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Effect of the circumferential resection margin on survival following colon cancer surgery

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An abstract of

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Abstract

Effect of the circumferential resection margin on survival following colon cancer surgery

By Guangnan Chen

Background: In rectal cancer, circumferential resection margin (CRM) has been demonstrated to be a very strong predictor of recurrence and survival. The primary goal of surgical resection for solid cancers is to have a negative CRM, the main factor in preventing recurrence. For colon cancer, studies on surgical margins have largely focused on proximal and distal margins. In 2015, Amri and colleagues, as well as Khan and colleagues, demonstrated that CRM is associated with a higher recurrence rate, and both a shorter disease-free survival and overall survival. These two studies are both hospital-based. Studies exploring the effect of CRM on prognosis and recurrence of colon cancer at the population level are lacking. The objective of this study is to assess the effect of CRM on survival in colon cancer, using population-based cancer registry data.

Methods: Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program for cases of first primary colon cancer diagnosed from 2010 to 2013. The study participants all received definitive surgical resection of their cancer. Unadjusted Kaplan-Meier survival curves and crude 47-month cause-specific survival estimates were used to compare survival between the CRM subgroups. A multivariable Cox proportional hazards model was used to calculate hazard ratios, controlling for age and marital status at diagnosis, insurance, tumor grade, and disease stage.

Results: The final study population included 15,803 cases with 1,761 defined as CRM positive (less than 1 mm or positive) and 14,042 defined as CRM negative (greater than or equal to 1 mm or negative). Unadjusted Kaplan-Meier survival curves and adjusted Cox-regression model estimates showed better survival for CRM negative versus CRM positive patients. For the 47-month unadjusted Cox proportional hazards model, patients with a positive CRM had an increased risk of death of 130% (HR=2.30; 95% CI: 1.97-2.70). Once adjusted for other covariates, the risk associated with a positive CRM was 60% (HR=1.63; 95% CI: 1.38-1.93).

Conclusions: Using a large national population-based cancer registry dataset, colon cancer survival disparities were shown to exist between CRM positive and CRM negative patients after controlling for stage and other covariates. Routine examination and documentation of the circumferential resection margin following colon resection should be considered for all patients.

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Chapter I: Background

Colon Cancer: Incidence and Mortality

In the US, colorectal cancer has the third highest incidence and mortality in both men and women. According to American Cancer Society, approximately 95,270 individuals were expected to be diagnosed with colon cancer in the US during 2016, and about 49,190 were expected to die of this disease.

Significant progress in the prevention and early detection of colorectal cancer has been made by increasing access to and utilization of colorectal cancer screening tests (fecal occult blood test and colonoscopy). While substantial declines in colorectal cancer incidence and mortality in the past decade have been observed due to increased use of screening, only 58% of people for whom screening is recommended have followed the recommended guidelines according to the National Health Interview Survey in 2013.

The lifetime risk of developing colorectal cancer is 5.0% in men and 4.7% in women. Incidence and mortality are 30% and 40% higher, respectively, in men than in women overall. The causes for higher incidence and mortality in men are not completely known, but are possibly associated with complex interactions between sex hormones and risk factor exposures, diet, and disparities in screening for people aged 50 and older (1, 2).

Incidence and mortality rates also vary significantly by race and ethnicity. Colorectal cancer incidence and mortality are highest in African American men and women; incidence is about 25% higher and mortality is about 50% higher than in whites. Incidence and mortality among other major racial/ethnic groups are lower than whites (3, 4). Much of this discrepancy is attributed to the disproportionately low socioeconomic status in the African American population. According to the US Census Bureau, in 2012, the poverty rate was 27.2 in blacks, compared with 9.7 in non-Hispanic whites and 11.7 in Asians (5). Low socioeconomic status has been shown in several studies to be associated with higher risk of colorectal cancer incidence and mortality (6, 7). Disparities in the prevalence of behavioral risk factors and obesity explain about 40% of the socioeconomic disparity

in colorectal cancer incidence (8). But there are other risk factors contributing to the higher rates in African Americans because colorectal cancer mortality rates are significantly higher compared to whites even after controlling for socioeconomic status (6, 9).

Subsite Distribution

Regarding risk factors and clinical and biological characteristics, colon cancers occur in different locations within the colon, suggesting different carcinogenic mechanisms (10-12). The most common location of colon cancer is the proximal colon (42%) (4). However, the subsite distribution varies according to sex. Women have a higher percentage of proximal colon cancers (46% vs 38%) and a lower percentage of rectal cancers (24% vs 31%) compared with men. There are also discrepancies in subsite distribution according to age at diagnosis, with an apparent increase in proximal cancers and decrease in rectal cancers with older age (4). For example, 56% of colorectal cancers in women aged 80 years and older are in the proximal colon, compared with 26% of colorectal cancers in women aged younger than 50 years. Thus, the median age at diagnosis for rectal cancer is younger (63 years in men and 65 years in women) than the median age at diagnosis for colon cancer (69 years in men and 73 years in women) (13).

Colon Cancer Staging

The TNM Staging System was developed and is maintained by the AJCC and the Union for International Cancer Control (UICC). It is the most commonly used staging system by medical professionals around the world. The TNM classification system was developed as a tool for doctors to stage different types of cancer based on certain, standardized criteria (14). For colon cancer, the tumor (T), node (N), metastasis (M) system is based on the extent of the tumor invasion into the colonic wall, the extent of spread to regional lymph nodes, and the presence or absence of distant metastasis. Stage I colon cancer is characterized by tumor invasion of the submucosa or muscularis propria**.** Stage II colon cancer is identified by tumor invasion through the muscularis propria into

pericolorectal tissues, tumor penetratation to the surface of the visceral peritoneum, or tumor invasion of other organs or structures in the absence of regional node involvement. Stage III colon cancer is characterized by lymph node involvement and is divided into three subcategories based on depth of invasion and number of lymph nodes involved. Stage IV colon cancer is identified by presence of distant metastasis (14).

