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ORIGINAL ARTICLE

Prognostic Factors Influencing The Recurrence Rate and Survival of Patients With Colorectal Cancer: A Single Institution Experience

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ABSTRACT:

Background: This study aims to determine the factors impacting the recurrence of colorectal carcinoma after resection and completion of the radio chemotherapy course.

Methods: The current single-center retrospective cohort study was conducted at Zagazig University Hospitals from November 2016 to November 2023. The study included 200 patients diagnosed with colorectal cancer (CRC) who underwent surgical resection and chemoradiotherapy.

Results: The study included 200 patients with colorectal cancer after a complete cure with surgery and chemoradiotherapy. During follow-ups for five years, 120 patients had no recurrence of the disease, while 80 patients had a disease recurrence. Recurrence was higher in male smokers with a positive family history. The mean age in recurrent cases was higher than that of non-recurrent cases. Receiving chemoradiotherapy, laparoscopic surgery, and mesocolic and mesorectal excision reduced the likelihood of recurrence. However, this risk increased with open surgery, soiling during surgery, and T3 and T4 tumors. The non-recurrent cases had a higher number of extracted lymph nodes (LNs) compared to the recurrent cases, with a P-value<0.001. The majority of recurring cases were asymptomatic and were discovered during follow-up investigations, while the liver represented the most common site for recurrence.

Conclusions: The recurrence of colorectal carcinoma is influenced by a combination of patient, pathological, surgical, and oncological factors. A total of thirty-three risk factors have been assessed.

Keywords: Colorectal cancer; Recurrence; L.N ratio; Mesocolic excision; Neoadjuvant therapy.

INTRODUCTION

Colorectal cancer recurrence is defined as a local, regional, or distant metastatic recurrence after a disease-free time [1]. Local recurrence refers to CRC relapses at the site of the initial surgical resection [2]. In contrast, regional recurrence occurs in draining lymph nodes and/or lateral pelvic lymph nodes [1]. Distant metastatic recurrence mainly occurs in the liver (40-50% of metastases), lungs (10-20% of metastases), peritoneum, ovaries, adrenal glands, bone, and brain [3]. The 5-year survival rates for CRC in the localized, regional, and distant metastatic phases are projected to be approximately 90%, 70%, and 10%, respectively [4].

It is necessary to validate individual risk factors, particularly multivariable prediction models of several risk factors for local, regional, or distant metastasis and recurrence. Therefore, outcomes can serve as guidance for primary tumor treatment and offer prognostic information to both patients and doctors [3].

This study aims to improve the survival and prognosis after a complete cure of colorectal cancer. This will be achieved by identifying the factors that

have an impact on the recurrence of colorectal cancer in a large group of Egyptian patients

METHODS

This study is a retrospective cohort study conducted at the Surgery, Gastroenterology, and Oncology Departments at Zagazig University Hospitals in Egypt from January 2013 to December 2022. Data was collected from the patient's records in the three departments. Colorectal cancer patients who achieved complete remission through surgery and chemoradiotherapy in this period were followed up (5-year follow-up).The study included a total of 200 patients. Exclusion criteria were patients ≤18 years old inoperable and metastatic cases at presentation.

The study protocol was approved by the Institutional Research Board (IRB) at Zagazig University with registration ID #11279-20-11-2023. The study procedures adhered to the Helsinki Declaration of 1975, as revised in 2000, and the STROBE guidelines. In addition, the study was registered in clinical trials by ID number NCT06325410.The study has assessed patient-related outcomes, such as age, sex, BMI, smoking, medical, surgical, or family history. Pathological risk factors, such as size, site, morphology, and histology of the tumor, were evaluated. Surgical risk factors included surgical margins, type of surgery and anastomosis, mesocolic and mesorectal excision, number of extracted LNs, positive lymph nodes, and lymph node ratio (the ratio of positive to examined lymph nodes LNR), stoma, and surgical complications. Factors related to oncology and gastroenterology, such as biomarkers, symptoms, TNM stage, and adjuvant and neoadjuvant therapy, were also assessed.For the SEER database, recurrence-free survival (RFS) was evaluated and defined as the time from the date of curative surgery to the time of recurrence or death.

Statistical Methods

The study used STATA statistical package for statistical analyses, comparing baseline characteristics, assessing differences between non-recurrent and recurrent groups, and comparing continuous and categorical variables. Logistic regression models were used to assess recurrence association with clinical variables, and Kaplan-Meier survival curves were used to estimate RFS probabilities.

