Article:
Elshaer, A.M. orcid.org/0000-0002-8178-303X, Jones, S., Cockbain, A.J. et al. (6 more authors) (2025) The prognostic value of circumferential resection margin (CRM) definition and location in esophageal cancer: A 12-year cohort study. European Journal of Surgical Oncology, 51 (8). 110138. ISSN 0748-7983

https://doi.org/10.1016/j.ejso.2025.110138

The prognostic value of circumferential resection margin (CRM) definition and location in esophageal cancer: A 12-year cohort study

Authors: Ahmed M ELSHAER[1,2*], Sian JONES[1], Andrew J COCKBAIN[1], SPL DEXTER[1], Heike I GRABSCH[3,4], Samir P MEHTA[1], Abeezar SARELA[1], Nicholas P WEST[4,5], Jeremy HAYDEN[1]

[1] Department of Upper Gastrointestinal Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom. [2] Cairo University Hospitals (Kasr-Alainy Hospital), Cairo, Egypt. [3] Department of Pathology, GROW Research Institute for Oncology and Reproduction, Maastricht University Medical Centre, Maastricht, The Netherlands. [4] Pathology and Data Analytics, Leeds Institute of Medical Research, University of Leeds, Leeds, United Kingdom. [5] Department of Histopathology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

***Corresponding author:**

Ahmed Mohammed Elshaer

Address: Department of Upper Gastrointestinal Surgery, Level 6 Bexley Wing, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Beckett Street, Leeds, United Kingdom. Postcode: LS9 7TF

Email: ams872004@gmail.com, ahmed.elshaer@bthft.nhs.uk

Tel: 0044-07398131931

Orcid ID: 0000-0002-8178-303X

This work is an original article and was conducted at Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

The prognostic value of circumferential resection margin (CRM) definition and location in esophageal cancer: A 12-year cohort study

Abstract:

Background:

The definition of the circumferential resection margin (CRM) involvement for esophageal cancer varies between the Royal College of Pathologists (RCP) and College of American Pathologists (CAP). There are insufficient data regarding the prognostic relevance of different sites of involvement at the CRM. In this study, we examined the prognostic impacts of different CRM definitions and different radial margin locations.

Methods:

This retrospective study included 449 patients who were treated by curative esophagectomy for esophageal or junctional cancers between 2010 and 2021. The distance of the closest tumour cells to the inked CRM was examined and site of CRM involvement was recorded. Patients with an involved longitudinal resection margin were excluded. Long-term follow up data were obtained from the hospital's electronic health records.

Results:

Tumour cells at or within 1mm from the CRM (*CRM-RCP R1≤1mm*) was observed in 196 patients (43.7%). CRM(*≤1mm*) was associated with poorer overall survival (OS) and disease-free survival (DFS) compared to CRM-*R0*, p-values <0.001 for both. Tumour cells at the CRM (*CRM-CAP R1-0mm*) was observed in 61 patients (13.6%). Patients with CRM-*0mm* had poorer OS and DFS compared to CRM*≤1mm,* p-values 0.039 and 0.013 respectively. Presence of tumour cells (CRM*≤1mm*) at multiple locations of the CRM was related to poorer survival compared to a single location; (OS p-value 0.008, DFS p-value 0.05). The posterior margin was the most common positive single CRM-positive site (44%), followed by anterior (39%) and lateral sites (17%). However, the anterior margins carried poorer OS and DFS compared to posterior and lateral sites, (p-values 0.37 and 0.39 respectively).

Conclusion:

This study demonstrated that CRM involvement as defined by RCP was an independent prognostic factor for both survival and recurrence in esophageal cancer. It promoted the value of additional reporting CRM-*0mm* in CRM-R1 cases. The study also investigated the relative importance of reporting CRM-R1 location, which might be a useful prognostic tool in the future.

Keywords: circumferential resection margin (CRM), esophageal cancer, esophagectomy, R1-resection, R0-resection, RCP definition, CAP definition.

Abbreviations: ADC: adenocarcinoma, CRM: Circumferential resection margin (esophagus), CAP: College of American Pathologists, CRT: chemoradiotherapy, CT: computerised tomography; DFS: disease free survival; LN: lymph node, MDT: multidisciplinary team; NAC: neoadjuvant chemotherapy; NAT: neoadjuvant treatment; NR: not reached; OS: overall survival; PET-CT: positron emission tomography CT; RCP: Royal College of Pathologists; SQCC: squamous cell carcinoma

Main Manuscript:

Introduction

The negative prognostic impact of microscopic involvement of the circumferential resection margin (CRM) on survival and recurrence was first reported by Sagar et al in 1993 in esophagectomy patients (1). Since then, the role of the CRM in esophageal cancer has been extensively investigated in the literature (2). However, there is heterogeneity in defining CRM involvement between the guidelines issued by the Royal College of Pathologists, London, UK (RCP) which defines a positive CRM as tumour cells at or within 1 mm of the cut margin; CRM ≤ 1mm) (3) and the College of American Pathologists (CAP) which defines a positive CRM as tumour cells present at the cut surface; CRM-0mm) (4). There is ongoing debate about the prognostic values of both CRM definitions and variable outcomes have been reported in the literature due to the use of different CRM definitions (2).

The anatomic boundaries of the esophagus hold special surgical challenges when compared to other viscera such as the rectum. In particular, proximity of the esophagus to central organs that cannot be resected like aorta, heart, spine and airways, impacts on the resectability of bulky tumours with a negative CRM. However, the pericardium anteriorly and pleurae or even lungs laterally could potentially represent resectable structures to achieve a negative CRM.

The difference in lymphatic drainage within the esophageal walls has been reported (5). Two previous studies evaluated the pre-treatment circumferential location of the tumour suggesting that tumour location within the wall was an independent predictor of survival (6,7). However, the prognostic value of the site/location of CRM involvement is currently unknown (6,7). We postulate that a difference in survival between CRM-R1 (RCP) radial margins could influence future treatment plans particularly for adjuvant treatment.

In this study, we investigated the prognostic value of the two CRM definitions (RCP versus CAP) and of CRM location in a large retrospective cohort of oesophageal cancer patients with locally advanced resectable disease treated by curative esophagectomy.

Methods:

Patient selection:

Patients were identified through a prospectively collected electronic database at a large tertiary referral centre for oesophageal cancer. The study included patients who underwent a potentially curative esophagectomy between 1st January 2010 and 31st December 2021. Patients with resectable adenocarcinoma (ADC) or squamous cell carcinoma (SQCC) of the mid or distal esophagus or esophagogastric junction (Siewert type I–II) were included. Patients with and without neoadjuvant treatment (NAT) were included. We excluded patients with alternative histology (5 patients), tumours within 1mm of the proximal or distal longitudinal resection margins in the pathology resection report (6 patients), who underwent salvage esophagectomy after definitive chemoradiotherapy (10 patients), who died within 30 days of surgery (7 patients) and patients who were lost during follow up or with unavailable accurate histopathological data (7 patients).

Preoperative investigations:

All patients underwent endoscopy with biopsy to confirm the diagnosis. Initial staging was performed through contrast enhanced computerised tomography (CT) of the chest, abdomen and pelvis followed by positron emission tomography-CT (PET-CT) scan. Endoscopic ultrasound (EUS) was used to complete staging if further assessment of tumour was still required after CT and PET-CT scans. All patients were discussed at the multidisciplinary team

(MDT) meeting following diagnosis and postoperatively with the pathology data of the resected specimens.

Neoadjuvant treatment (NAT) and surgery:

Patients who had locally advanced resectable cancer underwent NAT (383 patients). This included MAGIC and OEO-2 (n=286) or FLOT (n=80) regimes for neoadjuvant chemotherapy (NAC) (8,9) or neoadjuvant chemoradiotherapy (nCRT) CROSS regimen (n=17) (10). Selection of NAT regimen was undertaken at the first diagnostic MDT meeting.

