

Risk Factors for Circumferential Resection Margin Positivity among Patients with Rectal Adenocarcinoma

Ralph Leo C. Villaflores*, Loreto B. Ong and Vicente Sotto

Department of General Surgery, Memorial Medical Center, Cebu City, Philippines

*Corresponding author:

Ralph Leo C. Villaflores,
Department of General Surgery, Memorial Medical
Center, Cebu City, Philippines

Received: 08 Feb 2025

Accepted: 17 Feb 2025

Published: 23 Feb 2025

J Short Name: AJSCCR

Copyright:

©2025 Ralph Leo C. Villaflores, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work

Citation:

Ralph Leo C. Villaflores. Risk Factors for Circumferential Resection Margin Positivity among Patients with Rectal Adenocarcinoma. *Ame J Surg Clin Case Rep.* 2025; 8(4): 1-10

1. Abstract

1.1. Background

Circumferential resection margin (CRM) has gained enormous importance in prognostication and indication for multimodal treatment. Advances in rectal cancer treatment in the past two decades were made surrounding the application of optimal surgical techniques, specifically the adoption of total mesorectal excision (TME), a potentially curative resection, and the increased use of neoadjuvant chemotherapy. We aim to review routine post-operative histopathologic examination of the CRM status and its risk factors possibly affecting CRM positivity rates.

1.2. Methods

In a study involving 82 patients who underwent surgery for rectal cancer in VSMMC during the 5-year period 2014 to 2019, the authors reviewed the risk factors affecting CRM positivity with special regard to its associations with patient, treatment and tumor factors as a predictor of probable outcome

1.3. Results

Circumferential Resection Margin (CRM) reading was found in 59 of the 82 rectal cancer patients (72.0%), while 23 (28%) has no CRM reading of the said population size. Out of the 59 patients with CRM reading, 17 (28.8%) were positive and 42 (71.2%) were negative. CRM involvement was not found to be associated with age and smoking history, significantly more common in men and in those with a high preoperative serum CEA level. Also, CRM involvement was associated in patients with tumor measuring ≥ 4 cm or a tumor located in anal canal, nodal metastasis and late stage at treatment, but with no significant association to level of differentiation.

1.4. Conclusions

The rate of CRM involvement after the surgical resection of rectal cancer was found to be high and to be associated with male sex, larger tumor size, tumor in anal canal, nodal metastasis and advanced stage at treatment. CRM positivity was also highly associated with those who underwent laparoscopic procedure and those who have not received any neoadjuvant therapy. But the most significantly related factor to CRM positivity was the lack of neoadjuvant chemotherapy.

2. Background of the Study

Surgery is the first-line treatment for nonmetastatic rectal cancer and the goal is complete removal of the tumor with no residual cancer cells left behind [1]. Recently, the CRM status, that is, the histologic findings at the circumferential resection margin (CRM), has gained enormous importance in prognostication and indication for multimodal treatment. Unfortunately, its significance in influencing post-operative surveillance and decision-making is still not internationally recognized among surgeons despite heavy emphasis placed on its role as an independent predictor of rectal cancer treatment outcomes [2]. Rectal cancers, although biologically identical to colon cancers, are more challenging to treat surgically because of their unfavorable location in the anatomically limited pelvis, making them more prone to recurrence and developing distant metastasis. However, the relative paucity of radiation-sensitive structures in the pelvis makes rectal cancers easier to treat with radiation without considerable collateral damage [3]. Advances in rectal cancer treatment in the past two decades were made surrounding the application of optimal surgical techniques, specifically the adoption of total mesorectal

excision (TME), a potentially curative resection, and the increased use of neoadjuvantchemoradiation therapies [4]. Through the years, researchers have demonstrated against this background the importance of routinely reporting on CRM status after TME is performed on resectable tumors as a means of monitoring surgical quality and predicting disease-free and/or overall survival [5]. Furthermore, researchers have substantiated that the prognostic value of CRM is independent of TNM (tumor-node involvement-metastasis) classification, as the presence of microscopic findings of tumor cells within 1^{mm} of the CRM is strongly associated with local recurrence and increased risk for developing distant metastasis irrespective of TNM stage at the time of treatment [5,6]. However, CRM is still not routinely employed in rectal cancer staging systems and post-operative surveillance despite the growing number of literature strongly linking CRM to prognosis and indication for multimodal treatment [6].

Vicente Sotto Memorial Medical Center has recently employed the routine post-operative histopathologic examination of the CRM status. However, patient and disease factors possibly affecting CRM positivity rates are not yet well documented in the local setting, thereby limiting the use of CRM status as a predictor for rectal cancer treatment outcomes.

3. Significance of the Study

Circumferential resection margin (CRM) is an established independent prognostic marker and indication for multimodal treatment for patients with rectal adenocarcinoma. Therefore, this study shall determine the risk factors that are strongly associated with higher CRM positivity rates in rectal adenocarcinoma patients in this institution. The results of this study shall serve as evidence for the use of CRM status as a clinical endpoint for predicting treatment outcomes that may be incorporated in the next revision of clinical practice guidelines for rectal cancer staging, morbidity and mortality appraisal, and treatment. The results of this study shall also help identify risk factors strongly associated with increased CRM positivity that may be modified by lifestyle changes, thereby reinforcing the importance of a holistic approach to care for rectal cancer patients. Furthermore, this study shall also validate the need for pre-operative neoadjuvanttherapies in selected rectal cancer cases and help surgeons predict which patients would further require post-operative adjuvant chemo-and/or radiotherapy, in order to allow effective communication between surgeon and patient regarding treatment approach and goals. Moreover, the results of this study shall provide future reference for younger researchers in conducting studies on rectal cancer treatment as we seek to continually adapt to the rapidly changing needs of the medical community.

