Kolon Kanserinde Radiyal Sınırın Prognostik Önemi

The Effect of Prognostic Importance Of Radial Margin In Colon Cancer

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ÖZ

GİRİŞ ve AMAÇ: *Kolon kanser cerrahisinde, tümör yerleşiminin kolonun peritonsuz kısmında ya da anatomik olarak dar mezenterli parçasında olması ile lokorejiyonel reküren hastalık ve azalmış sağkalım arasında ilişki olduğu gösterilmiştir. Çalışmada küratif rezeksiyon geçiren kolon kanserinde radiyal sınır (sirkumferansiyel rezeksiyon marjin (CRM)) tutulumunun prognostik öneminin araştırılması amaçlanmıştır.*

YÖNTEM ve GEREÇLER: *Dokuz Eylül Üniversitesi Tıp Fakültesi,2005–2008 arasında radikal rezeksiyon yapılan 179 kolon kanserli (sadece pT3-pT4 kolon tümörleri) hastanın kayıtları retrospektif olarak değerlendirildi. Histopatolojik incelemede CRM; tümörün en derin penetrasyonununa en yakın retroperitoneyal ya da peritoneyal adventisyal yumuşak doku marjini olarak değerlendirildi.*

BULGULAR: *CRM pozitifliği %14 bulundu. CRM tutulumu ile; diferansiyasyon derecesi, tümör invazyon derinliği, lenf nodu tutulumu, venöz invazyon, lenfatik invazyon, tümör invazyon sınır tipi ve lokal nüks gelişimi arasında anlamlı ilişki saptandı. Venöz invazyon pozitifliği ve tümör invazyon derinliği ile CRM arasında anlamlı ilişki saptandı.Lokal nüks;CRM pozitiflerde artmış olarak bulundu.CRM pozitiflerde hastalarda hastalıksız sağ kalım(355±74 gün),CRM negatiflere göre (609±45 gün) anlamlı düzeyde azalmıştı.*

TARTIŞMA ve SONUÇ*: Bu çalışmada kolon kanserlerinde CRM pozitifliği, ilerlemiş tümör yayılımının göstermiştir. CRM pozitifliği onkolojik açıdan nüks ve sağkalımda önemli bir belirleyicidir. Kolon kanserli hastaların histopatolojik raporlarında bu prognostik faktörün yorumlanmasının rutin olmasını düşünmekteyiz.*

Anahtar ***Kelimeler:*** *Radiyal sınır, kolon kanseri, prognostik önemi*

ABSTRACT

INTRODUCTION: *In colon cancer surgery, tumor's existence in the colon not covered with peritoneum or its being in the narrow mesenteric compartment is related with locoregional recurrence of the cancer and decreased survival. This study investigates the prognostic significance of the involvement of the radial margin (circumferential resection margin (CRM)) in colon cancer patients undergoing curative resection.*

METHODS: *The records of 179 colon cancer patients (only pT3-pT4 colon tumors) undergoing radical resection in the Medical Faculty of Dokuz Eylul University between 2005 and 2008 were evaluated retrospectively. In the histopathologic examination, CRM was evaluated as the retroperitoneal or peritoneal adventitial soft tissue margin nearest to the deepest penetration of the tumor.*

RESULTS: *CRM was present in 14% of the patients. CRM involvement was significantly correlated with differentiation grade, tumor invasion depth, lymph node involvement, venous invasion, lymphatic invasion, tumor invasion margin type and local recurrence development and also with the presence of venous invasion and tumor invasion depth. Local recurrence frequency was higher in patients with CRM. Disease free survival significantly decreased in patients with CRM involvement (355±74 days) than in patients without CRM involvement (609±45 days).*

DISCUSSION AND CONCLUSION: *In this study, the presence of CRM involvement in colon cancers is the marker of advanced tumor spread. The presence of CRM is an important determinant of the possibility of recurrence or survival. Therefore, interpretation of this prognostic factor should be routine in the histopathological reports of colon cancer patients.*

Keywords: *Radial margin, colon cancer, prognostic ımportance*

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Başvuru Tarihi: 19.03.2018
Kabul Tarihi: 20.06.2018

