tests.
[e]Data reported as median (IQR), with overall p-value from Kruskal-Wallis tests, and pairwise comparisons from Dunn's tests.

Hybrid - laparoscopic gastric mobilisation and open right thoracotomy
MIO - Fully Minimally Invasive Oesophagectomy

Table 2 – Univariable survival analysis by resection margin for the whole cohort

	Overall Survival			Recurrence-Free Survival		
Resection Margin	***HR (95% CI)***	***Median (95% CI)***	***p-Value***	***HR (95% CI)***	***Median (95% CI)***	***p-Value***
Three Categories			**0.001**			**<0.001**
R0	0.84 (0.59 - 1.20)	25.1 (17.3 - 32.9)	0.334	0.76 (0.55 - 1.05)	21.5 (16.9 - 26.0)	0.095
R1a	-	27.0 (10.2 - 43.8)	-	-	16.5 (11.9 - 21.1)	-
R1b	1.57 (1.03 - 2.40)	14.9 (10.9 - 18.8)	**0.037**	1.56 (1.06 - 2.30)	11.2 (8.7 - 13.6)	**0.026**
CAP Guidelines			**<0.001**			**<0.001**
R0	-	26.3 (19.4 - 33.3)	-	-	20.1 (16.5 - 23.6)	-
R1	1.80 (1.30 - 2.50)	14.9 (10.9 - 18.8)	**<0.001**	1.92 (1.42 - 2.61)	11.2 (8.7 - 13.6)	**<0.001**
RCPath Guidelines			**0.006**			**<0.001**
R0	-	25.1 (17.3 - 32.9)	-	-	21.5 (16.9 - 26.0)	-
R1	1.48 (1.12 - 1.95)	18.0 (10.1 - 25.8)	**0.006**	1.62 (1.25 - 2.10)	13.6 (10.8 - 16.4)	**<0.001**

Hazard ratios and p-values are from univariable Cox regression models, and median survival times are Kaplan-Meier estimates
Bold p-values are significant at p<0.05.

CAP - College of American Pathologists definition with CRM involvement defined as at the margin only(22)
RCPath - Royal College of Pathologists definition with CRM involvement defined as within 1mm of the margin(23)

Table 3 – Subgroup analyses

Resection Margin	Overall Survival		Recurrence-Free Survival	
	HR (95% CI)	*p-Value*	*HR (95% CI)*	*p-Value*
		Chemotherapy Not Used (N=91)		
CAP (R1)	2.32 (1.21 - 4.46)	**0.012**	2.37 (1.31 - 4.31)	**0.005**
RCPath (R1)	2.02 (1.11 - 3.70)	**0.022**	2.05 (1.18 - 3.57)	**0.011**
		Chemotherapy Used (N=298)		
CAP (R1)	1.64 (1.11 - 2.43)	**0.013**	1.76 (1.22 - 2.54)	**0.003**
RCPath (R1)	1.35 (0.99 - 1.85)	0.060	1.50 (1.12 - 2.00)	**0.007**
		T-Stage 3 (N=260)		
CAP (R1)	1.38 (0.94 - 2.00)	0.097	1.41 (1.00 - 2.00)	0.051
RCPath (R1)	1.10 (0.80 - 1.52)	0.545	1.14 (0.85 - 1.54)	0.379
		N-Stage 0 (N=153)		
CAP (R1)	1.39 (0.63 - 3.08)	0.417	1.79 (0.88 - 3.63)	0.110
RCPath (R1)	0.94 (0.50 - 1.77)	0.843	1.05 (0.58 - 1.89)	0.883
		N-Stage 1-3 (N=237)		
CAP (R1)	1.74 (1.20 - 2.51)	**0.003**	1.70 (1.01 - 2.40)	**0.002**
RCPath (R1)	1.52 (1.10 - 2.10)	**0.012**	1.58 (0.17 - 2.13)	**0.003**

Hazard ratios and p-values are from univariable Cox regression models, and are for R1, relative to R0. Bold p-values are significant at p<0.05