RESULTS

Table 1 shows the baseline characteristics of the studied patients. The study included a total number of 200 patients, with 120 (60%) non-recurrent and 80 (40%) recurrent patients. Among non-recurrent patients, 55.0% were male and 45.0% were female, whereas the recurrent group consisted of 62.5% males and 37.5% females. The mean age of non-recurrent patients was 57.65 years (SD = 9.69), slightly higher than the mean age of recurrent patients at 54.66 years (SD = 10.72). The median body mass index (BMI) for both groups was 24, with an interquartile range (IQR) of 21-26 for non-recurrent patients and 21-29.5 for recurrent patients.A higher proportion of non-recurrent patients were non-smokers (71.7%) compared to recurrent patients (52.5%). Regarding comorbidities and medical diseases, 66.7% of non-recurrent patients and 61.3% of recurrent patients had no comorbidities. Non-recurrent patients had a lower prevalence of family history, with only 10.8% reporting a family history compared to 28.8% of recurrent patients. A higher proportion of patients in the recurrent group (51.3%) had previous surgeries, compared to 34.2% of non-recurrent patients. The most common previous surgeries in the recurrent group included laparoscopic cholecystectomy (21.3%) and inguinal hernia repair (15.0%).There were significant variations in the tumor characteristics among the groups. Among non-recurrent patients, the most common tumor macroscopic appearance was ulceration (44.2%), followed by fungation (30.8%) and infiltration (25.0%). In recurrent patients, infiltrating tumors were the most common type (48.1%), followed by ulcers (40.5%) and fungation (11.4%). Positive surgical margins were more frequently observed in recurrent patients (36.3%) compared to non-recurrent patients (4.2%).

Neoadjuvant therapy was administered to 35.8% of non-recurrent patients and 25.0% of recurrent patients. In addition, 83.3% of non-recurrent patients received adjuvant therapy, while 85.0% of recurrent patients received it. Laparoscopic surgery was more common in non-recurrent patients (64.2%) than in recurrent patients (75.0%), who demonstrated a higher incidence of open surgery (35.8%). The occurrence of soiling during surgery was observed in 85.0% of recurrent patients compared to only 16.7% of non-recurrent patients.Furthermore, 63.8% of recurrent patients underwent a hand-sewn anastomosis, whereas 83.3% of non-recurrent patients had a stapled anastomosis. Mesocolic or

mesorectal excision was performed in 90.8% of non-recurrent patients and 25.0% of recurrent patients. Recurrent patients had a higher incidence of postoperative complications, with 33.8% experiencing fecal fistula and 16.3% with wound infections. Conversely, 79.2% of non-recurrent patients had no postoperative complications. Stoma formation was observed in 61.7% of non-recurrent patients and 28.8% of recurrent patients. The primary tumor site varied among the groups, with rectal tumors being most common in both non-recurrent (38.3%) and recurrent (42.5%) patients. The incidence of grade 1 tumors was higher in non-recurrent patients (53.3%), while recurrent patients had a higher prevalence of higher-grade tumors (grades 3 and 4) (76.3%).The analysis of tumor histology revealed that non-recurrent patients had a higher occurrence of papillary adenocarcinoma (51.7%), while recurrent patients had a higher prevalence of mucinous adenocarcinoma (28.8%) and undifferentiated tumors (23.8%). The types of anastomosis varied between non-recurrent and recurrent patients. Colorectal anastomosis was the most common type in non-recurrent patients, accounting for 36.7% of cases, while colocolic anastomosis was the most common type in recurrent patients, accounting for 30.0% of cases. The tumor stage (TN) at diagnosis showed that the majority of non-recurrent patients had T1 and T2 tumors (96.7%), while the majority of recurrent patients had T3 and T4 tumors (77.6%). The Node stage was also more advanced in recurrent patients, with 42.5% having N2 stage compared to none in the non-recurrent group.The clinical presentation of recurrent cases is detailed in **Table 2.** Among the 80 recurrent cases, the most common clinical presentation was accidental during a follow-up, accounting for 36 patients (45.0%). Obstruction was observed in 34 patients (42.5%) while bleeding per rectum was reported in 10 patients (12.5%). Regarding the recurrence sites, the liver was the most common site, with 20 patients (25.0%) experiencing recurrence there. Recurrence occurred at the anastomosis site in 12 patients (15.0%), and a combination of recurrence at the anastomosis and liver was found in 10 patients (12.5%). Additionally, 18 patients (22.5%) had recurrence at both the peritoneum and liver.Other recurrence sites included the peritoneum (7.5%), lymph nodes (5.0%), and combined sites such as anastomosis and peritoneum (3.8%), liver and lymph nodes (3.8%), adrenal and lymph nodes (2.5%), and peritoneum and lymph nodes (2.5%).

