

Lack of Independent Significance of Close (Less Than 1 mm) Circumferential Resection Margin; After Neoadjuvant Treatment for Esophageal Cancer

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Abstract

Esophageal cancer is ranked sixth on cancer related deaths. There is gradually increasing interest in circumferential resection margin (CRM) and in comparison to rectal cancer where margin of less than 1 mm as involved is standardized debate is still open in esophageal cancer. There are currently two different criteria being used to define circumferential resection margin, the College of American Pathologist (CAP) used microscopic disease at the margin as involved margin, while the UK Royal College of Pathologist (RCP) take anything less than 1 mm as involved margin. There are studies in favor of both groups and no consensus has been reached yet. We also looked at which definition of CRM impacts overall and disease free survival more.

Methods: We retrospectively reviewed all patients with esophageal cancer who underwent neoadjuvant treatment followed by surgery at Shaukat Khanum Memorial Cancer Hospital, from January 2004 to June 2012. Minimum follow up period of 2 years was chosen as majority of recurrences occur within first 2 years. We divided our patients according to both CAP and RCP criteria into those with CRM involved and not involved. Cox univariate analysis was performed to determine variables which impact overall and disease free survival. Finally multivariate analysis was performed to determine independent significance of CRM. Data was analyzed using spss version 19.

Results: Squamous cell carcinoma was the most common diagnosis 72% (n 84/116) followed by adenocarcinomas 28% (n 32/116). Our median follow up was 26 months. According to RCP criteria 14% (n 16/116) patients had CRM positive while 86% (n 100/116) were negative. Mean survival in CRM negative group was 69 months (95% Confidence interval 58.9 to 79.7 months) compared to 37 months (95% CI 16.9 to 57.7 months) in CRM positive group. This difference was statistically significant (p value 0.009). According to CAP criteria 10 patients were CRM positive. Mean survival for patients with margins not involved according to CAP criteria was 68 months (95% CI 57.9 to 78.1 months) while it was only 20 months (95% CI 13.5 to 26.9 months) for CRM positive patients. It was again statistically significant difference (p value 0.002).

On performing univariate analysis following factors had significant impact on overall survival, CRM involvement both by CAP (Hazard ratio 3.3) and RCP (HR 2.4) criteria, pathological stage III (HR 3.1), perioperative morbidity (HR 1.8), recurrence of disease (HR 3.3), and pathological nodal disease (HR 1.8). Multivariate cox regression was performed using factors that were statistically significant on univariate analysis to determine the independent significance of CRM status using RCP and CAP criteria. Only CRM involvement according to CAP criteria (HR 2.6 p value 0.04), perioperative morbidity (HR 1.9 p value 0.04) and recurrence (HR 3.3 p value 0.001) had independent impact on survival.

Conclusion: In T3 esophageal cancer after neoadjuvant treatment there is lack of independent significance of close circumferential resection margin (less than 1mm). But involved CRM impacts survival.

Keywords: Circumferential Resection Margin; Neoadjuvant Treatment; Esophageal Cancer

Introduction

Esophageal cancer is ranked sixth on cancer related deaths [1]. Neoadjuvant treatment followed by surgery is the preferred treatment option for locally advanced esophageal cancer [2-4]. There is gradually increasing interest in circumferential resection margin (CRM) and in comparison to rectal cancer where margin of less than 1 mm as involved is standardized; debate is still open in esophageal cancer. This is mainly owing to lack of mesentery and serosa as well as close proximity to major vascular structures which limit the en block resection with wider margins.

There are currently two different criteria being used to define circumferential resection margin, the College of American Pathologist (CAP) used microscopic disease at the margin as involved margin, while the UK Royal College of Pathologist (RCP) take anything less than 1 mm as involved margin. There are studies in favor of both groups and no consensus has been reached yet [5,6]. One problem with majority of these studies is lack of neoadjuvant treatment in majority of their locally advanced patients. Only study to look at the CRM after neoadjuvant treatment has looked at adenocarcinomas only [7-10].