Surgery was typically a 2-stage esophagectomy (Ivor-lewis) approach with 2-field lymphadenectomy. This was performed either open, hybrid (with laparoscopic abdominal part) or minimally invasive esophagectomy with right thoracoscopic approach. Five cases required 3-stage (McKeown) esophagectomy. Surgery was performed 4-6 weeks after completion of NAC and 6-8 weeks after neoadjuvant CRT therapy. Adjuvant chemotherapy or radiotherapy was offered, after discussion in the MDT, in NAC group with advanced nodal disease or margin involvement and after clinical evaluation of patient fitness postoperatively

Pathological examination:

Resected specimens were examined according to a standardized protocol by specialized gastrointestinal pathologists. The resected specimens were fixed in formalin for 24-48 hours. Specimens were sliced transversely into cross-sections of 3-5mm thickness for macroscopic assessment of the tumour and its relationship to the CRM. Areas including the tumour closest to the CRM were processed into paraffin blocks, and subsequent haematoxylin and eosin-stained slides were examined microscopically to assess the distance of tumour cells from CRM in millimetres. Resection specimens were orientated by the surgeon for the pathologist with anterior and right lateral sutures placed on the oesophagus and anterior suture on the stomach.

Pathologists then inked the anterior, posterior, left and right lateral surfaces with different colours to enable identification of the radial margin location. Furthermore, Furthermore, the pT-stage and pN-stage, according to TNM version 7 (2010-2019) or 8 (2019-2021) were reported by the pathologist along with histological tumour type, tumour grade, angioinvasion, and perineural tumour growth. The post-operative pathology results were discussed in the MDT meeting. Resections with an involved CRM were routinely reported according to the RCP definition (tumour cells at or within 1mm of margin) (3)**.** The CRM sites were identified as: Anterior; which was usually related to the pericardium, posterior; related to the aorta side, right or left lateral: related to the pleura.

Data collection and follow up:

Patients were followed up initially at 4-6 weeks postoperatively at cancer clinics, then at 3, 6 and 12 months in the first year. Annual follow up was conducted to complete 5 years of oncological surveillance postoperatively or up to death if that occurred in less than 5 years. Follow up data were collected from the electronic health records until July 2022. This included patient demographics, disease characteristics, pathological data, treatment details (oncological and surgical) and survival outcomes. Data were collected and stored in an encrypted folder. Ethical approval was obtained local Research Ethics Committee at our institution in June 2022. All work in this study was performed in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments. Individual patient consent was not required for this study.

Interpretations and Outcomes of the study:

We analysed the clinicopathological data of CRM and its relationship to survival. We compared CRM R0-resection (no tumour cells in more than 1mm of cut margins) with CRM R1-resection

according to RCP definition (tumour cells within 1mm of cut margins). Additionally, we compared the outcomes between CRM-R1 (tumour cells ≤1mm but not at cut margins; >0.1-1mm) and CRM R1-CAP (0mm: tumour cells found at the cut margins). We conducted further subgroup analysis to patients with ≥ pT3 and pN-positive cancers who received NAT for those two comparisons.

We completed our analysis by interpreting the outcomes for each CRM margin according to the site. We also evaluated the outcomes between cases with multiple involved sites in CRM against the cases of single site involvement.

Primary outcome was to identify the overall survival (OS) and disease-free survival (DFS) between the above groups. Secondary outcomes included recurrence rates, 5-year survival rates and identifying factors affecting survival.

Statistical analysis:

All statistical analyses were performed using SPSS (version 20.0; IBM Corp, Armonk, NY). A two-sided p-value <0.05 was considered statistically significant. Clinicopathological data were compared by using chi-square tests or Fisher's exact tests for categorical data and Mann–Whitney U-test or Kruskal Wallis test for continuous variables. OS and DFS were estimated from time of surgery using the Kaplan-Meier method, and a log-rank test was performed to compare the groups. Univariate and multivariate Cox proportional hazards models were used to analyse the hazard ratios (HRs) for OS and DFS. Variables with p-values <0.05 in univariate analysis were included in the multivariate analysis.

Results:

During the period of the study, 449 patients fulfilled our inclusion criteria. Among the 449 cases, pT3 was the commonest T-stage in final pathology in 248 (55.2%) cases and N-positive

was observed in 236 (52.6%) cases. 397 (88.4%) cases were adenocarcinoma (ADC) while only 52 (11.6%) cases were squamous cell carcinoma (SQCC). Tumours were mainly situated in the lower esophagus 336 (74.8%) cases, then junctional 87 (19.4%) cases with only 26 (5.7%) cases were in middle third. Median overall survival was 61 months. Recurrence was detected in 204 (45.4%) patients, with 156/204 (76.5%) patients demonstrating systemic recurrence.

CRM-RCP R1(≤1mm) vs CRM-RCP R0:

253 (56.3%) patients had CRM-R0 resection, while 196 (43.7%) had CRM-R1 (≤1mm). Patient and tumour characteristics can be found in table 1. Tumour characteristics were more favourable in the R0 group. Tumours ≥pT3 were 190/196 (96.9%) in R1, while only 86/253 (33.9%) in R0 (p-value 0.04). pN-positive status was observed in 143/196 (72.9%) in R1 and 93/253 (36.7%) in R0 (p-value <0.0001).

Median OS was not reached in R0 cases compared to 26 months for R1 cases, p-value <0.001). 5-year OS rates between R0 and R1 were 69.9% and 21.1%, p-value<0.001. This was also noted in median DFS; not reached (NR) and 20.4 months respectively, p-value <0.001) (Figure 1).

On further analysis of patients with ≥pT3 and pN-positive cancers who had neoadjuvant therapy (NAT). 192 cases were involved in this analysis; 60 (31.2%) CRM-R0 and 132 (68.7%) CRM-R1 cases. Both median OS (26.8 and 19.5 months respectively, HR 1.615, 95%CI 1.107-2.355, p-value 0.012), and median DFS (18.6 versus 12.9 months respectively, p-value 0.031) were significantly better for R0 cases compared to R1 cases (Figure 1).

CRM-R1: R1 (0.1-1mm) versus R1(0 mm):

185 patients with CRM-R1 were analysed. 124/185 (67%) patients had R1(0.1-1mm) margins, while 61/185 (32.9%) had R1(0mm). Patients' and tumour characteristics are shown in table 2.

Median OS was 22 months in R1(0 mm) compared to 27 months R1(0.1- 1mm), p-value 0.039. 5-year OS rates between R1 (0 mm) and R1 (0.1-1mm) were 13.7% and 23.2% respectively, p-value 0.03. Median DFS was 12.9 months and 25 months respectively, p-value 0.013 (Figure 2).

After analysis for patients with ≥ T3 and N-positive cancers with NAT; 125 patients were included. 83/125 (66.4%) patients had R1(0.1-1mm). OS was better but insignificant for R1(0.1-1mm) compared to R1(0mm); 21.9 and 14.8 months respectively, p-value 0.08. 5-year survival rates between R1 (0 mm) and R1 (0.1-1mm) after adjustment were 7.4% and 14.3% respectively, p-value 0.07. However, DFS was better and significant; 18.1 and 11.8 months respectively, p-value 0.032 (Figure 2).

Analysis of different CRM-RCP R1 margin locations:

117 patients post NAT with CRM-RCP R1(≤1mm) margins were analysed for the location of involvement. 84 (71.8%) cases had single site involvement while 33 (28.2%) cases had multiple site involvement. For those with single site involvement; posterior margin was the commonest compared to anterior and lateral margins (37(44%), 32(38.1%) and 15(17.9%) cases respectively). Demographics and tumour characteristics for all margins are presented in table 3. There was no difference in pT-stage, pN-stage and NAT between the all single-margin groups (p-values 0.12, 0.4 and 0.19 respectively). Patients with multiple involved margins carried worse prognosis compared to single involved margin cases; either for OS (median 19

versus 32 months respectively; p-value 0.008) or DFS (median 12.1 versus 27.6 months respectively; p-value 0.05) (Figure 3). 5-year OS rates between those with multiple and single CRM-positive margins were 10.3% and 29.2% respectively, p-value 0.037.

