

EFFECT OF NEOADJUVANT THERAPY ON TUMOR SIZE AND SURGICAL MARGINS
IN COLORECTAL CANCER

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ABSTRACT

Background: The standard management approach for colorectal cancer (CRC) is surgical resection followed by adjuvant chemotherapy. The risk of cancer recurrence after adjuvant therapy reaches 20-30% in CRC. The existing literature suggests potential benefits of neoadjuvant chemotherapy over adjuvant chemotherapy in GI cancers by reducing tumor size prior to surgery which helps to avoid incomplete resection of tumor. **Purpose:** In this single-center, retrospective study, we aim to investigate the effects of neoadjuvant chemotherapy on CRC regression after surgical resection by evaluating tumor size and surgical margins in a Jordanian population of CRC patients. **Methods:** We will implement a retrospective design at King Hussein Medical Center (KHMC), Amman, Jordan for CRC patients who underwent surgical resection from 2016 to 2024. The cohort will include CRC patients who took neoadjuvant chemotherapy prior to surgery (Group A), and those who did not take neoadjuvant therapy (Group B). Demographic and clinical data will be retrieved for the following variables: patients' ID, national number, age, gender, body-mass index (BMI), smoking history, tumor site, mode of surgery (Laparoscopic, or open), and presence of perforation. Outcome variable will include the proximal and distal tumor margins in centimeters (cm), and tumor diameter (cm). Continuous data will be reported as mean (standard deviation) and analyzed with the student's t-test for normally distributed data and using median (Range) with the Mann-Whitney U test for non-normally distributed data. Categorical variables will be reported with frequencies and percentages and analyzed using the Chi-square test. A logistic regression model will be developed to assess the association between neoadjuvant chemotherapy and outcome variables (Tumor Size and Margins). All analyses will be conducted using R statistical software.

KEYWORDS: Colorectal Cancer, Neoadjuvant chemotherapy, Tumor regression, Surgical resection, Jordan.

INTRODUCTION

Recently, neoadjuvant therapy has been extensively utilized in the treatment of solid tumors, including those of the breast, esophagus, stomach, and rectum.^[1] Additionally, the management of colorectal cancer (CRC) has improved substantially over the past decade, guided by clinical guidelines that emphasize a multidisciplinary and multimodal approach involving preoperative (neoadjuvant), surgical management, and postoperative (adjuvant) chemo- or chemoradiotherapy.^[2,3]

In patients with non-metastatic locally advanced (stage II-III) colon cancer, surgical resection followed by adjuvant chemotherapy is the treatment of choice. However, there is a high risk of recurrence and systemic relapse highlighting the need to assess the use of

neoadjuvant chemotherapy.^[4,5] In addition, in patients with locally advanced rectal cancer, current guidelines recommend trimodal therapy, which includes surgery, chemotherapy, and radiation therapy. This approach has been shown to improve local control and reduce recurrence rates but its effect on survival rates is still controversial.^[6,7] Since 2016, the National Comprehensive Cancer Network (NCCN) Guidelines for colon cancer have recommended that neoadjuvant chemotherapy may serve as an alternative primary treatment for tumors with clinical T4b stage. This approach enhances tumor resection with reduced local recurrence, improve postoperative recovery, and optimize survival outcomes.^[8]

Despite the observed benefits of neoadjuvant chemotherapy in CRC, there remains a significant

controversy in the literature regarding its selective use in CRC patients and overall effect. While guidelines generally recommend neoadjuvant therapy for patients with advanced disease, the criteria for selecting patients who may safely forgo this treatment are not well-defined.^[1,9] However, there is a lack of consensus on which patients might benefit from a more tailored approach, and the long-term implications of omitting neoadjuvant therapy in these cases remain uncertain. In this retrospective study, we aim to compare the surgical and tumor margins between CRC patients with or without neoadjuvant chemotherapy in the Jordanian population.

MATERIALS AND METHODS

Study design

We conducted a single-center, retrospective comparative study at King Hussien Medical Center (KHMC) in Jordan between the period of May 2014 to April 2024. Patients with non-metastatic locally advanced CRC were included and divided into those who had neoadjuvant chemotherapy prior to surgery, and those who had surgical resection followed by adjuvant chemotherapy. The primary outcome was the surgical margins and tumor diameter between the study groups.

We retrieved patients' data retrospectively through accessing the medical records between the period May 2014 to April 2024. Demographic and clinical data included hospital ID, national ID, age, gender, mode of surgery (Laparoscopic, or open resection), duration of hospital stay in days, presence of perforation, proximal and distal tumor margins, and tumor diameter.