Table 3 shows a comparison of clinical characteristics between non-recurrent and recurrent patients using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. The median number of resected lymph nodes was significantly higher in non-recurrent patients (median: 14, IQR: 11-17) compared to recurrent patients (median: 10, IQR: 6-14), with a p-value of 0.0001. Similarly, Non-recurrent patients had a significantly lower median lymph node ratio (median: 0.1, IQR: 0-0.3) compared to recurrent patients (median: 0.5, IQR: 0.3-0.8), with a p-value of 0.0001.Logistic regression was used to assess the association between neoadjuvant chemotherapy and recurrence in different primary tumor sites, as shown in **Table 4.** Overall, neoadjuvant therapy was associated with a significant reduction in the odds of recurrence, with an odds ratio (OR) of 0.54 (95% CI: 0.30 to 0.97, p = 0.038). Neoadjuvant therapy was found to significantly decrease the odds of recurrence (OR = 0.21, 95% CI: 0.08 to 0.56, p = 0.002). Similarly, for rectosigmoid cancer, neoadjuvant therapy was associated with a significant reduction in the odds of recurrence (OR = 0.05, 95% CI: 0.005 to 0.49, p = 0.010).

The variable was omitted for the splenic flexure, left colon, right colon, transverse colon, and sigmoid sites due to accurate prediction, indicating different outcomes depending on the neoadjuvant therapy status. In contrast, neoadjuvant therapy did not show a statistically significant effect on recurrence for hepatic flexure cancer (OR = 3.2, 95% CI: 0.23 to 45.19, p = 0.389). These findings highlight the varying impact of neoadjuvant therapy on recurrence risk in different primary tumor sites, with significant protective effects observed, particularly in rectal and rectosigmoid cancer cases.

The logistic regression analyses revealed several significant predictors of recurrence, as shown in **Table 5.** Higher tumor grade was strongly associated with increased odds of recurrence, with Grade 2 (OR = 11.33, 95% CI: 2.50 to 51.42, p = 0.002), Grade 3 (OR = 187.43, 95% CI: 37.11 to 946.75, p = <0.001), and Grade 4 (OR = 640, 95% CI: 55.10 to 7434.39, p = 0.000). All of these grades showed a substantial

increase in the risk of recurrence compared to Grade 1. The risk of recurrence was significantly higher in advanced tumor stages, with T2 (OR = 9.65, 95% CI: 1.24 to 75.10, p = 0.030) and T3 stages (OR = 556.50, 95% CI: 59.94 to 5167.10, p = 0.000) showing higher odds of recurrence compared to T1 stage. Nodal involvement was another critical factor, with the N1 stage (OR = 9.98, 95% CI: 4.50 to 22.13, p = 0.000) significantly increasing the odds of recurrence compared to the N0 stage as a reference.For patients with rectal tumors, the presence of a stoma was significantly associated with lower odds of recurrence, with an OR of 0.10 (95% CI: 0.03 to 0.30, p = <0.001). This suggests that the stoma reduced the odds of recurrence by 90%. Similarly, the presence of a stoma significantly reduced the odds of recurrence (OR = 0.07, 95% CI: 0.01 to 0.73, p = 0.026) in patients with rectosigmoid tumors, indicating a 93% reduction in recurrence risk. Conversely, in patients with sigmoid tumors, the OR for recurrence with a stoma was 0.22 (95% CI: 0.03 to 1.49, p = 0.122). This result indicates that there is no clear association between the presence of a stoma and recurrence.Additionally, patients with a more significant number of resected lymph nodes (≥ 12) had significantly lower odds of recurrence compared to those with fewer than 12 resected lymph nodes (OR = 0.02, 95% CI: 0.01 to 0.04, p < 0.001).

Table 5 shows associations between specific biochemical parameters and odds of recurrence. The strongest predictor was the Carcinoembryonic Antigen (CEA), with patients who had high CEA levels exhibiting significantly higher odds of recurrence than those with normal levels (OR: 40.45, 95% CI: 14.81 - 110.47, p < 0.001). Similarly, elevated C-reactive protein (CRP) levels were linked to increased odds of recurrence (OR: 5.67, 95% CI: 3.05 - 10.53, p < 0.001). High D-Dimer levels were also significantly associated with higher odds of recurrence (OR: 5.71, 95% CI: 3.06 - 10.68, p < 0.001). Lactate Dehydrogenase (LDH) emerged as another significant predictor, with patients exhibiting high LDH levels showing an OR of 3.33 (95% CI: 1.73 - 6.42, p < 0.001) for recurrence. Lastly, fecal calprotectin levels were predictive of recurrence risk, with patients exhibiting high levels having significantly higher odds of recurrence (OR: 3.12, 95% CI: 1.73 - 5.64, p < 0.001).