For those with single margin involvement; anterior margins had poorer survival compared to posterior and lateral margins either for OS (median 29, 32 and 41 months respectively; p-value 0.37) or DFS (median 19.2, 28.7 and 32.1 months respectively; p-value 0.39) (Figure 3). 5-year OS rates between the different margins were; anterior (20.6%), lateral (47.7%) and posterior (30.2%), with p-value 0.39.

Uni- and multi-variate analysis for whole cohort group (table 4):

Univariate analysis for OS and DFS showed that pT-, pN- stages, CRM involvement (R0 vs R1-RCP), CRM-R1 types (0mm versus 0.1-1mm), multiple margin involvement, NAT, lymph node ratio (LNR) (number of positive lymph nodes/ total number of lymph nodes%) were significant factors. While on multi-variate analysis; CRM involvement, NAT and LNR remained significant. (p-values 0.000, 0.000 and 0.01 respectively)

Discussion:

The prognostic value of CRM status in oesophageal cancers has been under investigation over the last two decades with some conflicting results (2). We have published 2 previous studies from our large tertiary referral centre to evaluate CRM. Dexter et al in 2001, demonstrated that CRM-R1 carried worse OS compared to CRM-R0 in 135 esophagectomies without neoadjuvant treatment (21 vs 39 months, p. 0.015). CRM involvement was an independent variable with lymph node status on survival in Cox's hazards model (11). The other study was in 2013, Salih et al, showed that CRM-R1 patients post NAC had worse cancer specific survival compared to R0 (p-value 0.008) in 232 patients. Yet, CRM status failed to be an

independent prognostic factor in multivariate analysis, only lymph node status remained significant in this analysis (12). In these both studies, we used the RCP definition to identify CRM-R1.

This current study demonstrated that CRM involvement carried a worse prognosis in patients with locally advanced esophageal cancer in a larger cohort of patients. The study demonstrated that involved CRM-RCP (*CRM ≤ 1mm*) carried significantly worse OS and DFS compared to CRM-R0 (*CRM>1mm*) resections either before or after adjustment to subgroup analysis. It was also an independent prognostic factor in multivariate analysis for both OS and DFS. This was supported to date, by three large meta-analyses using the RCP definition which demonstrated survival benefit for CRM-R0 against R1-RCP (13–15)**.** It is noteworthy that many confounding variables might be encountered across the individual studies included in these meta-analyses. These variables include pT-stage, NAT and lymph node status. On subgroup analysis in these meta-analyses; both pT3 cancer group and cohort of patients with neoadjuvant treatment only, showed persistence of survival benefits for R0 compared to R1-RCP groups, yet lymph node status wasn't properly presented in most of the individual studies to achieve proper analysis.

On the other hand, fewer studies were not able to demonstrate a considerable effect of CRM-R1 on OS (16–19)**.** In a recent study by Ghadban et al. (20), in total 180 patients neither CRM-R1 RCP (p-value 0.655) nor CRM-R1 CAP (p-value 0.317) criteria yielded an association to overall survival.

There's a lack of consensus on the CRM-R1 definition to use across the literature between RCP and CAP (2). In our study, we compared R1 (0.1-1mm) group to R1 (0mm) group to precisely recognise the survival benefits between the two definitions. Most of our R1 resections

could not be classified as R1 by CAP definition (67%). This was similar to other studies (60-80%) (12,13,17,21–23)**.** The OS and DFS were significant better in R1 (0.1-1mm) compared to R1-CAP (0mm) but when adjusted to patients with ≥ypT3, ypN-positive and had NAT; only DFS remained significant. This difference in survival and recurrence rates supports the value of reporting both CRM-R1 definitions (RCP R1≤*1mm* and CAP R1 *0mm*) in esophageal cancers.

The published results are hugely contentious which prompt a genuine debate. For instance, Zhayong et al displayed no significant difference in survival between CRM (0mm) and CRM (0-1mm) in 376 patients without NAT within the pN0 group, but worse survival in the pN1-2 group towards CRM 0mm (OS, p-value 0.00, DFS p-value 0.001). This difference in CRM definition was an independent factor for survival in their multivariate analysis (23)**.** However, Depypere et al, demonstrated no difference between median OS and DFS between RCP and CAP for ypT3 patients post CRT, (p-value 0.06 and 0.075 respectively). Nevertheless, the number of patients in each group was relatively small; 37 and 8 patients respectively (24)**.** In another recent study for 105 pT3 oesophageal SQCC cases, R1 (0mm) carried worse OS compared to R1 (0-1mm) in the upfront surgery group (p-value<0.001). On the contrary, it didn't show any survival superiority in the group with neoadjuvant CRT (p-value 0.39) (25)**.** It's worth considering that some studies displayed a paramount difference in survival when CAP was used to identify R1 in comparison with R0 resections, but not witnessed with RCP (17,21,22,24,26).

In our study, biological features of tumour were more aggressive in R1-CAP (0mm) compared to R1 (0.1-1mm) group despite not being statistically significant for any feature. For instance, pT4-stage disease was higher (21.3% and 8.9% respectively, p-value 0.05), poor differentiation

(67% and 54% respectively, p-value 0.15) and pN-positive disease (78% and 70% respectively, p-value 0.13). This was also noticed by O'farrell et al, as they demonstrated that CRM-R1 (CAP) was significantly (p-value 0.036) associated with nodal disease, in contrast to CRM-R1 (RCP) (p-value 0.447). Nonetheless, there was no difference in tumour differentiation or in perineural or lymphovascular invasion between the two groups (21)**.** This was also supported in other studies which concluded that positive CRM with CAP criteria identified a higher-risk group of patients compared to RCP criteria (13,14).

For patients who received NAT, the rate of CRM involvement was 11.5% vs 26% in CAP and RCP groups respectively (p-value 0.02). This was supported by other studies which demonstrated that NAT affected the CRM towards less margin involvement (13,21,26)**.** It was also noticeable in our study, that no difference was related to type of NAT either chemotherapy or radiotherapy between both groups (p-value 0.51).

We further examined the anatomical sites in 117 CRM-RCP R1 patients post NAT to evaluate their prognostic significance. We noticed that multiple-site involvement was a higher risk factor for survival compared to single-site involvement for both OS and DFS. This was a significant independent factor on univariate analysis for OS and DFS, yet it failed to be an independent prognostic factor in multivariate analysis. This could be plausible to the tumour biology (pT, pN, tumour type or differentiation) which was supposed to be more aggressive in multiple positive sites tumour, however these characteristics didn't show any differences between both groups in this study.

When we analysed the patients with single site involvement, posterior margins (towards aorta) were the commonest (44%). However, anterior margins, which usually face the pericardium, carried the worst prognosis compared to posterior and lateral margins. This was observed for

OS and DFS, however, this difference in survival failed to reach a significance level in this study. There was also a trend for higher recurrence rates in anterior margins compared to other margins. This might be explained by the conclusion drawn by Doubliet et al, who discovered more nerve fibres in anterior wall of esophagus after examining 32 cadavers (27)**.** This could potentially lead to higher perineural and lymphatic invasion which can worsen the survival rates (28,29).