Standard of Care

Treatment for colon cancer varies by the stage of disease. Surgical removal of the primary cancer and surrounding lymph nodes, or colectomy, is the most effective treatment for potentially curable colon cancer. The safety and efficiency of colectomy have been improved through developments in surgical techniques, anesthesia, and other medical supportive systems (15). Curative colon excision followed by adjuvant chemotherapy has been the standard of care for stage III colon cancer patients for prolonged disease free survival and overall survival since the early 1990s (16, 17). Generally, those who do not receive adjuvant chemotherapy have inferior outcomes, with reported recurrence rates of 30.8% among patients with stage III colon cancer (18). In addition, a curative surgical procedure accompanied by adjuvant chemotherapy reduces the risk of mortality by one third as compared to surgery alone (16, 19). This reduction in mortality and recurrence due to use of chemotherapy has been observed across all age groups, indicating the benefit of adjuvant chemotherapy is similar in patients across age groups (20). However, in practice, older patients with stage III colon cancer are less likely to receive adjuvant chemotherapy (20-22).

Survival and Stage Distribution

Colon cancer survival rates are similar by sex; thus data are shown for both sexes combined. The 5-year relative survival rate for patients diagnosed from 2003 to 2009 (all followed through 2010) was 64.9% (15). The survival rate declines to 58.1% at 10 years after diagnosis, although this estimate does not reflect recent improvements in early detection, prevention and treatment because it is based

on patients diagnosed as far back as 2004. Overall the 5-year survival rate is slightly higher for rectal cancer (66.5%) than for colon (64.2%) cancer; however, this may reflect the higher percentage of rectal tumors diagnosed at a localized stage (44% vs 38%) because stage-specific survival is similar. Patients younger than 65 years have higher 5-year survival rates than those 65 years and older (68.9% vs 62.0%). However, this advantage is only regarding tumors in the distal colon and rectum since the 5-year survival rate for patients with proximal tumors is approximately 65% for each age group. Only 40% patients with colorectal cancer are diagnosed when the cancer is at a local stage, for which the 5-year survival rate is 90.3%. The survival rate declines to 70.4% and 12.5% for patients presenting with regional and distant metastasis, respectively (15). Though non-Hispanic whites have the highest probability to have a localized stage for the cancer, APIs (Asian/Pacific Islanders) have the highest overall 5-year survival rates (23). African Americans have the lowest survival for all stages combined, 10% less than that for APIs. Factors that contribute to discrepancies in colorectal cancer survival include differences in access to cancer screening, timely and high-quality treatment, and the prevalence of comorbidities (24-27). Many studies have demonstrated that black patients with colorectal cancer are less likely than patients of other races/ethnicities to have appropriate treatments, including surgery, adjuvant chemotherapy, and radiation therapy (24, 28-31). Adjuvant chemotherapy doubles the probability of surviving 5 years for patients with stage III colon cancer (32). Interestingly, compared to white patients, black patients have fewer toxicities in the treatment and have a similar survival rate from adjuvant chemotherapy (33). Survival rate discrepancies mostly disappear after controlling for tumor characteristics, patient demographics, and treatment.

CRM (circumferential resection margin)

In 1986, the circumferential resection margin (CRM), also known as the radial, lateral, or mesorectal resection margin, was introduced as a powerful prognostic factor for rectal cancer (34). The CRM is defined as the closest distance between the radial resection margin and tumor tissue by either direct tumor spread, areas of neural or vascular invasion, or the nearest involved lymph node.

Since then, many studies have been published establishing the value of CRM, not only for local recurrence, but also for the development of distant metastases and patient survival. (35-36)

Due to the measurement of CRM, the treatment of rectal cancer has changed dramatically. The appearance of total mesorectal excision (TME) and the enhancement of its value by the discovery of the mesorectum and CRM led to fewer positive CRM and consequently fewer local recurrences. (40) Short-term preoperative radiotherapy (dose: 5 x 5 Gy) has been used as neoadjuvant therapy for resectable rectal cancer. For locally advanced rectal cancer, various long-term radiotherapy schedules have been used, with or without chemotherapy. All treatment modalities result in improved prognosis and decreased local recurrence rates (37-40); however, there are increased side effects (41). Moreover, the improvement of diagnostic imaging allowing the accurate prediction of a potential CRM, will lead to better treatment plans and, thus, further decrease the percentage of positive CRM at surgery (42, 43).

Standardized method of CRM assessment

Accurate reporting of the CRM for colon cancer, requires serial cross sectioning of the cancer, a visual inspection of the cancer slices, and adequate histologic sampling of areas suspicious of cancer. In the Medical Research Council CR07 and Conventional Versus Laparoscopic-Assisted Surgery in Patients with Colorectal Cancer (CLASICC) trials, the Dutch TME trial, and the Mercury study, pathologists were trained before the start of the trial and filled in standardized forms at the time of pathology report. The frequency of CRM involvement is associated with high positive lymph node yields (35).