INTRODUCTION

The basic treatment method in multidisciplinary treatment of colon cancer is surgical resection. Pathologic analysis of the resection piece after surgical intervention is the strongest basis for assessment of prognosis, to monitor surgical sufficiency and to ensure quality control. Though pathologic stage is the strongest predictor of postoperative outcomes, there are a group of pathologic properties with prognostic meaning independent of stage. These are histologic degree, lymphatic and venous invasion, type of margin of tumor invasion and surgical margins. When CRM is assessed on solid organ resection specimens, information about whether the tumor was fully cleaned in terms of oncologic surgery may be learned. This "sufficient resection" principle in colon tumors is a very important prognostic facter for oncologic principles (1).

Colorectal cancer specimens include proximal and distal margins of traditional surgical resection. A study by Quirke et al. at the beginning of the 1980s, currently accepted as foundational, defined a new resection margin in rectum cancer resection specimens and gave it the name "circumferential resection margin" or "radial margin". They emphasized that this surgical margin was very important in terms of oncologic outcomes and defined it as the adventitial margin of soft tissue closest to the deepest penetration point of tumors in the mesorectum appropriately resected with surgical technique and dissected as a block without disrupting integrity. Rectum tumors below the peritoneal reflection are at risk of CRM positivity due to retroperitoneal localization and the difficulty in accessing the region due to anatomic structure. Though tumors below the reflection have total mesorectal excision (TME) fully applied, if the desire is to reduce the high local recurrence rates, firstly care must be taken that the dissection is radial margin negative (tumor-free) during tumor resection (2). The basis of this information is that the circumferential resection margin in colon cancers can be used as a variable or predictor affecting local recurrence, distant metastasis, general survival and disease-free survival. Good evaluation of this potential margin will strongly affect the decision for adjuvant therapy after surgery, especially for cases with controversial indications. However, to the best of our knowledge, there are insufficient studies in the literature about this topic.

In this study, the effect of CRM in colon cancer on local recurrence, distant metastasis, general survival and disease-free survival was researched.

