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Prognostic significance of positive circumferential resection margin post neoadjuvant chemotherapy in patients with esophageal or gastro-esophageal junction adenocarcinoma

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ABSTRACT

Background: The aim of the present study was to assess the prognosis of patients with esophageal or gastroesophageal junction (E/GEJ) adenocarcinoma extending beyond the muscularis propria layer (≥ypT3) and positive circumferential resection margin (CRM), post neoadjuvant chemotherapy.
Methods: 177 patients were retrospectively studied. The majority (94.9%) received ECX (epirubicin, cisplatin, capecitabine), and all had clear proximal/distal resection margins. CRM was defined as positive (CRM+) when it was directly infiltrated (infiltrated CRM) or when tumor cells were detected within 1 mm from CRM (close CRM) and as negative (CRM-) when tumor cells were found in a distance > 1 mm from CRM.
Results: CRM+ was found in 83 patients (46.9%). Of them, infiltrated CRM was recorded in 36 (20.3%) and close CRM in 47 (26.6%). Adjuvant chemotherapy was administered to 132 patients (74.6%). Lymphovascular invasion and primary site in the lower esophagus were independently associated with higher risk of CRM+. Patients with infiltrated CRM, compared to those with close CRM and those CRM-, had the shortest median time-to-relapse (11.4 vs. 15.6 vs. 22.1 months, respectively, $p = 0.005$) and overall survival (18.7 vs. 23.1 vs. 38.8 months, respectively, $p = 0.001$). However, CRM status was not an independent predictor of poor outcome. Symptomatic isolated locoregional recurrences were rare in both CRM+ and CRM-patients (4/56 [7.1%] vs. 5/52 [9.6%], $p = 0.736$), as well as in infiltrated vs. non-infiltrated CRM (CRM- and close CRM) (0/26 [0%] vs. 9/82 [11.0%], $p = 0.110$).
Conclusion: Although CRM status is associated with poor outcome, it does not represent an independent prognostic factor. The status of CRM did not significantly influence the pattern of cancer relapse.

Introduction

Esophageal cancer is the 9th most common cancer and a leading cause of cancer-related death worldwide [1]. Despite the advances in its management, 5-year survival remains below 20% [2]. The main histological subtypes of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma. These two histological subtypes have different anatomical distributions, with SCC usually involving the upper and middle esophagus, while adenocarcinoma involving the mainly the lower esophagus and gastroesophageal junction (E/GEJ). SCC is more common in Asia compared to adenocarcinoma which is more prevalent in Western counties. Moreover, recent evidence suggests that adenocarcinoma has a molecular profile similar to a subtype of gastric adenocarcinoma

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with chromosomal instability [3]. As such, adenocarcinoma should be studied separately from SCC of the esophagus [1].

Surgery represents the cornerstone of curative treatment, while the introduction of neoadjuvant/adjuvant chemotherapy and chemoradiotherapy has improved the outcome of this disease [4,5]. It is widely accepted that SCC is more radiosensitive than adenocarcinoma [5], thus current treatment guidelines present both neoadjuvant chemoradiotherapy as well as perioperative chemotherapy as treatment options for locally advanced E/GEJ adenocarcinoma [6,7]. In the UK perioperative chemotherapy is considered as a standard of care.

Tumor-free circumferential resection margin (CRM) is considered one of the most important components of optimal surgical treatment of E/GEJ cancer. Two definitions of CRM positivity are currently in use; the Royal College of Pathologists (RCPath) defines it as the presence of tumor cells within 1 mm from the margin [8], whilst the College of American Pathologists (CAP) defines it as tumor presence at the cut edge of the resection margin [9]). The prognostic significance of positive CRM has long been debated, most of the studies showing an adverse impact in cancer outcome [7]. Nevertheless, the majority of these studies include both adenocarcinoma and SCC cases along with diverse treatment strategies, making it difficult to draw any conclusions [7]. Therefore, the prognostic impact of positive CRM in patients receiving perioperative chemotherapy is largely unknown.

The aim of this study was to evaluate the significance of positive CRM in a homogeneous cohort of patients with E/GEJ adenocarcinoma treated with similar perioperative chemotherapy.