CRM positivity

There has been an ongoing debate about the definition of CRM positive. The TNM definition of a positive margin (R1) is 0 mm; in most cases, CRM is considered positive when ≤ 1mm. On the basis of prognostic value for local recurrence, 2 mm has also been considered as a cutoff point. In

general, it can be stated that the larger the distance of the tumor from the CRM, the better the prognosis. When tumor cells are reaching into the resection margin (0 mm), prognosis is worst (35). Large discrepancies exist regarding the percentage of CRM-positive patients, with percentages ranging from 1% to 28% in curatively operated patients (35). Various factors should be considered when reviewing these percentages. The percentage of CRM-positive cases is dependent on patient selection, quality of preoperative imaging, preoperative long course treatment, surgical technical skills, and skill of the pathologist. In several studies, patients with locally advanced rectal cancer are included; however, the term locally advanced has no consistent definition and varies from one positive lymph node to a clinical T4 tumor. Percentages of CRM-positive patients in these scenarios vary accordingly, thus such studies cannot be compared with each other. Skill of the pathologist may be one of the key factors. Two early studies (34, 44) showed that CRM involvement is not always present in the macroscopically most suspect area but might be present in other areas, requiring more extensive sampling. The examination of additional microscopic slides in some studies has led to more CRM-positive patients, from 6% to 27% (34). Frequencies of CRM involvement in single-center studies should be treated with caution. Reports from trials (45) in which "both tumor spread and tumor-free radial margins are reported suboptimally" (i.e., missing in 79% and 68% of patients, respectively) are still being published. However, less variability is present in the population-based studies, with the percentage of CRM-positive patients ranging from 8% to 13% (35). In these population-based studies, there is a difference in patient selection as well, reflected by differences in the percentage of node-positive patients, which ranges from 21% to 40%. In unpublished data from Yorkshire, United Kingdom, the frequency of CRM positivity was associated with the median number of lymph nodes found at individual hospitals; thus, the CRM rate can be interpreted in the light of the median lymph node yield from any individual study. Good quality of pathology (as indicated by high median lymph node yields (46, 47)) results in increased frequencies of CRM involvement.

Randomized neoadjuvant trials give insight to how negative CRMs can be obtained. When comparing short-course radiotherapy with long-course chemoradiotherapy, there is a difference in margin involvement (13% *v* 4% involved margins, respectively; *P* = .017 (48)); in this study, downstaging is observed as well (48% *v* 32% TNM stage III, respectively; *P*= .007). The addition of fluorouracil/folinic acid to long-term radiotherapy did not decrease the number of positive margins, although there was more downstaging in the radiochemotherapy arm (*P* = .001) (49).

Mode of CRM involvement

The following six different types of CRM involvement have been described (34, 51): direct tumor spread (28% to 29%), discontinuous tumor spread (14% to 67%), lymph node metastases (12% to 14%), venous invasion (14% to 57%), lymphatic invasion (9%), and perineural tumor spread (7% to 14%). In about 30% patients, the cancer showed more than one mode of CRM involvement. Lymph node metastases in the CRM were associated with a lower than expected local recurrence rate in two independent studies (51, 52); however, these results were based on only 19 and 67 patients, respectively, and require further studies to establish their true importance.

CRM-associated risk factors

Tumor-Related Factors

There is a significant association between CRM and TNM stage (35). The more advanced the stage, the greater the chance of CRM involvement (34). Both increasing depth of tumor invasion and the presence of tumor deposits and involved lymph nodes contribute to association.

More positive CRMs are present in cancers that have an ulcerative growth pattern (44, 53) and in cancers that show a stenosing growth pattern (53). Bigger tumors more often have a positive CRM (53). Histologic factors that are associated with positive CRM include an infiltrating margin (34), poor differentiation (34, 53-54), and vascular invasion (53-54). No significant relationship with tumor budding was observed (54). Moreover, poor differentiation in submucosal transanal biopsies

is predictive of CRM involvement (odds ratio=10.8; 95% CI, 1.7 to 67.1), as is vascular invasion (odds ratio=16.1; 95% CI, 1.9 to 139.2) (54).

Surgical Factors

Variation between surgeons is also reflected by the difference in the proportion of positive CRMs in single-center studies. In a study by Birbeck et al (51), the variability between surgeons and their improvement over time was demonstrated. The frequency of CRM involvement can be used both for overall surgical audit and for monitoring the value of training programs in improving rectal surgery by individual surgeons. The decrease in positive CRMs was also accompanied by a decreased local recurrence rate and improved survival. In a multicenter study, Tekkis et al (55) showed between-center variability ranging from 1% to 33% (*P*=.001). They did not observe any influence of timing of surgery (day or night), but there were fewer positive margins in emergency operations (2.7% in emergency operations *v* 13% in elective cases); the reasons for this are unclear.

By judging the quality of the surgery performed through evaluating the completeness of mesorectal excision, an association between CRM positivity and quality of surgery was demonstrated (35). In two large randomized multicenter trials (56-58), the authors showed that, if the mesorectum is removed as a whole (ie, the CRM is on the mesorectal plane), few positive CRMs are present, and local recurrence rates are low (1, 57-58). In contrast, when the plane of resection is on the muscularis propria (39), CRM involvement is common, and local recurrence rates are high. The plane of resection can explain why, in a few cases (1.1% (51) and 2.0% (52)), positive CRMs are present in TNM stage I tumors. There are more positive CRMs in cancers located in the lower rectum than in the middle and upper rectum (56). It was believed that the main cause of this is the difference in surgical technique applied and the different local anatomy. Many studies observed higher CRM positivity in patients who underwent abdominoperineal resection (APR) compared with patients who underwent low anterior resection (56). Perforations are more common in APR (56) and are associated with an increased CRM positivity (53). The mesorectal excision plane is more often on

the muscularis propria (56), and in the sphincter area, the plane of resection is often in the lumen, submucosa, or sphincters.

Patient-Related Factors

Surprisingly few studies have investigated patient-related factors for CRM involvement. Sex of patients seems important in APR patients, with CRM involvement in 39% of female and 24% of male patients ($P = .003$), but not in low anterior resection–operated patients (CRM involvement in 12% of female and 12% of male patients). This is probably a result of selection because APR is less frequently performed in women than men (26% *v* 33%, respectively; $P=.09$). No difference was found by Tekkis et al (55), and Chapuis et al (53) found more positive margins in men than women (9% *v* 6%, respectively; $P=.023$). In a logistic regression model, Luna-Perez et al (59) demonstrated an association between CRM involvement and age. However, this is not confirmed in other studies (53, 55).

