



IMPACT OF SMOKING ON SURGICAL OUTCOMES AND COMPLICATIONS IN COLORECTAL CANCER PATIENTS

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ABSTRACT

Background: It is undebatable that smoking is a major risk factor for various diseases, and the leading cause of morbidity and mortality. Colorectal cancer (CRC) patients undergoing surgical resection are under possible complications including infections, leakage, and anastomosis. However, the effect of smoking on the post-operative complications of CRC patients undergoing surgical resections needs further investigation. **Purpose:** We aim to investigate the association between pre-operative smoking on the post-operative outcomes in a population of CRC patients from Jordan undergoing surgical resection. In addition, we aim to investigate if the risk of post-operative complications are linked to other demographic and clinical factors. **Methods:** A retrospective, single-center study from King Hussien Medical Center in the period between 2016 to 2024. Patients' information will be recruited by accessing electronic hospital records. Demographic data will be collected for patients' ID, national number, age, and gender. Clinical variables will include body-mass index (BMI), smoking history (Smoker, Non-smoker, or Former-smoker), type of surgery (elective, or emergency), and mode of surgery (laparoscopic, or open). Post-operative evaluation will be determined by length of hospitalization in days, and post-operative complications. **Results:** We included 542 CRC patients who with a mean age of 58 years, and 58% are males. Smoking status varied, with 24% of patients being current smokers, 72% non-smokers, and 3% ex-smokers. There was a significant gender difference in smoking status, with 91% of smokers being male and 54% of non-smokers being female. Postoperative complications occurred in 26.4% of patients. The mortality rate was 1.5%. There was a trend toward higher postoperative pain in current smokers. Ever smokers had a lower rate of wound infections compared to non-smokers (2.7% vs. 7.4%). Logistic regression revealed that males had a higher likelihood of postoperative complications, and laparoscopic surgery was associated with better outcomes compared to open surgery.

KEYWORDS: Colorectal cancer, Jordan, Smoking, Colectomy, Hemicolectomy, Complications.

INTRODUCTION

Smoking has been established to be associated with various fatal diseases and cancers. It is one of the main causes of death in coronary heart diseases, stroke, lung cancer, and others. Cigarette smoking is the most used type of tobacco smoking.^[1] It is estimated by the World Health Organization (WHO) that tobacco smoking cause premature deaths in around 6 million people globally.^[2] There are significant levels of known carcinogens along with numerous other toxic chemicals in tobacco smoke. In addition, the nicotine in tobacco smoke showed an association with the rise in cardiovascular disease but plays little to no role in the increased risk of respiratory disease or cancer.^[3]

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths worldwide, and first cause of cancer-related mortality in men under the age of 50 years.^[1] The prevalence of CRC has been increasing in the middle eastern region including Jordan. The annual CRC incidence in Jordan reached 17.7% from 1996 to 2000, and it ranked the second most common cancer in both sexes in 2018 with and overall incidence of 10.6%. Mortality reduction for CRC resulted from the reduction of smoking and increased screening uptakes.^[4]

Organs not exposed to cigarette smoke are also expected to develop cancer such as the colon and rectum. In CRC, it has been shown that smoking is a significant risk factor for the development and worse prognosis of CRC.^[5,6] The mechanism by which smoking affect the

pathogenesis of CRC has been suggested to be linked to the gut microbiota and causes impairment of the gut barrier in animal models exposed to smoking. The MAPK/ERK pathway also showed significant enrichment in models exposed to cigarette smoke which can induce the development of CRC.^[7,8]

The association of smoking and colorectal cancer incidence has been well-investigated. However, there is still lack of research on the effect of smoking on the postoperative outcomes of CRC surgery. Therefore, in this retrospective study, we aim to investigate the association of postoperative outcomes of CRC surgery, and smoking in Jordanian population of CRC patients.

