Does the Margin Matter in Esophageal Cancer?

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Keywords

Esophageal cancer · Surgery · Resection margin

Abstract

Background: The prognostic impact of circumferential resection margin (CRM) involvement in resected esophageal cancer (EC) is controversial discussed. The College of American Pathologists (CAP) and the Royal College of Pathologists (RCP) provide 2 different definitions of CRM involvement. The aim of this systematic review was to evaluate the clinical significance of CRM involvement on patients' survival following esophagectomy due to EC. **Methods:** PubMed, Science Direct, and Google scholar were searched for studies analyzing the clinical impact of CRM in EC. **Summary:** A total of 28 studies analyzed the prognostic effect of a positive CRM in EC. A wide range of CRM involvement (8.6–83.1%) was reported. Both available meta-analyses found a significant association between a positive CRM and patients' survival irrespective of RCP (OR 2.52 [95% CI 1.96–3.25; $p < 0.001$]) or CAP (OR 4.02 [95% CI 2.25–7.20; $p < 0.001$]) criteria. The influence of neoadjuvant therapy on the CRM remains unclear. **Key Messages:** CRM involvement is a useful parameter for EC patients' prognosis. The application of CAP criteria should be preferred since patients with a poor prognosis can be identified more sufficiently. Neoadjuvant therapy and en bloc transthoracic esophagectomy show favorable results for achievement of negative CRM.

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Introduction

Esophageal cancer (EC) is an aggressive cancer with an increasing incidence worldwide [1, 2]. Reductions in postoperative mortality and morbidity have been achieved in recent years by improved perioperative care, implementation of EC centers, and development of minimal invasive techniques [3]. However, EC remains associated with a high mortality [1, 2]. Complete resection of the primary tumor with an adequate resection margin to healthy tissue is the main goal of curative therapy. Remaining tumorous tissue is usually regarded as a failed surgical therapy. Despite the effort to perform en-bloc resection of the tumor, loco-regional recurrence rates of EC are reported to be as high as 52% [4, 5]. The anatomical position of EC often hinders removal with wide circumferential resection margins (CRM) so incomplete tumor resection might occur. Histologic characteristics like depth of tumor invasion, lymph node involvement, and proximal and distal resection margins are accepted risk factors for patients' survival and tumor recurrence [6–8], while the role of CRM in patients with EC is still under controversial discussion in the literature. To complicate the controversy even more, definition of a positive CRM+ and a negative CRM– in EC differs between The Royal College of Pathologists (RCP) and The College of American Pathologists (CAP; Fig. 1). The RCP defines a positive CRM as a tumor at or within 1 mm of the resection margin [9] while The CAP only regards the occurrence of tu-

Fig. 1. Definitions of the CRM according to the College of American Pathologists (CAP) and the Royal College of Pathologists (RCP). R0, microscopical tumor free margin, CRM negative; R1, microscopical tumor involvement of the margin, CRM positive.

mor at the resections margins as CRM positive [10]. This is of great importance when comparing international trials. Since the TNM staging systems are identical, the CRM status acts as a confounding factor in survival analyses. Few studies have directly compared the prognostic significance of the different classification systems with conflicting results [11–16].

In this article, we review the current literature in regard to the prognostic and clinical significance of resection margins in EC. We especially focus on the impact of the CRM and critically discuss the results.

Methods

A comprehensive search of electronic databases (PubMed, Science Direct, and Google scholar) using the key words “esophageal cancer and/or carcinoma or tumor or neoplasm” and “resection margin circumferential/radial” was performed. The reference lists provided by the identified articles were additionally hand-searched for additional studies missed by the search strategy, and this method of cross-referencing was continued until no further relevant publications were identified. Evidence from these data was critically analyzed and summarized to produce this article. All studies reporting outcomes on resection margins in EC were included in the review process. The available published data on resection margins in EC comprise non-randomized retrospective case comparison series, case series, and case reports. The studies were subject to significant bias, both in terms of the selection criteria for the study participants and also the reporting of data.