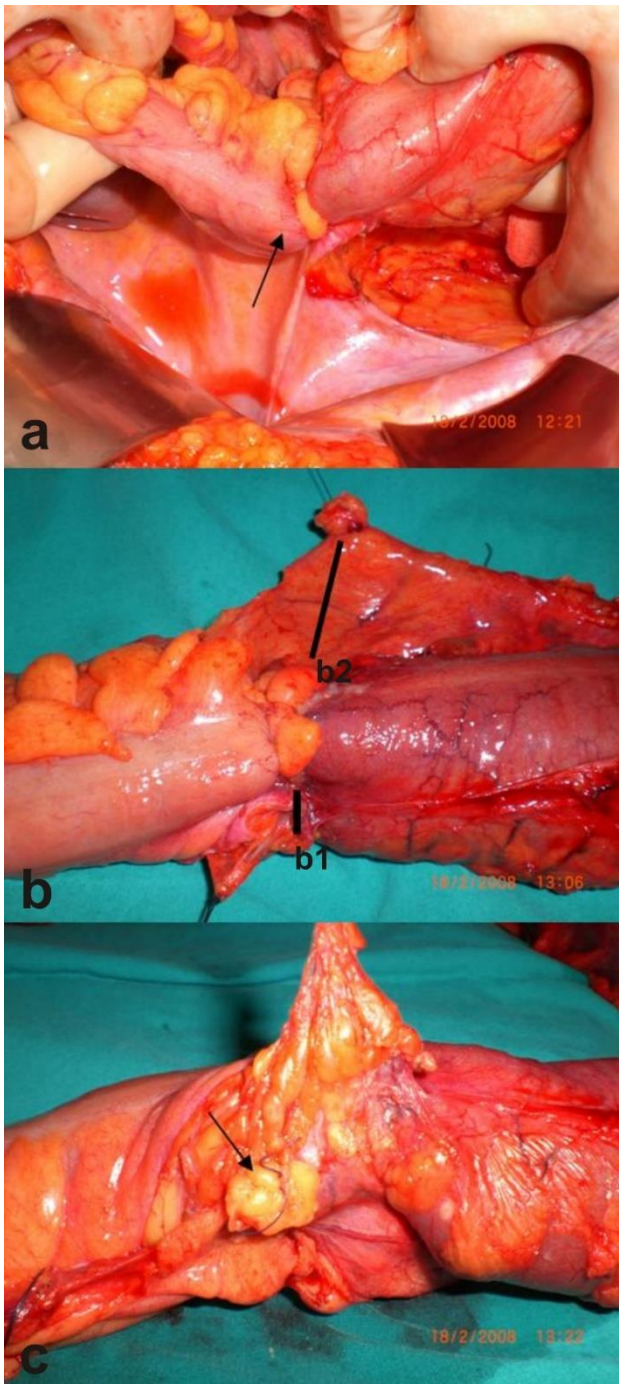
MATERIAL AND METHODS

The study prospectively collected clinicopathologic data of 179 colon cancer patients attending Dokuz Eylül University Medical Faculty, General Surgery Department Colorectal Surgery Unit from January 2005 to January 2008 and retrospectively assessed this data.

The study defined CRM as the soft tissue adventitial margin of the point where the tumor showed deepest penetration.

1.Demographic characteristics and clinical properties of the tumor: The clinical characteristics and following factors were reviewed for every patient included in the study. Age information was obtained from the pathology reports of cases. For statistical analysis, cases were divided into two groups as those above and below 65 years. Sex information was obtained from the pathology reports. Tumor localization was examined in two groups as those in the narrow mesentery compartment of the colon (cecum, hepatic flexure, splenic flexure) and those in the wide mesentery compartments (emerging, transverse, descending, sigmoid). Clinical diagnosis was assessed during surgery as obstruction linked to the tumor.

2.Histopathologic investigation and properties: Macroscopic investigation determined specimen size, tumor size, localization, and distance from surgical margins **(Plates 1 and 2).** All of the external face of the tumoral region segment was stained with India ink. Then this region was sliced at 1 cm intervals perpendicular to the lumen. Samples were taken for microscopic examination including the mesenteric surgical margin (one block) marked clinically and if present the main lymph node (one block) in the area, and in areas observed to be closest to the tumor separately in areas covered and not covered by the peritoneum (2-6 blocks). Additionally, at least 3 tissue blocks were prepared from the tumor. Lymph node dissection was performed. A block was prepared from lymph nodes with diameter under one cm. For larger nodes, blocks were prepared for each 0.5 cm. Proximal and distal surgical margins and other variations identified in colon mucosa were sampled for investigation under a microscope.



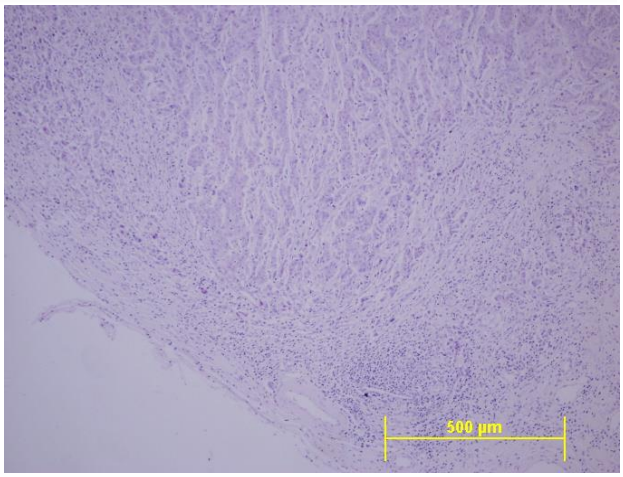


Plate 3. Radial (circumferential) surgical margin positive. Red arrow shows distance less than 1 mm from the tumor area surgical margin (H&E, x10)