Table1. Baseline Demographics of Study Patients

Variable	Non-recurrent (N=120)	Recurrent (N=80)
Patient Sex		
Male	66 (55.0%)	50 (62.5%)
Female	54 (45.0%)	30 (37.5%)
Patient Age		
Mean (SD)	57.65 (9.69)	54.66 (10.72)
Body Mass Index		
Median (IQR)	24 (21-26)	24 (21-29.5)
Smoking Status		
No	86 (71.7%)	42 (52.5%)
Yes	34 (28.3%)	38 (47.5%)
Comorbidities		
No	80 (66.7%)	49 (61.3%)
Hypertensive	20 (16.7%)	11 (13.8%)
Diabetic	20 (16.7%)	11 (13.8%)
Cardiac	-	2 (2.5%)
Hepatic	-	4 (5.0%)
Hypertensive & Diabetic	-	3 (3.8%)
Family History		
No	107 (89.2%)	57 (71.3%)
Yes	13 (10.8%)	23 (28.8%)
Previous Surgery		
No	79 (65.8%)	39 (48.8%)

Variable	Non-recurrent (N=120)	Recurrent (N=80)
PUH	11 (9.2%)	9 (11.3%)
Inguinal Hernia	13 (10.8%)	12 (15.0%)
Lap Cholecystectomy	17 (14.2%)	17 (21.3%)
Sleeve	-	1 (1.3%)
Splenectomy	-	2 (2.5%)
Tumor Macroscopic		
Fungating	37 (30.8%)	9 (11.4%)
Infiltrating	30 (25.0%)	38 (48.1%)
Ulcer	53 (44.2%)	32 (40.5%)
Surgical Margins		
Free	115 (95.8%)	51 (63.8)
Positive	5 (4.2%)	29 (36.3%)
Neoadjuvant Therapy		
No	77 (64.2%)	60 (75.0%)
Yes	43 (35.8%)	20 (25.0%)
Adjuvant Therapy		
No	20 (16.7%)	12 (15.0%)
Yes	100 (83.3%)	68 (85.0%)
Surgery Type		
Laparoscopic	69 (57.5%)	38 (47.5%)
Open	51 (42.5%)	42 (52.5%)
Soiling During Surgery		
No	113 (94.2%)	26 (32.5%)
Yes	7 (5.8%)	54 (67.5%)
Handsewn/Stappled		
Hand Sewn	20 (16.7%)	51 (63.8%)
Stapled	100 (83.3%)	29 (36.3%)
Mesocolic/Mesorectal Excision		
No	11 (9.2%)	60 (75.0%)
Yes	109 (90.8%)	20 (25.0%)
Postoperative Complications		
No	95 (79.2%)	34 (42.5%)
Wound Infection	8 (6.7%)	13 (16.3%)
Fecal Fistula	6 (5.0%)	27 (33.8%)
Pneumonia	11 (9.2%)	6 (7.5%)
Stoma Formation		
No	46 (38.3%)	57 (71.3%)
Yes	74 (61.7%)	23 (28.8%)
Primary Tumor Site		
Rectal	46 (38.3%)	34 (42.5%)
Rectosigmoid	18 (15.0%)	11 (13.8%)
Splenic Flexure	7 (5.8%)	7 (8.8%)
Lt Colon	4 (3.3%)	7 (8.8%)
Rt Colon	18 (15.0%)	4 (5.0%)
Hepatic Flexure	9 (7.5%)	7 (8.8%)
Transverse Colon	3 (2.5%)	2 (2.5%)
Sigmoid	15 (12.5%)	8 (10.0%)
Tumor Grade		

Variable	Non-recurrent (N=120)	Recurrent (N=80)
1	64 (53.3%)	2 (2.5%)
2	48 (40.0%)	17 (21.3%)
3	7 (5.8%)	41 (51.3%)
4	1 (0.8%)	20 (25.0%)
Tumor Histology		
Signet Ring	5 (4.2%)	18 (22.5%)
Undifferentiated	1 (0.8%)	19 (23.8%)
Papillary Adenocarcinoma	62 (51.7%)	6 (7.5%)
Tubular Adenocarcinoma	40 (33.3%)	14 (17.5%)
Mucinous Adenocarcinoma	12 (10.0%)	23 (28.8%)
Anastomosis		
Colorectal	44 (36.7%)	17 (21.3%)
Coloanal	17 (14.2%)	13 (16.3%)
Colocolic	19 (15.8%)	24 (30.0%)
Abdominoperineal	13 (10.8%)	15 (18.8%)
Ileocolic	27 (22.5%)	11 (13.8%)
Tumor Stage (T)		
T1	4 (3.3%)	1 (1.3%)
T2	74 (61.7%)	17 (21.3%)
T3	39 (32.5%)	53 (66.3%)
T4	3 (2.5%)	9 (11.3%)
Node Stage (N)		
N0	61 (50.8%)	11 (13.8%)
N1	29 (24.2%)	35 (43.8%)
N2	30 (25.0%)	34 (42.5%)