3. Objectives of the Study

This study generally aims to review and determine the risk factors that affect the CRM positivity rates in rectal adenocarcinoma in

Vicente Sotto Memorial Medical Center (VSMMC) from January 2014 to December 2017.

3.1. Specifically, This Study Aims to:

- 1) To determine the rate of CRM reading in rectal histopathological studies in our institution.
- 2) To determine the rate of CRM positivity in our institution.
- 3) To determine the patient related factors with CRM negative vs CRM positive:
 - a. age group (<40, 40-60, 60-80, >80 years old);
 - b. sex (males, females);
 - c. BMI (<20 kg/m², 20-25 kg/m², >25 kg/m²);
 - d. Smoking history (0-1 pack-year, 1-10 pack-years, >10 pack-years);
 - e. Pre-operative carcinoembryogenic antigen (CEA) levels (≤5 ng/ml, >5 ng/ml);
- 4) To determine the tumor related factors with CRM negative vs CRM positive
 - a. Tumor size (< 4 cm, ≥ 4 cm);
 - b. Distance of tumor from the anal verge (<4 cm, ≥4 cm)
 - c. Tumor histologic grade (1-4)
 - d. Tumor cell differentiation (well-, moderately-, and poorly-differentiated); and
 - e. Stage of disease upon treatment (I-IV);
- 5) To determine the treatment related factors with CRM negative vs CRM positive;
 - a. neoadjuvant treatment
 - b. APR vs LAR
 - c. Open vs laparoscopic

3.2. Scope and Limitations of the Study

This study shall determine the risk factors affecting CRM positivity rates in patients with rectal adenocarcinoma in Vicente Sotto Memorial Medical Center (VSMMC) from January 2014 to December 2017. This study shall make use of information reflected in the patients' charts only within the period of their admission. Thus, no data will be available regarding outpatient course.

This study shall also make use of histopathologic results of said patients issued by the Department of Pathology of VSMMC.

Patients with rectal adenocarcinomas admitted for other reasons shall be exempted, as well as patients with colonic adenocarcinoma admitted within the same time frame.

4. Review of Related Literature

Rectal cancer care has become increasingly multidisciplinary. Treatment guidelines have evolved to suggest that neoadjuvant therapy, including chemotherapy and radiation, be considered in the treatment of stage II and III rectal cancers in order to shrink

and render the tumor resectable before surgery, treat micrometastases without the delay of post-operative recovery, and improve surgical and overall outcomes. Despite improved surgical treatment strategies, however, 5 to 15% of all patients still developed local recurrence [7]. Therefore, as early as the 1970s, the circumferential resection margin (CRM), also called the radial margin, was adopted for the surgical treatment of rectal cancer at least in specialized European centers [8]. As a result of the activities of the pathologists from Leeds, U.K., the pathological examination of the CRM has become more widespread. However, it has not yet become clinical practice to include CRM in rectal cancer staging systems, despite the fact that almost all current recommendations for pathological examination of rectal cancer resection specimens include an obligatory histological assessment of the CRM and despite the growing number of literature emphasizing the role of CRM in prognostication and indication for multimodal treatment [9]. As proposed by the pathologists from Leeds, U.K., the currently accepted definition of a positive CRM is the presence of microscopic tumor cells at the margin or a minimal distance between tumor and margin of 1 mm or less, while a negative CRM is a minimal distance between tumor and margin of more than 1 mm [10]. The integral link between suboptimal surgery, a positive CRM, and poor oncological outcome has been recognized at a national healthcare policy level in many countries, leading to the establishment of quality assurance programs in several northern European countries during the 1990's [11]. Changes included in the treatment of rectal cancer were the introduction of newer surgical techniques (total mesorectal excision, or TME, and laparoscopy) and neoadjuvant therapy (short-course radiotherapy, long-course radiotherapy, and combination with different types of chemotherapy). Some of these changes have caused a decrease in the incidence of positive CRMs; well-performed TMEs with a resection margin on the mesorectal plane show margin positivity in less than 10%, and in most laparoscopic series, margin positivity is also less than 10% [12]. Since then, many case series have been published establishing the value of CRM involvement not only for local recurrence, but also for the development of distant metastases and patient survival. Initial series were relatively small, single-center studies, but in recent years, population studies and randomized trials have been added to the literature [13]. In a study done by Birbeck, et al. in 2002 (n = 586), 28.2% had CRM involvement by carcinoma on pathologic examination. Up to the end of 1998, 17.9% of patients had developed local recurrence, 38.2% of which were CRM-positive while 10.0% were CRM-negative. Kaplan-Meier survival analysis showed significant improvements in survival for CRM-negative patients over CRM-positive patients. Nagtegaal, et al. [14]. in 2002 also showed that a margin of ≤ 2 mm is associated with a local recurrence risk of 16% compared with 5.8% and an increased risk for distant metastases (37.6% versus 12.7%, $p < 0.0001$) and shorter survival for patients