Results

A total of 28 studies over the last 24 years analyzed the prognostic effect of a positive CRM in EC. Of these studies, 24 performed retrospective analyses, 2 studies a prospective analysis, and 2 studies were meta-analysis. Only few studies investigated the prognostic significance for squamous cell carcinoma ($n = 4$) or adenocarcinoma ($n = 2$) exclusively. Most of the studies used RCP criteria

($n = 12$). Only 2 studies used CAP criteria alone. A total of 9 studies directly compared RCP and CAP criteria while 5 studies used different criteria of which RCP or CAP criteria could be derived. A mean overall CRM involvement was found in 40.7% (range 18.1–83.1%) of the patients according to RCP criteria and in 11.8% (range 5.0–25.5%) of the patients when applying CAP criteria (Table 1).

Survival

The CRM in EC yielded a prognostic impact on patient survival in the majority of the studies (Table 1). Both available meta-analysis found a significant association between a positive CRM and patients’ survival irrespective of RCP or CAP criteria. Chan et al. [16] found an increased OR of 4.02 (95% CI 2.25–7.20; $p < 0.001$) when applying RCP criteria and an increased OR of 2.52 (95% CI 1.96–3.25; $p < 0.001$) when using CAP criteria in 5-year mortality rates of patients with a CRM involvement. The CAP criteria resulted in larger ORs than the RCP criteria [16]. In addition, Wu et al. [11] found an increased hazards ratio (HR) of 1.510 (95% CI 1.329–1.717; $p < 0.001$) and a HR of 2.053 (95% CI 1.597–2.638; $p < 0.001$), respectively. They also found a lower heterogeneity of the comprised study in the analyzed CAP group as compared to the RCP group [11]. These results were supported in other recent retrospective studies [3, 14, 17, 18]. A multicenter study comprising a total of 2,815 patients after esophagectomies found a reduced overall survival for patients with a positive CRM as compared to patients with tumor-free margins (17.1 vs. 28.0 months; $p < 0.001$) irrespective of the nodal status [3]. In addition, Gilbert et al. [17] reported a decreased median survival of 12 months in the CRM positive group (median survival 13 months; 95% CI 7–26) as opposed to the CRM negative group (median survival 25 months; 95% CI 20–30) [17]. Interestingly, another study was only able to demonstrate a negative effect on overall survival in ESCC for CRM positive patients when judged by CAP

