Original Article

The prognostic role of positive circumferential resection margins after curative intent surgery for locally advanced esophageal adenocarcinoma

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Background: Controversy exists regarding the prognostic role of positive circumferential resection margins (CRMs) after resection of esophageal adenocarcinoma (ADC). This study aims to evaluate the influence of positive CRM on disease-free survival (DFS) and overall survival (OS) in esophageal ADC.

Methods: A retrospective review of a prospective esophageal cancer database from a tertiary center was performed. Patients with curative-intent resections of locally advanced esophageal ADC (T3/4, any N) were included. Two definitions of CRM were compared: College of American Pathologists (CAP) (cancer cells at margin) and Royal College of Pathologists (RCP) (cancer cells ≤1 mm from margin). Primary outcomes were DFS and OS.

Results: One hundred and sixty-seven patients met inclusion criteria, 134 were male, and mean age was 65.8. Seventy-six percent received neoadjuvant therapy. A positive CRM was found in 6.0% by CAP and 23.4% by RCP definitions. Mean follow-up was 22 months (range, 1–119), and 75/167 (44.9%) developed recurrence, of which 7 (4.2%) were local. Sixty-seven/167 (40.1%) patients died during the follow-up period. CRM status, irrespective of definition, did not impact DFS or OS; neoadjuvant therapy and lymph-node positivity were the only significant factors on multivariate analyses.

Conclusions: Positive CRM is not a prognostic marker for worse DFS or OS in esophageal ADC regardless of margin definition.

Keywords: Esophageal adenocarcinoma (esophageal ADC); circumferential resection margins (CRMs); disease-free survival (DSF); overall survival (OS)

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Introduction

The use of the circumferential resection margin (CRM) in esophageal carcinoma stems from rectal carcinoma literature which was extrapolated to esophageal cancers (1). It has since become a standard of pathological reporting and a prognostic marker over the last 20 years. However, the usefulness of CRM as a prognostic marker in locally advanced esophageal adenocarcinoma (ADC) has been a

matter of significant debate. Discrepancies in pathological definitions between societies have further muddied the waters, with the College of American Pathologists (CAP) defining a positive CRM as tumor cells at the inked margin (2) and the Royal College of Pathologists (RCP) in the United Kingdom defining it as tumor cells at or within 1 mm of the margin (3).

In an attempt to elucidate this, many retrospective studies evaluating disease-free survival (DFS) and overall survival (OS) in patients with a positive CRM (1,4-13). However, this literature has been extremely heterogeneous, with many including both esophageal squamous cell carcinoma (SCC) and ADC. It is well accepted that the tumor biology of esophageal SCC and ADC are diverse, and that the natural history of these diseases differ greatly (14). These entities should therefore be studied in isolation. Other studies have included early-stage esophageal cancers (T1–T2), in which a positive CRM is more reflective of an inadequate surgical resection rather than a prognostic marker.

A meta-analysis performed in 2019 found that both CAP and RCP positive CRMs were associated with poorer prognosis; however, the authors caution that many studies pooled data from both SCC and ADC without reporting the underlying histology (15). They further warn that many papers included T2 tumors, which may falsely inflate the prognostic role of a positive CRM, and the authors were also not able to report on the role of lymph node status on prognosis given the low rates of reporting in the included studies (15). In contrast, a previous meta-analysis had concluded that lymph node positivity negated the impact of a positive CRM, at least on 3-year survival (16). Therefore, high-quality data regarding the prognostic role of a positive CRM is missing. In this study, we aim to evaluate the role of CRM positivity by either CAP or RCP definitions on DFS and OS in locally advanced esophageal ADC. We present the following article in accordance with the STROBE reporting checklist (available at https://aoe.amegroups.com/article/view/10.21037/aoe-20-94/rc).