To date, no reports correlated between CRM-R1 margins and survival. However, two studies examined the prognostic value of circumferential tumour location detected at time of diagnosis. Both studies included esophageal SQCC cases only, analysed the location prior to treatment (not in CRM pathological status) and didn't identify lateral (left/right) sites separately. Nagasawa et al, concluded that left or anterior (L/A) location carried worse 3-year OS and DFS compared to right or posterior position (R/P) (p-value 0.007 and 0.005 respectively). All patients in this study received NAT (6)**.** This was in contrary to the study done by Mine et al who reported that R/P sites carried worse DFS compared to L/A sites (p-value 0.02) (7)**.** They hypothesised their results on the concept that lymphatic drainage from posterior wall of oesophagus is likely to enter systemic circulation directly by the thoracic duct (30,31)**.** However, it's noted that Mine et al included patients who didn't receive neoadjuvant therapy which can theoretically control hematogenous micro-metastases and reduce its spread (7).

The findings of this study may play a potential role in tailoring adjuvant therapy, particularly in complex clinical scenarios where the benefits of adjuvant treatment must be weighed against patient deconditioning. It underscores the importance of reporting CRM-R1*(0mm)* status (CAP definition) (3) in esophageal cancer cases and its potential value to personalise adjuvant

therapy for such complex cases. This study also provides a stimulus to examine the anatomical boundaries of the circumferential resection margin (CRM), which can serve as a prognostic factor and may help refine adjuvant therapy strategies in these complex cases. This concept has not been previously explored in the literature.

This study has many merits; it involved a relatively large homogonous cohort of patients with long term follow up. We had no patients lost in follow up. We intensely evaluated CRM in different aspects with trying to eliminate confounding factors.

However, it has some inherited limitations related to its retrospective character. Furthermore, it didn't incorporate the effect of adjuvant therapy on survival analysis. Finally, the relatively small number used in comparison of each single margin group could make the statistical interpretation difficult due to lack of statistical power.

Conclusion: This study demonstrated that CRM-R1 was an independent prognostic factor for both survival and recurrence in oesophageal cancer. It promoted the value of reporting CRM-0mm in CRM-R1 cases. The study also stimulated the role of reporting different positive margins within CRM which might be a useful prognostic tool in the future.

Conflict of interests: The authors have no conflict of interests to declare. The results were presented as an oral presentation at the European Society of Surgical Oncology congress in 2022 and as an oral poster at the 20th International Society for Diseases of Esophagus congress in 2024.

Funding: Not applicable

Acknowledgements: HG and NW are supported in part by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre (BRC) (NIHR203331). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

References:

1) Sagar, P. M., Johnston, D., McMahon, M. J., Dixon, M. F., & Quirke, P. (1993). Significance of circumferential resection margin involvement after esophagectomy for cancer. Journal of British Surgery, 80(11), 1386–1388.

2) Karstens, K.-F., Izbicki, J. R., & Reeh, M. (2018). Does the Margin Matter in Esophageal Cancer. *Digestive Surgery*, *35*(3), 196–203.

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

4) Mapstone N. (2006). Dataset for the Histopathological Reporting of Oesophageal Carcinoma, 2nd ed. London. Royal College of Pathologists

5) Wang, Y., Zhu, L., Xia, W., & Wang, F. (2018). Anatomy of lymphatic drainage of the esophagus and lymph node metastasis of thoracic esophageal cancer. *Cancer Management and Research*, *Volume 10*, 6295–6303.

6) Nagasawa S, Oshima T, Hara K, Nakazono M, Kumazu Y, Aoyama T, Yamada T, Ogata T, Rino Y, Saito A, Yokose T, Grabsch HI. Clinical Significance of Pre-treatment Circumferential Tumor Location in Patients With cStage IB-III Esophageal Squamous Cell Cancer. Anticancer Res. 2023 Jun;43(6):2697-2705

7) Mine S, Yamada K, Grabsch H, Sano T, Ishiyama A, Hirasawa T, Yamamoto N, Hiki N and Yamaguchi T: The prognostic significance of tumor laterality in patients with esophageal squamous cell carcinoma. J Surg Oncol 105(1): 66-70, 2012.

8) Cunningham, D., Allum, W. H., Stenning, S. P., et al. (2006). Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. New England Journal of Medicine, 355(1), 11–20.

9) Al-Batran, S.-E., Homann, N., Pauligk, C., et al (2019). Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. The Lancet, 393(10184), 1948–1957.

10) Van Hagen, P., Hulshof, M. C. C. M., et al. (2012). Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. New England Journal of Medicine, 366(22), 2074–2084.

11) Dexter SPL, Sue-Ling H, McMahon MJ, et al Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer Gut 2001;48:667-670

12) Salih, T., Jose, P., Mehta, S. P., et al. (2013). Prognostic significance of cancer within 1 mm of the circumferential resection margin in oesophageal cancer patients following neo-adjuvant chemotherapy. European Journal of Cardio-Thoracic Surgery, 43(3), 562–567.

13) Chan, D. S. Y., Reid, T. D., Howell, I., & Lewis, W. G. (2013). Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. In British Journal of Surgery (Vol. 100, Issue 4, pp. 456–464).

14) Wu, J., Chen, Q. X., Teng, L. S., & Krasna, M. J. (2014). Prognostic significance of positive circumferential resection margin in esophageal cancer: A systematic review and meta-analysis. Annals of Thoracic Surgery, 97(2), 446–453.

15) Evans, R., Bundred, J. R., Kaur, P., Hodson, J., & Griffiths, E. A. (2019). Meta-analysis of the influence of a positive circumferential resection margin in oesophageal cancer. BJS Open, 3(5), 595–605

16) Thompson, S. K., Ruszkiewicz, A. R., Jamieson, G. G., Esterman, A., Watson, D. I., Wijnhoven, B. P. L., Lamb, P. J., & Devitt, P. G. (2008). Improving the Accuracy of TNM Staging in Esophageal Cancer: A Pathological Review of Resected Specimens. Annals of Surgical Oncology, 15(12), 3447–3458

17) Harvin, J. A., Lahat, G., Correa, A. M., Lee, J., Maru, D., Ajani, J., Marom, E. M., Welsh, J., Bhutani, M. S., Walsh, G., Roth, J., Mehran, R., Vaporciyan, A., Rice, D., Swisher, S., & Hofstetter, W. (2012). Neoadjuvant chemoradiotherapy followed by surgery for esophageal adenocarcinoma: Significance of microscopically positive circumferential radial margins. The Journal of Thoracic and Cardiovascular Surgery, 143(2), 412–420.

18) Khan, O. A., Fitzgerald, J. J., Soomro, I., Beggs, F. D., Morgan, W. E., & Duffy, J. P. (2003). Prognostic significance of circumferential resection margin involvement following esophagectomy for cancer. British Journal of Cancer, 88(10), 1549–1552.

19) Rao, V. S. R., Yeung, M. M. Y., Cooke, J., Salim, E., & Jain, P. K. (2012). Comparison of circumferential resection margin clearance criteria with survival after surgery for cancer of esophagus. Journal of Surgical Oncology, 105(8), 745–749.

20) Ghadban, T., Reeh, M., Koenig, A. M., Nentwich, M. F., Bellon, E., Izbicki, J. R., Vashist, Y. K., & Kutup, A. (2017). Prognostic Significant or Not? The Positive Circumferential Resection Margin in Esophageal Cancer. Annals of Surgery, 266(6), 988–994.

21) O'Farrell, N. J., Donohoe, C. L., Muldoon, C., Costelloe, J. M., King, S., Ravi, N., & Reynolds, J. v. (2013). Lack of independent significance of a close (<1 mm) circumferential resection margin involvement in esophageal and junctional cancer. Annals of Surgical Oncology, 20(8), 2727–2733.

22) Verhage, R. J. J., Zandvoort, H. J. A., ten Kate, F. J. W., & van Hillegersberg, R. (2011). How to Define a Positive Circumferential Resection Margin in T3 Adenocarcinoma of the Esophagus

23) Yang, Z., Lin, H., Wang, Z., Rong, L., Zhang, X., Wang, L., Qin, J., Xue, X., Li, Y., & Xue, L. (2022). The prognostic significance of the circumferential resection margin in esophageal squamous cell carcinoma patients without neoadjuvant treatment. BMC Cancer, 22(1).