Table 1. Included studies for evaluation of the clinical impact of CRM in EC

Study	Study design	Number of patients	Entities (n)	Stage	Neoadjuvant treatment (n)	Criteria	CRM+, n (%)		CRM+ of T3, n (%)		Influence on survival
							RCP	CAP	RCP	CAP	
Sagar et al. [25], 1993	R	50	ESCC (21), EAC (28), other (1)	np	None	RCP	20 (40.0)				s
Dexter et al. [45], 2001	P	135	ESCC (37), EAC (98)	T1–3	None	RCP	64 (47.1)		60 (63.0)		s
Khan et al. [20], 2003	R	329	ESCC (128), EAC (201)	T1–3	None	RCP	67 (20.0)				ns
Griffiths et al. [40], 2006	R	249	ESCC (61), EAC (178), other (10)	T1–3	CT (34)	RCP	79 (31.7)		79 (50.9)		s
Sujendran et al. [30], 2008	R	242	ESCC (50), EAC (185), other (7)	T1–4	CT (142), RCT (9)	RCP	53 (39.2)		56 (38.6)		s
Thompson et al. [28], 2008	R	240	ESCC (49), EAC (191)	T1–4	RCT (124)	RCP	85 (35.4)				s
Deeter et al. [12], 2009	R	135	ESCC (15), EAC (117), other (3)	T3	CT (24), RCT (35)	RCP, CAP	83 (61.5)	16 (11.8)	83 (61.5)	16 (11.8)	ns (RCP), s (CAP)
Scheepers et al. [32], 2009	R	110	ESCC (29), EAC (81)	T1–3	none	3 groups	42 (38.0)		42 (48.0)		s
Saha et al. [36], 2009	P	105	Not provided	T0–4	CT (105)	RCP	38 (36.0)	16 (15.5)	37 (53.0)		s
Sillah et al. [46], 2009	R	320	ESCC (65), EAC (248), other (7)	T1–3	CT (121)	RCP	91 (28.4)		np		np
Mirnezami et al. [21], 2010	R	314	ESCC (51), EAC (263)	T1–4	None	RCP	146 (46.0)				ns
Pultrum et al. [33], 2010	R	98	ESCC (22), EAC (76.5), other (1)	T1–4	None	3 groups	47 (48.0)	25 (25.5)	43 (84.0)		s
Chao et al. [26], 2011	R	151	ESCC (151)	T3	RCT (151)	3 groups	77 (51.0)	26 (17.2)	77 (51.0)	26 (17.2)	s
Verhage et al. [13], 2011	R	132	EAC (132)	T3	None	RCP, CAP	89 (67.4)	26 (19.7)	89 (67.4)	26 (19.7)	ns (RCP), s (CAP)
Harvin et al. [19], 2012	R	160	EAC (160)	T3	RCT (160)	RCP, CAP	42 (26.0)	8 (5.0)	42 (26.0)		ns (RCP), s (CAP)
Rao et al. [37], 2012	R	115	ESCC (36), EAC (79)	T1–4	CT (37)	3 groups	57 (49.6)	17 (14.8)			s (RCP), ns (CAP)
Reid et al. [29] (2012)	R	269	ESCC (57), EAC (212)	T1–4	CT (124), RCT (42)	RCP	98 (36.4)				s
Salih et al. [38], 2013	R	232	ESCC (45), EAC (183), other (4)	T1–4	CT (232)	3 groups	105 (45.3)	38 (16.4)			ns
O'Farrell et al. [15], 2013	R	157	ESCC (33), EAC (122), other (2)	T3	RCT (82)	RCP, CAP	94 (60.0)	29 (18.0)	94 (60.0)	29 (18.0)	ns
Liu et al. [47], 2013	R	94	ESCC (94)	T0–4	RCT (94)	RCP	17 (18.1)				s
Park et al. [22], 2013	R	71	ESCC (71)	T3	None	RCP	59 (83.1)				ns
Hulshoff et al. [14], 2015	R	209	ESCC (37), EAC (172)	T0–4	RCT (104)	RCP, CAP	89 (42.5)	36 (17.2)			ns
Gilbert et al. [17], 2015	R	154	ESCC (27), EAC (123), other (5)	T3–4	CT (22), RCT (35)	CAP	30 (19.0)				s
Markar et al. [3], 2015	R	2,815	ESCC (1294), EAC (1521)	T1–4	CT (1272), RCT (788)	CAP	242 (8.6)				s
Ghadban et al. [23], 2016	R	180	ESCC (107), EAC (73)	T3	None	RCP, CAP	76 (42.2)	44 (24.4)	76 (42.2)	44 (24.4)	ns
Okada et al. [18], 2016	R	160	ESCC (160)	T3	CT (67)	RCP, CAP	113 (70.6)	16 (10.0)	113 (70.6)	16 (10.0)	s

Table 1. (continued)

Study	Study design	Number of studies and patients	Entities	Neoadjuvant therapy	Criteria	CRM+, n (%)		CRM+ of T3, n (%)		Influence on survival
						RCP	CAP	RCP	CAP	
Chan et al. [16], 2013	M	14 (2,433 patients)	ESCC, EAC, other	CT, RCT	RCP, CAP	889 (36.5)	173 (15.3)	597 (42.5)	110 (14.6)	s
Wu et al. [11], 2014	M	19 (3,543 patients)	ESCC, EAC, other	CT, RCT	RCP, CAP	1,417 (40.0)	609 (17.2)	np	np	s

Main characteristics of the eligible studies.
 R, retrospective; P, prospective; M, meta-analysis; ESCC, esophageal squamous cell carcinoma; n, number of patients; CT, chemo therapy; RCT, radio-chemotherapy; CAP, College of American Pathologists; RCP, Royal College of Pathologists; CRM, circumferential resection margin; s, significant; ns, not significant; np, not provided; 3 groups: tumor cells found at, within, and at more than 1 mm of the surgical margin.

criteria (HR 5.26; 95% CI 2.37–11.32; $p < 0.001$) and not RCP criteria (HR 1.3; 95% CI 0.62–2.98; $p = 0.50$) in multivariate analysis [18]. Similar results were found in 3 other studies where CAP criteria yielded a significant prognostic influence on overall survival while RCP criteria did not [12, 13, 19].