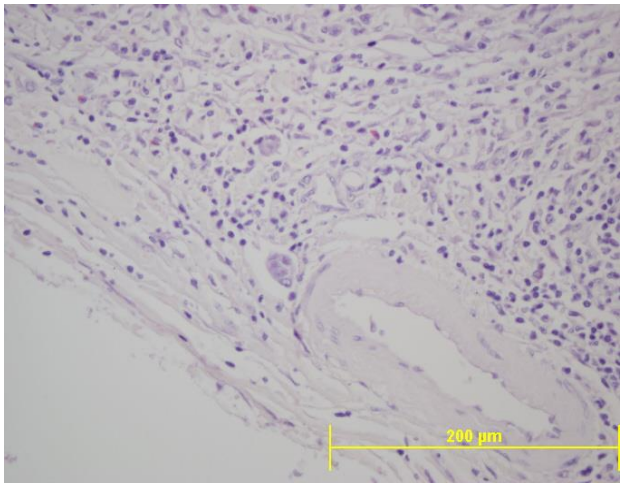


Plate 4. Tumor positivity at larger magnification (H&E, x40)

Patients with suspected endocrine differentiation had chromogranin-A etc. immunohistochemical investigations performed. Pathology reports were completed considering the report recommendations of the "American College of Pathologists" and the AJCC/UICC TNM, 6th reprint (updated January 2005) list.

Pathology reports were assessed by organizing data as follows.

1)Histopathologic type: classified as adenocarcinoma and others for statistical analysis.

2) Hıstologic grade: cases were divided into 3 groups according to glandular structuring. Tumors with more than 95% glandular structuring were Grade 1 (well-differentiated), tumors with 50-95% glandular structuring were Grade 2 (moderately differentiated) and tumors with 5-50% glandular

structuring were Grade 3 (poorly differentiated). In statistical studies Grade 1 and 2 were low-grade and Grade 3 was classified as high grade (3,4,5).

3)Local invasion: According to degree of local penetration tumors were pT1 if they invaded the submucosa, pT2 if they invaded the muscularis propria, pT3 if they invaded the subserosa or pericolic tissue, and pT4 if they invaded neighboring organs or structures. The study included pT3 and pT4 tumors.

4) Presence of venous invasion.

5) Presence of lymph vein invasion.

6) Presence of perineural invasion.

7) Tumor invasion margin type: The invasion of the tumor into surrounding tissue was divided into expansive (growing by pushing) and infiltrative types (growing by extending between normal structures).

8) Lymph node status: the number of dissected lymph nodes and number of lymph nodes with involvement were examined. For statistical analysis lymph node status was grouped as (+) and (-).

9) Form of lymphatic invasion: investigated in three groups as intramural including invasion of the muscularis propria and mucosa; extramural including invasion of areas outside the muscularis propria; and intramural + extramural.

10) Stage: Staging was determined using the TNM system.

3. Follow-up protocol: Follow-up after surgery at the Dokuz Eylül University General Surgery Department Colorectal Surgery Unit included history, physical examination and CEA levels every three months for the first two years, thorax radiography and especially abdominal ultrasonography (USG) or computed tomography (CT) for the liver and colonoscopy once per year.

4. Oncologic outcomes: Recurrence and treatment were investigated along with survival outcomes.

Statistical method

When the study data was assessed, descriptive statistical methods (mean, standard deviation) along with one-way ANOVA and independent variables t-test were used for comparison of quantitative data. The chi-square test was used for comparison of qualitative data. The Kaplan-Meier method and log-rank test were used for survival analysis. The correlation between CRM status and clinicopathologic variables was assessed with univariate analysis. Variables identified to have significant correlation were tested with the multivariate analysis method (binary logistic regression test). The correlation between CRM positivity and disease-free survival was assessed with the Cox regression analysis. Results are in the 95% confidence interval with significance assessed as $p<0.05$.

RESULTS

From January 2005 to January 208, a total of 210 patients had surgery for colon cancer in Dokuz Eylül University General Surgery Department Colorectal Surgery Unit. Histopathologically, 22 patients had tumor penetration into the submucosa (pT1) and muscularis propria (pT2). For CRM assessment, cases with pT1 and pT2 tumors were excluded from the study as there is no effect on local recurrence and general survival, so only 179 patients with pT3-pT4 tumors were included in the study. The demographic characteristics of 179 patients included in the study are shown on **Table 1.** Of patients 112 were male (62.6%) and 67 were female (37.4%).