24) Depypere, L., Moons, J., Lerut, T., de Hertogh, G., Peters, C., Sagaert, X., Coosemans, W., van Veer, H., & Nafteux, P. (2018). Prognostic value of the circumferential resection margin and its definitions in esophageal cancer patients after neoadjuvant chemoradiotherapy. Diseases of the Esophagus, 31(2), 1–8

25) Liu, C. Y., Hsu, P. K., Hsu, H. S., Wu, Y. C., Chuang, C. Y., Lin, C. H., & Hsu, C. P. (2020). Prognostic impact of circumferential resection margin in esophageal cancer with or without neoadjuvant chemoradiotherapy. Diseases of the Esophagus, 33(9).

26) Hulshoff, J. B., Faiz, Z., Karrenbeld, A., Kats-Ugurlu, G., Burgerhof, J. G. M., Smit, J. K., & Plukker, J. T. M. (2015). Prognostic Value of the Circumferential Resection Margin in Esophageal Cancer Patients After Neoadjuvant Chemoradiotherapy. Annals of Surgical Oncology, 22, 1301–1309.

27) Doubilet H, Shafiroff BG and Mulholland JH: The anatomy of the peri-esophageal vagi. Ann Surg 127(1): 128-135, 1948.

28) Gao A, Wang L, Li J, Li H, Han Y, Ma X and Sun Y: Prognostic value of perineural invasion in esophageal and esophagogastric junction carcinoma: a meta-analysis. Dis Markers 2016: 7340180, 2016.

29) Xu G, Feng F, Liu Z, Liu S, Zheng G, Xiao S, Cai L, Yang X, Li G, Lian X, Guo M, Sun L, Yang J, Fan D, Lu Q and Zhang H: Prognosis and progression of ESQCC patients with perineural invasion. Sci Rep

30) Kuge K, Murakami G, Mizobuchi S, et al.: Submucosal territory of the direct lymphatic drainage system to the thoracic duct in the human esophagus. J Thorac Cardiovasc Surg 2003;125: 1343–1349

31) Saito H, Sato T, Miyazaki M: Extramural lymphatic drainage from the thoracic esophagus based on minute cadaveric dissections: Fundamentals for the sentinel node navigation surgeryfor the thoracic esophageal cancers. Surg Radiol Anat 2007;29: 531–542.

Tables Index:

Table 1: Comparison between CRM-R0 and CRM-R1* characteristics.

***CMR-R1: RCS definition (1mm or less)**

	For whole cohort (449 patients)			For ≥ pT3, pN+ve and NAT (192 patients)		
	CRM-R0 (n=253)	**CRM-R1 (n=196)**	**P-value**	**CRM-R0 (n=60)**	**CRM-R1 (n=132)**	**P-value**
Males	199 (78.7%)	162(82.7%)	0.29	50 (83%)	109(82%)	0.89
Age (years)-median	64.4	65.1	0.35	64.3	65.2	0.3
Charlson Comorbidity Index (CCI)	4.83	4.9	0.82	4.84	4.9	0.8
Type of Tumour						
AC	221(87.4%)	176(89.8%)	0.422	55(91.7%)	120(90.9%)	0.86
SCCC	32 (12.6%)	20 (10.2%)		5 (8.3%)	12 (9.1%)	
Tumour location						
Middle third	15 (5.9%)	11 (5.6%)	0.431	5 (8.3%)	8 (6.1%)	0.68
Lower third	191(75.5%)	145 (74%)		38(63.4%)	94 (71.2%)	
Junctional	47 (18.6%)	40 (20.4%)		17(28.3%)	30 (22.7%)	
Pathological T-stage			**0.000**			0.05
pT0	29 (11.5%)	0 (0%)		-	-	
pT1	95 (37.5%)	0 (0%)		-	-	
pT2	43 (17%)	6 (3%)		-	-	
pT3	82 (32.4%)	166 (84.6%)		58 (97%)	112 (85%)	
pT4	4 (1.6%)	24(12.3%)		2 (3%)	20 (15%)	
Pathological N-stage			**0.000**			**<0.001**
pT0	160(63.2%)	53(27%)		-	-	
pT1	56 (22.1%)	36(18.4%)		32 (53.3%)	34 (25.8%)	
pT2	29 (11.5%)	56(28.6%)		21 (35%)	49 (37.1%)	
pT3	8 (3.2%)	51 (26%)		7 (11.7%)	49 (37.1%)	
Total Lymph nodes			0.835			0.153
<15	30 (11.9%)	22 (11.2%)		2 (3%)	13 (9.8%)	
>15	223(88.1%)	174(88.8%)		58 (97%)	119 (90.2%)	
Neoadjuvant therapy	203 (80.2%)	180 (91.8%)	**0.001**			
Type of neoadjuvant treatment						
NAC	191 (94.1%)	175 (97.2%)	0.137	59 (98%)	129 (97.7%)	0.14
CRT	12 (5.9%)	5 (2.8%)		1 (2%)	3 (2.3%)	

Type of operation						
Hybrid (lap-assisted)	21 (8.3%)	8 (4%)	0.104	6 (10%)	3 (2%)	**0.01**
Minimally invasive	25 (9.9%)	17 (8.7%)		10(16.7%)	12 (9%)	
Open	207 (81.8%)	171 (87.3%)		44(73.3%)	117 (89%)	
Clavin-Dindo classification			0.1			0.82
≥ 3	47 (18.6%)	49 (25%)		15 (25%)	35 (26.5%)	
<3	206 (81.4%)	147 (75%)		45 (75%)	97 (73.5%)	

Table 2: Comparison between CRM-R1 (0mm) and CRM-R1 (0.1-1mm) characteristics.

	For whole CRM-R1 (185 patients)			For ≥ pT3, pN+ve and NAT (125 patients)		
	R1 (0 mm) (n=61)	**R1 (0.1-1mm) (n=124)**	**P-value**	**R1 (0 mm) (n=42)**	**R1 (0.1-1mm) (n=83)**	**P-value**
Males	49 (80.3%)	102 (82.3%)	0.75	34 (80.9%)	68 (81.9%)	0.89
Age (years)-median	64.8	65.5	0.35	64.6	65.4	0.3
Charlson Comorbidity Index (CCI)	5	5	0.82	4.8	4.9	0.8
Type of Tumour						
ADC	58 (95.1%)	108 (87.1%)	0.07	40 (95%)	73 (88%)	0.33
SQCC	3 (4.9%)	16 (12.9%)		2 (5%)	10 (12%)	
Tumour location						
Middle	2 (3.3%)	9 (7.3%)	0.27	2 (4.8%)	6 (7.2%)	0.68
Lower	49 (80.4%)	86 (69.4%)		30 (71.4 %)	58 (69.9%)	
Junctional	10 (16.3%)	29 (23.3%)		10 (23.8%)	19 (22.9%)	
Pathological T-stage			0.05			**0.02**
pT2	1 (1.6%)	3 (2.4%)		-	-	
pT3	47 (77%)	110 (88.7%)		31 (73.8%)	74 (89.1%)	
pT4	13 (21.3%)	11 (8.9%)		11 (26.2%)	9 (10.8%)	
Pathological N-stage			0.137			0.15
pT0	13 (21.3%)	37 (29.8%)		-	-	
pT1	9 (14.8%)	26 (20.9%)		8 (19%)	26 (31.3%)	
pT2	17 (27.9%)	35 (28.2%)		14 (33.3%)	31 (37.4%)	
pT3	22 (36.1%)	26 (20.9%)		20 (47.6%)	26 (31.3%)	
Total Lymph nodes			0.97			1.0
<15	7 (11.5%)	14 (11.3%)		4 (9.5%)	8 (9.6%)	
>15	54 (88.5%)	110 (88.7%)		38 (90.5%)	75 (90.4%)	
Neoadjuvant therapy	52 (85.2%)	118 (95.2%)	0.02			
Type of neoadjuvant treatment			0.51			0.5
NAC	51 (98.1%)	113 (95.7%)		42 (100%)	80 (96.4%)	
CRT	1 (1.6%)	5 (4.3%)		0 (0%)	3 (3.6%)	

Type of operation						
Hybrid (lap-assisted)	2 (3.3%)	4 (3.3%)	0.75	1 (2.4%)	2 (2%)	0.3
Minimally invasive	7 (11.5%)	10 (8.1%)		6 (14.3%)	6 (7%)	
Open	52 (85.2%)	110 (88.6%)		35(83.3%)	75 (91%)	
Clavin-Dindo classification			0.95			0.45
≥ 3	16 (26.6%)	33 (26.6%)		10 (23.8%)	25 (30.1%)	
<3	45 (73.8%)	91 (73.4%)		32 (76.2%)	58 (69.9%)	

Table 3: Characteristics of different involved CRM sites in CRM-RCP R1 cases.