with ≤ 1 mm margins after a median follow-up of 35 months (n = 656). Nagtegaal and Quirke further demonstrated in 2008 (n = 17,500) that after neoadjuvant therapy (both radiotherapy and chemotherapy), the predictive value of the CRM for local recurrence is significantly higher than when no preoperative therapy has been applied (hazards ratio [HR] = 6.3 versus 2.0, respectively; $p < 0.05$) (14). They further added that involvement of the CRM is a powerful predictor of both development of distant metastases (HR = 2.8) and survival (HR = 1.7), leading to the conclusion that CRM involvement is even more important in the neoadjuvant setting than it was in the era before its introduction [15]. If in advanced tumors with a positive margin on preoperative imaging, the margin becomes free after treatment, prognosis is good. If, in contrast, the margin remains positive, the prognosis is worse because the remaining tumor consists of a selected population of tumor cells resistant to therapy. Nagtegaal and Quirke therefore concluded that CRM might function as a better marker of tumor regression than tumor response since not only can the CRM be predicted reliably before treatment starts, but also the different treatment modalities (surgery, chemotherapy, and radiotherapy) can be monitored by the CRM, combining pathology and imaging (magnetic resonance imaging), making it valuable in the evaluation of the various steps during treatment. Building on this conclusion, they further recommended the use of CRM by radiologists and pathologists alike and that the use of CRM as an immediate endpoint in neoadjuvant studies should be further explored [16]. Safety resection margins for rectal cancer may vary across institutions and among surgeons. However, the most commonly practiced Japanese general rules for clinical and pathologic studies on rectal cancer state that a 3-cm distal resection margin is needed with a distal edge above and a 2-cm margin with a distal edge below the peritoneal reflection [17]. In a study of 381 patients by Shimada, et al., the maximum extent of distal spread in patients with rectal cancer with the distal edge above the peritoneal reflection was 3.8 cm, whereas it was 3.5 cm with the distal edge below the peritoneal reflection [18]. Therefore, a further increase of 1-2 cm beyond the recommended distal resection margin may contribute to improved local control for patients with distant metastasis [19]. Studies have demonstrated the risk factors that strongly correlate with a positive CRM. In a study done by Sung and Jin in 2011, these factors include the male sex, a large BMI, high preoperative serum CEA level, larger tumor size (≥ 4 cm), distance of tumor of less than 4 cm from the anal verge, T stage higher than T3, poor tumor differentiation, nodal metastasis, tumor perforation, non-sphincter-preserving proctectomy, and open surgery. Logistic regression analysis showed that CRM involvement was significantly associated with male sex, larger tumor size, an advanced T stage, nodal metastasis, and non-sphincter-preserving proctectomy. This study focused on risk factors associated with CRM involvement in the hope that

identification of such risk factors would provide data regarding the indications for adjuvant therapy. The CRM involvement rate of 28.8% in this study is high compared to the results of multicenter studies focusing on evaluating risk factors and prognostic significance of CRM, which reported CRM positivity for all rectal cancer patients of around 10%. This study, however, excluded patients that underwent neoadjuvantchemoradiation to enable use of select indications for post-operative adjuvant management, which may have caused skewed statistical outcomes. While most studies done surrounding the association between the male sex and rectal cancer morbidity suggest that females have higher morbidity rates, other studies suggest a strong association between the male sex and CRM positivity. This phenomenon remains poorly defined as of the moment. Advanced age is traditionally thought to adversely affect any disease, including rectal cancers. While the association between advanced age and poorer overall survival is well documented, however, the association between advanced age and CRM positivity is still to be determined. A large BMI is also suggested by Sung and Jin in 2011 to greatly affect CRM positivity rates. However, theories as to why are still scarce. Of the risk factors mentioned by Sung and Jin, preoperative serum CEA level, larger tumor size (≥ 4 cm), distance of tumor of less than 4 cm from the anal verge, T stage higher than T3, poor tumor differentiation, nodal metastasis, and tumor perforation affecting CRM positivity rates are more or less adequately explained by the advanced state of the disease. This is, however, an oversimplification, since some of these factors only affect CRM positivity rates (as well as disease-free and/or overall survival) in the presence of one or two others. For example, a larger tumor size alone may be inadequate to cause a positive CRM involvement on a single case since adequate surgical technique may compensate.

5. Operational Definition of Terms

1. Circumferential resection margin (CRM) – corresponds to the non-peritonealized surface of the resection specimen created by dissection of the subperitoneal aspect at surgery
2. Positive CRM – tumor at the CRM or minimal distance between tumor and CRM 1mm or less, as determined by histopathology;
3. Negative CRM – Minimal distance between tumor and CRM more than 1 mm, as determined by histopathology;
4. Rectal adenocarcinoma – Neoplasia of epithelial tissue of glandular origin involving the rectum;
5. Total mesorectal excision (TME) – A surgical technique that uses sharp dissection along anatomic planes to ensure complete resection of the rectal mesentery during low and extended low anterior resections; this term shall refer to the surgical technique employed in this retrospective cross-sectional study;
6. Neoadjuvant therapy – A type of adjuvant therapy administered before surgery done to downsize or render a tumor resectable, treatment of micrometastases, and increase treatment response;

