

Importance of Circumferential Resection Margin in Management of Esophageal Cancer

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ABSTRACT

Esophagectomy (R0) remains the gold standard for the management of esophageal cancer. But due to close vicinity of esophagus with the major structures like heart, aorta, vertebral column, tracheobronchial tree and lungs, a wider circumferential resection is generally not possible and a R1/ R2 resection might occur. Therefore, locoregional recurrence rates of esophageal cancer are reported to be as high as 52%. The Royal College of Pathologists (RCP) and The College of American Pathologists (CAP) define circumferential resection margin (CRM) differently. A mean overall CRM involvement was found to be 40.7% (RCP criteria) and 11.8% (CAP criteria). Two meta-analyses have shown poor survival in CRM positive cases. CRM positivity in T1/ T2 lesions should not occur unless there is a surgical fault. For T3 lesions, a higher rate of CRM positivity has been documented. Therefore, a wider CRM using transthoracic approach appears mandatory, especially for T3 lesions.

Keywords: Esophageal cancer; Esophagectomy; Resection margin.

Introduction

Esophageal cancer is one of aggressive cancers with an increasing incidence worldwide.^{1,2} There has been persistently improvement in diagnostic and therapeutic modalities which have reduced the morbidity and post-operative mortality.³

Usual treatment protocols include preoperative chemoradiation for squamous cell carcinoma and perioperative chemotherapy for adenocarcinoma. Hence, Surgery remains the gold standard treatment at present.^{4,5}

Like any other gastrointestinal malignancies, achieving R0 resection remains the main goal of surgery. But due to close vicinity of esophagus with the major structures like heart, aorta, vertebral column, tracheobronchial tree and lungs, a wider circumferential resection is generally not possible and a R1/ R2 resection might occur. Therefore, locoregional recurrence rates of esophageal

cancer are reported to be as high as 52%.^{6,7} 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 recurrence⁸⁻¹⁰, while the role of circumferential resection margin (CRM) is still debatable in the literature.

There is no unanimous definition of CRM in esophageal cancer. The Royal College of Pathologists (RCP) defines a positive CRM as a tumor at or within 1 mm of the resection margin¹¹ while The College of American Pathologists (CAP) only regards the occurrence of tumor at the resection margins as CRM positive.¹² In metanalysis, Chan et al showed Rates of CRM involvement were 15.3 per cent (173 of 1133) and 36.5 per cent (889 of 2433) according to the CAP and RCP criteria respectively.¹³ The median CRM positive rates 40.0% (range, 20.3% to 67.4%) and 17.2% (range, 5% to 25.5%) according to the RCP and CAP criteria, respectively were reported in another metanalysis by Wu et.al.¹⁴ Few studies

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have directly compared the prognostic significance of the different classification systems with conflicting results.¹³⁻¹⁸ These data suggest, there is an urgent need to redefine the technique of esophagectomy where the boundaries of excision would follow embryological or fascial plane rather than simply adventitial plane. Motivated by results of total mesorectal excision for rectal cancer from the point of view of reducing CRM rates and locoregional recurrences¹⁹, there has been a growing evidence suggesting existence of “Meso-esophagus”.²⁰⁻²² The procedure has been named as Total Mesoesophageal excision (TME).^{21,23} TME for esophageal cancer appears to decrease the incidence of locoregional recurrence by reducing the rates of CRM positivity.²³

Here, we review the importance of CRM and effect of CRM positivity on locoregional recurrence and overall survival.