Methods

Study population

A retrospective analysis of a prospectively maintained esophageal cancer database at a single, referral-based academic center was performed. The study population included patients with locally advanced (T3 and T4) esophageal ADC who underwent curative-intent esophagectomy between 2006 and 2016. Patients who had post-operative survival of under 3 months, who underwent palliative surgery, who underwent surgery for recurrent disease, or who had stage IV disease at the time of surgery were all excluded. Further excluded were those who had a positive proximal or distal resection margin (see *Figure 1*). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics review board of the McGill University Health Center (ID number 2020-5850) and individual consent for this retrospective analysis was waived, with the Director of Professional Services providing consent in lieu of individual patient consent.

Outcomes and variable definitions

Electronic medical records were used to retrospectively collect demographic, clinical, pathologic, and radiologic data, as well as data specific to each patient's operation These included age at the time of surgery, pre-operative clinical staging information, operative information, final pathological information, information about neoadjuvant and adjuvant locoregional and systemic treatments, and post-operative complications and recurrences. Patients' final pathological stage was uniformized to follow the 8th edition of the American Joint Committee on Cancer staging manual [2017] (17).

We then employed and compared two definitions of CRM. The CAP defines an R1 resection as malignant cells at the margin (CRM =0 mm) whereas the RCP defines it as malignant cells at or within 1 mm of the margin (CRM ≤1 mm) (2,3). Patients for whom the CRM was qualitatively described as "negative" or "uninvolved" by the pathologist were considered to have both CAP and RCP R0 resections.

Follow-up consisted of computed tomography scans every 3 months and upper endoscopy every 6 months for the first 2 years following surgery, then yearly. The primary outcomes of interest were DFS and OS.

Statistical analysis

Data are represented as n (%) for categorical variables and mean [standard deviation (SD)] or median [interquartile range (IQR)] for continuous variables. Univariate analyses were performed using student *t*-test to compare means and two-sample Wilcoxon rank-sum (Mann-Whitney) test for medians of continuous variables. Two-sided Fisher exact and chi-square tests were used for categorical variables.

Adjusting for confounders, multiple regression analyses were performed to identify independent predictors of OS and DFS. To compare CAP positive and RCP positive patients, Kaplan-Meier estimator and log-rank test were used to estimate survival functions for both OS and DFS. A P value of P<0.05 was used to reject the null hypothesis and determine statistical significance. All statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX, USA).

Results

Patients

Patient characteristics are summarized in *Table 1*. Of 517 patients who underwent esophagectomies from 2006 to 2016, 167 patients met inclusion criteria (see *Figure 1*). 134 patients (80.2%) were male, and the mean age at the time of surgery was 65.8 (range, 26–85, SD: 10.7). Most patients had Siewert gastroesophageal junction tumors [128 patients

Table 1 Baseline characteristics and pathological data presented as n (%) unless otherwise specified

Variables	CAP			Total	RCP		
	Negative	Positive	P value		Negative	Positive	P value
Total	157 (94.0)	10 (6.0)		167	128 (76.6)	39 (23.4)	
Male sex	125 (76.5)	9 (90.0)	0.424	134 (80.2)	103 (80.5)	31(79.5)	0.893
Mean age, years (SD)	65.9 (10.8)	65.8 (8.9)	0.989	65.8 (10.7)	65.0 (10.8)	68.6 (10.0)	0.064
Location			0.001				0.056
EGJ Siewert I	23 (14.8)	1 (10.0)		24 (14.6)	18 (14.2)	6 (15.8)	
EGJ Siewert II	55 (35.5)	6 (60.0)		61 (37.0)	44 (34.7)	17 (44.7)	
EGJ Siewert III	41 (26.5)	2 (20.0)		43 (26.1)	39 (30.7)	4 (10.5)	
Distal thoracic	36 (23.2)	0 (0.0)		26 (21.8)	26 (20.5)	10 (26.3)	
Proximal thoracic	0 (0.0)	1 (10.0)		1 (0.61)	0 (0.0)	1 (2.6)	
Neoadjuvant therapy			0.145				0.046
None	35 (22.3)	5 (50.0)		40 (24.0)	26 (20.3)	14 (35.9)	
Chemotherapy	115 (73.3)	4 (40.0)		119 (71.7)	97 (75.8)	22 (56.4)	
Radiotherapy	1 (0.6)	0 (0.0)		1 (0.6)	0 (0.0)	1 (2.6)	
Chemoradiotherapy	6 (3.8)	1 (10.0)		7 (4.2)	5 (3.9)	2 (5.1)	
Adjuvant therapy			<0.001				0.251
None	62 (45.3)	1 (10.0)		63 (42.9)	47 (41.6)	16 (47.1)	
Chemotherapy	57 (41.6)	1 (10.0)		58 (39.5)	49 (43.4)	9 (23.5)	
Radiotherapy	3 (2.2)	2 (20.0)		5 (3.4)	3 (2.7)	2 (5.9)	
Chemoradiotherapy	15 (11.0)	6 (60.0)		21 (14.3)	14 (12.4)	7 (20.6)	
Procedure			0.637				0.079
Ivor-Lewis	82 (52.2)	6 (60.0)		88 (52.7)	65 (50.8)	23 (59.0)	
LTA	39 (24.8)	2 (20.0)		41 (24.6)	35 (27.3)	6 (15.4)	
Extended total gastrectomy	11 (7.0)	0 (0.0)		11 (6.6)	11 (8.6)	0 (0.0)	
Three holes	15 (9.6)	2 (20.0)		17 (10.2)	11 (8.6)	6 (15.4)	
Transhiatal	10 (6.4)	0 (0.0)		17 (10.2)	6 (4.7)	4 (10.3)	