Distant metastases and survival for rectal cancer CRM

All studies with distant metastases as an outcome variable show a significant difference between the CRM-positive and the CRM-negative patients with rectal cancer (HR=2.8; 95% CI, 1.9 to 4.3) (35). No difference is observed between the patients treated with or without neoadjuvant therapy. The association between CRM involvement and patient survival is not clear from all studies, probably due to the lack of statistical power. However, when all studies are summarized, there is a significant association between CRM involvement and patient survival, both in the neoadjuvant setting as well as in the patients treated with surgery alone (HR=1.7; 95% CI, 1.3 to 2.3). A recent study investigated the value of CRM on survival in a multivariate model and found that CRM is a more important predictor than T stage. In combination with lymph node status, CRM status provides a better prognostic model than the current TNM system (35).

Locally recurrent disease for rectal cancer CRM

The association between CRM involvement and locally recurrent disease for rectal cancer has been reviewed by Caricato et al (50). In this systematic review, they included 24 observational studies in which a total of 2,206 patients were investigated. They conclude that "the only reliable prognostic marker is microscopically negative margins after surgery."

Colon cancer CRM and survival

In 2015, Amri and colleagues (60) have carried out a retrospective study on the effect of radial margin positivity (CRM<1 mm) on survival in patients with colon cancer. They demonstrated that, although rare, CRM positivity is associated with a higher recurrence rate, and both a shorter disease-free survival and overall survival. In the study, positive CRM was shown to be an independent predictor of survival. Using the Surveillance, Epidemiology, and End Results database in 2010, Gundrson et al (61) found that patients with T2N2a tumors have a prognosis that is similar to that of patients with T4aN0 tumors. Due to CRM, the study by Amri and colleagues provides a justification for the population review of Gunderson et al. Both studies emphasize the importance of meticulous pathological evaluation of surgical technique. Also in 2015, Khan and colleagues (62) demonstrated CRM in colon cancer resection is an important marker for advanced disease and a prognostic factor for disease free survival and overall survival. Therefore, like rectal cancers, it is important that colon cancers are evaluated by the pathologist in a standard format, generating standard reports for CRM.

The abovementioned two studies are both hospital-based. Studies on the effect of CRM on prognosis and recurrence of colon cancer at the population level are lacking. The objective of this study is to assess the effect of CRM on cause-specific survival in colon cancer, using SEER data from 2010-2013. Our hypothesis is that positive CRM is associated with higher risk of death. Thus the main objective is to assess the effect of CRM on survival in colon cancer controlling for staging or other predictors that may be confounders.

Chapter II: Manuscript

Title: Effect of the circumferential resection margin on survival following colon cancer surgery

Author(s): Guangnan Chen, Kevin C. Ward

Abstract:

In rectal cancer, circumferential resection margin (CRM) has been demonstrated to be a very strong predictor of recurrence and survival. The primary goal of surgical resection for solid cancers is to have a negative CRM, the main factor in preventing recurrence. For colon cancer, studies on surgical margins have largely focused on proximal and distal margins. In 2015, Amri and colleagues, as well as Khan and colleagues, demonstrated that CRM is associated with a higher recurrence rate, and both a shorter disease-free survival and overall survival. These two studies are hospital-based. Studies exploring the effect of CRM on prognosis and recurrence of colon cancer at the population level are lacking. The objective of this study is to assess the effect of CRM on survival in colon cancer, using population-based cancer registry data.

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program for cases of first primary colon cancer diagnosed from 2010 to 2013. The study participants all received definitive surgical resection of their cancer. Unadjusted Kaplan-Meier survival curves and crude 47-month cause-specific survival estimates were used to compare survival between the CRM subgroups. A multivariable Cox proportional hazards model was used to calculate hazard ratios, controlling for age and marital status at diagnosis, insurance, tumor grade, and disease stage.

The final study population included 15,803 cases with 1,761 defined as CRM positive (less than 1 mm or positive) and 14,042 defined as CRM negative (greater than or equal to 1 mm or negative). Unadjusted Kaplan-Meier survival curves and adjusted Cox-regression model estimates showed better survival for CRM negative versus CRM positive patients. For the 47-month unadjusted Cox proportional hazards model, patients with a positive CRM had an increased risk of death of 130% (HR=2.30; 95% CI: 1.97-2.70).Once adjusted for other covariates, the risk associated with positive CRM was 60% (HR=1.63; 95% CI: 1.38-1.93).

Using a large national population-based cancer registry dataset, colon cancer survival disparities were shown to exist between CRM positive and CRM negative patients after controlling for stage and other covariates. Routine examination and documentation of the circumferential resection margin following colon resection should be considered for all patients.

Introduction

Colorectal cancer has the third highest incidence and mortality in both men and women. The circumferential resection margin (CRM) is defined as the closest distance between the radial resection margin and tumor tissue by either direct tumor spread, areas of neural or vascular invasion, or the nearest involved lymph node. In rectal cancer, CRM has been demonstrated to be a very strong predictor of both recurrence and survival (35).

The primary goal of surgical resection for solid cancers is to have a negative circumferential resection margin (in rectal cancer, CRM<1 mm is considered positive), the main factor in preventing recurrence of solid cancers (35). However, for colon cancer, research on surgical margins has largely focused on proximal and distal margins (60).