Methods

Study design

A retrospective, single-center observational study was conducted at King Hussien Medical Center in Jordan spanning the period of May 2014 to April 2024. Patients who were diagnosed with colorectal cancer and went surgical resection were included.

Study outcomes

The primary outcome of this study was postoperative complications and included wound infection, ileus, stoma, anastomosis, renal complications, death, and postoperative pain. Patients were stratified based on their smoking history into three groups: current smoker, ex-smoker, non-smoker. Additional stratification was carried out by including ex-smokers and current smokers to ever smoker group. Demographic and clinical data were collected retrospectively for the following variables: hospital record ID, national ID, age (years), sex, smoking status, type of surgery (elective, or emergency), mode of surgery (laparoscopic, open, or laparoscopic converted to open), and post-operative complications. Records with missing information were removed and a final count of 542 CRC patients were included.

Ethical approval

Ethical approval for this study was provided by the Ethics Committee at King Hussien Medical Center. As this was a retrospective study involving de-identified data from existing medical records, informed consent was not required, following the Declaration of Helsinki.

Statistical analysis

Continuous data will be presented as mean (standard deviation) and assessed using the Student's t-test for data that is normally distributed. For data that is not normally distributed, median (range) will be used, and the

Wilcoxon rank-sum test will be applied. Categorical variables will be reported as frequencies and percentages and analyzed using the Chi-square test. A logistic regression model will be developed to investigate the relationship between smoking and post-operative complications. A P-value of <0.05 is considered to be statistically significant. All analyses will be conducted using R statistical software.

RESULTS

We included a total of 542 CRC patients who underwent surgical resection at our hospital. The mean age was 58.0 (14.0) years, and 312 (58%) were males (**Table 1**). The majority (95%) of patients had elective colectomy, with 367 (68%) having laparoscopic colectomy, and 133 (25%) having open colectomy. A total of 131 () were smokers, 393 () were non-smokers, and 18 () were ex-smokers. There was a significant difference between smoking and gender, in which 91% of current smokers were males, and 54% of non-smoker were females (p-value<0.001). No significant difference in age was observed.

Postoperative complications were seen in 143 (26.4%) patients, and included wound infection in 33 (6.1%), ileus in 19 (3.5%) of patients, 13 (2.4%) patients had stoma, and 10 (1.8%) patients had anastomosis. Eight (1.5%) patients died following the operation. No significant differences were found between the post-operative complications and smoking groups. There was a trend towards a higher percentage of post-operative pain in 3.1% of current smokers compared to 0.5% in non-smokers (p-value=0.062).

After including ex-smokers with current smokers (Ever smoker, n=149), there was a significant difference in sex, in which 89% of ever smokers were males, compared to 54% of non-smokers being females (p-value<0.001) as shown in (**Table 2**). There was a significant difference in the rate of wound infections between smoking groups, in which 29 (7.4%) of non-smokers had wound infections compared to 4 (2.7%) in ever smokers (p-value=0.041). The logistic regression model showed a significant association with gender and postoperative complications, in which males had 1.6 higher likelihood of developing postoperative complications (OR: 1.58, 95% CI: 1.02-2.46, p-value=0.041) as shown in (**Table 3**). In addition, the mode of surgery was significantly associated with surgical outcomes, in which patients who had laparoscopy had better postoperative outcomes compared to those who converted to open surgery (OR: 0.46, 95% CI: 0.23-0.92, p-value=0.029).

Table 1: Patients' demographics based on smoking status.