Methods

This was a retrospective study of consecutive patients treated at a central tertiary referral centre. The inclusion criteria were histological confirmation of adenocarcinoma of the lower esophagus or Siewert type I-II of the GEJ. Patients must have received at least one cycle (maximum 3) of neoadjuvant chemotherapy followed by tumor resection with curative intent. The mainstay of neoadjuvant chemotherapy regimen used was ECX (epirubicin, cisplatin, capecitabine). Patients with renal dysfunction (glomerular filtration rate < 40 ml/min) received EOX (epirubicin, oxaliplatin, capecitabine) or ECarboX (epirubicin, carboplatin, capecitabine). Patients with cardiac dysfunction (left ventricular ejection fraction < 50%) were treated with MCX (mitomycin, cisplatin, capecitabine), while patients who wanted to avoid alopecia underwent chemotherapy with cisplatin-capecitabine (CisCap). Finally, patients who were unable to swallow tablets received ECF (epirubicin, cisplatin, 5-fluorouracil). Patients who did not undergo radical surgery were excluded. Only patients at high risk of resection with positive CRM were selected, i.e. those with postoperative pathology stage being at least ypT3 (tumor extension beyond the muscularis propria layer). Neoadjuvant or adjuvant radiotherapy were exclusion criteria. Finally, tumor infiltration of the proximal and/or distal surgical resection margin was also an exclusion criterion. Patient inclusion according to the above criteria is described in CONSORT diagram (Fig. 1). Patients were included if they started perioperative chemotherapy from July 2009 to December 2014, and were operated from November 2009 to May 2015.

Following resection, the tumor was placed in formalin for approximately 24 h, then the CRM was painted with ink and the E/GEJ was horizontally sectioned at the level of the tumor into slices measuring approximately 3 mm in thickness. The CRM for each resection was assessed by specialist gastrointestinal pathologists according to the RCPath criteria [8], and was defined as a positive CRM (CRM+) when either the CRM was directly infiltrated (infiltrated CRM) or when tumor cells were detected within 1 mm from the CRM (close CRM) and the CRM was defined as negative (CRM) when tumor cells were found at a distance greater than 1 mm from the CRM. Macroscopic tumor-free CRM were obtained by removing pleural, diaphragm, lung or aortic adventitia where necessary [10]. All patients had follow-up appointments every 3 months for the first 2 years postoperatively, then every 6 months for the next 3 years. Follow-up included medical history, clinical examination, blood tests and a chest x-ray.

Data was collected retrospectively from case notes and pathology reports were reviewed. All cases were reclassified according to the Eighth Edition of the American Joint Committee on Cancer staging (AJCC8) of the esophagus or GEJ into neoadjuvant pathological stage groups (ypTN) [11]. The current study was performed as part of a clinical audit approved by the Audit Department of the Christie NHS Foundation Trust (CE15/1604). All procedures were conducted in accordance with the Helsinki Declaration, as revised in 2013.

Statistical analysis

Statistical analysis was performed using statistical package SPSS® version 22.0 (SPSS, Chicago, Illinous, USA). Survival curves were constructed by the Kaplan-Meier method, and survival comparisons were performed using the log-rank test. Cases were classified according to sex (male vs. female), age (≥65 vs. <65 years), primary tumor site (GEJ vs. esophagus), T stage (ypT3 vs. ypT4a), ypN stage (ypN0 vs. ypN1 vs. ypN2 vs. ypN3), lymph node ratio (LNR) (0 vs. 1–19% vs. 20–100%), CRM status (CRM + vs. CRM- by RCPath criteria or infiltrated CRM vs. non-infiltrated CRM by CAP criteria), tumor histological differentiation (well/moderate vs. poor), lymphovascular invasion (LVI) (yes vs. no) as defined by RCPath [8], type of surgery (esophagectomy vs. extended gastrectomy) and adjuvant chemotherapy (at least one cycle administered vs. not administered). These subgroups were used for univariate and multivariate analysis by logistic regression to determine independent predictors of CRM+. Cox proportional hazards models were used to identify independent prognostic factors for time-to-

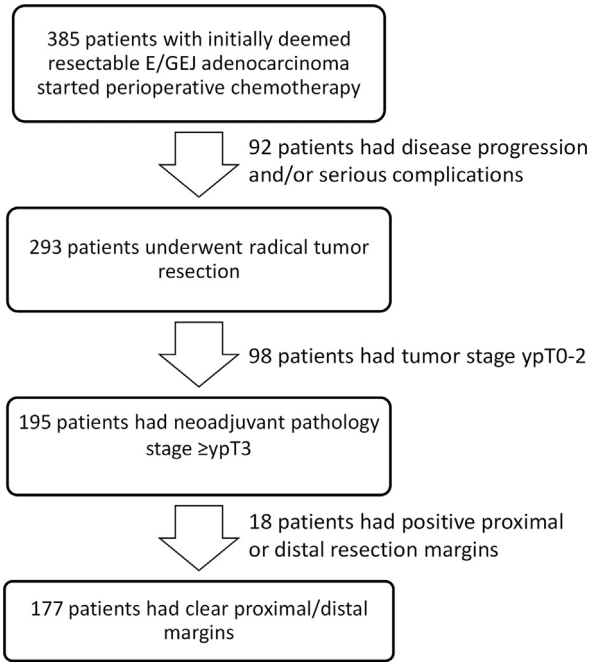

Fig. 1. CONSORT diagram showing patient selection for the study according to inclusion criteria.