Notably, some studies were not able to show an effect of the CRM status on overall survival [15, 20–23]. Khan et al. [20] investigated 329 patients treated for ESCC by esophagectomy. No statistically significant association between the CRM status and survival was observed ($p = 0.57$). In multivariate analysis, only tumor stage, nodal stage, and tumor grade were prognostic markers [20]. In a study by O’Farrell et al. [15], a positive CRM according to RCP or CAP criteria did not show any influence on survival in multivariate analysis. In a recent study of our institution by Ghadban et al. [23], a total of 180 patients following esophagectomy were compared. Neither RCP (HR 1.081; 95% CI 0.769–1.518; $p = 0.655$) nor CAP (HR 1.214; 95% CI 0.830–1.777; $p = 0.317$) criteria yielded an association to overall survival. Only nodal status remained to have a prognostic influence on patient survival in multivariate analysis ($p = 0.003$) [23].

Recurrence

Most of the studies have assessed the CRM status in regards to patients’ survival, but not in terms of tumor recurrence. Despite advances in surgical techniques local, regional and distant recurrences frequently occur after resection [24]. Loco-regional recurrences seem to be the predominant failure pattern in CRM positive patients [22]. In the first study of CRM involvement by Sagar et al. [25], significantly ($p < 0.01$) more patients with a positive CRM (55%) developed a local recurrence as compared to those without involvement of the CRM (13%) [25]. These results were later proven by other studies, which also identified a prognostic role of a positive CRM on recurrences [3, 13, 14, 17, 18, 22, 26]. Chao et al. [26] found a significant influence of an involved CRM not only on loco-regional but also on distant recurrences, while an involvement to the CRM of less than 1 mm was associated with early loco-regional recurrences. In another study, involvement of the CRM was only associated to recurrences, being outside the lymphatic drainage of the esophagus and the gastroesophageal junction [17]. Interestingly, Verhage et al. [13] were able to demonstrate a prognostic effect only when using CAP criteria in multivariate analysis (HR 2.086; 95% CI 1.320–3.296; $p = 0.002$). CRM involvement was the strongest predictor of recurrence in their analysis comprising only pT3 adenocarcinomas

[13]. The results of the latter study were supported by Hulshoff et al. [14] who identified margin involvement according to CAP criteria to be associated with local recurrence in surgically treated patients ($p = 0.004$) as well as in patients who also received neoadjuvant therapy prior to surgery ($p = 0.001$). However, when applying RCP criteria, no significant associations were observed [14]. In a study of 160 ESCC, the usage of RCP criteria also did not show any relationship to local recurrence ($p = 0.64$) while judging by CAP criteria did ($p = 0.02$) [18].

In contrast to the latter studies, the paper of Harvin et al. [19] investigated only pT3 adenocarcinomas that failed to detect an effect of a positive CRM on recurrences after performing a propensity score matching by histopathological and clinical parameters [19]. The latter results were supported by a recent study, which failed to demonstrate an influence on local or distant recurrences when applying either CAP or RCP criteria. In the latter study, only nodal status remained to have a significant influence in multivariate analysis [23].

Neoadjuvant Therapy

Recent studies have proven survival advantages of neoadjuvant chemo- and radio-chemotherapy in EC [27]. However, the influence of neoadjuvant therapy on the CRM remains unclear.

Chao et al. [26] reported a decline in CRM involvement when comparing patients treated with surgery alone (CAP 22.2%, RCP 40.1%), chemotherapy prior to surgery (CAP 15.8%, RCP 34.3%), and radio-chemotherapy prior to surgery (CAP 11.2%, RCP 31.9%). In a subset of 123 patients, Thompson et al. [28] found significantly less CRM involvement in patients treated with neoadjuvant radio-chemotherapy as compared to patients who were treated by surgery alone (22 vs. 50%; $p < 0.001$). However, no association between CRM status and survival was observed in these patients ($p = 0.184$) [28]. The influence of neoadjuvant therapy on CRM status was supported by Reid et al. [29], who found a reduction of CRM involvement in patients treated with radio-chemotherapy in multivariate analysis (OR 0.116; 95% CI 0.035–0.382; $p < 0.0001$). Interestingly, neoadjuvant chemotherapy without radiation did not show any association to the CRM status (OR 0.641; 95% CI 0.289–1.420; $p = 0.273$) [29]. In contrast, Sujendran et al. [30] observed a reduction of CRM positivity in patients treated with neoadjuvant chemotherapy alone as compared to those who did not receive any treatment prior to surgery (31 vs. 55%; $p = 0.005$). In another study, the CRM had no significant influence on disease-free survival after neoadjuvant treat-