Table 1 (*continued*)

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Variables	CAP			Total	RCP		
	Negative	Positive	P value		Negative	Positive	P value
Clinical T stage			0.061				0.489
N/A	34 (21.7)	0 (0.0)		34 (20.4)	24 (18.8)	10 (25.6)	
T1	4 (2.6)	0 (0.0)		4 (2.4)	2 (1.6)	2 (5.1)	
T2	5 (3.2)	2 (20.0)		7 (4.2)	5 (3.9)	2 (5.1)	
T3	112 (71.3)	8 (80.0)		120 (71.9)	95 (74.2)	25 (64.1)	
T4	2 (1.3)	0 (0.0)		2 (1.2)	2 (1.6)	0 (0.0)	
Clinical N stage			0.644				0.205
N/A	35 (22.3)	1 (10.0)		36 (21.6)	24 (18.8)	12 (30.8)	
Uninvolved	37 (23.6)	3 (30.0)		40 (24.0)	30 (23.4)	10 (25.6)	
Involved	85 (54.1)	6 (60.0)		91 (54.5)	74 (57.8)	17 (43.6)	
(y)pTNM			0.907				0.389
IIA	2 (1.3)	0 (0.0)		2 (1.2)	2 (1.6)	0 (0.0)	
IIB	24 (15.3)	1 (10.0)		25 (15.0)	21 (16.4)	4 (10.3)	
IIIB	68 (433.3)	4 (40.0)		72 (43.1)	57 (44.5)	15 (38.5)	
IVA	63 (40.1)	5 (50.0)		68 (40.7)	48 (37.5)	20 (51.3)	
Pathologic T stage			0.022				0.813
2	1 (0.6)	0 (0.0)		1 (0.6)	1 (0.8)	0 (0.0)	
3	134 (85.4)	5 (50.0)		139 (83.3)	105 (82.0)	34 (87.2)	
4a	21 (13.4)	5 (50.0)		26 (15.6)	21 (16.4)	5 (12.8)	
4b	1 (0.6)	0 (0.0)		1 (0.6)	1 (0.8)	0 (0.0)	
Pathologic N stage			0.789				0.138
0	27 (17.2)	2 (20.0)		29 (17.4)	24 (18.8)	5 (12.8)	
1	30 (19.1)	1 (10.0)		31 (18.6)	23 (18.0)	8 (20.5)	
2	42 (26.8)	2 (20.0)		44 (26.4)	38 (29.7)	6 (15.4)	
3	58 (36.9)	5 (50.0)		63 (37.7)	43 (33.6)	20 (51.3)	
Recurrence			0.689				0.568
None	86 (54.8)	6 (60.0)		92 (55.1)	73 (57.0)	19 (48.7)	
Local	6 (3.8)	1 (10.0)		7 (4.2)	4 (3.1)	3 (7.7)	
Regional	7 (4.5)	0 (0.0)		7 (4.2)	5 (3.9)	2 (5.1)	
Distant	58 (36.9)	3 (30.0)		61 (36.5)	46 (35.9)	15 (38.5)	

CAP, College of American Pathologists; RCP, Royal College of Pathologists; SD, standard deviation; EGJ, esophagogastric junction; LTA, left thoracoabdominal.