The mean age was 63.7±13.3 years with patient ages ranging from 18 to 86 years. Ninety-seven patients (54.2%) were in the group aged 65 years and above.

Of tumors, 118 (65.9%) were in the wide mesentery compartments (emerging colon, transverse colon, descending colon, sigmoid colon) and 61 (34.1%) were in the narrow mesentery compartments (cecum, hepatic flexure, splenic flexure). Of patients, 88 (49.2%) had obstruction linked to the tumor during diagnosis. Of cases, 48 (26.8%) developed morbidity in the period after surgery.

Table 1. Demographic characteristics of patients

	Number, (%)
Sex	
Female	67 (37.4)
Male	112 (62.6)
Age	
<65	82 (45.8)
≥65	97 (54.2)
Clinical diagnosis	
Non-obstructed	91 (50.8)
Obstructed	88 (49.2)
Metastasis at time of diagnosis	
None	156 (87.2)
Present	23 (12.8)

The basic histopathologic characteristics of patients are summarized in **Table 2.** Patients with lymph node involvement had mean lymph node involvement number of 3.8±6.4, with the mean number of lymph nodes microscopically investigated 19.9±9.6.

CRM was positive for 25 patients (14%) and negative for 154 (86%). The appearance of the tumor during surgery and CRM status are shown in Plate 1. In terms of tumor invasive margin type, 120 patients (67%) had infiltrative and 54 (30.2%) of patients had expanding type, with data not found for 5 patients (2.8%). In the postoperative period, some patients received adjuvant therapy, while some did not. The mean follow-up duration in our study was 375.8 (±311.6) (range 0-1104) days.

Table 2. Histopathologic characteristics of patients

	Number, (%)
Depth of tumor invasion	
T3	75 (41.8)
T4	104(58.2)
Lymph node involvement	
N0	67 (37.5)
N+	112(62.5)
Form of lymphatic invasion	
Intramural (IM)	42 (23.5)
Extramural (EM)	25 (14.0)
IM+EM	30 (16.8)
Stage	
II	64 (35.8)
III	92 (51.4)
IV	23 (12.8)
Histopatologic type	
Adenocarsinoma	152 84.9)
Other	27 (15.1)
Histologic degree	
Low	143(79.8)
High	36 (20.2)
Venous invasion	
None	136(77.7)
Present	39 (22.3)
Lymph vein invasion	
None	77 (44.5)
Present	96 (55.5)
Perineural invasion	
None	129(72.5)
Present	**49 (27.5)**

There were statistically significant correlations identified between the clinicopathologic variables of differentiation, tumor invasion depth, lymph node involvement, venous invasion, lymphatic invasion, tumor invasion margin type and local recurrence development with CRM status **(Table 3).**

Histopathologic factors (differentiation degree, tumor invasion depth, lymph node involvement, venous invasion, lymphatic invasion, tumor invasion margin type) correlated with CRM status in univariate analysis results were included in multivariate analysis. Multivariate analysis identified statistically significant correlations between venous invasion positivity and tumor invasion depth with CRM (p=0.049 and p=0.046, respectively) **(Table 4).**

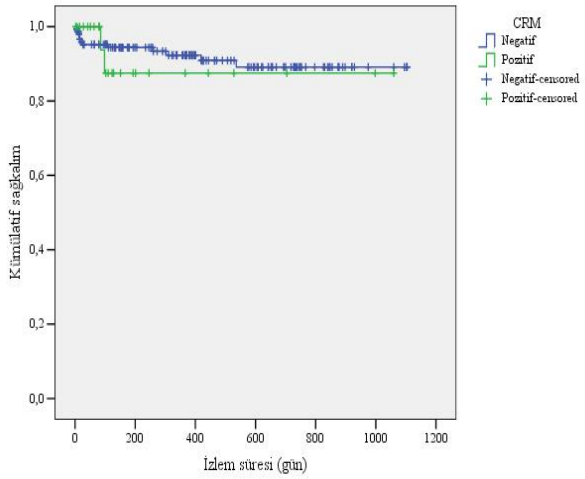
Table 3. Correlation between clinicopathologic variables and CRM status