7. Post-operative adjuvant therapy – Refers to radiation therapy and systemic therapies, including chemotherapy, immunotherapy, and hormonal therapy offered post-operatively to patients included in this study, as indicated in advanced stages of the disease and/or a positive CRM on histopathologic examination

8. Conservative post-operative management – Refers to timed diligent post-operative surveillance using diagnostic tests such as CEA level monitoring or proctoscopy, without the interference of post-operative adjuvant therapies, as indicated in non-metastatic stages of the disease and/or a negative CRM on histopathologic examination;

9. Body mass index (BMI) – The body mass in kilograms divided by the square of the body height in meters, used in classifying individuals as underweight, normal, overweight, obese I, and obese II;

10. Distance from anal verge – Distance in centimeters measured between tumor and anal verge that is a key determinant for measurement-based suitability for neoadjuvant therapy in rectal cancer;

11. Histologic grade – The description of a tumor based on cell atypia, extent of local invasion, and cell differentiation; refers to the grade assigned to rectal cancer patients involved in the study (1 – resembles benign growth but with local invasion; 2 – cell atypia but well differentiated; 3 – cell atypia with moderate differentiation; 4 – poorly differentiated, undifferentiated, or anaplastic structures);

12. Stage at treatment – The description of a primary tumor based on size and extent with description of tumor spread using the number of lymph nodes involved, metastasis to adjacent organs, and distant metastasis, currently known as the TNM classification; refers to the stage assigned to rectal cancer patients involved in the study (I – T1-T2, N0; IIa – T3, N0; IIb – T4, N0; IIIa – T1-T2, N1; IIIb – T3, N1; IIIc – T3, N2 or T4, N1-N2; IV – any T, any N, M1);

13. Number of lymph nodes examined – Refers to the number of pelvic lymph nodes surgically obtained and examined histopathologically; current practice guidelines recommends examining at least 12 lymph nodes as adequate;

14. Erroneous pertinent data – Data that can potentially confound study outcomes that are included in a patient's chart and/or histopathologic results including, but not limited to, ambiguous discharge diagnosis, incongruent patient data, etc.;

15. Missing pertinent data – Data that can potentially alter study outcomes that are absent in either a patient's chart or histopathologic results or both including, but not limited to, final diagnosis, surgical records, intraoperative findings, histologic grade, etc.

6. Methodology

6.1. Study Design

This study is a case-control study on the risk factors affecting

CRM positivity rates among patients with rectal adenocarcinoma in VSMMC.

6.2. Study Setting

This study was conducted at Vicente Sotto Memorial Medical Center (VSMMC), a 1200-bed capacity tertiary hospital that is committed to research and training. This study was conducted within the jurisdiction of the Department of General Surgery of VSMMC, which caters to all surgical patients hailing from the province of Cebu as well as from neighboring and even distant provinces.

7. Study Population

7.1. Inclusion Criteria

- All patients with rectal adenocarcinoma admitted at VSMMC from January 2014 to December 2017 that underwent rectal adenocarcinoma surgery whose post-operative histopathologic results are available for access at the Department of Pathology of the said institution;

Exclusion Criteria

- Patients whose charts contain missing pertinent data.

7.2. Data Collection Procedure

Approval from the Research Committee was obtained prior to conducting data collection. The researcher acquired a list of all rectal adenocarcinoma cases using the patient database at the medical records department. A chart review was done and a data collection form be filled up for each patient. The researcher also acquired histopathologic results of said patients issued by and with permission from the Department of Pathology.

8. Statistical Analysis

Results were presented using frequencies, percentages, and mean \pm standard deviation (SD). Data analysis was performed with an aid of statistical software, namely, IBM SPSS version 21. The proportion between patients with CRM regarding two modalities of treatment (conservative and surgery) will be analyzed using χ^2 test. Odds ratios were computed to determine association between patient characteristics and CRM positivity.

Sample Size: 58

Confidence level: 95% Margin of Error: 7% Population Size: 82
 $n = N1 + Ne2$

9. Ethical Considerations

The researcher acquired approval from the Ethics Review Board prior to retrieval of the needed charts and histopathologic results for data collection. There shall be no actual patient interaction in the collection of data; hence no informed consent is warranted. The researcher acquired the charts and histopathologic results after approval from the Medical Records Section head and

the Department of Pathology, respectively, are obtained. The researcher observed confidentiality in that data collection shall be done only in the Medical Records Section and the Department of Pathology, respectively, where each chart and histopathologic result was assigned a patient number. Data pertaining to each patient was recorded in a separate data collection form. These data collection forms were accessed only by the researcher.