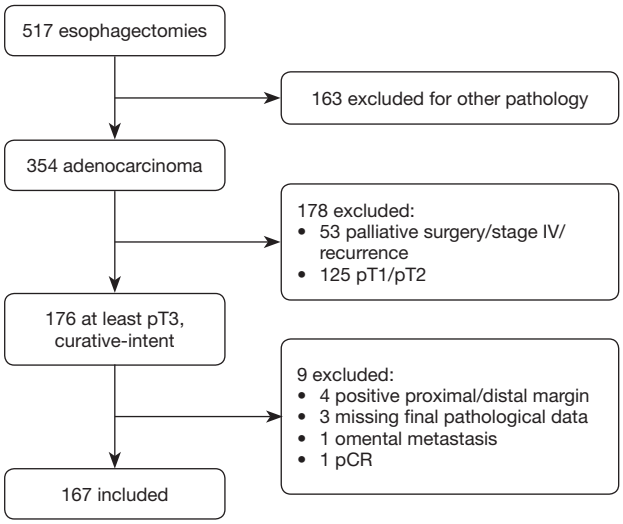

Figure 1 Flowchart of inclusion/exclusion of patients. pCR, pathological complete response.

(76.7%)], of which the most common subtype was Siewert II (37.0%). The clinical T stage for 120 patients (71.9%) was T3, with 54.5% of patients having clinically suspicious lymph nodes on imaging. The majority of patients (52.7%) underwent an Ivor-Lewis esophagectomy, with most commonly grade 3 (59.9%), T3 (83.2%), N3 (37.7%) disease. 76.1% patients received neoadjuvant therapy, of which 119 (71.3%) received neoadjuvant chemotherapy. Regarding adjuvant therapy, there was no data available for 20 (12.0%) patients. Of the remaining patients for whom data was available, 63 (42.9%) did not receive adjuvant therapy, and 21 (14.3%) received combination adjuvant chemoradiotherapy.

CRM status

Of the 167 patients, 27 (16.2%) had a CRM that was described as "negative" or "uninvolved" by the pathologist without a clear distance reported from the CRM. These were assigned the predetermined status of R0 resection according to both CAP and RCP definitions of CRM. Using the CAP definition (CRM =0 mm), 10 patients (6.0%) had an R1 resection for the CRM. According to the RCP definition (CRM ≤1 mm), 39 patients (23.4%) had an R1 resection.

Prognosis

Univariate and multivariate evaluation of DFS are summarized in *Table 2*. Mean follow-up for the cohort was 22 (range, 1–119) months. Of 166 patients, 75 (44.9%) developed a recurrence during the follow-up period, of which most (81.3%) developed distant recurrence. On univariate regression analysis, positive CRM by neither CAP nor RCP definitions were associated with increased risk of recurrence [hazard ratios (HRs): 1.56 (P=0.39) and 1.26 (P=0.40), respectively]. The only variable which improved DFS on univariate analysis was use of neoadjuvant chemotherapy (HR: 0.57, P=0.03). Factors which negatively impacted DFS were use of adjuvant radiotherapy alone (HR: 4.08, P=0.02) and a higher pathological N-stage, with all positive N-stages conferring an increased risk of recurrence, but N3 being the worst prognostic marker (HR: 9.15, P<0.001). On multivariate analysis, neither CAP nor RCP CRM positive status affected DFS nor OS. Only pathological N-stage conferred an increased risk of recurrence, with N3 disease being associated with the worst DFS (HR: 8.69, P<0.001 and HR: 8.41, P=0.001 for CAP and RCP, respectively).