relapse (TTR) and overall survival (OS). TTR was defined as the time from the date of surgery until the date of disease relapse and OS as the time from the date of operation until the date of death from any cause. Differences were considered statistically significant for a two-sided p value < 0.05.

Results

In total, 177 eligible patients were included in the analysis. Of them, 168 (94.9%) had received at least one pre-operative cycle of epirubicin, cisplatin and capecitabine (ECX) chemotherapy, while the rest had received other regimens (3 MCX, 2 EOX, 2 CisCap, 1 ECF, 1 ECarboX). Also, 164 patients (92.7%) underwent two-stage transabdominal and transthoracic resection of the esophagus, while 13 (7.3%) underwent extended total gastrectomy.

CRM+ was found in 83 patients (46.9%). Infiltrated CRM (CAP criteria) was recorded in 36 patients (20.3%), while 47 patients (26.6%) had close CRM. Patient and tumor characteristics are described in Table 1. The presence of LVI (LVI+) was strongly associated with CRM+, while lower esophageal primaries were weakly associated with higher risk of CRM+. Multivariable logistic regression analysis suggested LVI+ (Odds ratio [OR] 4.77, 95% confidence intervals [CI] 2.39–9.51, $p < 0.001$) and location of the tumor within the esophagus (OR 2.89, 95%CI 1.32–6.30, $p = 0.008$) were independently associated with higher risk of CRM+.

Adjuvant chemotherapy was administered to 132 patients (74.6%), which was generally the same regimen that was offered before operation. When comparing CRM+ and CRM-cases there was no significant difference in the numbers receiving adjuvant chemotherapy (Table 1). The majority of patients (125/132, 94.7%) underwent adjuvant chemotherapy with ECX, while 4 (3.0%) were treated with adjuvant ECarboX, 1 (0.8%) with EOX, 1 with ECF and 1 (0.8%) with MCX. Ninety-seven patients (73.5%) received 3 cycles of adjuvant chemotherapy, 22 (16.7%) received 2 cycles and 13 (9.8%) only one cycle.

Median follow-up time was 43.5 months (range, 0.4–81.5), by which time 108 patients (61.0%) had relapsed and 111 (62.7%) had died. Median TTR was 17.5 months (95%CI 14.9–20.0) and median OS was 25.4 months (95%CI 20.0–30.7). Three-year TTR was 25.5% and 3-year OS was 41.8%. Patients with infiltrated CRM, compared to those with close CRM and those with CRM-, had the shortest TTR (11.4 [95%CI 6.7–16.2] vs. 15.6 [95%CI 11.2–19.9] vs. 22.1 [95%CI 16.2–28.1] months, respectively, $p = 0.005$, Fig. 2a) and OS (18.7 [95%CI 9.0–28.4] vs. 23.1 [95%CI 18.2–28.1] vs. 38.8 [95%CI 24.5–53.1] months, respectively, $p = 0.001$, Fig. 2b). Three-year TTR was 10.3% vs. 20.7% vs. 32.2% and 3-year OS was 25.3% vs. 37.2% vs. 50.5% for patients with infiltrated CRM, compared to those with close CRM and those with CRM-, respectively. In contrast, patients with ypT3 and ypT4 stages did not demonstrate any difference in TTR ($p = 0.166$, $p = 0.130$, respectively), as well as in OS ($p = 0.075$, $p = 0.057$, respectively), according to the status of CRM, most probably due to insufficient sample size (Fig. S1 and S2).

Table 2 describes the results of univariate Cox proportional hazard model for TTR and OS. This confirmed the strong prognostic significance of already established parameters, such as ypT and ypN stage, LNR, histological differentiation, LVI and R margin. In addition it showed that patients who received adjuvant chemotherapy had a significantly better outcome. Multivariate Cox proportional hazard model indicated ypT stage, LNR and histological differentiation as the strongest prognostic factors (Table 3). Also, LVI+ was an independent predictor of poor outcome. Patients who received at least 1 cycle of adjuvant chemotherapy were confirmed to have better prognosis. Notably, CRM status as defined by both RCPath and CAP criteria was not an independent predictor of poor outcome in this analysis.