10. Results

In this study, Circumferential Resection Margin (CRM) reading was found in 59 of the 82 rectal cancer patients (72.0%), while 23 (28%) has no CRM reading of the said population size (Table 1). Mean patient age was 58 years (range, 30 to 60 years), and with significance level of 0.05. Risk Factors for CRM involvement were summarized and further sub classified in Tables 3, 4 and 5, as to patient-related, tumor-related and treatment-related factors, respectively. As shown in Table 3, CRM involvement was not found to be associated with age and smoking history. However, CRM involvement was significantly more common in men and in those with a high preoperative serum CEA level. The patient's sex had the highest influence to CRM, with a p-value of 0.037. As shown in Table 4, the rate of CRM involvement was associated in patients with tumor measuring ≥ 4 cm or a tumor located in anal canal, nodal metastasis and late stage at treatment, but with no significant association to level of differentiation. Patients with lymph node metastasis were found to be significantly more likely to have CRM involvement ($P = 0.019$). A significant correlation was found between late stage at treatment and the proportion of patients with CRM positivity ($P = 0.01$). To demonstrate the relation between rate of CRM involvement and tumor distance from the anal verge, we classified tumors based on preoperative colonoscopy findings into two groups; 0 to 4.0 cm ($n = 20$) and 4.1 cm or more ($n = 39$). The frequency of CRM involvement was found to increase as tumor level decreased; with high rate of CRM involvement for tumors 0 to 4.0 cm from the anal verge (7 of 20, 35%), and low rate of CRM involvement for tumors 4.1 cm or more from anal verge (4 of 39, 10.3%). Both stage treatment and distance from anal verge influence the most to CRM, with a p-value of < 0.001 . Finally, treatment-related factors were summarized in Table 5. The treatment factors that have significant influence to CRM are neoadjuvant treatment, type of procedure, and type of surgical approach with a p-value of < 0.001 . Patients who have not received any neoadjuvant therapy have higher rate of CRM involvement than those patients who had neoadjuvant therapy. There was noted higher rate of CRM positivity for low anterior resection (64.7%) as compared to with abdominoperineal resection (35.3%). The rate of CRM involvement was higher in patients who underwent laparoscopy as compared to those who underwent open procedure, with 37.5% (3 of 8) and 27.5% (14 of 51), respectively.