ment, irrespective of CAP or RCP criteria. Thus, the authors proposed an additional CRM cutoff of 0.3 mm for patients treated with neoadjuvant therapy [14]. Okada et al. [18] demonstrated that the usage of CAP criteria as opposed to RCP criteria in regards to CRM status was of greater prognostic significance after neoadjuvant therapy in multivariate analysis [18].

Adjuvant Therapy

A majority of the patients treated for EC receive adjuvant therapy. The prognostic influence of the CRM still remains unclear and only very few studies have addressed this issue. Markar et al. [3] demonstrated a significant benefit for CRM positive patients treated with adjuvant therapy comprising either radiotherapy or radio-chemotherapy ($p = 0.015$). The results indicated improved overall survival ($p = 0.087$) and reduced distant recurrences ($p = 0.058$). However, no effect ($p = 0.851$) on loco-regional recurrences was found.

Park et al. [22] investigated the effect of postoperative radiotherapy in esophageal squamous cell carcinomas (ESCC) only. They were not able to demonstrate a significant survival benefit between patients with positive or negative CRM ($p = 0.883$) treated with adjuvant radiotherapy. Only patients with a positive CRM and pN2-3 stage yielded a benefit from this treatment in regards to loco-regional recurrences. However, the latter finding failed to reach statistical significance ($p = 0.057$) [22].

Surgical Approach

Esophagectomies can be done using either transhiatal or a transthoracic (Ivor Lewis) technique. Both techniques can be performed by a minimal invasive or open approach. The influence of the surgical approach on CRM involvement is still unclear. Suttie et al. [31] found an increased number of positive CRM involvement in patients treated with a transhiatal approach as compared to a transthoracic approach. This is in line with a recent study of our institution, which also found an increased CRM involvement in patients treated with a transhiatal approach as compared to patients treated with a transthoracic approach using CAP criteria ($p = 0.026$). However, when applying RCP criteria, the difference did not remain significant ($p = 0.086$) [23]. Scheepers et al. [32] further divided transhiatal esophageal resections into a laparoscopic and an open group. However, they were not able to detect any significant differences in regards to CRM involvement ($p = 0.192$) [32]. In another study by Pultrum et al. [33], the type of surgery did not influence the extension of CRM involvement ($p = 0.693$) at all.

Discussion

A positive resection margin after radical oncologic resection for cancer has been proposed as a prognostic marker for survival in different entities. While the longitudinal margins are widely accepted parameters for patients' prognosis and being used on a routine basis, the prognostic role of circumferential margins is still being discussed. Especially for EC, the data are very heterogeneous, and interpretation is hampered by several factors. In the reviewed literature, a wide range of CRM involvement (8.6–83.1%) has been reported [3, 22]. The difference can be explained by the varying pathologic classification systems (RCP and CAP criteria; Fig. 1) being used [9, 10]. This is a major issue when comparing international studies. The criteria of positive CRM in EC by the RCP are partially derived from rectal cancer [34, 35]. However, a comparison between esophageal and rectal cancer in regards to resection criteria is questionable since anatomic boundaries are different. Even though both entities are localized in an extraperitoneal position and miss a serosal cover, only the rectum is surrounded by the mesorectum and Denonvilliers fascia. Bulky T3 tumors of the rectum can be resected anatomically with negative margins, while the same principles do not apply for bulky T3 tumors of the esophagus. This is caused by the proximity of the esophagus to central organs that cannot be resected like aorta, atrium, trachea, spine and lung. So close margins have to be anticipated in a high number of such tumors leading to larger amount of CRM positive tumors in regards to RCP as opposed to CAP criteria. In consequence, the meta-analysis of Wu et al. [11] reported an advantage of the CAP criteria over the RCP criteria in terms of prognostic significance, risk stratification [11]. However, CAP criteria missed a subgroup of patients with poorer survival due to extended infiltration >1 mm in the peripheral tissue [16]. Another problem is to clearly distinguish the prognostic effect of a positive CRM from other factors like lymph node invasion or tumor stage. Respectively, several studies reported a close association of CRM involvement to nodal stage and tumor stage [36–38], other studies described that only lymph node invasion and tumor stage are proved to be of prognostic significance [19, 20, 23]. In addition, Gilbert et al. [17] reported CRM positive tumors to exclusively be of T3 and T4 stage ($p < 0.01$) and to be longer (50 vs. 35 mm; $p > 0.01$) and wider in diameter (35 vs. 29 mm; $p = 0.01$). Markar et al. [3] showed that 21.9% of the vertical margins were positive if a positive CRM occurred, while only 3.2% of the vertical margins were positive in the CRM negative group ($p > 0.001$). This