Amri and colleagues (60) carried out a retrospective study on the effect of radial margin positivity (CRM<1 mm) on survival in patients with colon cancer. They demonstrated that, although rare, radial margin positivity is associated with a higher recurrence rate, and both shorter disease-free survival and overall survival. In their study, a positive radial margin was shown to be an independent predictor of survival. Using the Surveillance, Epidemiology, and End Results database in 2010, Gunderson et al (61) found that patients with T2N2a tumors have a prognosis that is similar to that of patients with T4aN0 tumors. Due to CRM, the study by Amri and colleagues provides a justification for the population review of Gunderson et al. Both studies emphasize the importance of meticulous pathological evaluation of surgical technique.

In a separate study, Khan and colleagues (62) demonstrated that CRM positivity in colon cancer resection is an important marker for advanced disease and a prognostic factor for disease free survival and overall survival. Therefore, like rectal cancers, it is important that colon cancers are evaluated by the pathologist in a standard format, generating standard reports for CRM.

The abovementioned two studies are, however, hospital-based with relatively small numbers. Studies on the effect of CRM positivity on prognosis and recurrence of colon cancer at the

population level are lacking. As such, the objective of the current study is to assess the effect of CRM on survival in colon cancer using population-based SEER data from 2010 to 2013. Our hypothesis is that a positive CRM is associated with higher risk of death even after controlling for staging and other potential confounders.

Methods

Study data and cohort

We conducted a retrospective cohort study using data obtained from the Surveillance, Epidemiology, and End Results (SEER) program. SEER registries routinely collect data on patient demographics, primary cancer site, tumor stage at diagnosis, and follow-up for vital status and data from these registries are a representative sample of all cancer cases among the US population. The SEER program publishes data on cancer survival and incidence for more than a quarter of the country's population. The initial dataset obtained for this work consisted of 103,486 diagnoses of invasive colon cancer between 2010 and 2013 (released in April 2016). Rectal cancers were not included. The last date of follow-up for the entire cohort was December 31, 2013. Following exclusions (Figure 1), the final analytic sample comprised 15,803 observations. Exclusions consisted of 1) patients not between 20 years old and 90 years old; 2) patients with histology not included in AJCC definition for colon staging (ICD-O-3 histology codes other than: 8000-8152, 8154-8231, 8243-8245, 8250-8576, 8940-8950, 8980-8981); 3) patients with colon cancer stage III or IV; 4) patients where colon cancer was not the only or first primary diagnosis; 5) patients without a definitive surgical resection; 6) patients for whom CRM was not assessed or results not available; and 7) patients with unknown values for covariates of specific interest (marital status, insurance status, race and tumor grade).

Dependent Variable

The primary outcome measure was 47-month cause-specific survival, with cause of death obtained from SEER data. SEER registries routinely link their data with both state vital records and the National Death Index to obtain vital status, date of death and cause of death. Survival time was defined as the number of months from the date of diagnosis until death from colon cancer or censoring. Survival time was censored at the time of death from another cause, at the time a patient was lost to follow-up or at the study endpoint of December 31, 2013.

Primary Exposure

The primary exposure of interest for this study was the CRM subgroup variable, CRM positive versus CRM negative. SEER registries began collecting circumferential resection margin for colon cancer in 2010 and collect this data in Site-Specific Factor 6. Patients were considered to have positive margin involvement if either the margins were coded positive or the size of the margin was less than 1mm. Patients were considered to have negative margin involvement if either the margins were coded negative or the size of the margin was greater than or equal to 1mm. In the primary analysis, there were 1,761 CRM positive cases and 14,042 CRM negative cases (Figure 2).

Covariates

Potential confounding variables available in SEER data included both demographic and clinical factors. Demographic variables included age at diagnosis (<50, 50-59, 60-69, 70-79, >80), sex, race, insurance status and marital status (Married vs Unmarried (single, separated, divorced, widowed, unmarried or domestic partner)). Clinical and pathologic variables included tumor grade (Grade I, II vs Grade III, IV), stage (I, IIA vs IIB, IIC, IINOS) and radiation (Yes, No). The rationale to group the stages is that stage I (tumor invades submucosa and muscularis propria) and stage IIA (tumor invades through the muscularis propria into pericolorectal tissues) are inside the colon. Stage IIB

(tumor penetrates to the surface of the visceral peritoneum) and stage IIC (tumor directly invades or is adherent to other organs or structures) have already penetrated to outside the colon.

Statistical Analyses

Demographic, clinical and pathologic variables for the two CRM subgroups were compared in order to assess whether there were any statistically significant differences between the two CRM subgroups. Categorical variables were analyzed using Pearson's chi-square test, at an alpha of 0.05. All of the categorical variables were presented as counts and percentages. Complete survival analysis included 47-month unadjusted Kaplan-Meier survival curves for CRM positive versus CRM negative patients with a corresponding log-rank test for comparison between subgroups. A single variable Cox regression model was used to obtain an unadjusted hazard ratio for CRM while a multivariate Cox regression model, controlling for confounders, was used to obtain adjusted hazard ratios. Proportional hazard assumptions were tested for all covariates using log-log survival curves, interaction with survival time, and Goodness of Fit tests. Variables that failed the proportional hazards assumptions were stratified on in the multivariate model and included radiation and gender. The stratified, multivariate cox regression model adjusted for gender, radiation therapy, race, age, marital status, tumor grade, and tumor stage. Interaction terms between the main exposure (CRM variable) and each of the covariates were assessed for effect modification. Backward elimination was used in the regression analysis, removing the interaction terms if it did not have a significant effect in the corresponding model. All of the models were analyzed at a 5% significance level**.** All interaction terms were found insignificant. All statistical tests were performed using the SAS 9.4 software.