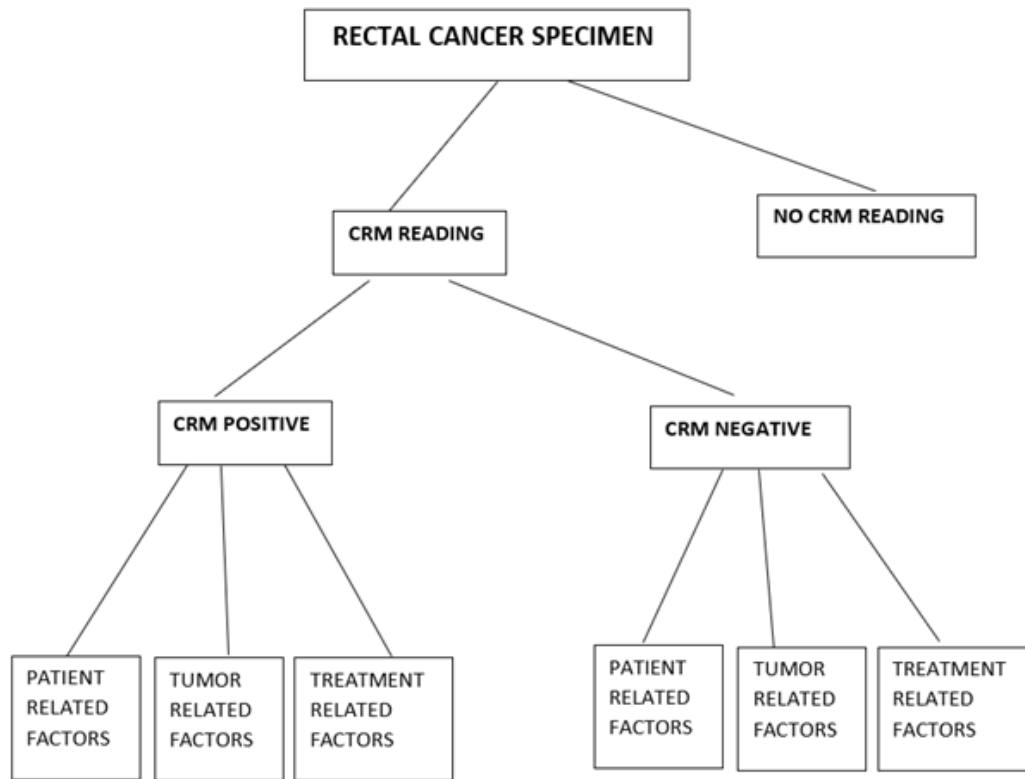


Figure 1

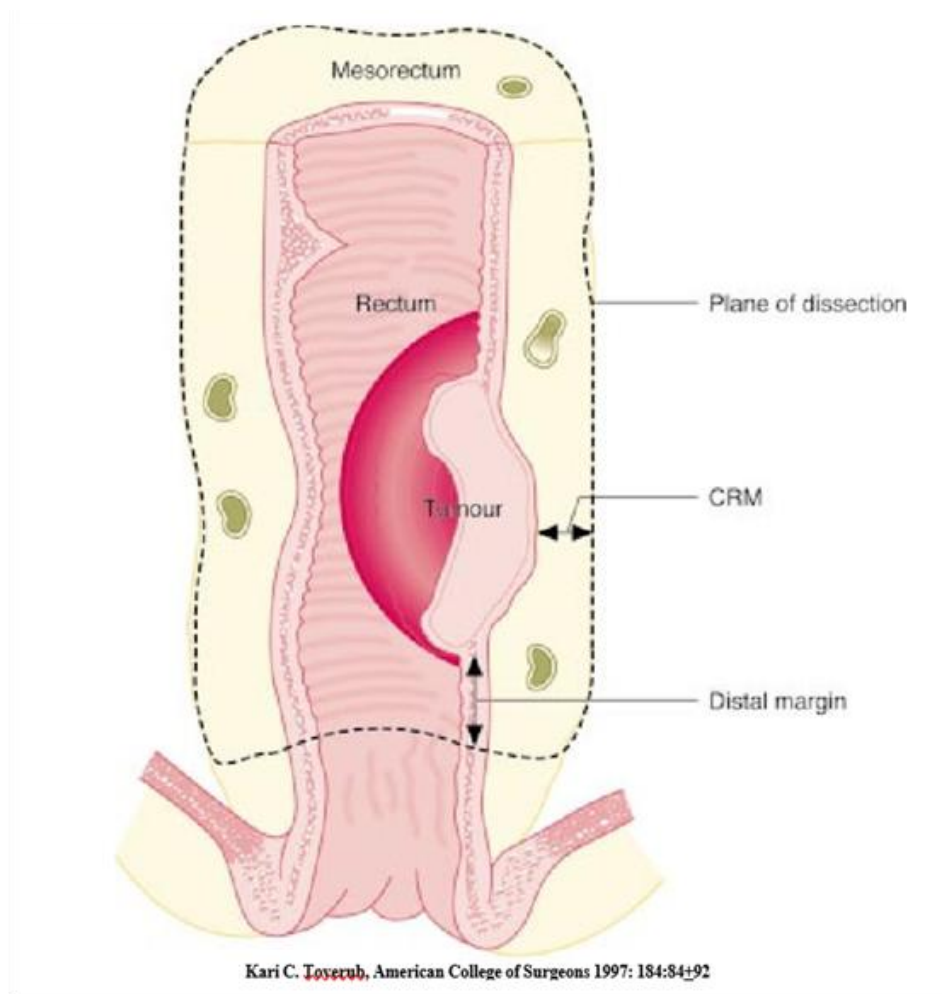


Figure 2.

Table 1: Rate in CRM reading inVSMCC.

Total Number of Rectal Adenocarcinomapatients	WithCRMreading (Percentage)	WithoutCRMreading (Percentage)
82	59 (72%)	23 (28%)

Table 2:Rate of CRM positivity of those with CRM reading.

Total Number of Patients with CRM reading	CRM (+)	CRM(-)
59	17 (28.8%)	42 (71.2%)

Meanpatientagewas58years(range,30to60years),andwithsignificancelevel of 0.05. Risk Factors for CRM involvement were summarized and further sub classified in Tables 3, 4 and 5, as to patient-related, tumor-related and treatment-related factors, respectively.

Table 3:Distribution of subjects according to patients related factors with CRM reading (negative vs positive).

VARIABLE	Negative CRM (N=42)	Positive CRM (N=17)	Proportion of Negative CRM	Proportion of Positive CRM	P value	Level of Significance
Age (yr.)						
<40	5(11.9)	2 (11.7)	(71.4)	(28.6)	0.687	0.05
40-60	17 (40.5)	5 (29.4)	(77.3)	(22.7)		
>60	20 (47.6)	10 (58.9)	(66.7)	(33.3)		
Sex						
Male	32(76.2)	14 (82.4)	(43.8)	(56.2)	0.0371	0.05
Female	10 (23.8)	3 (17.6)	(76.9)	(23.1)		
BMI (kg/m2)						
<20	11(26.2)	3 (17.6)	(78.6)	(21.4)	0.0453	0.05
20-25	22 (52.4)	8 (47.1)	(73.3)	(26.7)		
>25	9 (21.4)	6 (35.3)	(60.0)	(40.0)		
Smoking history (pack yr.)						
0-1	18 (42.9)	7 (41.2)	(72.0)	(28.0)	0.458	0.05
1-10	10 (23.8)	6 (35.3)	(62.5)	(37.5)		
>10	14(33.3)	4 (23.5)	(77.8)	(22.2)		
CEA (ng/ml)						
w/o	20 (47.6)	5(29.4)	(80.0)	(20.0)	0.042	0.05
<5	15 (35.7)	3(17.6)	(83.3)	(16.7)		
>5	7 (16.7)	9(53.0)	(43.8)	(56.2)		

Table 4: Distribution of subjects according to tumor related factors with CRM reading (negative vs positive).

VARIABLE	Negative CRM (n=42)	Positive CRM (n=17)	Proportion of Negative CRM	Proportion of Positive CRM	P Value	Level of Significance
Tumor size (cm)						
<4cm	26 (61.9)	7(41.2)	(78.8)	(21.2)	0.046	0.05
>4cm	16 (38.1)	10(58.8)	(61.5)	(38.5)		
Distance from anal verge (cm)						
<4cm	7 (16.7)	13(76.5)	(35.0)	(65.0)	0.0415	0.05
>4cm	35 (83.3)	4(23.5)	(89.7)	(10.3)		
Differentiation						
Well	11(26.2)	4(23.5)	(73.3)	(26.7)	0.491	0.05
Moderately	21 (50.0)	7(41.2)	(75.0)	(25.0)		
Poorly	10 (23.8)	6(35.3)	(62.5)	(37.5)		
Nodal Status						
(+)	18 (42.9)	13	(58.1)	(41.9)	0.019	0.05
(-)	24 (57.1)	(76.5) 4(23.5)	(85.7)	(14.3)		
Stage at treatment						
Stage I	9 (21.5)	0 (0)	(100)	(0)	0.01	0.05
Stage II	10(23.8)	2(11.8)	(83.3)	(16.7)		
Stage III	19(45.2)	6 (35.3)	(76.0)	(24.0)		
Stage IV	4(9.6)	9 (52.9)	(44.4)	(55.6)		

Table 5: Distribution of subjects according to treatment related factors with CRM reading (negative vs positive).