Since neoadjuvant treatment is standard for clinically T3 esophageal cancers, we performed this review to look at the impact of neoadjuvant treatment on circumferential resection margin of this group. We would like to determine how many of these patients were left to have close (less than 1 mm CRM) or involved (microscopically positive) margins, and how it affected the overall survival. We also want other studies with neoadjuvant treatment to separately publish their results to help us better understand the impact of neoadjuvant on CRM.

Methods

We retrospectively reviewed all patients with esophageal cancer who underwent neoadjuvant treatment followed by surgery at Shaaukat khanum memorial cancer hospital, from January 2004 till June 2012. Ethical review committee approval was taken. 135 patients were identified, after excluding patients with T2N1 and T4 disease, 116 patients were available for final analysis. Minimum follow up period of 2 years was selected as majority of recurrences occur within first 2 years. Patients were staged using endoscopy, endoscopic ultrasound, computerized tomography and PET/CT. Patients were staged according to 7th edition AJCC classification [11].

Patients received external beam radiation between 45 and 55 Gy with concurrent cisplatin and 5FU. Patients were restaged with CAT scan after 4 weeks of completing neoadjuvant treatment and were then planned for surgery depending on the resectability status. Patients with metastasis or T4b disease were not offered surgery. Patients were followed quarterly for first 2 years and then semiannually for 1 year and yearly thereafter till completion of 5 years. Patients required CAT scan every year to look for any radiological evidence of recurrence [12]. All patients had documented circumferential margin status. We divided our patients according to both CAP and RCP criteria into those with CRM involved and not involved.

Chi square test was used to compare categorical variables while t test was used to compare means. Kaplan Meir survival curves were used to analyze overall and disease free survival and log rank test was used to compare survival for both groups using both CAP and RCP criteria. Cox univariate analysis was performed to determine variables which impact overall survival. Finally multivariate analysis was performed to determine independent significance of CRM. Data was analyzed using spss version 19.

Results

Mean age of our patients was 51 years (Std dev. 11years). Males were 55% (n 64/116) while females were 45% (n 52/116). Squamous cell carcinoma was the most common diagnosis 72% (n 84/116) followed by adenocarcinomas 28% (n 32/116). Tumors were poorly differentiated in 26% (n 30/107) patients. On preoperative staging 66% (n 77/115) of our patients were Stage III. Majority of our patients received chemoradiotherapy as neoadjuvant treatment, which was used in 93% (n 108/116) patients. Transhiatal esophagectomy was the most commonly performed procedure and was used in 50% (n 58) of study population. Other baseline characteristics were shown in table 1.

Characteristics	Value	%
Age	51.3 years +/- 11.2 years	
Gender		
Male	64	55.2
Female	52	44.8
Diagnosis		
Adenocarcinoma	32	27.6
Squamous Cell Cancer	84	72.4
Grade		
Well	14	12.1
Moderate	63	54.3
Poor	30	25.9
Missing	09	07.8
Location		
Upper Thoracic	01	0.9
Mid Thoracic	29	25
Lower Thoracic	78	67.2
GE junction	08	06.9
Procedure		
Transhiatal	58	50
Hybrid 3 stage	14	12
Minimally Invasive	28	24
Open 3 Stage	09	08
Lap Transhiatal	07	06
pStage		
pCR	49	42.2
Stage I	04	03.4
Stage II	51	44
Stage III	12	10.3
CAP		
CRM Involved	10	08.6
CRM Not Involved	106	91.4
RCP		
CRM Involved	16	13.8
CRM Not Involved	100	86.2

Table 1: Baseline patient characteristics.

Our median follow up was 26 months. According to RCP criteria 14% (n 16/116) patients had CRM positive while 86% (n 100/116) were negative. When looked at overall survival, there were 44 events during our study period. There were 11 deaths in CRM positive while 33 deaths in CRM negative groups. The median survival of CRM negative group was 68 months; compared to 19 months in CRM positive group, log rank was 0.009 (Figure 1).