Results

A total of 15,803 patients comprised our study population. Among these, 1,761 (11.1%) were CRM positive and 14,042 (88.9%) were CRM negative, showing a large difference between CRM

subgroups in the study population. (Figure 2). Patient characteristics according to CRM subgroups are presented in Table 1. Patients were similar across strata of CRM by sex, age, and race. Patients with positive CRM were significantly more like to be unmarried (47.8% versus 43.7%), be uninsured, have higher tumor grades (28.7% versus 13.5%), have more advanced stage disease (29.4% versus 7.7%), receive radiation therapy (5.0% versus 0.7%), and have died from colon cancer (11.1% versus 4.8%), relative to patients with negative margins.

The unadjusted 47-month survival probabilities by CRM status are presented in Figure 3. The Kaplan-Meier (KM) survival curves differed significantly by CRM status (Log-Rank 112.9; p<.0001). The results of an unadjusted Cox model shows that patients with positive CRM have a 2.3 times increased risk of death compared to patients with negative CRM (HR=2.30; 95% CI: 1.97-2.70) (Table 2). This result will be compared to the multivariate model that adjusted for confounders. Race, marital status, age, cancer grade, and cancer stage satisfied the proportional hazards assumption, while gender and radiation status did not. A multivariate Cox model adjusting for covariates that satisfied the PH assumption and stratifying on those that did not showed that patients with positive CRM had an increased risk for colon cancer death of 60% (HR=1.6; 95% CI: 1,4-1.9) (Table 3). Despite the fact that this was not a predictive model, the hazard ratio for other variables was assessed and stage was of course the strongest predictor of mortality (HR=3.1, 95%CI: 2.7-3.7) as it is for most cancers. Grade (HR=1.4; 95% CI: 1.2-1.7), age and marital status (HR=1.4; 95% CI: 1.2-1.6) were also predictors of colon cancer death.

Discussion

Among the large population-based cohort of US SEER patients diagnosed with a primary stage I or II colon cancer between 2010 and 2013, we found a strong association between CRM and survival. Patients with positive CRM had less favorable outcomes compared to those with negative margins (HR=1.63; 95% CI: 1.38-1.93).

These findings are consistent with the previous two hospital-based studies exploring the association between CRM and survival (60, 62). In a 9-year hospital-based retrospective study, Amri and colleagues (60) showed a 239% increase in risk of death from colon cancer with positive CRM, controlling for adjuvant chemotherapy (P<.001), AJCC stage (P<0.001), Charlson (P<.001), and smoking (P=.01). Khan and colleagues (62) carried out an 8-year hospital-based retrospective analysis, demonstrating a 35% increase in risk of death from colon cancer with positive CRM, controlling for age (<.001), cancer differentiation (<.001), and cancer stage (<.001). The results of our study confirm the results of other authors who have explored the influence of CRM on colon cancer survival.

To our knowledge, this is the first study using population-based data to demonstrate the effect of CRM on survival of patients with colon cancer. Although having a positive CRM is a relatively rare event (11.1%), the effect of CRM on outcome demonstrates its clinical effect and the importance of our findings. In rectal cancer, the effect of CRM on survival of patients with cancer is much more frequently studied and validated due to the much higher prevalence of CRM in rectal cancer, i.e., 22% in population-based studies (63) and 28% in a single-center study (51).

Despite our findings, this study has limitations. One limitation is that our study population was restricted to patients with early stage disease (stage I and II). This decision was made due to the fact that chemotherapy, a strong predictor of survival in node positive disease, is not made available in the SEER research dataset. Despite the fact that the CRM positive disease is more common with nodal involvement, we believed it was important to restrict on stage since chemotherapy use would be a known unmeasured confounder in our study. As such, the generalizability of our findings is limited to those with early stage disease.. In addition, since this is a retrospective study some cases had to be excluded, despite all efforts to collect data as accurately and completely as possible, due to the lack of data on CRM (excluded 14,487 observations from 31,836 observations, i.e., almost half of observations).

In contrast to these limitations, our study has several strengths. Our study is the first, to our knowledge, to use population-based data to demonstrate the effect of CRM on survival of patients with colon cancer. It used registry data from the SEER program, which is known to have very high quality, complete case capture and comprehensive data on long term patient follow-up and survival Compared to the previous two hospital-based studies, our study has a much larger sample size as well (15, 803 observations) leading to more stable results.

Using a large national population-based cancer registry dataset, colon cancer survival disparities were shown to exist between CRM positive and CRM negative patients after controlling for stage and other covariates. Routine examination and documentation of the circumferential resection margin following colon resection should be considered for all patients.

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Tables and Figures

Table 1. Descriptive statistics of 15,803 stage I and II colon cancer patients treated with colon resection, by CRM (circumferential resection margin), SEER 2010-2013

		CRM, No. (%)		p-Value
Variable	All Patients, No. (%)	Negative	Positive	
No. (%)	15,803	14,042(88.9)	1,761(11.1)	
Sex				0.09
Male	7,629(48.3)	6,812(48.5)	817(46.4)	
Female	8,174(51.7)	7,230(51.5)	944(53.6)	
Age at Diagnosis				0.27
<50	1,224(7.8)	1,084(7.7)	140(8.7)	
50-59	2,722(17.2)	2,406(17.1)	316(17.9)	
60-69	3,871(24.5)	3,436(24.5)	435(24.7)	
70-79	4,130(26.1)	3,708(26.4)	422(24.0)	
≥80	3,856(24.4)	3,408(24.3)	448(25.4)	
Race				0.56
White	12,841(81.3)	11,426(81.4)	1,415(80.4)	
African American	1,631(10.3)	1,443(10.3)	188(10.7)	
Other	1,331(8.4)	1,173(8.4)	158(9.0)	
Insurance				<.0001
Uninsured	418(2.7)	346(2.5)	72(4.1)	
Any Medicaid	1,744(11.0)	1,498(10.7)	246(14.0)	
Insured	11,181(70.8)	1,0035(71.5)	1,146(65.1)	
Insured/No specifics	2,460(15.6)	2,163(15.4)	297(16.9)	
Marital status				0.001
Married	8,826(55.9)	7,907(56.3)	919(52.2)	
Unmarried	6,977(44.2)	6,135(43.7)	842(47.8)	
Grade				<.0001
Grade I ,II	13,579(85.9)	12,147(86.5)	1,432(81.3)	
Grade III, IV	2,224(14.1)	1,895(13.5)	329(28.7)	
AJCC stage				<.0001
I, IIA	1,4208(89.9)	12,964(92.3)	1,244(70.6)	
IIB, IIC, IINOS	1,595(10.1)	1,078(7.7)	517(29.4)	
Radiation				<.0001
None	15,610(98.8)	1,3937(99.3)	1,673(95.0)	
Radiation	192(1.2)	104(0.7)	88(5.0)	
Colon cancer death				<.0001
Dead	874(5.5)	678(4.8)	196(11.1)	
Alive or dead of other cause	14,929(94.5)	13,364(95.2)	1,565(88.9)	