Characteristic	Smoker N ¹ = 131	Ex-Smoker N ¹ = 18	Non-Smoker N ¹ = 393	p-value ²	Overall N ¹ = 542
Gender				<0.001	
Male	119 (91%)	13 (72%)	180 (46%)		312 (58%)
Female	12 (9.2%)	5 (28%)	213 (54%)		230 (42%)
Age	56 (13)	61 (11)	58 (14)	0.11	58 (14)

Type of surgery				0.5	
Elective	122 (93%)	18 (100%)	375 (95%)		515 (95%)
Emergency	9 (6.9%)	0 (0%)	18 (4.6%)		27 (5.0%)
Mode of surgery				0.4	
Laparoscopy	86 (66%)	16 (89%)	265 (67%)		367 (68%)
Open	36 (27%)	2 (11%)	95 (24%)		133 (25%)
Laparoscopy converted to open	9 (6.9%)	0 (0%)	33 (8.4%)		42 (7.7%)
Postoperative complications					
Ileus	8 (6.1%)	1 (5.6%)	10 (2.5%)	0.1	19 (3.5%)
Anastomosis	2 (1.5%)	1 (5.6%)	7 (1.8%)	0.4	10 (1.8%)
Stoma	5 (3.8%)	0 (0%)	8 (2.0%)	0.6	13 (2.4%)
Renal	4 (3.1%)	1 (5.6%)	4 (1.0%)	0.066	9 (1.7%)
Dead	3 (2.3%)	0 (0%)	5 (1.3%)	0.6	8 (1.5%)
Pain	4 (3.1%)	0 (0%)	2 (0.5%)	0.062	6 (1.1%)
Wound infection	4 (3.1%)	0 (0%)	29 (7.4%)	0.15	33 (6.1%)
None	91 (69%)	15 (83%)	293 (75%)	0.4	399 (74%)

¹ n (%); Mean (SD)

² Pearson's Chi-squared test; Kruskal-Wallis rank sum test; Fisher's exact test.

Table 2: Patients' demographics based on smoking vs no smoking.

Characteristic	Smoker N ¹ = 149	Non-Smoker N ¹ = 393	p-value ²	Overall N ¹ = 542
Gender			<0.001	
Male	132 (89%)	180 (46%)		312 (58%)
Female	17 (11%)	213 (54%)		230 (42%)
Age	57 (13)	58 (14)	0.13	58 (14)
Type of surgery			0.5	
Elective	140 (94%)	375 (95%)		515 (95%)
Emergency	9 (6.0%)	18 (4.6%)		27 (5.0%)
Mode of surgery			0.6	
Laparoscopy	102 (68%)	265 (67%)		367 (68%)
Open	38 (26%)	95 (24%)		133 (25%)
Laparoscopy converted to open	9 (6.0%)	33 (8.4%)		42 (7.7%)
Postoperative complications				
Ileus	9 (6.0%)	10 (2.5%)	0.048	19 (3.5%)
Anastomosis	3 (2.0%)	7 (1.8%)	>0.9	10 (1.8%)
Stoma	5 (3.4%)	8 (2.0%)	0.4	13 (2.4%)
Renal	5 (3.4%)	4 (1.0%)	0.069	9 (1.7%)
Dead	3 (2.0%)	5 (1.3%)	0.7	8 (1.5%)
Pain	4 (2.7%)	2 (0.5%)	0.051	6 (1.1%)
Wound infection	4 (2.7%)	29 (7.4%)	0.041	33 (6.1%)
None	106 (71%)	293 (75%)	0.4	399 (74%)

¹ n (%); Mean (SD)

² Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Table 3: Logistic regression model.

Predictor	Odds ratio	95% CI		p-value
		Lower	Upper	
Age	0.996	0.9825	1.011	0.617
Gender:				
Male – Female	1.584	1.0195	2.462	0.041
Type of surgery:				
Emergency – Elective	1.257	0.5401	2.924	0.596
Mode of surgery:				
Laparoscopy – Laparoscopy converted to open	0.463	0.2324	0.923	0.029
Open – Laparoscopy converted to open	1.156	0.5523	2.418	0.701
Smoking:				
Non-Smoker – Ex-Smoker	1.558	0.4294	5.652	0.5

Smoker – Ex-Smoker	1.599	0.4261	6	0.487
Odds of "Postoperative complications = "Yes vs. No"				