Ethical approval

This study was approved by the Institutional Review Board at King Hussein Medical Center. Since it was a retrospective study using de-identified data from existing medical records, the need for informed consent was waived in accordance with the Declaration of Helsinki. All procedures adhered to relevant ethical standards and institutional guidelines.

Statistical analysis

Continuous data will be presented as mean (Standard deviation) and analyzed with the student's t-test for normally distributed variables, while median (Range) and the Wilcoxon rank-sum test will be applied for non-normally distributed variables. Categorical data will be expressed as frequencies and percentages and analyzed using the Chi-square test. A linear regression model will be constructed to evaluate the association between study variables and tumor margins. A P-value of <0.05 will be considered statistically significant. All analyses will be performed using R statistical software.

RESULTS

We included a total of 288 CRC patients and were grouped into those who took neoadjuvant chemotherapy (N=118, %), and who did not have neoadjuvant

chemotherapy (N=170, %). The mean age was 59.0 (13.0) years, and 165 (57%) were males (**Table 1**). The majority (61%) of patients underwent laparoscopic resection, while 89 (31%) underwent open surgery, and 24 (8.3%) had laparoscopy but converted to open surgery. Perforation was seen in 32 (11%) of patients. Marginal tumor characteristics was 7.5 (7.5) cm for distal margins, 14.0 (8.0) cm for proximal margins, and the mean tumor diameter was 4.70 (5.03) cm. The mean length of hospitalization was 4.17 (3.11) days.

Patients who had neoadjuvant chemotherapy were significantly younger than those who didn't (mean: 56.0 vs. 61.0, p-value=0.003, **Figure 1A**). There was no significant difference in sex, presence of perforation, and mode of surgery between the study groups (P-value>0.05, **Table 1**). While distal and proximal tumor margins, and tumor diameter were significantly different across study groups. The neoadjuvant chemotherapy group had a significantly lower distal tumor margins (mean: 3.3 cm vs. 10.3 cm, p-value<0.001) as shown in **Figure 1B**. While the proximal tumor margins were significantly higher in the neoadjuvant group (mean: 15.0 cm vs. 13.0 cm, p-value=0.004) as shown in **Figure 1C**. Tumor diameter was significantly lower in the neoadjuvant group (mean: 4.39 cm vs. 4.92 cm, p-value<0.001, **Figure 1D**).

The linear regression model for distal tumor margins showed significant negative association with the neoadjuvant chemotherapy group, in which patients who had neoadjuvant chemotherapy had a significantly lower distal margins (estimate: -0.90, 95% CI: -1.12;-0.69, p-value<0.001) as shown in **Table 2**. While there was no significant association in the model for proximal tumor margins and neoadjuvant group (p-value >0.05). However, patients who had laparoscopic resection had a significantly lower proximal tumor margin compared to patients who had laparoscopy but converted to open resection (estimate: -0.46, 95% CI: -0.88; -0.03, p-value=0.035) as shown in **Table 3**. The linear model for tumor diameter did not show significant association with neoadjuvant group (p-value>0.05), while presence of perforation was associated with a significantly higher tumor diameter (estimate: 0.54, 95% CI: 0.15; 0.94, p-value=0.007) as shown in **Table 4**.

DISCUSSION

Surgical resection is the mainstay treatment for localized non-metastatic colorectal cancer. Postoperative observation is crucial for early detection of tumor recurrence and metastasis. The main objective of surgical resection in CRC treatment is to fully remove the tumor while maintaining optimal bowel function and reducing the risk of complications. Preoperative or neoadjuvant chemotherapy for CRC treatment is still under investigation. Therefore, in this retrospective study, we aimed to analyze and investigate the postoperative surgical margins after CRC surgery and compare between patients who underwent neoadjuvant

chemotherapy and patients who underwent surgical resection alone.