Table 2. 47-month Single Variable (CRM) Cox Model for Risk of Colon Cancer Mortality for primary invasive colon cancer patients who received colon resection, diagnosed from 2010 to 2013

Variable	Hazard Ratio	95% CI	p-Value
CRM			
CRM negativity	Reference		
CRM positivity	2.30	(1.97, 2.70)	<.0001

Table 3. 47-month Multivariable Cox Proportional Hazard Model[1] for Risk of Colon Cancer Mortality by CRM subgroups for primary invasive colon cancer patients who received colon resection, diagnosed from 2010 to 2013

Variable	Hazard Ratio	95% CI	p-Value
CRM			
CRM negativity	Reference		
CRM positivity	1.63	(1.38, 1.93)	<.0001
Grade			
I and II	Reference		
III and IV	1.43	(1.22, 1.68)	<.0001
AJCC Stage			
I and IIA	Reference		
IIB, IIC, IINOS	3.14	(2.68, 3.68)	<.0001
Age at Diagnosis			
<50	0.09	(0.06, 0.16)	<.0001
50-59	0.17	(0.13, 0.22)	<.0001
60-69	0.28	(0.23, 0.34)	<.0001
70-79	0.47	(0.41, 0.56)	<.0001
≥80	Reference		
Marital Status			
Married	Reference		
Unmarried	1.42	(1.23, 1.65)	<.0001
Race			
White	Reference		
African American	1.12	(0.89, 1.41)	0.32
Other	0.68	(0.51, 0.92)	0.01
Insurance			
Uninsured	Reference		
Any Medicaid	1.14	(0.67, 1.94)	0.62
Insured	0.73	(0.44, 1.22)	0.23
Insured/No specifics	0.92	(0.54, 1.56)	0.75

1. Adjusted Cox Model, stratified on gender and radiation.

Figure 1. Flowchart to show inclusion/exclusion criteria for the creation of Final Cohort, SEER 2010-2013 (N=15,803)

Invasive colon cancer excluding rectal cancer (103,486)

↓

Enrollees with colon resection between 20 years old and 90 years old (number included: 103,373, number excluded: 113)

↓

Histology included in AJCC definition 8000-8152, 8154-8231, 8243-8245, 8250-8576, 8940-8950, 8980-8981(number included: 101,378, number excluded: 1,995)

↓

Colon cancer Stage I and II only (number included: 47,226, number excluded: 54,152)

↓

Colon cancer only and first primary (number included: 32,969, number excluded: 14,257)

↓

Definitive surgical resection (number included: 31,836, number excluded: 1,133)

↓

Colon cancer with CRM documented (number included: 17,349, number excluded: 14,487)

↓

Married status excluding Unknown value (number included: 16,438, number excluded: 911)

↓

Insurance status excluding Unknown value (number included: 16,254, number excluded: 184)

↓

Race excluding Unknown value (number included: 16166, number excluded: 88)

↓

Grade excluding Unknown value (number included: 15,803, number excluded: 363)

Final cohort total: 15,803

Figure 2. Percentage of CRM positivity and CRM negativity in 15,803 stage I and II colon cancer patients treated with colon resection