Data regarding univariate and multivariate analyses for OS are summarized in *Table 3*. Of the total number of patients, 67 (40.1%) died during the follow-up period. On univariate regression analysis, positive CRM by neither CAP nor RCP definitions were associated with increased risk of death (HR: 1.56, P=0.39 and HR: 1.20, P=0.52, respectively). Here again, use of neoadjuvant chemotherapy predicted a better OS (HR: 0.48, P=0.005), as did adjuvant chemotherapy (HR: 0.53, P=0.04). Factors which predicted a worse OS were use of extended total gastrectomy (HR: 2.19, P=0.045) and pathological N-stage N3 (HR: 3.21, P=0.009). On multivariate analysis, N3 was also associated with a worse OS (HR: 2.82, P=0.028 and HR: 2.83, P=0.029 for CAP and RCP, respectively). Use of neoadjuvant chemotherapy was associated with a slightly improved OS (HR: 0.58, P=0.054 and HR: 0.57, P=0.047 for CAP and RCP, respectively). On Kaplan-Meier survival analysis for both DFS and OS for CAP and RCP, DFS and OS did not significantly differ between patients with a positive CRM and those with a negative CRM for either definition (*Figures 2,3*).

Discussion

Interpreting the significance of a positive CRM in esophageal ADC remains challenging given the heterogeneity in the data, the lack of prospective trials, and conflicting meta-analysis results (15,16,18). A further

Table 2 Univariate and multivariate Cox proportional analysis for DFS

Variables	Univariate			Multivariate					
				CAP			RCP		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.97–1.01	0.229	0.98	0.96–1.01	0.147	0.98	0.96–1.00	0.126
Male sex	0.77	0.44–1.32	0.340	0.99	0.55–1.78	0.975	1.03	0.58–1.84	0.925
ASA 3	0.62	0.27–1.41	0.256						
Neoadjuvant therapy				0.75	0.43–1.32	0.319	0.73	0.42–1.29	0.283
Chemotherapy	0.57	0.34–0.95	0.031						
Radiotherapy	1.38	0.18–10.31	0.754						
Chemoradiotherapy	0.95	0.33–2.78	0.931						
Adjuvant therapy				0.82	0.46–1.48	0.515	0.88	0.50–1.55	0.654
Chemotherapy	0.72	0.41–1.27	0.260						
Radiotherapy	4.08	1.20–13.82	0.024						
Chemoradiotherapy	1.74	0.91–3.32	0.094						
pN									
N1	4.09	1.16–14.38	0.028	4.04	1.13–14.49	0.032	3.84	1.06–13.88	0.040
N2	4.43	1.31–15.00	0.017	4.43	1.25–15.67	0.021	4.28	1.22–15.08	0.024
N3	9.15	2.82–29.70	<0.001	8.69	2.62–28.81	<0.001	8.41	2.53–27.93	0.001
CRM CAP	1.56	0.56–4.30	0.392	1.61	0.55–4.72	0.388			
CRM RCP	1.26	0.74–2.12	0.395				1.25	0.70–2.24	0.450

DFS, disease-free survival; CAP, College of American Pathologists; RCP, Royal College of Pathologists; HR, hazard ratio; CI, confidence interval; CRM, circumferential resection margin.

challenge is the lack of clarity in what defines a positive CRM (2,3). In this study, we aimed to evaluate the prognostic implication of a positive CRM by either CAP or RCP definitions on DFS and OS in locally advanced esophageal ADC.

Of the 167 patients in this cohort, most had negative CRMs by both definitions. However, in those that did have positive margins, neither CAP nor RCP definitions of positive CRM affected DFS or OS on univariate nor multivariate analyses, nor was there any relationship found between survival and CRM on Kaplan-Meier survival analyses. The main prognostic factors for both measurements of survival were nodal status and use of neoadjuvant chemotherapy.

Use of neoadjuvant chemotherapy is a relatively recent development in the care of esophageal ADC, but one that has demonstrated a significant impact on survival in this disease (19). Most evaluations of the role of the CRM in esophageal ADC failed to control for administration of neoadjuvant therapies, and our findings supporting that CRM is not an independent risk factor when controlling for administration of such therapies. This echoes the findings of some studies which controlled for this factor (8,20), though the data remain quite heterogeneous in this regard (21).