VARIABLE	Negative CRM (n=42)	Positive CRM (n=17)	Proportion of Negative CRM	Proportion of Positive CRM	P Value	Level of Significance
Neoadjuvant treatment With/without	23 (54.8) 19 (45.2)	7 (41.2) 10 (58.8)	(76.7) (65.5)	(23.3) (34.5)	0.01	0.05
APR LAR	17 (40.5) 25 (59.5)	6 (35.3) 11 (64.7)	(73.9) (69.4)	(26.1) (30.6)	0.001	0.05
Open Procedure Lap Procedure	37(88.1) 5 (11.9)	14 (82.4) 3 (17.6)	(72.5) (62.5)	(27.5) (37.5)	0.001	0.05

11. Discussion

Rectal cancer outcome and survival have considerably improved with the adoption of a multidisciplinary model of care. Outcome in rectal cancer depends on stage, use of adjuvant and neoadjuvant chemo-radiation, and technical aspects of surgical excision. One of the main objectives of surgical treatment is to provide adequate safety margins of healthy tissue around the tumor, since positive resection margins are associated with high risk for local recurrence, distal metastases and eventually death. It is well-documented that circumferential resection margin (CRM) status remains a strong predictor of local recurrence, a measure of quality of surgery and an indicator of the need for multimodal treatment for patients with rectal adenocarcinoma. This was well emphasized in a large meta-analysis performed by Nagtegaal et al on 17,000 patients, which showed that a CRM of ≤ 1 mm was a strong predictor of local and distant recurrence [21]. This study, therefore, was conducted to determine the risk factors that are significantly associated with higher CRM positivity rates in rectal cancer. The predictive patient-related factors for CRM involvement were, male sex, BMI of 20-25 and CEA >5 . But contrary to previous studies which associated higher BMI to CRM positivity, this study observed patients with positive CRM involvement to have a normal BMI. The association between a male sex and greater CRM involvement may be due to difficult surgical access in the narrower male pelvis, which is consistent with a previous study that also reported that male patients were a risk factor for CRM involvement. A large BMI is also suggested by Sung and Jin in 2011 to greatly affect CRM positivity rates. However, in this study it was observed that patients with positive CRM status have normal BMI. This may correlate a bigger role of treatment factors on CRM positivity in this institution [22]. Tumor-related factors identified which include, a larger tumor size (>4 cm), distance of tumor <4 cm from anal verge, nodal metastasis, and late stage at treatment (Stage IV), concur with those reported in previous studies that sought to identify predictive factors of CRM involvement for 'all' types of rectal cancers. They are more or less adequately explained by the advanced state of the disease. A previous study by Sung and Jin in 2011 showed similar association with tumors located less than 4 cm from anal verge and a high CRM positivity rate. It suggests that a tumor location around the anal canal necessitates pre and postoperative adjuvant therapy regardless of the type of surgical resection, which is in-line with the recommendation that postoperative chemoradiotherapy is necessary for patients with CRM involvement [23].

A study by concluded that neoadjuvant chemoradiotherapy not only can reduce tumor size and recurrence, but it also increase tumor resection rate and anus retention rate and increase sphincter preservation with very slight side effect [24]. In this study, the rate of

CRM involvement was 37.5% (3 of 8) for patients who underwent laparoscopic surgery as compared to those who underwent open procedure with 27.5% (14 of 51). This is in contrast to the study conducted in 2011 by Sung and Jin, which showed lower CRM (+) positive involvement in patients who underwent laparoscopy with only 3.5 %, as compared to a higher rate of 18.9% for those who underwent open procedure. However, a previous multicenter trial on conventional versus laparoscopic-assisted surgery in colorectal cancer would show a similar result, showing a high positive CRM rate of 16% in the laparoscopic group as compared with a rate of 14% in the open group [25]. A Study by Fleshman et al. [26], the ACOSOG Z6051 randomized control trial a negative circumferential resection margin was observed in 90% of the overall group (87.9% laparoscopic resection and 92.3% open resection. This showed the potential of laparoscopic approach in rectal cancer to be inferior in terms of pathological outcomes [26]. A Study done by Hussain and Mahmood et al in 2018 showed 17.1% had a CRM positive margin post abdominoperineal resection which resulted in significantly increased local recurrence with a trend towards poorer survival outcomes. Overall CRM positivity rate of 28.8% were higher compare to a study done by Warriar & Guerra et al in. [27-29] and with 7.5% and 9.2% respectively maybe because of the newness of the standardization of the CRM resection of the institution [27].

12. Conclusion

The rate of CRM involvement after the surgical resection of rectal cancer was found to be high and to be associated with male sex, larger tumor size, tumor in anal canal, nodal metastasis and advanced stage at treatment. CRM positivity was also highly associated with those who underwent laparoscopic procedure and those who have not received any neoadjuvant therapy. But the most significantly related factor to CRM positivity was the lack of neoadjuvant chemoradiotherapy.