Impact on Survival

Majority of studies confirmed a prognostic impact of CRM on survival. Two available meta-analysis found a significant association between a positive CRM and patients' survival irrespective of RCP or CAP criteria. In the meta-analysis by Chan et al., 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 was found. The CAP criteria resulted in larger ORs than the RCP criteria.¹³ In addition, Wu et al.¹⁴ in another meta-analysis of 19 studies (2 prospective and 17 retrospective) found the pooled hazard ratio (HR) for survival to be 1.510 (95% CI, 1.329–1.717; $p < 0.001$) and 2.053 (95% CI, 1.597–2.638; $p < 0.001$) according to the RCP and CAP criteria, respectively. Positive circumferential resection margin was associated with worse survival in patients with T3 stage disease according to the RCP (HR, 1.381; 95% CI, 1.028–1.584; $p < 0.001$) and CAP (HR, 2.457; 95% CI, 1.902–3.175; $p < 0.001$) criteria, respectively. Positive circumferential resection margin was associated with worse survival in patients receiving neoadjuvant therapy according to the RCP (HR, 1.676; 95% CI, 1.023–2.744; $p = 0.04$) and CAP (HR, 1.847; 95% CI, 1.226–2.78; $p = 0.003$) criteria, respectively. Both the meta-analyses showed poor survival of CRM positive patients. Other recent retrospective studies also supported these results.^{3,17, 24,25} 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 However, some studies were not able to show an effect of the CRM status on overall survival.^{18, 26-29} Khan et al.²⁶ investigated 329 patients treated for esophageal squamous cell carcinoma (SCC) by esophagectomy. No statistically significant association between the CRM status and survival was observed ($p = 0.57$). In a study by O'Farrell et al., a positive CRM according to RCP or CAP criteria did not show any influence on survival in multivariate analysis.¹⁸ In a recent study by Ghadban et al., a total of 180 patients following esophagectomy were compared.²⁹ 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.

While analyzing specifically pT3N0M0 in SCC in 112 patients without neoadjuvant treatment, CRM+ was found in 77.7% with median overall survival (OS) of 29.1 months according to RCP; whereas CRM+ was found in 21.4% with median OS of 24.3 months according to CAP ($p = ns$). Reclassifying CRM with a cutoff value of 600 microns showed better OS with CRM > 600 microns than CRM < 600 microns ($p = .003$).³⁰

Impact on Locoregional Recurrence

Loco-regional recurrences seem to be the predominant failure pattern in CRM positive patients.^{28,31} In the first study of CRM involvement by Sagar et al., 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%).³² These results were later proven by other studies, which also identified a prognostic role of a positive CRM on recurrences.^{3,16,17,24,25,28,33} Chao et al.³³ found a significant influence of an involved CRM not only on locoregional but also on distant recurrences, while an involvement to the CRM of less than 1 mm was associated with early locoregional 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.²⁴ Interestingly, Verhage et al. were able to demonstrate a prognostic effect only when using CAP criteria in multivariate analysis (HR 2.086; 95% CI 1.320–3.296; $p = 0.002$).¹⁶ CRM involvement was

the strongest predictor of recurrence in their analysis comprising only pT3 adenocarcinomas.¹⁶ The results of the latter study were supported by Hulshoff et al. who identified margin involvement according to CAP criteria to be associated with local re-currence in surgically treated patients ($p = 0.004$) as well as in patients who also received neoadjuvant therapy prior to surgery ($p = 0.001$).¹⁷ However, when applying RCP criteria, no significant associations were observed.¹⁷ 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 ($p = 0.02$).²⁵ In contrast to the latter studies, the paper of Harvin et al. investigated only pT3 adenocarcinomas and authors failed to detect an effect of a positive CRM on recurrences after performing a propensity score matching by histopathological and clinical parameters.³⁴

Impact of Neoadjuvant Treatment

Perioperative chemotherapy and preoperative chemoradiotherapy has become the standard of treatment for esophageal cancer.^{4,5} However, the influence of neoadjuvant therapy on the CRM remains unclear. Chao et al. reported a decline in CRM involvement when comparing patients treated with surgery alone (CAP 22.2%, RCP 40.1%), preoperative chemotherapy (CAP 15.8%, RCP 34.3%), and preoperative chemoradiation (CAP 11.2%, RCP 31.9%).³³ In a subset of 123 patients, Thompson et al. found significantly less CRM involvement in patients treated with neoadjuvant chemoradiotherapy as compared to patients who were treated by surgery alone (22 vs. 50%; $p < 0.001$).³⁵ However, no association between CRM status and survival was observed in these patients ($p = 0.184$).³⁵ The influence of neoadjuvant therapy on CRM status was supported by Reid et al.³⁶, who found a reduction of CRM involvement in patients treated with neoadjuvant chemoradiotherapy in multivariate analysis (OR 0.116; 95% CI 0.035–0.382; $p < 0.0001$). In contrast, Sujendran et al.³⁷ 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 treatment, irrespective of CAP or RCP criteria. Thus, the authors proposed an additional CRM cutoff of 0.3 mm for patients treated with neoadjuvant therapy.¹⁷ Okada et al. 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.²⁵ Another retrospective study in 177 patients specifically looked at perioperative chemotherapy and surgery and CRM. The majority (94.9%) received ECX (epirubicin, cisplatin, capecitabine), and all had clear proximal/distal resection margins. CRM was defined as positive 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. Positive CRM was found in 46.9%. Of them, infiltrated CRM was recorded in 20.3% and close CRM in 26.6%. Adjuvant chemotherapy was administered to 74.6% patients. Lympho-vascular invasion and primary site in the lower esophagus were independently associated with higher risk of CRM positivity. 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 positive and CRM-patients (7.1% vs. 9.6%, $p = 0.736$), as well as in infiltrated vs. non-infiltrated CRM (CRM- and close CRM) (0% vs. 11.0%), $p = 0.110$). Authors concluded, although CRM status is associated with poor outcome, it does not represent an independent prognostic factor.³⁸