Our cohort included 288 CRC patients who underwent surgical resection of which 118 had neoadjuvant chemotherapy. Our findings showed that the neoadjuvant group had a significantly younger age, with no difference in sex. Similar to our findings, a retrospective study of 921 CRC patients by Dehal et al. showed that patients who received neoadjuvant chemotherapy had a significantly younger age and higher-grade and advanced T-stage tumors, but with less lymph node involvement compared to the surgery with adjuvant chemotherapy group.^[10] The use of neoadjuvant chemotherapy for elderly patients, who are often above the median age in clinical trials, careful consideration is needed to balance treatment benefits with potential risks.^[11] Similarly, a study by Kamel et al. on non-metastatic CRC patients comparing neoadjuvant chemotherapy with surgery alone showed that younger age was significantly associated with the use of neoadjuvant chemotherapy in addition to male sex.^[12] In an international randomized controlled-trial for localized operable colon cancer, there was no age cutoff for the choice of neoadjuvant chemotherapy, and both groups receiving neoadjuvant chemotherapy and the control group were age-balanced. Therefore, there is still a need to evaluate the effect of age while giving preoperative chemotherapy.^[13]

Regarding the effect of neoadjuvant chemotherapy on tumor margins, our findings showed a significant decrease in distal tumor margins and tumor diameter in the neoadjuvant chemotherapy group. Neoadjuvant

therapy is being used more frequently in CRC patients, but there is still controversy in clinical practice regarding a standardized criterion to determine the safe distance of the distal margin post-therapy. As neoadjuvant chemotherapy works by decreasing the tumor margins and volume preoperatively, this can result in removing extra normal tissue especially in tumors in the lower rectum.^[14] Interestingly, a study by Yunlong et al. comparing mismatch repair (MMR) status in patients with or without neoadjuvant chemotherapy.^[15] They showed that in patients with MMR deficiency, neoadjuvant chemotherapy was associated with larger tumor diameter postoperatively compared to patients with MMR deficiency who did not have neoadjuvant chemotherapy. In addition, they showed that overall survival and disease-free survival were not significantly different in patients with and without neoadjuvant chemotherapy for advanced tumors.^[15] The FOxTROT trial showed that 50% of patients with locally advanced colon cancer and MMR deficiency did not have a pathological response while patients with MMR proficiency exhibited 23% greater regression and significant reduction in the 2-year recurrence rate.^[13] A study by Kim et al. for the use of neoadjuvant chemoradiotherapy in locally advanced rectal cancer showed that disease-free survival and overall survival were significantly associated with lymphovascular and perineural invasion.^[16] Neoadjuvant chemoradiotherapy has been recommended for patients with node positive rectal cancer and has been shown to be superior to adjuvant chemotherapy based on the results from a randomized controlled trial.^[17]

Table 1: Patients' demographics based on Chemotherapy treatment.

Characteristic	Neoadjuvant, N ¹ = 118	No neoadjuvant, N ¹ = 170	p-value ²	Overall, N ¹ = 288
Gender			0.11	
Male	61 (52%)	104 (61%)		165 (57%)
Female	57 (48%)	66 (39%)		123 (43%)
Age	56 (13)	61 (12)	0.003	59 (13)
Mode of surgery			0.4	
Laparoscopy	70 (59%)	105 (62%)		175 (61%)
Open	35 (30%)	54 (32%)		89 (31%)
Laparoscopy converted to open	13 (11%)	11 (6.5%)		24 (8.3%)
Perforation	11 (9.3%)	21 (12%)	0.4	32 (11%)
Distal margins (cm)	3.3 (2.1)	10.3 (8.5)	<0.001	7.5 (7.5)
Proximal margins (cm)	15 (6)	13 (9)	0.004	14 (8)
Tumor diameter (cm)	4.39 (7.38)	4.92 (2.27)	<0.001	4.70 (5.03)
Length of hospital stay (Days)	4.43 (3.79)	3.98 (2.52)	0.2	4.17 (3.11)
¹ n (%); Mean (SD)				
² Pearson's Chi-squared test; Wilcoxon rank sum test				

Table 2: Linear regression model for distal tumor margins (cm).

Predictor	Stand. Estimate	95% CI		p-value
		Lower	Upper	
Gender:				
Male – Female	0.0805	-0.1331	0.294	0.459
Age	0.0815	-0.0259	0.189	0.136