Clinicopathologic variables	CRM (-)	CRM (+)	*P*
Sex			
Male	99	13	**0.269**
Female	55	12	
Age			
<65	69	13	**0.503**
≥65	85	12	
Degree of differentiation			
Low degree	128	15	**0.007**
High degree	26	10	
Depth of tumor invasion			
T3	71	4	**0.004**
T4	83	21	
Lymph node involvement			
N (-)	62	5	**0.043**
N (+)	92	20	
Tumor localization			
Narrow mesentery	52	9	**0.823**
Wide mesentery	102	16	
Venous invasion			
None	125	11	**0.000**
Present	26	13	
Perineural Invasion			
None	114	15	**0.132**
Present	39	10	
Lymphatic invasion			
None	73	4	**0.002**
Present	75	21	
Preop clinical assessment			
Non-obstructive	77	14	**0.668**
Obstructive	77	11	
Metastasis at time of diagnosis			
None	136	20	**0.249**
Present	18	5	
Tumor Invasion Margin Type			
Infiltrative	98	22	**0.034**
Expanding	51	3	
Local Recurrence			
None	144	19	**0.004**
Present	10	6	
Metastasis			
None	121	18	**0.464**
Present	**33**	**7**	

Tablo 4. CRM durumu ile tek değişkenli analiz sonuçlarında anlamlı ilişki saptanan histopatolojik değişkenler arasındaki ilişkinin, çok değişkenli analiz sonuçları

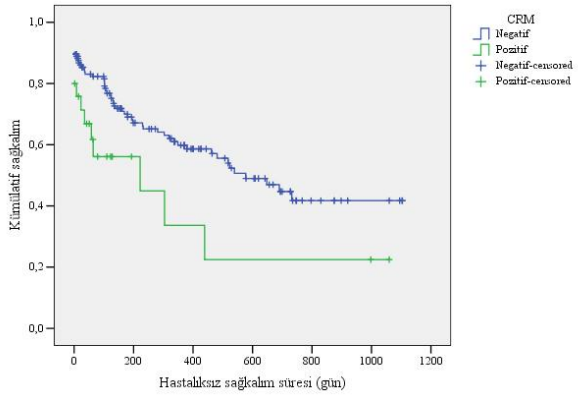
	B	*P*	Multivariate OR	%95 güven aralığı	
				Alt sınır	Üst sınır
Venöz invazyon	-1,057	**0.049**	0.347	0.122	0.994
Tümör invazyon derinliği	-1,298	**0.046**	0.273	0.072	0.912

The general survival duration was 1003 (±25) (range 0-1104) days with disease-free survival 581 (±42) (range 0-732) days. The graph of the correlation between CRM positivity and general survival is shown in **Graph 1.**



Graph 1. Correlation of CRM with general survival

There was a statistically significant correlation between CRM positivity and disease-free survival. This is shown on **Graph 2.**



Graph 2. Correlation of CRM with disease-free survival

When the correlation between CRM positivity and disease-free survival is assessed with the Cox regression analysis method, it was found to be significant (p =0.027; CI=0.276-0.926).

DISCUSSION

CRM forms in the large intestine segments not fully covered with peritoneum (emerging colon, descending colon, sigmoid colon and upper rectum) or without any peritoneum (lower rectum) with definite dissection of the retroperitoneal or subperitoneal area in surgery (6). Even proponents and opponents of total mesorectal excision (TME) in rectum cancer surgery accept that resection ensuring the largest CRM possible during dissection and full mobilization of the rectum is an important part of oncologic surgery. This is because radial margin is one of the rare factors that can be controlled by the intervention technique of surgery among tumor-based and patient-sourced prognostic factors.

The importance of measurement of the circumferential resection margin is that it provides reliable data. Currently obtaining negative CRM is accepted as reflecting accurate surgical technique. In the literature, there are studies using positive or negative circumferential resection margin to assess the sufficiency of surgical treatment in addition to assessing the aggressiveness of the tumor (7,8).