Table 2: Clinical Presentation of recurrent cases

Clinical Presentation	
Follow Up	36 (45.0%)
Bleeding Per Rectum	10 (12.5%)
Obstruction	34 (42.5%)
Recurrence Site	
Adrenal and Lymph Nodes	2 (2.5%)
Anastomosis	12 (15.0%)
Anastomosis and Liver	10 (12.5%)
Anastomosis and Peritoneum	3 (3.8%)
Liver	20 (25.0%)
Liver and Lymph Nodes	3 (3.8%)
Lymph Nodes	4 (5.0%)
Peritoneum	6 (7.5%)
Peritoneum and Lymph Nodes	2 (2.5%)
Peritoneum and Liver	18 (22.5%)

Table 3: Comparison of Clinical Characteristics by Recurrence Status

Variable	Non-recurrent (N=120)	Recurrent (N=80)	P value*
Number of Resected Lymph Nodes			**<0.001**
Median (IQR)	14 (11-17)	10 (6-14)	
Lymph Node Ratio			**<0.001**
Median (IQR)	0.1 (0-0.3)	0.5 (0.3-0.8)	
* P values for Mann-Whitney U test for continuous variables and Chi-squared test for categorical variables			

Table 4: Odds Ratios for Neoadjuvant Therapy by Primary Tumor Site

Primary Site	OR	P value	95% CI
Overall	0.54	**0.038**	0.30 - 0.97
Rectal	0.21	**0.002**	0.08 - 0.56
Rectosigmoid	0.05	**0.010**	0.005 - 0.49
Splenic Flexure	1 (omitted)	-	-
Left Colon	1 (omitted)	-	-
Right Colon	1 (omitted)	-	-
Hepatic Flexure	3.2	0.389	0.23 - 45.19

Table 5: Odds Ratios for Various Predictors of Recurrence

Variable	Odds Ratio	P value	95% CI
Tumor Grade			
Grade 1	Reference	-	-
Grade 2	11.33	**0.002**	2.50 - 51.42
Grade 3	187.43	**<0.001**	37.11 - 946.75
Grade 4	640	**<0.001**	55.10 - 7434.39
Tumor Stage (T)			
T1	Reference	-	-
T2	9.65	**0.03**	1.24 - 75.10
T3	556.50	**<0.001**	59.94 - 5167.10
Nodal Stage (N)			
N0	Reference	-	-
N1	9.98	**<0.001**	4.50 - 22.13
Stoma			
Rectal	0.10	**<0.001**	0.03 - 0.30
Rectosigmoid	0.07	**0.026**	0.01 - 0.73
Splenic Flexure	1	-	-
Left Colon	1	-	-
Right Colon	1	-	-
Hepatic Flexure	1	-	-
Transverse Colon	1	-	-
Sigmoid	0.22	0.122	0.03 - 1.49
Number of Resected Lymph Nodes			
< 12	Reference	-	-
≥ 12	0.02	**<0.001**	0.01 - 0.04
biochemical parameters			

Variable	Odds Ratio	P value	95% CI
Carcinoembryonic Antigen (CEA)		-	-
Normal	Reference	-	-
High	40.45	**<0.001**	14.81 - 110.47
C-Reactive Protein (CRP)		-	-
Normal	Reference	-	-
High	5.67	**<0.001**	3.05 - 10.53
D-Dimer		-	-
Normal	Reference	-	-
High	5.71	**<0.001**	3.06 - 10.68
Lactate Dehydrogenase (LDH)		-	-
Normal	Reference	-	-
High	3.33	**<0.001**	1.73 - 6.42
Fecal Calprotectin		-	-
Normal	Reference	-	-
High	3.12	**<0.001**	1.73 - 5.64

Kaplan-Meier Survival Analysis Results

The recurrence-free survival (RFS) probability was evaluated among patients stratified by a variety of factors, such as the N-stage, T-stage, and lymph node (ln) ratio quartiles, using Kaplan-Meier survival curves. The survival functions were compared across various strata using the log-rank test.

N-Stage Analysis

The Kaplan-Meier survival curves for patients with different N-stages (N0, N1, and N2) are shown in **Figure 1.** The log-rank test indicated a borderline significant difference in RFS across N-stage groups (chi-square = 5.89, P = 0.0525).