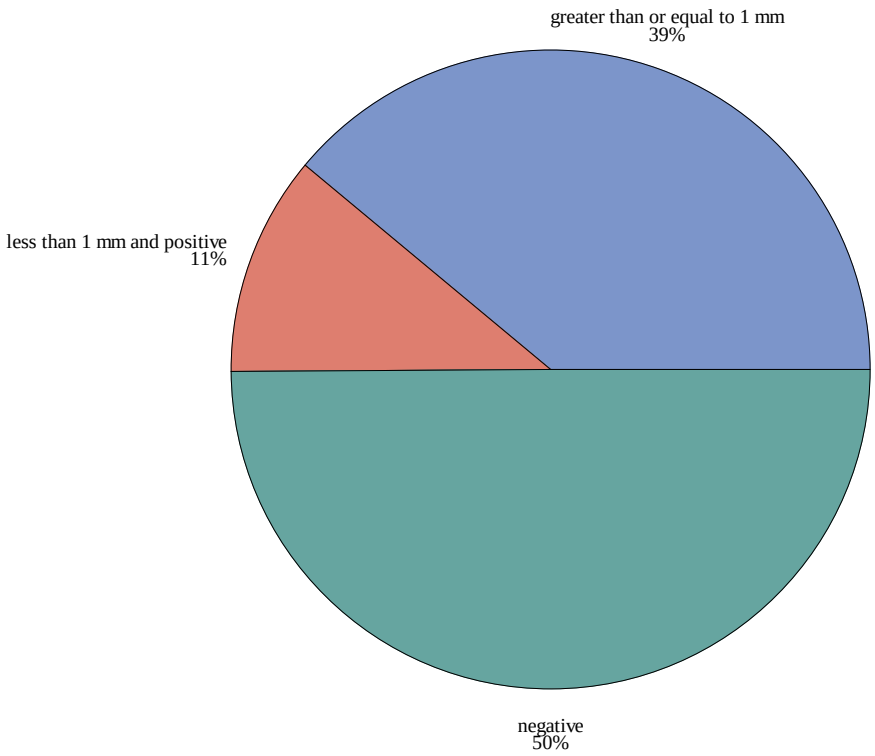
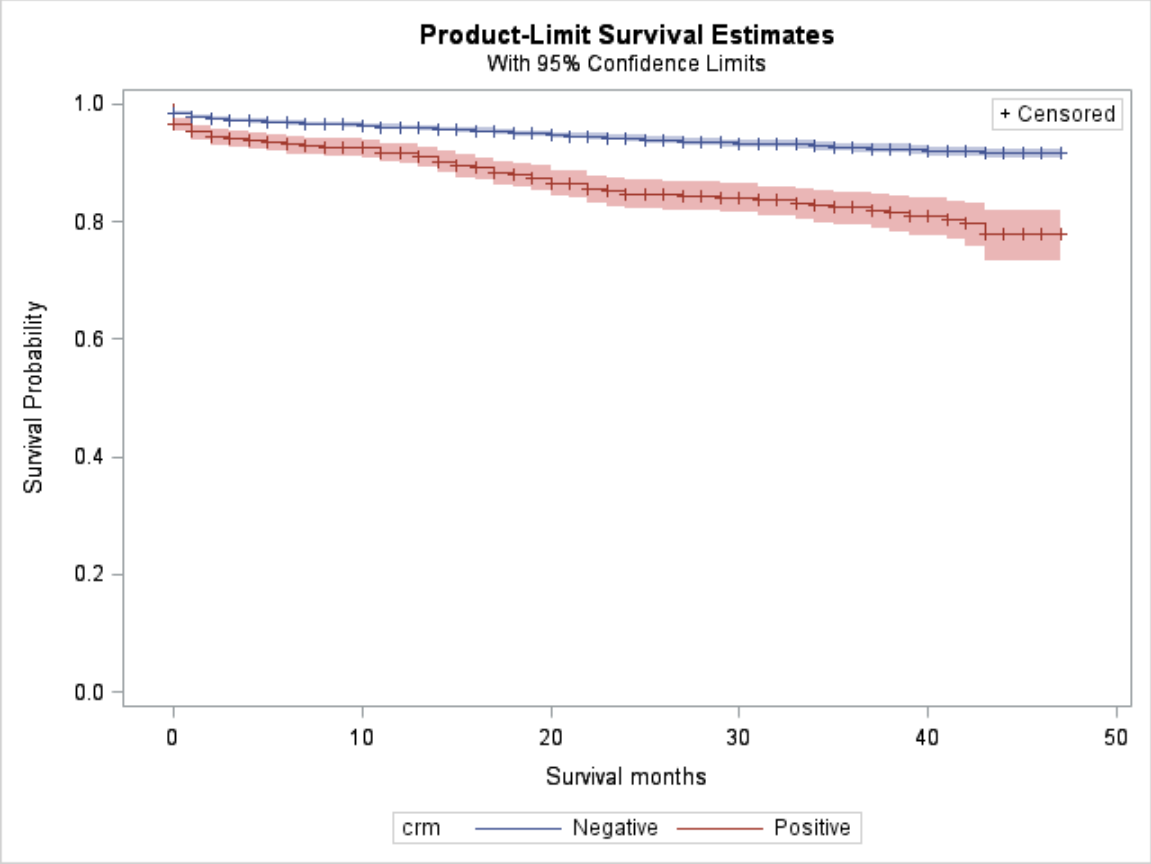


Figure 3. Kaplan-Meier Curve of Survival Probability by Survival Months, According to CRM (N=15,803)



Chapter III: Summary, Public Health Implications, and Possible Future Directions

As colorectal cancer has the third highest incidence and mortality in both men and women, improvements in health care and long-term survival for colon cancer are very important. According to the SEER statistics, the 5-year survival probability for colon cancer is 64% for all cancer stages. The higher the stage, the lower the survival probability for colon cancer. The 5-year survival probabilities for localized, regional and metastatic colon cancer are 90.8%, 70.9%, and 12.7% respectively. Our study confirms the previously observed significant improvement in survival among colon cancer patients treated with colon cancer resection with a negative CRM compared to those with a positive CRM. This is an important finding in improving colon cancer treatment and long-term survival. CRM should be a standard component of preoperative evaluation and postoperative pathological assessment. Indication of CRM positivity in preoperative examination should be considered carefully for optimal treatment plans. It is very important to realize the financial burden from colon cancer because of colon cancer treatments. Being the third highest incidence and mortality in cancer in both men and women, colon cancer has a great impact on the cost of health care. In 2010, the cost of colon cancer treatments was estimated over $14 billion. It is also very important to know that CRM positivity is associated with increased cancer recurrence and decreased survival. Therefore, with the high incidence and high cost of colon cancer, improvements in colon cancer treatments should be one of the strategies in decreasing the recurrence of colon cancer and decreasing the cost of colon cancer. Reducing the number of patients with positive CRM may decrease the cost of colon cancer treatments by decreasing colon cancer recurrence and improving colon cancer long-term survival.

Further study is needed to evaluate the mechanisms through which CRM negativity improves colon cancer outcomes. Our study suggests that CRM positivity is an important indicator for 47-month mortality. Although this finding is consistent with previous study, there is still disagreement on how to define CRM positivity. Further study is needed to explore the association between CRM positivity (e.g., CRM≥2 mm) and survival from colon cancer.