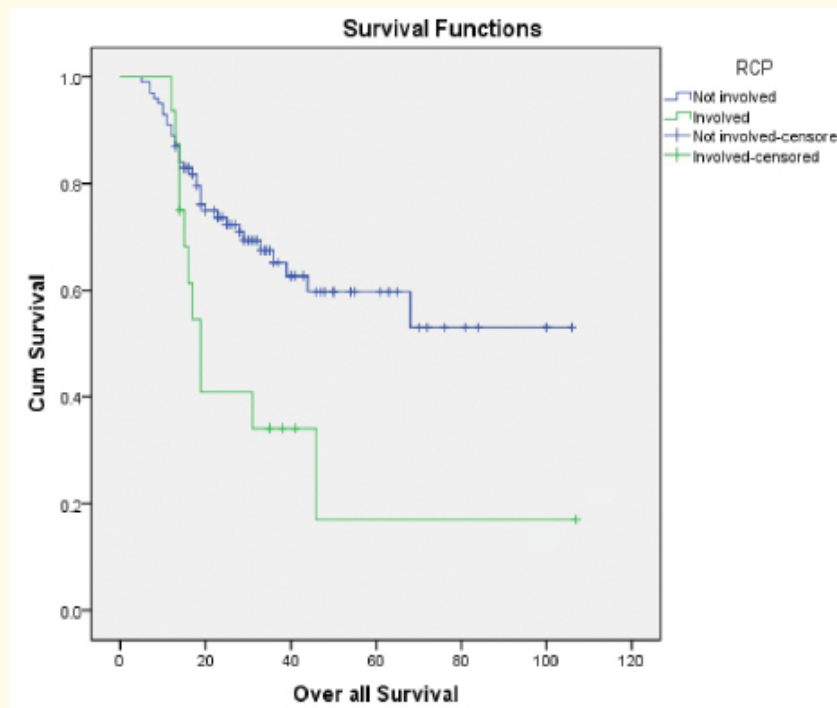


Figure 1: Impact of CRM involvement on overall survival. Log rank was 0.009.

According to CAP criteria 10 patients were CRM positive. There were 7 deaths in CRM positive patients. Median survival for patients with margins not involved according to CAP criteria was 68 months, while it was 15 months for those with positive margins. It was again statistically significant difference on log rank test (p value 0.002) (Figure 2).