CAP - College of American Pathologists definition with CRM involvement defined as at the margin only(22)

RCPath - Royal College of Pathologists definition with CRM involvement defined as within 1mm of the margin(23)

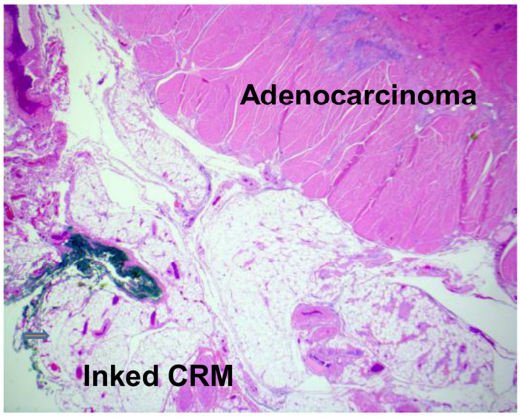
Table 4 – Multivariable analysis of overall survival and recurrence free survival

		CAP		RCPath	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Overall Survival	Resection Margin (R1)	1.21 (0.81 - 1.81)	0.352	1.02 (0.73 - 1.44)	0.907
	Age (Years)		**0.039**		**0.030**
	<60	-	-	-	-
	60-64	0.69 (0.41 - 1.16)	0.161	0.67 (0.40 - 1.13)	0.135
	65-69	0.92 (0.58 - 1.47)	0.742	0.93 (0.58 - 1.49)	0.761
	70-74	1.00 (0.61 - 1.64)	0.989	1.00 (0.61 - 1.63)	0.988
	75+	0.48 (0.28 - 0.82)	**0.007**	0.47 (0.28 - 0.81)	**0.006**
	N-Stage		**0.004**		**0.002**
	N0	-	-	-	-
	N1	1.03 (0.66 - 1.63)	0.889	1.02 (0.65 - 1.62)	0.921
	N2	1.65 (1.00 - 2.71)	**0.049**	1.65 (1.00 - 2.72)	0.051
	N3	2.17 (1.32 - 3.58)	**0.002**	2.23 (1.35 - 3.68)	**0.002**
	Lymphovascular Invasion	2.70 (1.85 - 3.93)	**<0.001**	2.74 (1.86 - 4.04)	**<0.001**
	Neoadjuvant Chemo.	0.65 (0.43 - 0.97)	**0.035**	0.64 (0.43 - 0.95)	**0.029**
Recurrence Free Survival	Resection Margin (R1)	1.37 (0.93 - 2.02)	0.107	0.99 (0.71 - 1.37)	0.936
	Age (Years)		**0.027**		**0.019**
	<60	-	-	-	-
	60-64	0.71 (0.43 - 1.18)	0.183	0.68 (0.41 - 1.12)	0.131
	65-69	0.94 (0.60 - 1.47)	0.774	0.94 (0.60 - 1.48)	0.804
	70-74	1.05 (0.65 - 1.69)	0.837	1.02 (0.63 - 1.64)	0.946
	75+	0.49 (0.30 - 0.82)	**0.006**	0.48 (0.29 - 0.80)	**0.005**
	N-Stage		**0.005**		**0.002**
	N0	-	-	-	-
	N1	1.03 (0.67 - 1.59)	0.893	1.03 (0.66 - 1.59)	0.906
	N2	1.54 (0.96 - 2.48)	0.076	1.56 (0.96 - 2.53)	0.074
	N3	2.11 (1.31 - 3.40)	**0.002**	2.23 (1.38 - 3.62)	**0.001**
	Lymphovascular Invasion	2.83 (1.97 - 4.05)	**<0.001**	2.91 (2.00 - 4.22)	**<0.001**
	Neoadjuvant Chemo.	0.73 (0.50 - 1.08)	0.114	0.71 (0.48 - 1.04)	0.075

Results are from multivariable Cox regression models. All factors in Table 1a/b were initially considered for inclusion in backwards stepwise models to identify significant independent predictors of outcome. Significant factors were then included in models alongside the resection margin. The final models are based on N=256, after excluding cases with missing data.