The Kaplan-Meier survival curves for different T-stages (T1, T2, T3, and T4) are shown in **Figure 2.** The T-stage groups did not exhibit a significant difference in RFS according to the log-rank test (chi-square = 6.65, P = 0.0840).

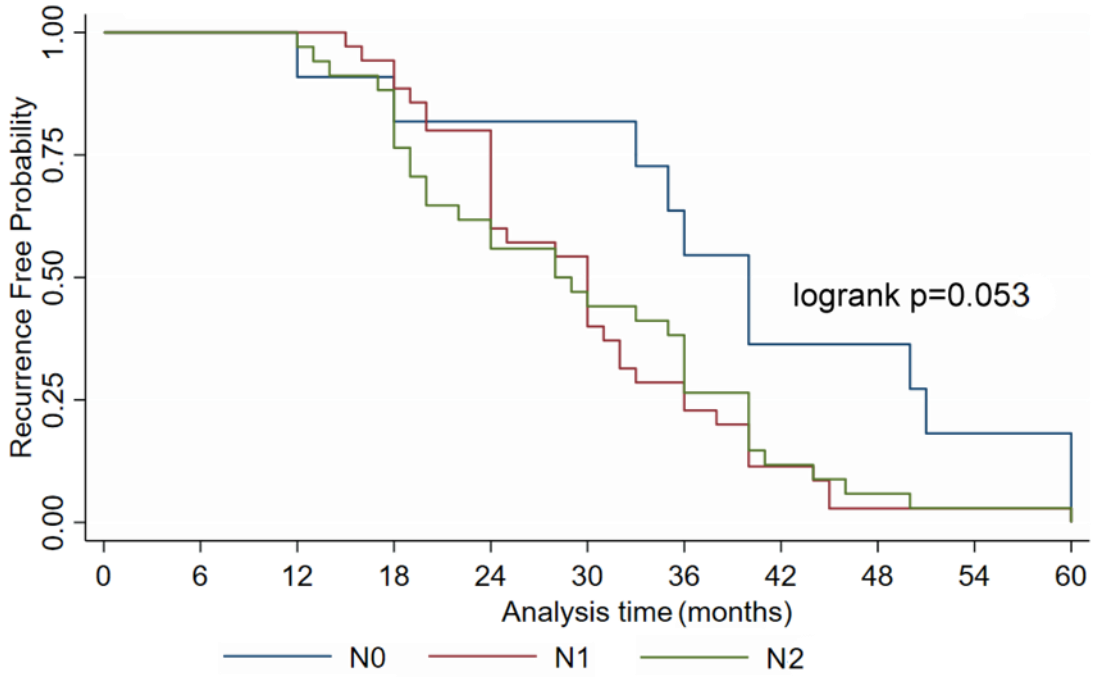

Figure 1: Recurrence Free Probability according to N Stages

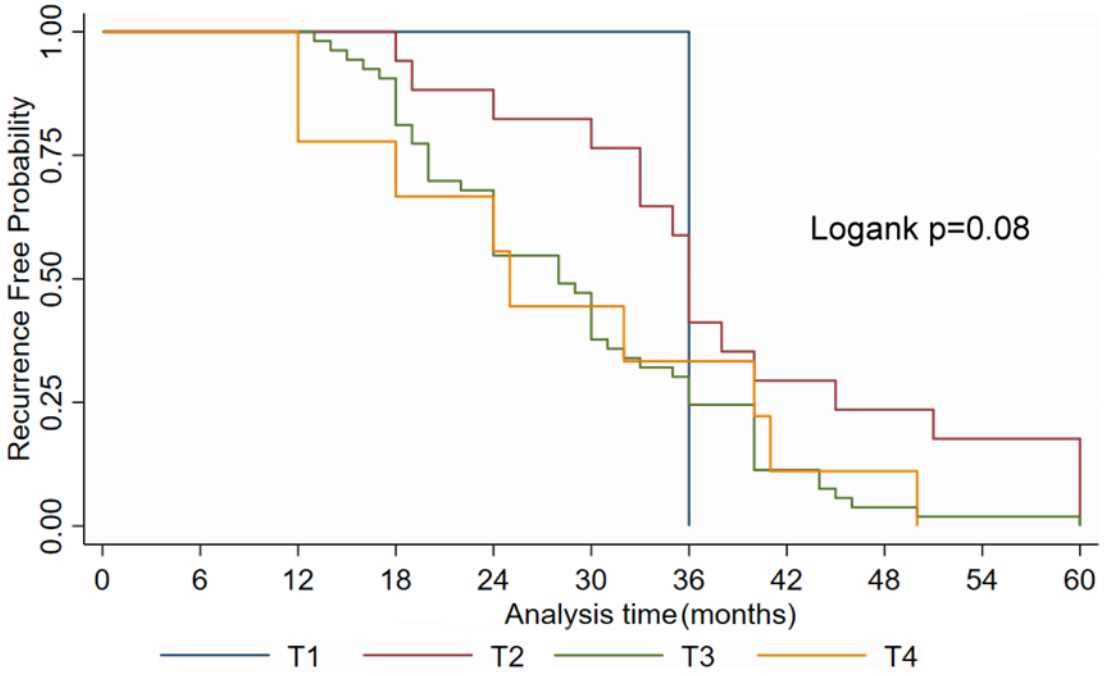

Figure 2: Recurrence Free Probability according to T Stages

DISCUSSION

There is an increasing need for the complete eradication of colorectal cancer and the provision of free survival to patients, as it is one of the most prevalent malignancies.This study aimed to determine multiple risk factors that impact on prognosis and recurrence of CRC. In the current study, male sex predominance was observed in both recurrent and non-recurrent groups, with the mean age at surgery being 54.66 (10.72) and 57.65 (9.69), respectively. These results align with those of Zare-Bandamiri et al. [5].Wei Xu et al. [6] found a weak correlation between recurrence and obesity and underweight. However, there was no correlation with overweight. Our study found that the median body mass index (BMI) was 24 for both groups. Additionally, we observed that BMI has a more significant impact on the overall condition and surgical complications than disease recurrence.A high proportion of recurrent cases were smokers compared to non-recurrent cases, as smoking was established as a causal factor for CRC almost ten years ago [7]. Regarding comorbidities, 66.7% of non-recurrent patients and 61.3% of recurrent patients had no comorbidities. However, recurrent patients demonstrated additional comorbidities, including cardiac (2.5%) and hepatic (5.0%) patients.The recurrent group had a higher prevalence of previous surgeries, with laparoscopic cholecystectomy being the most common procedure, which we ascribed to coincidence. Family history was more evident in the recurrent group, which aligns with the findings of the Mehraban Far et al. study [8]. The liver was the most frequent site of recurrence, accounting for 63.8% of cases, followed by the peritoneum at 36.3% and the anastomosis site at 31.3%. Most cases were discovered during follow-up investigations, e.g., colonoscopy and CT, followed by intestinal obstruction.Hung et al. [9] found that pre-operative CEA levels were high in recurrent cases, unlike the recurrent cases. In this study, the pre-operative CEA level was significantly higher in the