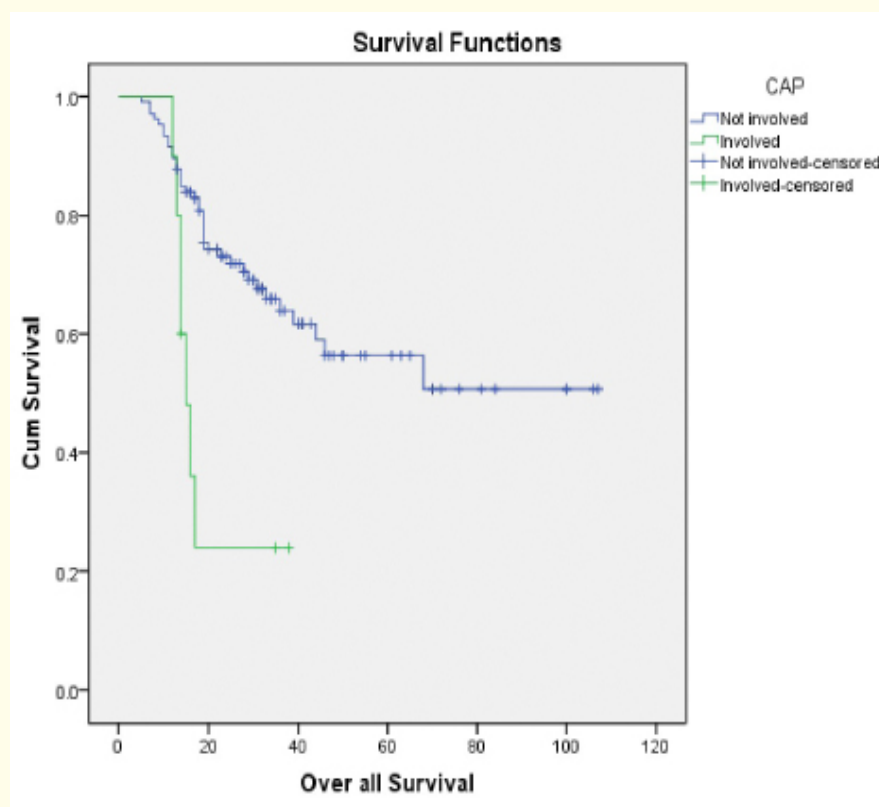


Figure 2: Impact of CRM involvement using CAP criteria. Log rank was 0.002.

On performing univariate analysis following factors had significant impact on overall survival, CRM involvement both by CAP (Hazard ratio 3.3) and RCP (HR 2.4) criteria, pathological stage III (HR 3.1), perioperative morbidity (HR 1.8), recurrence of disease (HR 3.3), and pathological nodal disease (HR 1.8). Multivariate cox regression was performed using the factors that were statistically significant on univariate analysis to determine the independent significance of CRM status using RCP and CAP criteria. Only CRM involvement according to CAP criteria (HR 2.6 p value 0.04), perioperative morbidity (HR 1.9 p value 0.04) and recurrence (HR 3.3 p value 0.001) had independent impact on survival. Results were shown in table 2.

Variable	Univariate			Multivariate		
	HR	95%CI	p- value	HR	95%CI	p- value
Age greater than 40 Age less than 40	0.51	0.20 - 1.29	0.16			
Gender Male Female	0.62	0.34 - 1.15	0.13			
Diagnosis Squamous cell cancer Adenocarcinoma	1.29	0.67 - 2.46	0.45			
Pathological node No Yes	1.82	0.97 - 3.40	0.06	0.86	0.39 - 1.94	0.73
p Stage pCR Stage I Stage II Stage III	0.96 2.02 3.14	0.13 - 7.39 1.01 - 4.04 1.29 - 7.63	0.97 0.05 0.01	1.05 1.52 1.16	0.14 - 8.16 0.71 - 3.27 0.35 - 3.88	0.96 0.28 0.80
Perioperative Morbidity No Yes	1.81	0.98 - 3.32	0.05	1.91	1.03 - 3.54	0.04
Recurrence No Yes	3.29	1.80 - 5.99	0.00	3.33	1.67 - 6.66	0.001
CAP Not involved Involved	3.37	1.47 - 7.74	0.004	2.64	1.05 - 6.63	0.04
RCP Not involved Involved	2.40	1.21 - 4.76	0.012	1.28	0.51 - 3.24	0.59

Table 2: Variables analyzed in Univariate and multivariate analysis. In addition comorbid conditions, procedure and grade of tumor were analyzed in univariate and were not significant.

Discussion

We had presented our data of clinically T3 esophageal cancers treated with neoadjuvant treatment to determine if their CRM status post neoadjuvant had impact on overall survival. Out of 116 patients who had clinically threatened CRM, on final histopathology only 13.8% patients had disease within 1 mm of CRM, while 8.6% had microscopic disease at CRM. This could help us conclude that neoadjuvant treatment improved patient outcome by reducing the risk of CRM involvement. We had shown that both RCP and CAP significantly impact survival on univariate analysis, however on multivariate analysis only CAP criteria impact survival while RCP lost its independent significance. This result was similar to various published series on the topic. But our result need to be looked carefully as we were reporting patients who had received neoadjuvant treatment prior to surgery, so did that had an added benefit for the patient with close margin or was it less number of patients need to be seen. More studies were required to answer this question clearly.