Of 108 patients who relapsed, only 9 (8.3%) developed

Table 1
Patient and disease characteristics according to the CRM status based on the criteria of the Royal College of Pathologists. Statistically significant p values are marked in bold.

Characteristics		CRM-		CRM+		p-value
		N	(%)	*N*	(%)	
Age (years)	<65	44	(46.8)	44	(53.0)	0.453
	≥65	50	(53.2)	39	(47.0)	
Gender	Male	82	(87.2)	68	(81.9)	0.403
	Female	12	(12.8)	15	(18.1)	
Primary site	Lower esophagus	18	(19.1)	28	(33.7)	**0.039**
	GEJ	76	(80.9)	55	(66.3)	
T stage	ypT3	89	(94.7)	72	(86.7)	0.113
	ypT4	5	(5.3)	11	(13.3)	
N stage	ypN0	30	(31.9)	15	(18.1)	0.098
	ypN1	19	(20.2)	24	(28.9)	
	ypN2	25	(26.6)	19	(22.9)	
	ypN3	20	(21.3)	25	(30.1)	
yp AJCC8 stage	II	30	(31.9)	15	(18.1)	**0.025**
	IIIB	41	(43.6)	39	(47.0)	
	IVA	23	(24.5)	29	(34.9)	
LNR	0	30	(31.9)	15	(18.1)	0.108
	1–19%	29	(30.9)	31	(37.3)	
	≥20%	35	(37.2)	37	(44.6)	
Differentiation	Well	5	(5.3)	5	(6.0)	0.277
	Moderate	36	(38.3)	22	(26.5)	
	Poor	53	(56.4)	56	(67.5)	
LVI	No	55	(58.5)	24	(28.9)	**<0.001**
	Yes	39	(41.5)	59	(71.1)	
Type of operation	Transthoracic esophageal resection	84	(89.4)	80	(96.4)	0.089
	Extended gastrectomy	10	(10.6)	3	(3.6)	
Adjuvant CT	Yes	75	(79.8)	57	(68.7)	0.119
	No	19	(20.2)	26	(31.3)	
Total		**94**	**(100)**	**83**	**(100)**	

CT, chemotherapy; GEJ, gastroesophageal junction; LVI, lymphovascular invasion; LNR, lymph node ratio; ypAJCC8 stage, neoadjuvant pathology stage according to the 8th Edition of the American Joint Committee of Cancer staging.

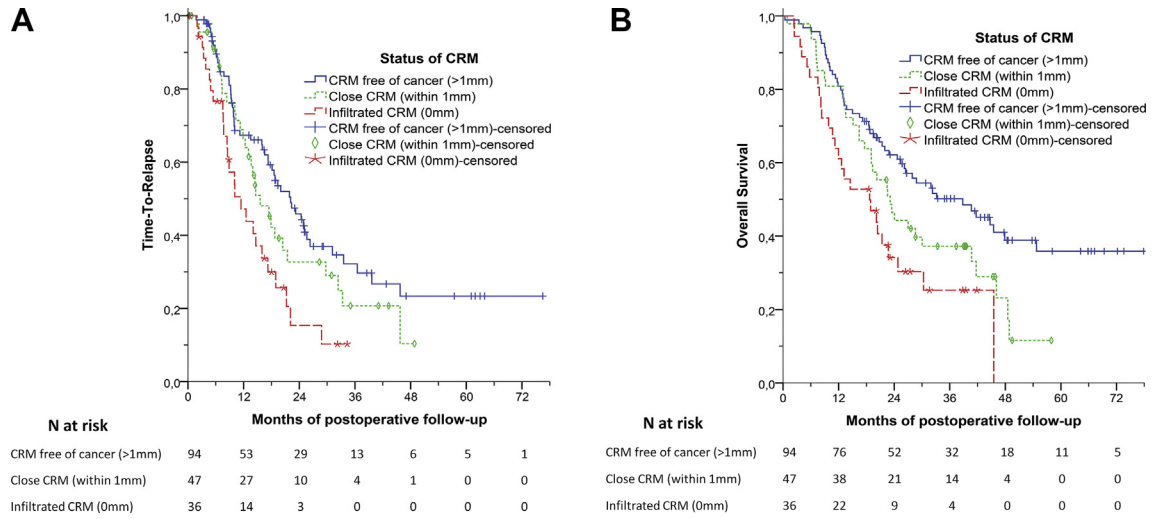

Fig. 2. Time-to-relapse (a) and overall survival (b) according to the status of circumferential resection margin (CRM).