could potentially be caused by a more aggressive tumor biology, which would also explain the previously mentioned association to higher T-stages and nodal affection. Nevertheless, R1 status in T2 tumors is considered to be caused by inadequate surgery [13, 14, 39, 40]. This influences the results of survival analyses towards a better survival in CRM positive cases, because of the inclusion of less invasive tumors with a false positive CRM. Thus, results of studies investigating the CRM status including early tumor stages have to be interpreted with caution.

Another factor that hampers the validity of the results is the composition of the analyzed EC. Most of the studies analyze different entities of EC (Table 1) though each of them has different tumor biology and different risk factors for tumor development. Consequently, different neoadjuvant and adjuvant therapies are used, which has to be taken into account if analyzing the prognostic effect of CRM involvement.

When reviewing the available data for neoadjuvant therapy a tendency to improvement in R0 resectability could be observed, but there are important limitations. It is still not possible to predict the response to such a treatment and patients might even suffer from a progress of cancer while being treated neoadjuvantly. In addition, the risk of morbidity and mortality by neoadjuvant therapy should not be taken lightly [41]. Mulligan et al. [42] demonstrated in their study that multimodal therapy including neoadjuvant treatment decreases margin involvement and as such significantly improves patients' prognosis. In addition, even patients with involved margin yielded decreased recurrence rate following a multimodal treatment [42]. The advantage of neoadjuvant therapy was recently proven by the CROSS trial [43]. Though, different amounts of vital tumor cells can be detected in the induced fibrosis [27]. This makes thoroughly investigation of the CRM more important.

The role of the surgical technique in regards to CRM involvement is still unclear. Few studies have investigated the direct impact on margin involvement. Two studies found higher positive CRMs after transhiatal resections while another failed to demonstrate any differences between surgical approaches [23, 31, 33]. A higher rate of CRM involvement might be due to failed en bloc resections, which are known to improve patients' prognosis [44]. Another study demonstrated malnutrition to be a predictor for CRM positive resections irrespective of tumor stage and other confounding variables [3]. Hence, resection planes might be tighter and missing fatty tissue might lead to further limitations in wide resections increasing the rate of positive CRM.

When looking at CRM involvement and adjuvant therapy it is very difficult to draw any conclusion. Few conflicting results of the prognostic effect of the CRM have been reported, which might again be explained by the inclusion of different histopathologic tumor types. In addition, if CRM involvement represents a more aggressive tumor type these tumors would consequently show a greater benefit of adjuvant therapy.

In conclusion, evaluation of the CRM involvement demonstrates to be a useful parameter for EC patients' prognosis. The application of CAP criteria should be preferred since patients with a poor prognosis can be

identified more distinct. When trying to achieve negative CRMs, neoadjuvant therapy and en bloc transthoracic esophageal resections show favorable results. Furthermore, further prospective studies with a precise differentiation of the pathologic classification system of tumor histopathology and use of multimodal therapy are needed.

Disclosure Statement

The authors declare no conflicts of interest.

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