A recent review on pT3 SCC of esophagus ($n = 217$) divided the patients in upfront surgery ($n = 138$) vs chemoradiation followed by surgery. CRM status was assessed and divided into CRM > 1 mm, $0 < CRM < 1$ mm, and tumor at CRM. In the upfront surgery group, patients with $0 < CRM < 1$ mm showed equivalent overall survival to those with CRM > 1 mm (log-rank $p = 0.817$) and significantly outlived those with tumor at CRM (log-rank $p < 0.001$). However, in the chemoradiation + surgery group, CRM > 1 mm failed to show survival superiority to CRM between 0 and 1 mm or involved by cancer (log-rank $p = 0.390$). Authors concluded, a negative CRM, even though being < 1 mm, is adequate for pT3 Esophageal SCC patients undergoing upfront esophagectomy. However, the CRM status is less prognostic in pT3 patients undergoing chemoradiation followed by esophagectomy.³⁹

Impact of Adjuvant Treatment

A majority of the patients treated for esophageal cancer 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 radiochemo-therapy ($p = 0.015$). 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.²⁸ investigated the effect of postoperative radiotherapy in esophageal squamous cell carcinomas 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 ($p = 0.057$).²⁸

Impact of Type of Surgery

Association of type of surgery and CRM has been also a controversial issue. Esophagectomies can be done using either transhiatal or a transthoracic technique. The influence of the surgical approach on CRM involvement is still debatable. Suttie et al.⁴⁰ found an increased number of positive CRM involvement in patients treated with a transhiatal approach as compared to a transthoracic approach. Another study 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 ($p = 0.086$).²⁹ Scheepers et al.⁴¹ further divided transhiatal esophageal resections into a laproscopic and an open group. However, they were not able to detect any significant differences in regards to CRM involvement ($p = 0.192$).⁴¹ Similarly, Pultrum et al.⁴² could not find an association between type of surgery and CRM ($p = 0.693$).⁴²

Conclusion and Future Direction

Hence, it is obvious from the literature that a wide range of CRM involvement (8.6–83.1%) has been reported.^{3,28} This is due to various pathologic classification systems -RCP and CAP criteria.^{11,12} The criteria of positive CRM

in esophageal cancer by the RCP are partially derived from rectal cancer.^{43,44} 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. 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.¹⁴ reported an advantage of the CAP criteria over the RCP criteria in terms of prognostic significance, risk stratification.¹⁴

Nevertheless, R1 status in early tumors (T1-2) is considered to be caused by inadequate surgery.^{16,17,45,46} Results of such studies investigating the CRM status including early tumor stages have to be interpreted with caution.

Whatsoever, evaluation of the CRM remains an extremely important prognostic factor in esophageal cancer.⁴⁷ A deep understanding of various surgical procedures would definitely show a transthoracic approach to be a better approach to achieve wider CRM, especially for T3 tumors. Though concept of TME sounds very scientific, evidences are still lacking. Logically, dissection in an mesoesophageal and embryological plane would definitely help in achieving an extra layer of dissection beyond the esophageal adventitia and this, in return, would reduce the locoregional recurrence.

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