Table 2
Univariable Cox proportional hazard models for time-to-relapse (TTR) and overall survival (OS). Statistically significant *p* values are marked in bold.

Covariates		TTR			OS		
		HR	95%CI	*p*-value	HR	95%CI	*p*-value
Age (years)	≥65 years vs.<65 years	0.95	0.65–1.38	0.773	1.02	0.70–1.48	0.930
Gender	Male vs.Female	0.81	0.49–1.34	0.407	1.04	0.62–1.74	0.888
Primary site	GEJ vs. Lower esophagus	1.00	0.64–1.56	0.987	0.79	0.52–1.19	0.255
T stage	ypT4 vs. ypT3	3.72	2.08–6.64	**<0.001**	3.07	1.74–5.41	**<0.001**
N stage	ypN1 vs.ypN0	2.03	1.04–3.96	**0.037**	1.95	1.01–3.76	**0.048**
	ypN2 vs.ypN0	3.45	1.81–6.60	**<0.001**	3.47	1.85–6.50	**<0.001**
	ypN3vs.ypN0	5.60	2.95–10.63	**<0.001**	6.62	3.57–12.28	**<0.001**
LNR	1–19% vs. 0%	2.00	1.06–3.79	**0.033**	2.06	1.10–3.83	**0.023**
	≥20% vs.0%	5.38	2.93–9.87	**<0.001**	5.52	3.07–9.91	**<0.001**
Differentiation	Poor vs. Well/Moderate	1.73	1.15–2.61	**0.009**	2.12	1.39–3.22	**<0.001**
LVI	Yes vs. No	2.35	1.57–3.53	**<0.001**	2.29	1.54–3.41	**<0.001**
CRM	CRM+ (0-<1 mm) vs.CRM-[a]	1.61	1.10–2.36	**0.014**	1.79	1.23–2.62	**0.003**
	CRM+ (0 mm) vs.CRM-[b]	1.97	1.26–3.09	**0.003**	1.92	1.23–3.00	**0.004**
Type of operation	Extended gastrectomy vs. Transthoracic esophageal resection	0.66	0.27–1.61	0.359	0.58	0.25–1.32	0.193
Adjuvant CT	Yes vs.No	0.63	0.41–0.96	**0.031**	0.54	0.36–0.81	**0.003**

CRM, circumferential margin; CT, chemotherapy; GEJ, gastroesophageal junction; LNR, lymph node ratio; LVI, lymphovascular invasion.
[a] CRM status definition according to the Royal College of Pathologists (RCPath).
[b] CRM status definition according to the College of the American Pathologists (CAP).

Table 3
Multivariable Cox proportional hazard models for time-to-relapse (TTR) and overall survival (OS).

Covariates		TTR			OS		
		HR	95%CI	*p*-value	HR	95%CI	*p*-value
T stage	ypT4 vs. ypT3	2.82	1.55–5.11	0.001	2.80	1.54–5.11	0.001
LNR	1–19% vs. 0%	1.39	0.71–2.71	0.333	1.46	0.75–2.81	0.263
	≥20% vs. 0%	3.72	1.96–7.07	<0.001	3.96	2.13–7.38	<0.001
Differentiation	Poor vs. Well/Moderate	1.78	1.15–2.74	0.009	2.11	1.37–3.23	0.001
LVI	Yes vs. No	1.60	1.03–2.49	0.037	1.63	1.05–2.54	0.031
Adjuvant CT	Yes vs. No	0.57	0.37–0.89	0.014	0.52	0.35–0.79	0.002

CT, chemotherapy; LNR, lymph node ratio; LVI, lymphovascular invasion.

symptomatic isolated loco-regional recurrence, while the majority of cases (N 99/108, 91.7%) presented with distant metastasis. Relapse in 1 distant site was observed in 32/108 patients (29.6%), in 2 different distant sites in 41 (38.0%), in 3 sites in 20 (18.5%) and in 4 sites in 6 (5.6%), as shown in Table 4. The incidence of symptomatic isolated local relapse did not significantly defer between patients with CRM + vs. CRM-by RCPath (4/56 [7.1%] vs. 5/52 [9.6%], $p = 0.736$), as well as by CAP criteria (0/26 [0%] vs. 9/82 [11.0%], $p = 0.110$). There was no difference in the number of involved distant organs between patients with CRM + vs. CRM-by RCPath (Mann-Whitney $Z = -0.74$, $p = 0.736$), as well as by CAP criteria (Mann-Whitney $Z = -0.608$, $p = 0.543$).