Characteristics (n= 117)		Multiple (n=33)	Anterior (n=32)	Lateral (n=15)	Posterior (n=37)	p value
Gender	**Male**	27 (81.8%)	24 (75%)	12 (80%)	31 (83.8%)	0.89
	Female	6 (18.2%)	8 (25%)	3 (20%)	6 (16.2%)	
Pathological N-stage	**pN0**	6 (18.2%)	13 (40.6%)	5 (33.3%)	10 (27%)	0.44
	pN1	7 (21.2%)	5 (15.6%)	2 (13.3%)	9 (24.3%)	
	pN2	12 (36.4%)	7 (21.9%)	2 (13.3%)	6 (16.2%)	
	pN3	8 (24.2%)	7 (21.9%)	6 (40%)	12 (32.4%)	
Histology	**ADC**	30 (90.9%)	26 (81.3%)	13 (86.7%)	33 (89.2%)	0.677
	SQCC	3 (9.1%)	6 (18.8%)	2 (13.3%)	4 (10.8%)	
Type of neoadjuvant treatment	**NAC**	31 (93.9%)	24 (75%)	13 (86.7%)	34 (91.9%)	0.192
	CRT	2 (6%)	8 (25%)	2 (13.3%)	3 (8.1%)	
Total LNs	**< 15**	3 (9.1%)	3 (9.4%)	1 (6.7%)	5 (13.5%)	0.924
	> 15	30 (90.9%)	29 (90.6%)	14 (93.3%)	32 (86.5%)	
Recurrence	**Yes**	24 (73%)	22 (69%)	8 (53%)	22 (59.5%)	0.48
	No	9 (27%)	10 (31%)	7 (47%)	15 (40.5%)	
Pathological T-stage	**pT2**	0 (0%)	1 (3.1%)	1 (6.7%)	2 (5.4%)	0.12
	pT3	26 (78.8%)	29 (90.6%)	13 (86.6%)	21 (56.8%)	
	pT4	7 (21.2%)	2 (6.3%)	1 (6.7%)	14 (37.8%)	

Table 4: Cox regression analysis for Overall survival and Disease-free survival.

	Overall survival (OS)				Disease free survival (DFS)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender (Males/females)	0.8(0.58 - 1.15)	0.25			0.7(0.53-1.11)	0.17		
Age	0.9(0.983 - 1.014)	0.81			0.9(0.97-1.009)	0.35		
CCI > 3	0.9 (0.652 - 1.243)	0.52			1(0.779 - 1.514)	0.62		
Type of Tumour (ADC/SQCC)	1.2 (0.803 - 1.84)	0.35			1.37(0.86-2.18)	0.17		
Neoadjuvant treatment	1.5 (1.063 - 2.375)	**0.024**		**<0.01**	2.3(1.43-3.86)	0.001		**<0.01**
Type of surgery								
Hybrid	0.6(0.35-1.34)	0.16			0.54(0.25-1.15)	0.11		
Minimally invasive	1.2(0.83- 1.88)	0.11			1.19(0.76-1.85)	0.43		
Open								
Pathological T-stage								
pT1-2	0.22 (0.165 - 0.319)	**0.00**	1.6(0.15- 18.03)	0.68	0.19(0.13-0.28)	**0.00**	0.8(0.30-2.60)	0.82
pT3-4								
Pathological N-stage (p N-ve/ p N+ve)	0.27 (0.204 - 0.367)	**0.00**	0.9(0.35-2.30)	0.83	0.21(0.155 - 0.299)	**0.00**	0.7(0.48-1.04).	0.08
Total Lymph nodes (>vs <15 LNs)	1.13 (0.751 - 1.723)	0.54			1.32(0.833 - 2.096)	0.23		
CRM (R0 vs R1)	0.33(0.256 - 0.438)	**<0.001**		**<0.001**	0.31(0.237 - 0.421)	**<0.001**		**<0.001**
CRM – R1 (0mm vs 0.1-1mm)	1.42 (1.013 - 2.017)	**0.042**	0.42(0.17- 1.04)	0.062	1.58(1.096 - 2.293)	**0.01**	1.2(0.929 - 1.624)	0.14
Sites of CRM-R1 positive								0.12
Anterior	1.34 (0.77 -2.362)	0.59	1.6(0.7-3.9)	0.232	1.4(0.79-2.60)	0.2		
Lateral	0.81(0.35 - 1.89)	0.17	1.4(0.41-5)	0.561	0.955(0.42-2.14)	0.91		
Multiple	2 (1.157 - 3.473)	**0.008**	1.9(0.7-4.9)	0.164	1.85(1.03-3.31)	**0.03**		
Posterior								
Positive LN ratio*	1.039 (1.033 - 1.046)	**0.00**	1.03(1.00-1.05)	**0.01**	1.04(1.036 - 1.050)	**0.00**	1.01(1.001-1.03)	**0.03**

Positive LN ratio: (number of positive lymph nodes/ total number of lymph nodes%)

Figures Legend:

Figure 1: Kaplan Meier survival curves between CRM-R0 and CRM-R1:

(a,b) Overall survival (OS) curves for (a) whole cohort, (b) for patients with ≥ pT3, pN+ve and neoadjuvant treatment (NAT).

(c,d) Disease-free survival (DFS) curves for (c) whole cohort, (d) for patients with ≥ pT3, pN+ve and neoadjuvant treatment (NAT).

Figure 2: Kaplan Meier survival curves between CRM-R1 (0mm) and CRM-R1 (0.1-1mm):

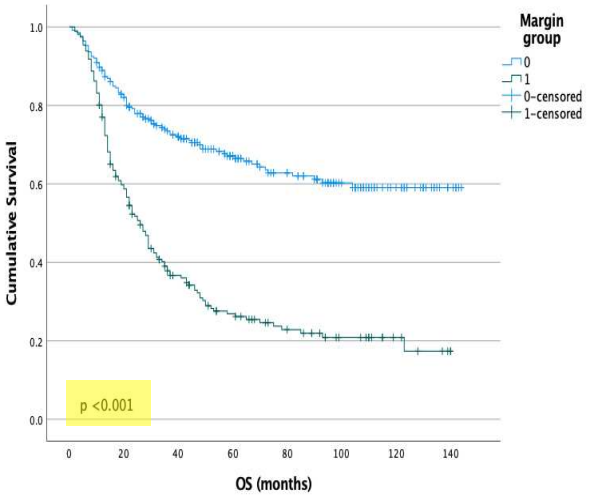
(a,b) Overall survival (OS) curves for (a) whole cohort, (b) for patients with ≥ pT3, pN+ve and neoadjuvant treatment (NAT).