recurrent group. Moreover, some biomarkers were found to be significantly higher in the recurrent group, like CRP, D-Dimer, LDH, and Fecal Calprotectin. This finding is consistent with the Lu et al. study, which demonstrated that high pre-operative plasma D-dimer predicts poor survival of colorectal cancer [10]. Elevated pre-diagnostic Fecal Calprotectin levels were common in patients with CRC in close proximity to diagnosis [11]. However, further research is needed to determine its impact on prognosis. Elevated levels

of LDH are linked to advanced stages of colorectal cancer [12]. CRP is a reliable indicator of the likelihood of postoperative recurrence and the overall prognosis of colorectal cancer. It has also been demonstrated as a predictor of chemo-sensitivity [13].

The most common site of the primary tumor was the rectum, followed by the rectosigmoid junction in both recurrent and non-recurrent groups. This finding agrees with the study of Zare-Bandamiri et al. [5]. However, the study by Holt et al. demonstrated that the rectosigmoid junction had the highest occurrence rate of recurrence[14].

According to Macias-Garcia et al., the infiltrative pattern of colorectal cancer was associated with a higher risk for submucosal invasion [15]. Our findings indicate that the majority of the recurring cases were of the infiltrative type, with ulcer being the second most common.

The primary tumor grade and histopathology are two of the most frequent parameters influencing the prognosis of colorectal cancer. According to the Holt et al. study [14], poorly differentiated tumors (grade 3) were the most prevalent in the recurrent group, followed by grade 2. In our study, grade 3 was the most common in the recurrent group, followed by grade 4 (undifferentiated).

The multivariate analysis revealed that a mucinous morphology did not exhibit independent prognostic significance. In contrast, a comprehensive study involving 2,764 cases of sporadic colorectal tumors revealed that the existence of signet ring histology was identified as an independent negative prognostic factor on multivariate analysis. It has been reported that it has different molecular pathways, which account for its aggressiveness [16]. Nevertheless, this study found that mucinous adenocarcinoma was the predominant histopathological type in the group of patients with recurrent cancer, while papillary adenocarcinoma constituted the majority of cases in the non-recurrent group.