Discussion

This study assesses the significance of positive CRM, by both RCPath and CAP criteria, in patients with E/GEJ adenocarcinoma who underwent perioperative chemotherapy and surgery with

Table 4
Number of involved distant organs at the time of cancer relapse.

N of involved organs		CRM by CAP criteria			CRM status by RCPath criteria		
		CRM- or close CRM	Involved CRM	*p*-value	CRM-	CRM+	*p*-value
1	N	23	9	0.634	16	16	0.491
	%	31.5	34.6		34.0	30.8	
2	N	29	12		17	24	
	%	39.7	46.2		36.2	46.2	
3	N	17	3		12	8	
	%	23.3	11.5		25.5	15.4	
4	N	4	2		2	4	
	%	5.5	7.7		4.3	7.7	
Total	N	73	26		47	52	
	%	100.0	100.0		100.0	100.0	

CAP, College of American Physicians; CRM, circumferential margin; RCPath, Royal College of Pathologists.

curative intent. Although the significance of CRM has been extensively studied by individual retrospective studies and meta-analyses, the heterogeneity of the results is significantly high, most probably due to the inclusion in the same analysis of both adenocarcinomas and SCC, (y)pT1/2 and (y)pT3/4 tumors, and of cases treated with different modalities and chemotherapy regimens [7]. The most important strength of this study is the inclusion of a homogeneous population of patients who were selected if they had adenocarcinoma of the lower esophagus or GOJ, and were at significant risk of getting a positive CRM (ypT3/4). In contrast, a positive CRM was observed only rarely in ypT2 tumors (2 out of 44 patients) and might reflect a suboptimal surgery. Therefore, these patients were excluded from the study. Additionally, all our patients received their systemic treatment in the same institution, consisting of the same neoadjuvant chemotherapy regimen ECX, with only slight variations in case of comorbidities.

Patient and disease characteristics predicting CRM status

We aimed to identify factors that could be linked with a likelihood of CRM+. Having a pure esophageal primary and LVI+ were the only independent factors associated with CRM+. This might be related with the constraints of surgery in the esophagus, related to its position within the chest very close to vital organs, and a more extensive microscopic spread unmasked by the LVI. Although LVI is a well documented prognostic factor for esophageal cancer [12–16], to our knowledge LVI is identified as a predictor of CRM + for the first time in this specific disease setting. Of note, other investigators did not show similar findings; there may be many reasons for this (e.g. the retrospective nature of these studies, the limited sample size). However the heterogeneity of patients' characteristics in previous studies, which is less of an issue in this study, may also have been an important factor.

Prognostic significance of CRM status

We demonstrated that patients with infiltrated CRM had worse TTP and OS, compared to those with negative CRM according to RCPath (>1 mm), while those with close CRM (<1 mm) showed a trend for intermediate prognosis compared to the above two groups. However, the prognostic significance of CRM status was not confirmed in multivariate analysis. One possible explanation might be the fact that numerically, but not statistically significantly, more CRM-positive patients were unable or declined receiving adjuvant chemotherapy, compared to those who underwent CRM-negative resections. Of note, receipt of adjuvant chemotherapy was an independent favorable prognostic factor, thus strengthening the argument that it might also represent a significant confounding factor.

The presence of tumor in the resection margin has long been considered a poor prognostic factor [17,18]. Nevertheless, recent studies have shown contradictory results, with some demonstrating the independent prognostic significance of CRM status [12,19–23], others showing a prognostic value only in univariate analysis [24–26], and others showing no association of CRM status with tumor relapse or survival [13,27–29]. The most likely explanation of this controversy might be the small sample sizes, as well as the heterogeneity of tumor characteristics and treatments within each cohort. With regard to the sample size, two large studies were published recently; the first including 2944 patients [30] and the second 3125 patients [31]. Both studies showed that infiltrated margins (by CAP criteria) were independently associated with adverse outcome. However, they included cases with positive longitudinal (proximal, distal) and/or lateral (circumferential) margins. Therefore, the relative impact of each type of surgical margin on prognosis was not estimated.