13. Recommendation

Based on this study, we suggest and highlight that by greater adherence to basic surgical tenets of rectal adenocarcinoma care such as advanced imaging modalities improved pathologic assessment, dedication to appropriate neoadjuvant therapy, and commitment to a multidisciplinary team approach to rectal adenocarcinoma care, a substantial reduction in CRM positivity and negative oncological outcomes can be delivered. CRM reading should be standardized and be routine on specimen readings. Neoadjuvant treatment should be standard of care. Neoadjuvant treatment should be stage considered for radical non-sphincter saving surgery. Follow up studies on CRM positivity and recurrence rates. Determine the rate of neoadjuvant therapy done on rectal adenocarcinoma patients. Lastly, include surgeon/operator related factors.

References

- DeCaria K. "Rectal cancer resection and circumferential margin rates in Canada: a population-based study" *Current Oncology*. 2015; 60-63.
- P Hermanek, T Junginger. "The circumferential resection margin in rectal carcinoma surgery" *T. Tech Coloproctology*. 2005; 9: 193.
- Brunnicardi C. *Schwartz's Principles of Surgery*, 10th ed. New York: McGraw-Hill Education. 2015; 29:1213.
- Gosens MJ. "Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma." *Clinical Cancer Res*. 2007;13(22) 200.
- Nagtegaal, I. "Circumferential resection margin is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit." *American Journal of Surgical Pathology*. 2002; 26(3): 350-7.
- Glynne-Jones R, "The clinical significance of the circumferential resection margin following preoperative pelvic chemo-radiotherapy in rectal cancer: why we need a common language." *Colorectal Diseases*. 2006; 8(9): 800-7.
- Birbeck, K. "Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery." *Annals of Surgery*. 2002; 235(4): 449-457.
- Nagtegaal I, Quirke P. "What is the role for the circumferential margin in the modern treatment of rectal cancer?" *American Journal of Clinical Oncology*. 2008; 26(2):303-12.
- Chen-Guo Ker, "Surgical safety margin of gastroenterological cancer surgery: A truth or a dream?" *Formosan Journal of Surgery*. 2014; 47(3): 83-89.
- Shimada. "Intramural and mesorectal distal spread detected by whole-mount sections in the determination of optimal distal resection margin in patients undergoing surgery for rectosigmoid or rectal cancer without preoperative therapy." *Disease of the Colon and Rectum*. 2011; 54(12):1510-20.
- Tekkis PP. "Comparison of circumferential margin involvement between restorative and nonrestorative resections for rectal cancer." *Association of Coloproctology of Great Britain and Ireland. Colorectal Diseases*. 2005; 7:369- 374.
- MERCURY Study Group. "Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study." *BMJ*. 2006; 333:779.
- Burton S. "MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins?" *Br J Cancer*. 2006; 94:351-357.
- Chau I. "Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging- defined poor-risk rectal cancer." *Journal of Clinical Oncology*. 2006; 24:668-674.
- Fernandez-Martos C. "Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study." *Journal of Clinical Oncology*. 2002; 10:859-865.
- Cercek A. "Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer." *Journal of National Comprehensive Cancer Network*. 2014; 12:513-519.
- Bhatti AB. "Can induction chemotherapy before concurrent chemoradiation impact circumferential resection margin positivity and survival in low rectal cancers?" *Asian Pacific Journal of Cancer Prevention*. 2015; 16:2993-2998.
- Deng Y "A multi-center randomized controlled trial with or without radiation in neo-adjuvant treatment of local advanced rectal cancer (FOWARC study): preliminary results." *Journal of Clinical Oncology*. 2015.
- Rosenberg AR "Insurance status and risk of cancer mortality among adolescents and young adults." *Cancer*. 2015; 121:1279-1286.
- Aizer AA. Cancer-specific outcomes among young adults without health insurance. *Journal of Clinical Oncology*. 2014; 32:2025-2030.
- Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol*. 2008; 26(2):303-12.
- Sung Jin Oh, Jin Yong Shin. Risk factors of circumferential resection margin involvement in the patients with extraperitoneal rectal cancer; *J Korean Surgical Society*. 2012; 82(3): 165-171
- Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet*. 2009;373:811-820.
- Yi Li. A Review of Neoadjuvant Chemotherapy for Locally Advanced Rectal Cancer; *International Journal of Biological Sciences*. 2016; 12(8): 1022-1031
- Fleshman J. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcome: The ACOSOG Z6051 Randomized Clinical Trial. 2015;314(13):1346-55.
- Anwar Hussain. Oncological outcomes of abdominoperineal resection for the treatment of low rectal cancer: A retrospective review of a single UK tertiary centre experience; *Annals of Medicine and Surgery*. 2018; 34:28-33.
- Warrier SK. Risk Factors Associated with Circumferential Resection Margin Positivity on Rectal Cancer: A Binational Registry Study. 2018;61(4):433-440.
- Roodbeen SX, de Lacy FB. Predictive Factors and Risk Model for Positive Circumferential Resection Margin Rate After Transanal Total Mesorectal Excision in 2653 Patients with Rectal Cancer: *Annals of Surgery*. 2019; 270(5):884-891.