Sagar, *et al.* in 1993 published his results of 50 esophagectomies. 20 patients in his series had CRM involvement of less than 1 mm. At a median follow up of 36 months, 11 of these 20 patients had developed recurrence while only 4 out of remaining 30 patients developed recurrence (p value < 0.01). This analysis led him to conclude that circumferential resection margin involvement lead to increase in local recurrence [13]. This study led to the development of RCP criteria for circumferential resection margin involvement. In 2001 Dexter, *et al.* reported his series of 135 resectable esophageal cancers, he kept the CRM involvement criteria as RCP (microscopic disease within 1 mm of CRM). He reported that 64 (47%) patients were CRM +ve and median survival for this group was 21 months compared to 39 months in CRM -ve group (p value 0.015) [14]. Griffiths., *et al.* in 2006 reported their results of 249 esophagectomies. They also kept CRM involvement criteria as RCP. In this study 79 patients had CRM involvement with median survival of 18 months compared to 37 months in CRM negative patients (p value 0.0001) [5]. All these studies supported RCP criteria of CRM involvement. Studies from North America had shown that only microscopic disease at circumferential inked resection margin impacts survival. And this had led to the controversy, as to which group to follow.

Recently studies had compared the two criteria to answer this question. In 2009 Deeter, *et al.* reported results for 135 patients with T3 disease. He showed that 83 patients had CRM +ve according to RCP criteria while 16 had CRM +ve according to CAP. Median survival for CAP CRM +ve patients was 8.33 months compared to 29.8 months in CRM -ve group. While median survival for RCP CRM +ve patients was 22.23 months compared to 28.47 months in CRM -ve patients. Also on univariate and multivariate analysis RCP failed to impact survival [6]. In 2012 Harvin, *et al.* looked at close (less than 1 mm) and involved (microscopic disease at Radial margin) after neoadjuvant chemoradiotherapy. In this study when comparing close margin with uninvolved margin, median survival was 28 months versus 50 months respectively (p value 0.81). While comparing those with microscopic disease at radial margin versus uninvolved margin, median survival was 8 months compared to 28 months (p value 0.01) [15]. This again showed lack of significance of close margin in esophageal cancer. Verhage, *et al.* in 2011 studied 132 patients with T3 disease, and compared the RCP criteria to CAP for impact on overall and disease free survival. He showed that median survival for 26 patients with CRM involvement according to CAP criteria was 9.4 months compared to 21.6 months in CRM negative patients (p value 0.000). In 89 CRM positive patients according to RCP criteria, median survival was 16.4 months compared to 21 months in CRM negative patients (p value 0.144) [16]. All these results were comparable to our study.

CRM involvement, residual disease after neoadjuvant treatment and pathological nodal disease were predictors of survival in esophageal cancer. However which CRM to be taken as positive remained controversial. With the upcoming data on comparative studies for RCP criteria versus CAP, there is growing evidence showing CAP criteria to be more meaningful and independent predictor of survival. Close margin lack independent impact on survival when used in multivariate analysis. This argument is important as close proximity of esophagus to major vascular and bronchial structures make en block resection difficult in bulky T3 tumors. Neoadjuvant treatment will reduce the bulk of disease and help in these patients.

Our study has limitation of being retrospective review. It has small sample size. Patients with positive margin are less. But this can at the same time be the strength of our study to show the true response to neoadjuvant treatment in T3 esophageal cancer patients. We have shown the true representation of clinical population. More such studies are needed to reach a consensus about the definition of CRM.

Conclusion

In T3 esophageal cancer after neoadjuvant treatment there is lack of independent significance of close circumferential resection margin (less than 1 mm) involvement.

Disclosure

We performed this retrospective review of T3 esophageal cancers, undergoing resection following neoadjuvant treatment. Ethical review committee approval was taken for this study. There is no conflict of interests and no financial support was provided for this study.

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