Bold p-values are significant at p<0.05

A



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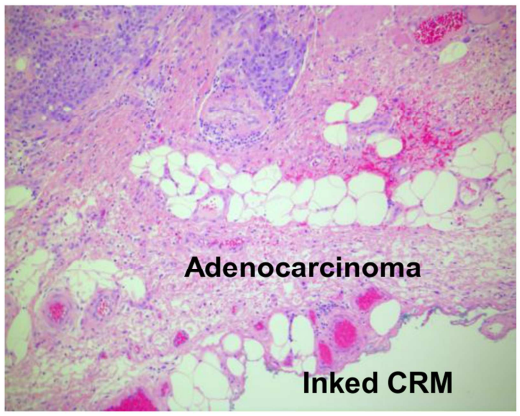

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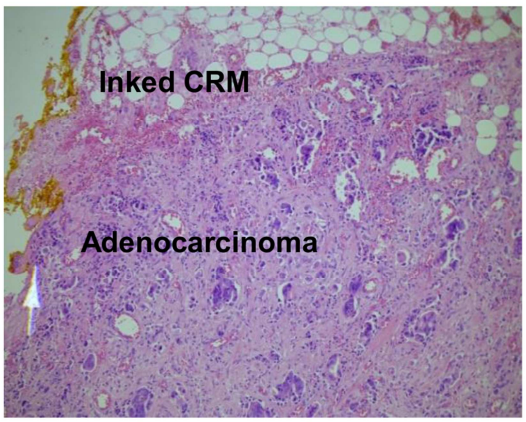
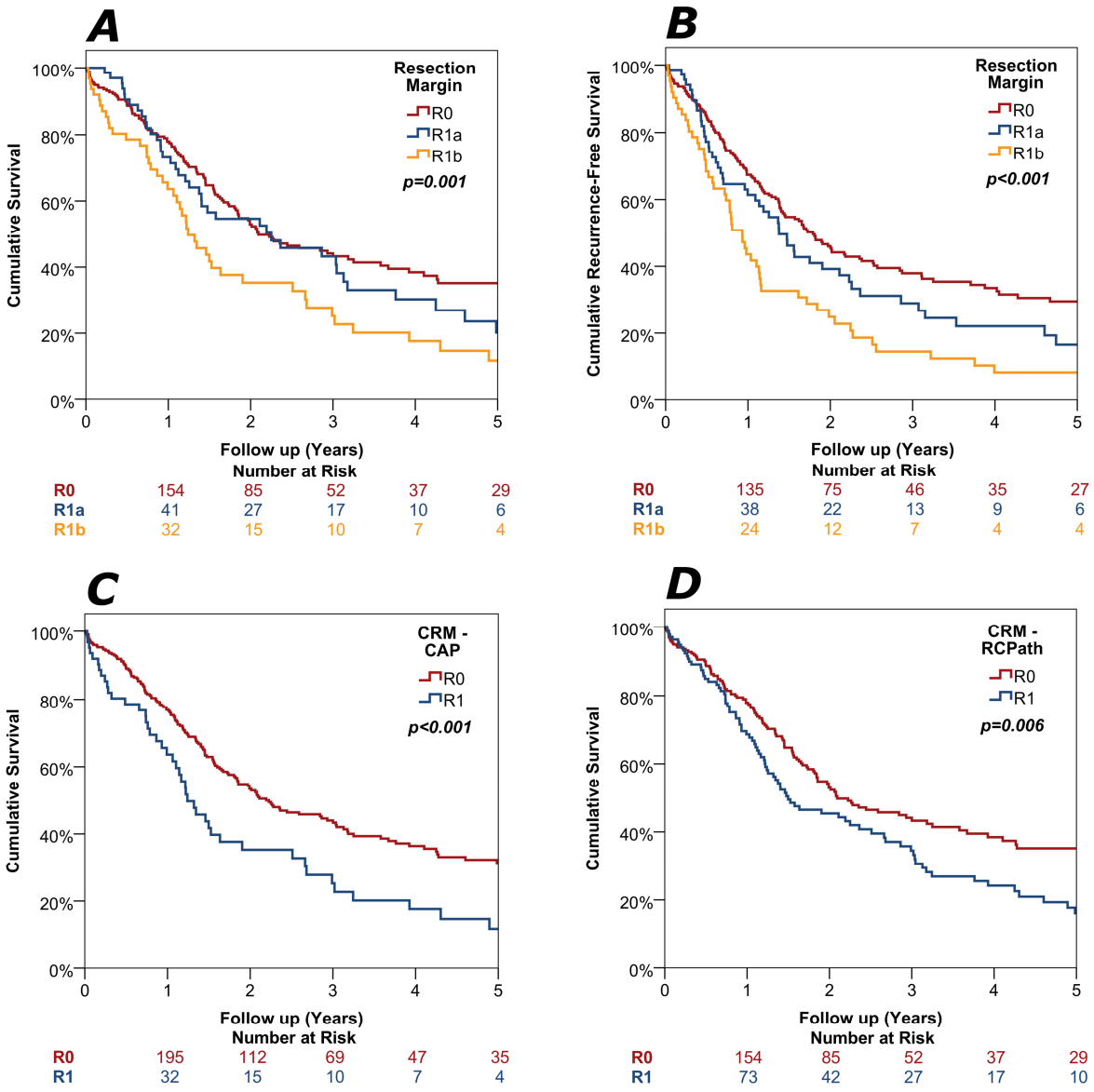
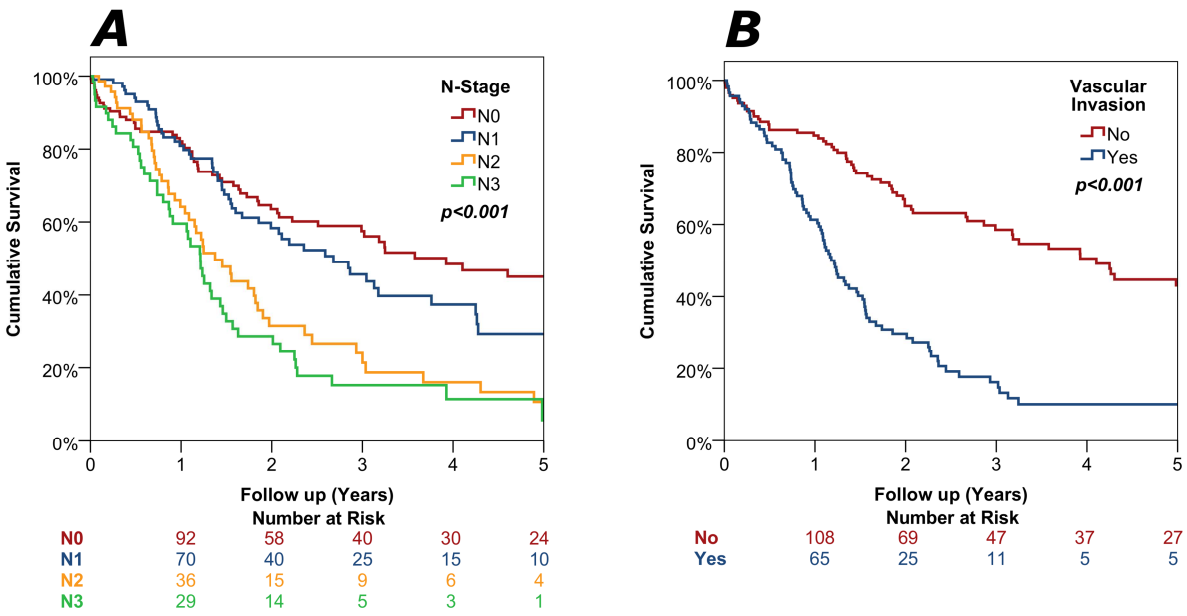