(c,d) Disease-free survival (DFS) curves for (c) whole cohort, (d) for patients with ≥ pT3, pN+ve and neoadjuvant treatment (NAT).

Figure 3: Kaplan Meier survival curves for all margin sites in CRM-RCP R1 cases

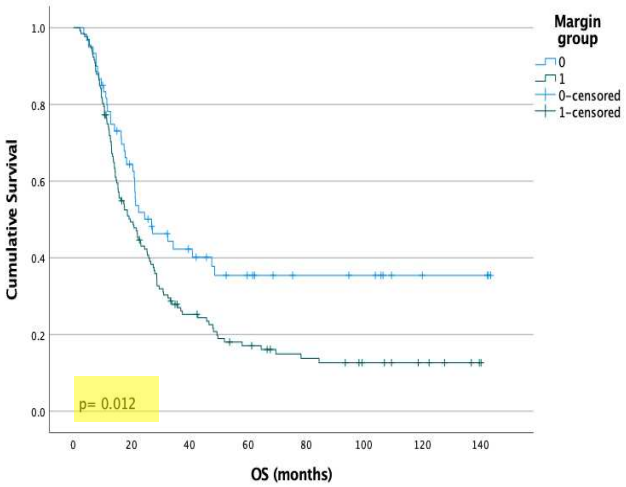
- Multiple-margin involvement versus single-margin involvement **(a)** Overall survival curves and **(b)** Disease-free survival curves
- Different CRM-RCP R1 margin sites (anterior, lateral and posterior) **(c)** Overall survival curves and **(d)** Disease-free survival curves

a) OS for whole cohort (CRM-R0 vs CRM-RCP R1)



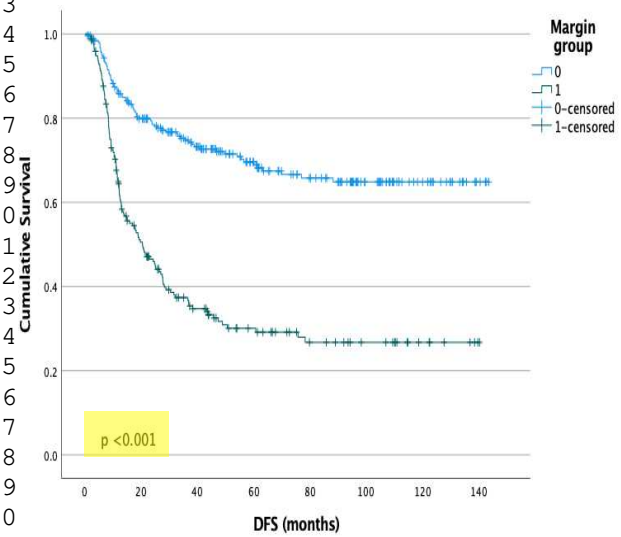
Median OS: R0 (not reached), R1 (26 months)

b) OS for patients with ≥ pT3, pN+ve and NAT (CRM-R0 vs CRM-RCP R1)



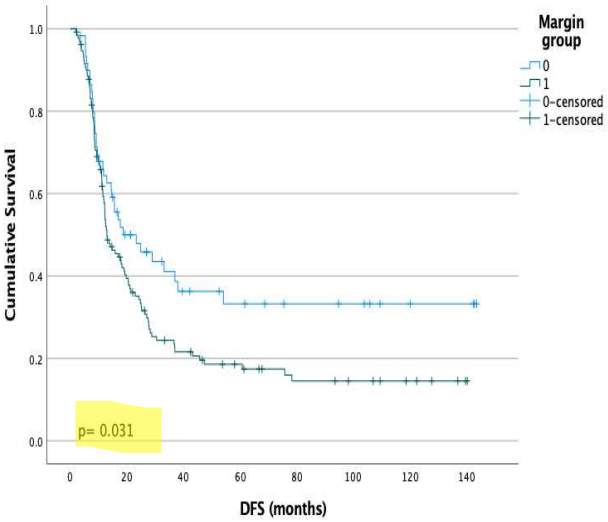
Median OS: R0 (26.8 months), R1 (19.5months)

c) DFS for whole cohort (CRM-R0 vs CRM-RCP R1)



Median DFS: R0 (not reached), R1 (20.4 months)

d) DFS for patients with ≥ pT3, pN+ve and NAT (CRM-R0 vs CRM-RCP R1)



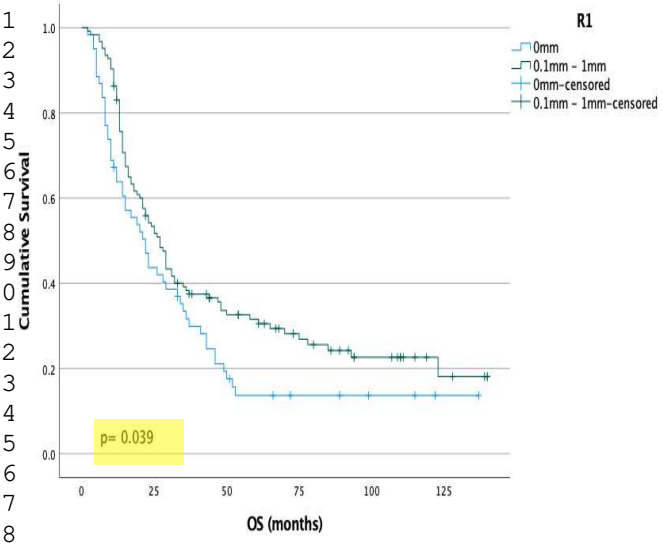
Median DFS: R0 (18.6 months), R1 (12.9months)

Figure 1: Kaplan Meier survival curves between CRM-R0 and CRM-RCP R1*:

- **Overall survival (OS) curves between CRM-R0 and CRM-RCP R1 for (a) whole cohort, (b) for patients with ≥ pT3, pN+ve and NAT.**
- **Disease-free survival (DFS) curves between CRM-R0 and CRM-RCP R1 for (c) whole cohort, (d) for patients with ≥ pT3, pN+ve and NAT.**

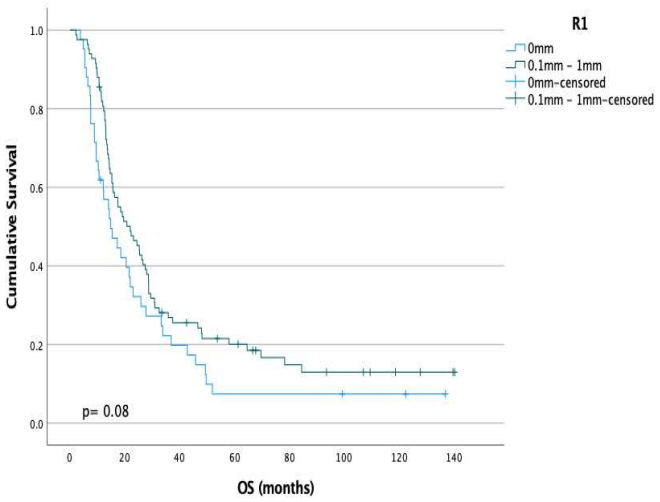
*CMR-R1: RCS definition (1mm or less)

a) OS for whole CRM-R1 cohort



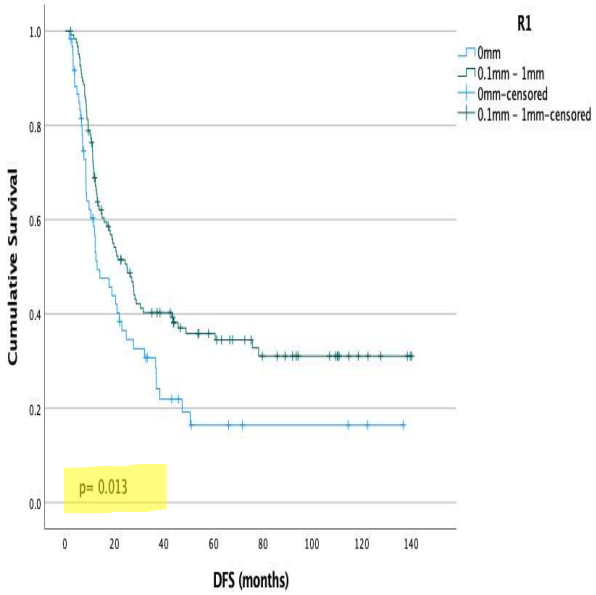
Median OS: R1-0mm (22 months), R1-(0.1-1mm) (27 months)