It is still controversial as to whether insufficient CRM (Figure 1 and Plate 1b) shows local aggressiveness of disease or systemic aggressiveness.

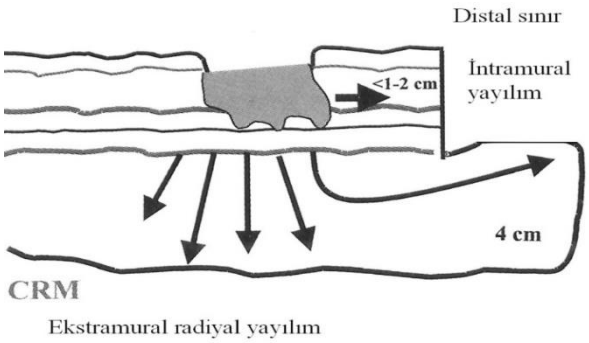


Figure 1. Schematic illustration of CRM

To date, studies of rectum and esophagus cancers have shown that CRM positivity (CRM ≤1 mm) has increased local recurrence (60-78%) and distant metastatic disease (10-17%) compared to negative cases (7,9).

Griffiths et al. prospectively collected and retrospectively assessed histopathologic records of patients undergoing curative resection for esophagus cancer. Among a total of 249 cases, 170 (68.3%)

were CRM negative and 79 (31.7%) were CRM positive. The mean survival of patients was identified as 37 and 18 months, respectively (10,11). This study noted accompanying lymph node positivity in CRM positive patients and stated the prognostic effect of CRM status was associated with degree of lymphatic nodal load and width of resection. The presence of better prognosis in the esophagus, especially for pT3 tumors, was only shown to be possible for cases with low lymph node metastasis percentage and cases with negative CRM obtained with radical resection.

Birbeck et al. in a 2002 study researched the effect of CRM status on survival in rectum tumors. This study including 608 patients undergoing rectum cancer surgery questioned the role of CRM status as an early predictor of oncologic outcomes. In conclusion, pathologic assessment of 586 patients with full clinical follow-up identified 165 had CRM positivity (28.2%). A significantly high proportion of CRM (+) cases (38.2%) had local recurrence, while only 10% of CRM (-) cases had local recurrence. These results showed that CRM status may be used as a survival predictor after rectal cancer surgery and is a beneficial indicator of surgical quality (12,13).

Luno-Perez et al. investigated the prognostic significance of CRM positivity in rectal cancer patients treated with preoperative CRT and LAR in 2005. They noted the importance of histologic assessment of CRM in determination of local and distant recurrence, especially in rectal cancer patients who had not received RT. This study identified that the incidence of distant metastasis and cancer-related deaths were higher in patients with CRM involvement (14,15).

There are many studies showing the relationship between lymph node involvement and CRM positivity in rectum cancer. A study by Nagtegaal et al. showed that the patients with lymph node positivity together with CRM positivity had integrity of the mesorectum more disrupted and as a result, higher rates of local recurrence and distant metastasis were observed in these cases. This study also showed that, contrary to previous studies, CRM (+) of 2 mm and below was associated with increased local recurrence and reduced survival. This research investigated the pathology reports of a total of 656 patients with mean follow-up duration of 35 months. While local recurrence was 16% among those with 2 mm or less margin in mesorectal tissue surrounding the tumor, the local recurrence was 5.8% in the CRM (-) group ($p<0.0001$). This study showed that CRM (+) was a prognostic marker independent of stage (8,16).

Bateman et al. in a 2005 study investigated pathology specimens from 100 patients with right colectomy and identified CRM positivity in 7% of cases. In this study CRM of 1 mm or less was accepted as positive. Cases included in the study were told that CRM positivity could cause local recurrence and this may be an indication for adjuvant radiotherapy. However, the researchers could not ensure pathologic and clinical staging and patients were not clinically followed-up (17). In our study CRM was positive in 25 patients (14%) and negative in 154 (86%) patients ($p=0.269$). Statistically the lack of significance for CRM positivity may be due to the small size of our patient sample. In our study, 112 patients were male (62.6%) and 67 were female (37.4%). There was no effect of patient sex on oncologic outcomes (local recurrence and survival) and on CRM positivity ($p=0.269$). There are studies supporting this in the literature (18), while there are also studies with contrary results (19).