Furthermore, large meta-analyses assessed the importance of CRM status for prognosis. Khan et al. [15] included in their analysis 4 studies with 763 patients who predominantly did not receive any neoadjuvant treatment and showed conflicting results with regard to the prognostic significance of CRM status. They also analyzed 457 patients from 3 studies who predominantly received neoadjuvant chemotherapy and showed prognosis was adversely impacted by the presence of positive CRM. They concluded that a positive CRM is an independent poor prognostic factor only for those patients who had received neoadjuvant chemotherapy. Wu et al. [32], in their meta-analysis including 19 studies with 3543 patients, confirmed the prognostic significance of an involved CRM for patient outcome. Chan et al. [33] conducted a meta-analysis of 2433 patients from 14 studies and demonstrated that patients with close CRM (<1 mm) were characterized by an intermediate prognosis compared to those with infiltrated CRM (0 mm) having poor prognosis and those with clear CRM by RCPath (>1 mm) who had the best outcome. However, the applicability of these results to an oesophageal adenocarcinoma cohort are limited by the large heterogeneity of the analyzed patient populations, with respect to the different inclusion criteria, stratification factors and type of treatments.

Pattern of tumor recurrence

We demonstrated that the great majority of relapses occurred at distant sites, while symptomatic isolated locoregional relapses were remarkably low. In the present study, patients underwent a basic clinical, laboratory and radiological follow-up, while more advanced imaging exams, such as computed tomography and magnetic resonance imaging, and gastrointestinal (GI) endoscopy were performed in case of suspicious clinical or laboratory findings. Therefore, virtually all relapses were diagnosed only when they

became symptomatic and probably at a relatively late stage, which might explain the very low incidence of isolated locoregional metastases. Additionally, many asymptomatic local recurrences might have been missed if not shown by radiological imaging. Thus, we could not reliably describe the total locoregional recurrence rate, because most probably it has been underestimated. Nevertheless, according to a recent study [34], adenocarcinomas of the esophagus have a higher tendency to metastasize than SCCs. Also, Harvin et al. [25] described local recurrences only in 7% of patients, and paradoxically their incidence was not correlated with CRM status, also shown in our cohort. These results led us to the conclusion that effective systemic treatment is of high importance and largely represents an unmet need in E/GEJ adenocarcinoma.

Limitations of the study

Significant weaknesses of this study were the retrospective nature of the analysis and the relatively small sample size. Also, the lack of central review of the pathology specimens might have biased the results due to interobserver variability. Finally, the potential bias caused by non-including advanced imaging methods in the routine follow-up of these patients was discussed above.

Conclusions

In summary, CRM involvement is frequent even following neoadjuvant chemotherapy in patients with deeply invasive E/GEJ adenocarcinomas (≥ypT3). CRM positive status is associated with poor outcome, but in this study it did not show an independent prognostic significance. Moreover, the pattern of tumor relapse did not differ significantly between patients with positive and negative CRM, with the great majority of them developing distant recurrences irrespective of CRM status.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Study concepts: AP, GP, BA, SG, WM; *Study design*: AP, GP, SG, WM; *Data acquisition*: AP, GP, ZK, JMJW, VO-H; *Quality control of data and algorithms*: AP, GP, WM; *Data analysis and interpretation*: AP, GP, WM; *Statistical analysis*: AP, GP; *Manuscript preparation*: AP, GP, WM; *Manuscript editing*: AP, GP, ZK, JMJW, VO-H, BA, SG, WM; *Manuscript review*: AP, GP, ZK, JMJW, VO-H, BA, SG, WM.

All authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.10.530.