According to the surgical records in our study, most non-recurrent cases were operated by laparoscopic technique, while most of the recurrent cases were operated by open surgery. The reasons for this can be attributed to the implementation of the 'no touch' technique, which reduces the need for physical contact during surgery, as well as the shorter duration of the operation and the reduced amount of bleeding that occurs in laparoscopic surgery.

Clear surgical margins are one of the most important prognostic factors in colorectal cancer. Surgical margins not only predict the risk of local recurrence, but also provide guidance for postoperative treatment [17]. This finding agrees with our results, as we found that 36.3% of the recurrent cases had positive surgical margins in their specimen compared to 4.2% in non-recurrent cases.

Hand-sewn anastomosis was more common in the recurrent cases. However, most of the non-recurrent cases had stapled anastomosis. Hand-sewn anastomosis requires a longer time and increased manipulation.

Several theories have been postulated for the local recurrence of colon cancer, and altered biological properties of colonic anastomosis are one of the most proposed theories [18]. In this study, it was found that 35.1% of the recurrent cases and 33% of the non-recurrent cases had altered anatomic anastomosis (coloanal and abdominoperineal). It was observed that the modified anatomical anastomosis had a more significant impact on physiological function compared to the recurrence.

This study demonstrated that the rate of recurrence was lower in cases that underwent mesocolic and mesorectal excision with extracted L.Ns $\geq$ 12 and median lymph node ratio $\geq$0.5. This finding agrees with the studies of Zare-Bandamiri et al. [5], Gupta et al. [19], and İmamoğlu et al. [20]. These studies concluded that the lymph node ratio can be used as a dependable prognostic indicator. Additionally, a ratio > 0.31 was identified as a poor prognostic factor in patients with surgically treated Stage III colorectal cancer.

Postoperative complications were found not to affect the recurrence. However, soiling during surgery was found to be more prevalent in recurrent cases. This can be due to the implantation of tumor buds or cells in different sites. While stoma did not impact the overall recurrence rate, there was a notable difference in the recurrence of rectal and rectosigmoid cancer. This can be attributed to reduced postoperative leakage and improved tumor aeration, particularly in emergency surgeries.

The study conducted by Paik et al. [21] revealed that the tumor size and T stage are significant risk factors for the recurrence of colorectal and rectal cancer but not for colon cancer recurrence. Similar results were reported in prior studies [22,23,24]. The study by Zare-Bandamiri et al. [5] found no significant association between the risk of recurrence and the size

of the tumor or the number of dissected lymph nodes [P<0.05 for all]. Our study revealed a significant correlation between the advanced tumor stage and an increased risk of recurrence. Specifically, the T2 and T3 stages exhibited higher odds of recurrence compared to the T1 stage. The presence of nodal involvement was found to be a critical factor, with the N1 stage significantly increasing the odds of recurrence compared to the N0 stage as a reference.

The analysis conducted by Cheong et al. [25] suggests potential benefits of using the neoadjuvant approach compared to adjuvant chemotherapy. While the efficacy of neoadjuvant chemotherapy is still under investigation for colon cancer, its use has been well-established for the treatment of rectal cancer. Similarly, we discovered that neoadjuvant therapy had a significant influence on recurrence. The majority of cases received adjuvant therapy, while only 25% of the recurrent cases had undergone neoadjuvant therapy. Neoadjuvant therapy demonstrated a notably robust effect on rectal cancer, substantially decreasing the likelihood of recurrence. Likewise, neoadjuvant therapy was found to be linked with a substantial decrease in the odds of recurrence.

CONCLUSIONS

Multivariate factors have an impact on the recurrence of colorectal cancer. Several factors, including smoking, a family history of colorectal cancer, high levels of pre-operative CEA, fecal calprotectin, D-dimer, CRP, LDH, and the presence of infiltrative high-grade mucinous histopathological types, can be used to predict the likelihood of recurrence. Microscopically involved surgical margins, open hand sewn anastomosis without mesocolic or mesorectal excision, soiling during surgery, extracted L.N≤12, higher lymph node ratio and tumor stage (TN), and tumors without neoadjuvant therapy was associated with increased rates of recurrence, poor prognosis, and low disease-free survival**.**

Ethics declarations

This study was conducted following the ethical principles of the Declaration of Helsinki (Edinburgh 2000) and the approval of the Institutional Review Board. The Institutional Review Board granted an exemption for informed consent.

All participants provided informed written consent.

This study was approved by the Institutional Research Board (IRB) at Zagazig University

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