DISCUSSION

The incidence of colorectal cancer (CRC) has increased in developing countries. In Jordan, CRC survival rates reached 58.2%, and 51.8% for the 5-year, and 10-year period.^[9] The gold-standard treatment approach for CRC is surgical resection which can be performed either using open surgery or laparoscopic-assisted technique.^[10] Despite improved treatment modalities, the recurrence rate of CRC after surgical resection is still high and can reach 30%-40%.^[11] To achieve better surgical outcomes after CRC surgery, functional capacity plays a key factor by providing a strong justification for enhancing physical, nutritional, and mental well-being prior to surgery.^[12] Therefore, in this retrospective study, our objective is to evaluate and compare postoperative outcomes, including postoperative complications and mortality rate, between CRC patients in the Jordanian population with and without preoperative smoking history.

Our cohort included a total of 542 CRC patients, grouped into current smokers (n=131), ex-smokers (n=18), and never smoker (n=393). There was no sex predominance in our cohort, and a mean age of 58 years in both study groups. Recently, several population studies showed a significant increase in CRC incidence among younger people.^[13] In addition to genetic conditions such as lynch syndrome and familial adenomatous polyposis (FAP) disease, smoking carries a significant risk for developing CRC, which can be attributed to the rapid increase in CRC incidence among younger patients.^[14] Additionally, there is still a low screening rate for CRC in Jordan, which has been attributed to several factors including people awareness of the necessity of CRC screening and access to screening facilities.^[15]

Surgical resection is the mainstay treatment approach in non-metastatic CRC patients followed by adjuvant chemotherapy in patients with stage II CRC. Advanced stages and metastatic CRC patients may also benefit from neoadjuvant chemotherapy, and/or targeted and immunotherapy.^[16] Recently, laparoscopic surgery rates increased in comparison to open surgery for both cancerous and non-cancerous colorectal surgery.^[17] In our study, all patients underwent surgical resection followed by adjuvant chemotherapy, with the majority of patients undergoing laparoscopic resection. Postoperative complications were seen in 26% of our cohort, ranging from ileus, anastomosis, wound infection, and postoperative pain, and the mortality rate was 1.5%. The Jordan Cancer Registry showed that cancer-related mortality from small intestine and colon origin reach a rate of 11.4% in males, and 8.7% in females.^[18] In our study, males were associated with a significantly higher odds of developing postoperative complications compared to females. These findings can also be explained by the significantly higher proportion of males

exposed to cigarette smoking (91% vs. 54%). Similarly, a study by Al-Amry et al. showed that smoking was linked to numerous risks and potential postoperative complications like wound infections and delayed wound healing, which was observed in 20% of the patients.^[19]

Interestingly, our findings showed that despite the low rate of wound infection, it was higher in non-smoker CRC patients compared to ever smokers (7.4% vs. 2.7%). In contrast, several studies showed that smoking increase the risk of infections by several mechanisms including lowering the immune system response.

Our study presents some limitations, thus the findings in our study need to be interpreted carefully. First, we conducted a single-center study in Jordan, this may limit the applicability of our findings to other regions and limit the generalizability of the results. Future studies including multi-center cohorts should be carried out to assess the results across different regions. Second, the retrospective design implemented in our study design can infer the causal relationship between events. Therefore, prospective randomized controlled studies with long-term follow-up are warranted to evaluate the long-term outcomes of smoking on CRC surgery.

However, our study have several strong points. This is the first study up to our knowledge in Jordan to evaluate the long-term outcomes of smoking association and postoperative outcomes of CRC surgery over a period of 10-years. Despite the low number of complications, our study included a large sample size which increases the power of our results.

In conclusion, this is the first study in Jordan to assess the long-term outcomes smoking in CRC patients who undergoing surgical resection. Our findings showed higher rates of postoperative complications in smokers, with no significant association in mortality rate between the two groups. These findings add to the available literature on the risk of worse prognostic outcomes associated with smoking in CRC patients. However, future multicenter studies are warranted to support these findings.

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