References

[1] Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet 2017 Jun 22;390. pii: S0140-6736(17)31462-31469.
[2] Cancer Research UK, Cancer statistics report for the UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-bycancer-type/oesophageal-cancer. (accessed 8 September 2017).
[3] Cancer Genome Atlas Research Network, et al. Nature 2017;541:169–75.
[4] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006 Jul 6;355(1):11–20.
[5] van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012 May 31;(22):366. 2074-84.
[6] Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D, ESMO Guidelines Working Group. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013 Oct;24(Suppl 6). vi51-6.
[7] Ronellenfitsch U, Schwarzbach M, Hofheinz R, et al. Predictors of overall and recurrence-free survival after neoadjuvant chemotherapy for gastroesophageal adenocarcinoma: pooled analysis of individual patient data (IPD) from randomized controlled trials (RCTs). Eur J Surg Oncol 2017 Aug;43(8):1550–8.
[8] Document G006 Dataset for the histopathological reporting of oesophageal carcinoma. second ed. The Royal College of Pathologists; February 2007. https://www.rcpath.org/resourceLibrary/g006oesophagealdatasetfinalfeb07-pdf.html. [Accessed 22 October 2017].
[9] Surgical pathology cancer case summary (checklist): esophagus. College of American Pathologists; January 2005.
[10] Theologou T, Diab M, Kyaw PA, et al. The impact of positive circumferential margin on survival following oesophagectomy using the new 7th TNM classification. Eur J Cardio Thorac Surg 2013 Nov;44(5):855–9.
[11] Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an Eighth edition staging primer. J Thorac Oncol 2017 Jan;12(1):36–42.
[12] Ahmad J, Loughrey MB, Donnelly D, et al. Prognostic value of added stratification of circumferential resection margin status in oesophageal carcinoma. Histopathology 2013 Apr;62(5):752–63.
[13] O'Farrell NJ, Donohoe CL, Muldoon C, et al. Lack of independent significance of a close (<1 mm) circumferential resection margin involvement in esophageal and junctional cancer. Ann Surg Oncol 2013 Aug;20(8):2727–33.
[14] Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. Gut 2011;60:1449–72.
[15] Khan OA, Cruttenden-Wood D, Toh SK. Is an involved circumferential resection margin following oesphagectomy for cancer an important prognostic indicator? Interact Cardiovasc Thorac Surg 2010 Nov;11(5):645–8.
[16] Okada N, Fujii S, Fujita T, et al. The prognostic significance of the positive circumferential resection margin in pathologic T3 squamous cell carcinoma of the esophagus with or without neoadjuvant chemotherapy. Surgery 2016 Feb;159(2):441–50.
[17] Skinner DB, Dowlatshahi KD, DeMeester TR. Potentially curable cancer of the esophagus. Cancer 1982 Dec 1;50(11 Suppl):2571–5.
[18] Dexter SP, Sue-Ling H, McMahon MJ, et al. Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer. Gut 2001 May;48(5):667–70.
[19] Pultrum BB, Honing J, Smit JK, et al. A critical appraisal of circumferential resection margins in esophageal carcinoma. Ann Surg Oncol 2010 Mar;17(3):812–20.
[20] Reid TD, Chan DS, Roberts SA, et al. Prognostic significance of circumferential resection margin involvement following oesophagectomy for cancer and the predictive role of endoluminal ultrasonography. Br J Canc 2012 Dec 4;107(12):1925–31.
[21] Scheepers JJ, van der Peet DL, Veenhof AA, Cuesta MA. Influence of circumferential resection margin on prognosis in distal esophageal and gastroesophageal cancer approached through the transhiatal route. Dis Esophagus 2009;22(1):42–8.
[22] Saha AK, Sutton C, Rotimi O, et al. Neoadjuvant chemotherapy and surgery for esophageal adenocarcinoma: prognostic value of circumferential resection margin and stratification of N1 category. Ann Surg Oncol 2009 May;16(5):1364–70.
[23] 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 2008 Feb;95(2):191–4.
[24] Salih T, Jose P, Mehta SP, et al. Prognostic significance of cancer within 1 mm of the circumferential resection margin in oesophageal cancer patients following neo-adjuvant chemotherapy. Eur J Cardio Thorac Surg 2013 Mar;43(3):562–7.
[25] Harvin JA, Lahat G, Correa AM, 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.
[26] Rao VS, Yeung MM, 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.
[27] Ghadban T, Reeh M, Koenig AM, 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;266(6):988–94 [Epub ahead of print].
[28] 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 Canc 2003 May 19;88(10):1549–52.
[29] Theologou T, Diab M, Kyaw PA, et al. The impact of positive circumferential margin on survival following oesophagectomy using the new 7th TNM classification. Eur J Cardio Thorac Surg 2013 Nov;44(5):855–9.
[30] Markar SR, Gronnier C, Duhamel A, et al. Significance of microscopically incomplete resection margin after esophagectomy for esophageal cancer. Ann Surg 2016 Apr;263(4):712–8.
[31] Javidfar J, Speicher PJ, Hartwig MG, et al. Impact of positive margins on survival in patients undergoing esophagogastrectomy for esophageal cancer. Ann Thorac Surg 2016 Mar;101(3):1060–7.
[32] Wu J, Chen QX, Teng LS, 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.
[33] Chan DS, 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.
[34] Xi M, Xu C, Liao Z, Hofstetter WL, et al. The impact of histology on recurrence patterns in esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol 2017 Aug;124(2):318–24.