In our study, increasing N-status was associated with the poorest DFS and OS. Previous research has demonstrated that more aggressive tumor characteristics such as higher grade and more advanced T-stage are independent predictors for increased numbers of involved lymph nodes, and this is thought to be a consequence of the more aggressive biology of the disease (22). This association holds especially true in esophageal ADC, further highlighting biological differences in the metastatic patterns of SCC and ADC (22). Other studies which controlled for lymph node burden also found that CRM had no impact on survival as the pathological N-stage increased (23,24).

Table 3 Univariate and multivariate Cox proportional analysis for OS

Variables	Univariate			Multivariate					
				CAP			RCP		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.01	0.99–1.03	0.554	0.99	0.97–1.02	0.485	0.99	0.97–1.02	0.591
Male sex	0.74	0.42–1.31	0.306	0.92	0.49–1.71	0.789	0.96	0.52–1.77	0.884
ASA 3	1.31	0.52–3.29	0.563						
Neoadjuvant therapy				0.58	0.33–1.01	0.054	0.57	0.33–0.99	0.047
Chemotherapy	0.48	0.29–0.80	0.005						
Radiotherapy	1.47	0.20–10.96	0.708						
Chemoradiotherapy	0.42	0.10–1.78	0.239						
Adjuvant therapy				0.56	0.30–1.05	0.073	0.61	0.33–1.11	0.107
Chemotherapy	0.53	0.29–0.95	0.035						
Radiotherapy	2.01	0.47–8.66	0.349						
Chemoradiotherapy	1.15	0.59–2.24	0.680						
pN									
N1	1.52	0.56–4.12	0.410	1.52	0.54–4.26	0.429	1.54	0.54–4.39	0.415
N2	1.90	0.75–4.80	0.174	2.00	0.74–5.40	0.172	1.90	0.71–5.11	0.203
N3	3.21	1.34–7.71	0.009	2.82	1.12–7.11	0.028	2.83	1.11–7.18	0.029
CRM CAP	1.56	0.56–4.32	0.390	1.74	0.58–5.24	0.328			
CRM RCP	1.20	0.69–2.08	0.520				0.96	0.52–1.78	0.897

OS, overall survival; CAP, College of American Pathologists; RCP, Royal College of Pathologists; HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; CRM, circumferential resection margin.

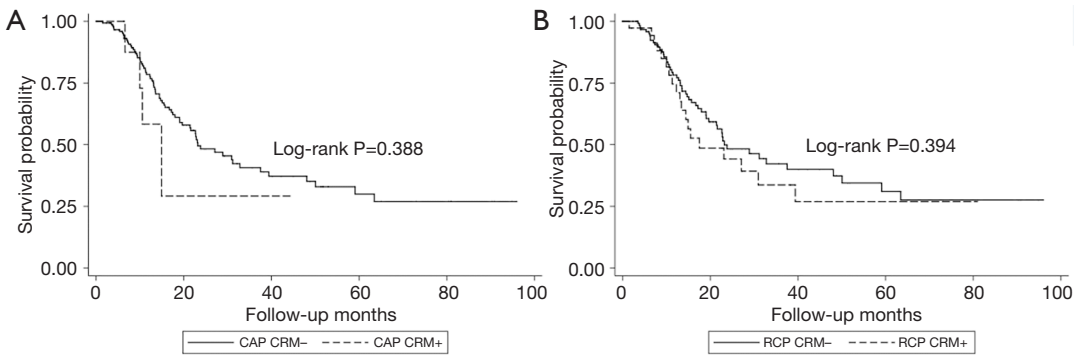

Figure 2 Kaplan-Meier survival curves of DFS for positive CRMs based on CAP (A) and RCP (B) definitions. DFS, disease-free survival; CRM, circumferential resection margin; CAP, College of American Pathologists; RCP, Royal College of Pathologists.