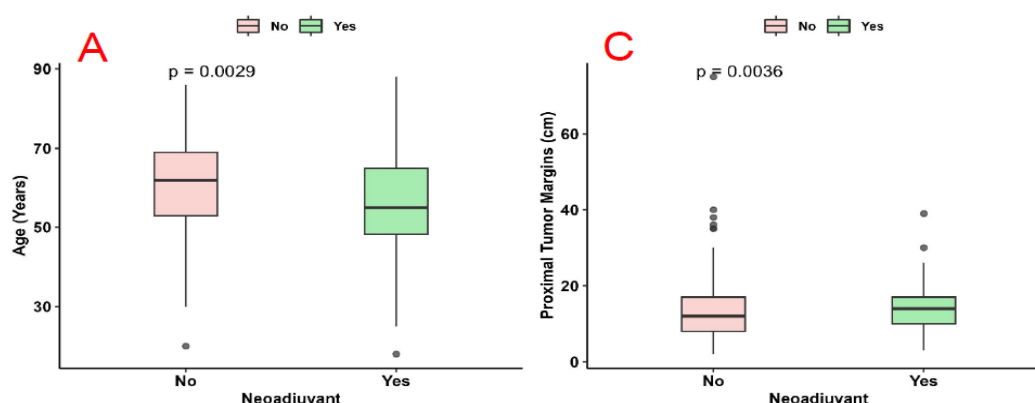
Mode of surgery:				
Laparoscopy – Laparoscopy converted to open	3.20E-04	-0.3859	0.387	0.999
Open – Laparoscopy converted to open	0.0642	-0.3477	0.476	0.759
Perforation:				
Yes – No	-0.0732	-0.4285	0.282	0.685
Neoadjuvant:				
Yes – No	-0.9035	-1.1219	-0.685	<.001
Length of hospital stay (Days)	0.0245	-0.086	0.135	0.663

Table 3: Linear regression model for proximal tumor margins (cm).

Predictor	Stand. Estimate	95% CI		p-value
		Lower	Upper	
Gender:				
Male – Female	0.2098	-0.0256	0.4452	0.08
Age	0.0309	-0.0874	0.1493	0.607
Mode of surgery:				
Laparoscopy – Laparoscopy converted to open	-0.4569	-0.8825	-0.0313	0.035
Open – Laparoscopy converted to open	-0.1045	-0.5585	0.3495	0.651
Perforation:				
Yes – No	0.1469	-0.2447	0.5384	0.461
Neoadjuvant:				
Yes – No	0.1981	-0.0427	0.4388	0.106
Length of hospital stay (Days)	-0.0153	-0.1371	0.1065	0.805

Table 4: Linear regression model for tumor diameter (cm).

Predictor	Stand. Estimate	95% CI		p-value
		Lower	Upper	
Gender:				
Male – Female	0.00169	-0.2358	0.2392	0.989
Age	-0.04229	-0.1613	0.0767	0.485
Mode of surgery:				
Laparoscopy – Laparoscopy converted to open	-0.07218	-0.4985	0.3541	0.739
Open – Laparoscopy converted to open	0.07163	-0.3853	0.5286	0.758
Perforation:				
Yes – No	0.54267	0.1492	0.9361	0.007
Neoadjuvant				
Yes – No	-0.11298	-0.3553	0.1293	0.359
Length of hospital stay	0.04659	-0.0761	0.1692	0.455



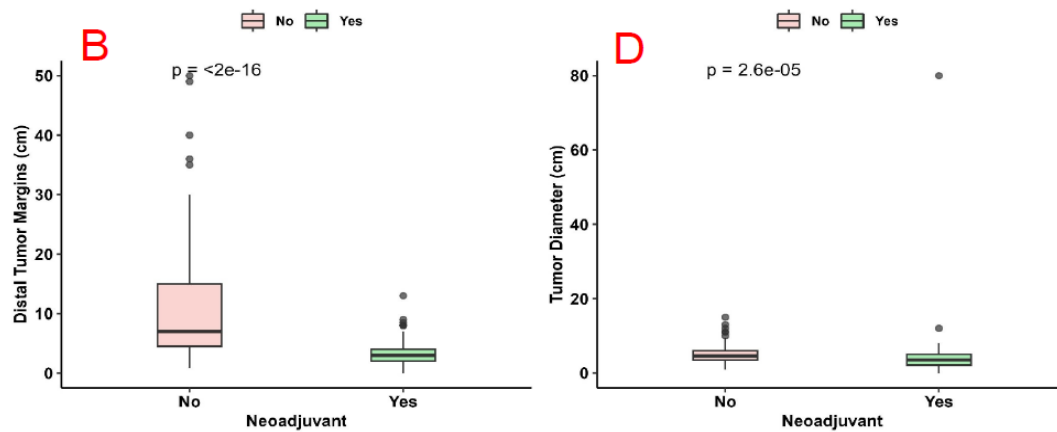


Figure 1: Boxplots showing the difference in age, Proximal and Distal tumor Margins and Tumor diameter between the study groups.