The mean age in our study was 63.7±13.3 years, with patients ages ranging from 18 to 86. Of patients, 97 (54.2%) were in the group aged 65 years and older. The effect of patient age on oncologic outcomes and CRM positivity was found to be statistically insignificant ($p=0.503$). In the literature, there are studies supporting the correlation between patient age with oncologic outcomes and CRM positivity (16,19), while there are also contrary studies with results similar to our study (20).

Though the correlation between tumor localization with oncologic outcomes and CRM positivity has been shown in the literature for rectum tumor patients (16,20), it is still controversial in colon cancer (16,21). In our study, 118 tumors (65.9%) were located in the wide mesentery compartment (emerging colon, transverse colon, descending colon, sigmoid colon), while 61 (34.1%) were located in the narrow mesentery compartment

(cecum, hepatic flexure, splenic flexure). CRM positivity is expected to be significant in colon regions with difficult resection due to their nature and narrow mesentery. In our study, due to the low number of samples from each tumor localization and the low number of CRM positive patients, no statistically significant results were obtained (p=0.823). Tumor localizations were 72 in the sigmoid colon (40.2%), 32 in the cecum (17.8%), 21 in the emerging colon (11.7%), 17 in the descending colon (9.4%), 15 in the hepatic flexure (8.3%), 14 in the splenic flexure (7.8%) and 8 in the transverse colon (4.4%).

In our study, obstruction linked to colon cancer had no statistically significant effect on oncologic outcomes and CRM positivity (p=0.668). There is no study in the literature showing the presence of any relationship between these variables.

Of cases, 48 (26.8%) developed morbidity in the period after surgery. The most common was respiratory system morbidity (22 cases). Seven patients (3.9%) were exitus in the perioperative period.

While adjuvant therapy was administered to 142 (79.4%) patients, it was not given to 37 (20.6%) patients. Patients receiving adjuvant therapy included 137 with SKT (76.5%), 3 with SKT+IPK (1.7%) and 2 with CT+RT (1.1%).

The mean follow-up duration was 375.8 (±311.6) (range 0-1104) days. Within this duration 16 patients (8.9%) had local recurrence and 40 patients (22.3%) had metastasis (distant metastasis) for a total of 51 patients (28.5%) with recurrence. Of cases with recurrence, 3 had only surgery (5.8%), 8 had chemotherapy after surgery (15.7%) and 40 had chemotherapy and/or radiotherapy (78.5%).

There was a statistically significant correlation between CRM positivity and disease-free survival. CRM negative patients had disease-free survival of 609±45 days, while CRM positive patients had 355±74 days (p =0.022).

The general survival duration was calculated as 1003 (±25) (range 0-1104) days with disease-free survival of 581 (±42) (range 0-732) days. There was no statistically significant correlation identified between CRM positivity and general survival (p=0.696). Among CRM negative patients, general survival was 1006±26 days while among CRM positive patients this duration was 938±80 days.

When the correlation between CRM positivity and disease-free survival is assessed with the Cox regression analysis method, there was a 0.5-times negative effect of CRM positivity on disease-free survival (p =0.027; CI=0.276-0.926).

Different to literature information showing CRM positivity reduced general survival, in our study no significant results were identified in the current data assessment stage. This situation may be explained by the small patient sample and the short follow-up duration.

CONCLUSION

Currently CRM is a leading independent factor in multidisciplinary treatment of rectum canser (at least as much as lymph nodes) and plays an effective role in shaping and timing of treatment methods. Though CRM positivity in rectum cancer is a well-defined prognostic factor for both local recurrence and metastatic disease, there are very few studies on this topic related to colon cancer. Moving from this point, CRM positivity in colon cancer should be researched for the effect on local recurrence, metastasis and survival.

CRM should be included in these topics as a "marker" on standard pathologic reporting in multidisciplinary assessment, in prognostic categorization, in the stage of deciding about adjuvant therapy and in testing the sufficiency of surgical interventions.

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