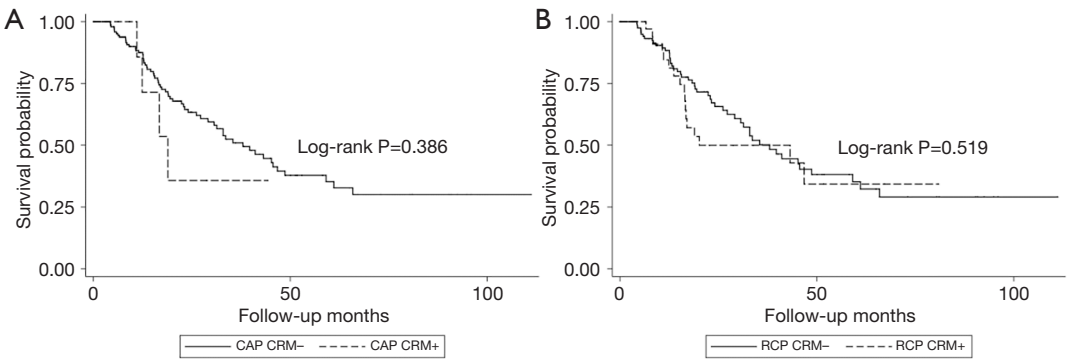

Figure 3 Kaplan-Meier survival curves of OS for positive CRMs based on CAP (A) and RCP (B) definitions. OS overall survival; CRM, circumferential resection margin; CAP, College of American Pathologists; RCP, Royal College of Pathologists.

Additionally, most of the patients in our cohort who recurred during the follow-up period did so distantly. This finding is in keeping with data demonstrating that patients with eight or more involved lymph nodes almost all recur systemically at 5 years (25). This also supports the concept of early dissemination of this disease and that local recurrence is not the main cause of cancer-related death. Thus, the crux of treatment for esophageal ADC remains systemic therapy, with local factors such as CRM and use of isolated adjuvant radiotherapy being less important in controlling the disease (26). The ongoing TIGER study aims to evaluate the prognostic implication of the distribution of lymph node metastases in esophageal carcinoma. This study should provide a deeper understanding of the optimal surgical strategy for patients with early disseminated disease (27).

Finally, most of the previous retrospective studies have evaluated CRM in esophageal SCC and ADC by pooling and analyzing these two diseases together. It has long been known that SCC and ADC present in distinct populations, with specific risk factors, and have different natural histories (14,28). Most notably, recurrence patterns between SCC and ADC differ greatly; SCC tends to recur regionally and less frequently with high pathological complete response rates, whereas ADC typically recurs distantly and responds more poorly to neoadjuvant therapies (29). This further highlights the importance of systemic therapies in the treatment of this disease. As next-generation sequencing techniques have begun to further highlight, esophageal SCC and ADC are two separate entities and should be studied as such in the future (30).

Strengths of this work include its homogeneous patient population with similar disease biology and T-stage. Restaging of all patients according to the most recent edition of the AJCC staging manual is also a strength of this study, as it allows for uniformization of the examined pathological stages. Limitations of this paper are its retrospective nature, the small number of patients, and the heterogeneity in the neoadjuvant and adjuvant therapies received. As patients with esophageal ADC increasingly receive neoadjuvant chemotherapy, downstaging will become more common and will be associated with better outcomes (31). In addition, a specific CRM distance was not noted in all pathological reports; however, these patients were considered to have an R0 resection according to both definitions.

Conclusions

In conclusion, this study demonstrates that a positive CRM in esophageal ADC by either CAP or RCP has no impact on DFS nor OS, while use of neoadjuvant chemotherapy and pathological N-stage significantly do. This is consistent with the biology and recurrence patterns of esophageal ADC, and may be generalizable to this patient population at other institutions.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://aoe.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aoe.amegroups.com/article/view/10.21037/aoe-20-94/coif). LF serves as an unpaid editorial board member of *Annals of Esophagus* from April 2020 to March 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics review board of the McGill University Health Center (ID number 2020-5850) and individual consent for this retrospective analysis was waived, with the Director of Professional Services providing consent in lieu of individual patient consent.

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