A
Cumulative Survival
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
Follow up (Years)
Resection Margin
R0
R1a
R1b
p=0.001
Number at Risk
R0 154 85 52 37 29
R1a 41 27 17 10 6
R1b 32 15 10 7 4
B
Cumulative Recurrence-Free Survival
Resection Margin
R0
R1a
R1b
p<0.001
Follow up (Years)
Number at Risk
R0 135 75 46 35 27
R1a 38 22 13 9 6
R1b 24 12 7 4 4
C
Cumulative Survival
CRM - CAP
R0
R1
p<0.001
Follow up (Years)
Number at Risk
R0 195 112 69 47 35
R1 32 15 10 7 4
D
Cumulative Survival
CRM - RCPath
R0
R1
p=0.006
Follow up (Years)
Number at Risk
R0 154 85 52 37 29
R1 73 42 27 17 10


A
Cumulative Survival
100%
80%
60%
40%
20%
0%
0
1
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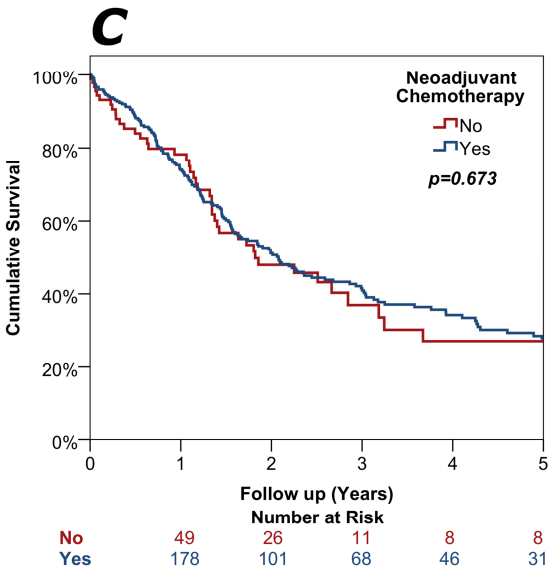
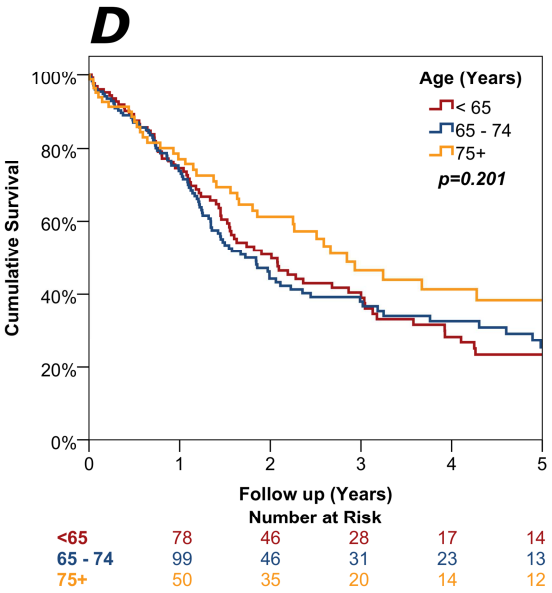
5
N-Stage
N0
N1
N2
N3
p<0.001
Follow up (Years)
Number at Risk
N0 92 58 40 30 24
N1 70 40 25 15 10
N2 36 15 9 6 4
N3 29 14 5 3 1

B
Cumulative Survival
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
Vascular Invasion
No
Yes
p<0.001
Follow up (Years)
Number at Risk
No 108 69 47 37 27
Yes 65 25 11 5 5


C
Cumulative Survival
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
Neoadjuvant Chemotherapy
No
Yes
p=0.673
Follow up (Years)
Number at Risk
No 49 26 11 8 8
Yes 178 101 68 46 31


D
Cumulative Survival
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
Age (Years)
< 65
65 - 74
75+
p=0.201
Follow up (Years)
Number at Risk
<65 78 46 28 17 14
65 - 74 99 46 31 23 13
75+ 50 35 20 14 12