b) OS for CRM-R1 patients with ≥ pT3, pN+ve and NAT



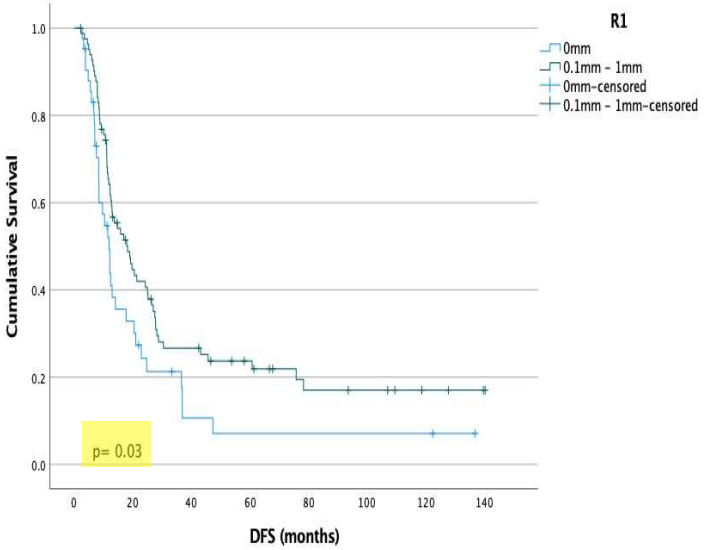
Median OS: R1-0mm (14.8 months), R1 0.1-1mm (21.9months)

c) DFS for whole CRM-R1 cohort



Median DFS: R1-0mm (12.9 months), R1 0.1-1mm (25 months)

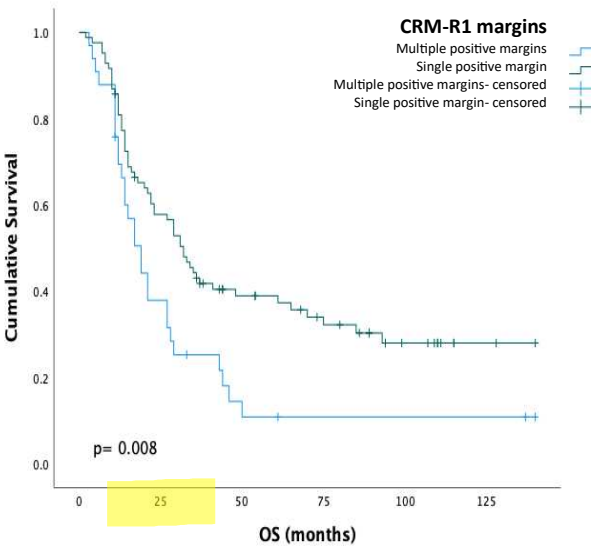
d) DFS for CRM-R1 patients with ≥ pT3, pN+ve and NAT



Median DFS: R1-0mm (11.8 months), R1 0.1-1mm (18.1months)

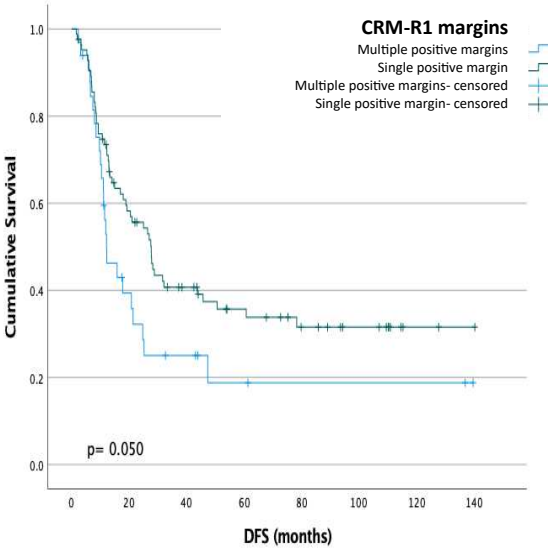
Figure 2: Kaplan Meier survival curves between CRM-R1 (0mm) and CRM-R1 (0.1-1mm):
-Overall survival (OS) curves between CRM-R1 (0mm) and CRM-R1 (0.1-1mm) for (a) whole cohort, (b) for patients with ≥ pT3, pN+ve and NAT.
-Disease-free survival (DFS) curves between CRM-R1 (0mm) and CRM-R1 (0.1-1mm) for (c) whole cohort, (d) for patients with ≥ pT3, pN+ve and NAT.

(a)



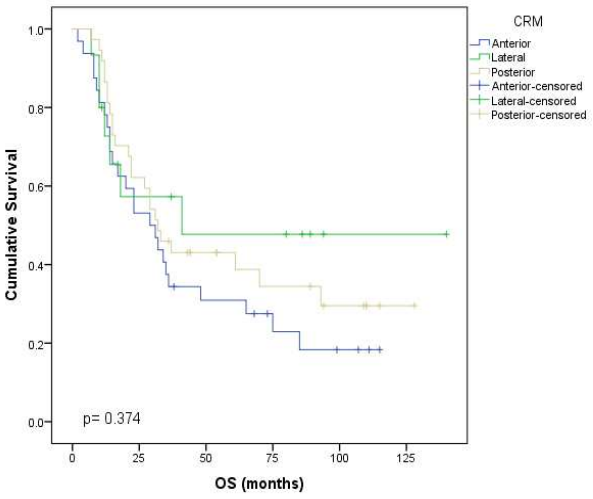
Median OS: Multiple positive margins (19 months), single positive margin (32 months).

(b)



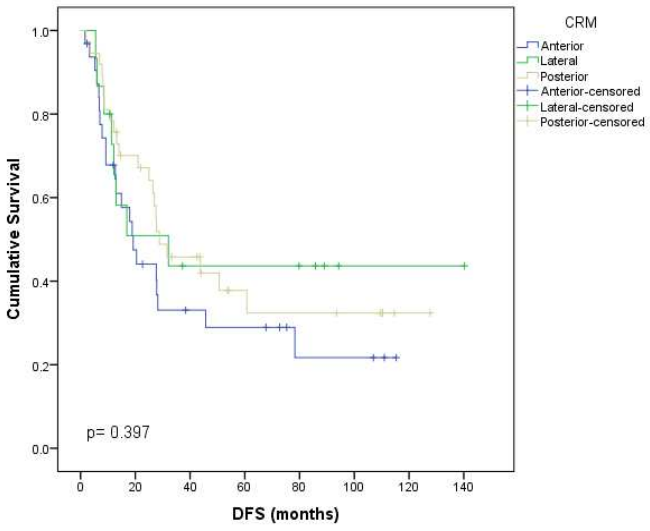
Median DFS: Multiple margins 12.1 months, single margin 27.6 months

(C)



Median DFS: Anterior (19.2 months), lateral (32.1 months), posterior (28.7 months)

(d)



Median OS: Anterior (29 months), lateral (41 months), posterior (32 months)

Figure 3: Kaplan Meier survival curves for all margin sites in CRM-RCP R1 cases

- Multiple-margin involvement versus single-margin involvement (a) Overall survival curves and (b) Disease-free survival curves

- Different CRM-RCP R1 margin sites (anterior, lateral and posterior) (c) Overall survival curves and (d) Disease-free survival curves