



## Survey the Prognostic Factors of Recurrence and Survival in Patients with Colorectal Cancer

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### Abstract

**Purpose:** Recurrence of colorectal cancers is considered to be one of the greatest post-surgical complications that is affected by various factors. This study design to investigate the prognostic factors that affect the recurrence and survival of patients with colon and rectal cancer.

**Methods:** A retrospective study was performed in 380 patients with colon and rectal cancer who underwent surgery; type of surgery, tumor size, differentiation grade, proximal, distal and radial, marginal involvement, total number of excision lymph nodes, number of involved lymph nodes and tumor stage was recorded. Also, the incidence of recurrence and metastasis was recorded during the study.

**Results:** 380 patients with mean age of 57.11 were enrolled to the study. 152 patients with an average age of 57.57 were diagnosed with colon cancer. Recurrence and metastasis occurred in 2 patients (1.3%) and 5 patients (3.3%), respectively. 18 patients (11.8%) died due to colon cancer. 228 patients with a mean age of 56.81 had rectal cancer. Recurrence was seen in 19 patients (8.3%) and metastasis in 33 patients (14.5%). 38 patients (16.7%) died due to rectal cancer. Tumor size and involved lymph nodes were independent prognosis factors of recurrence and metastases of colon cancer. Only involved lymph nodes were associated with death due to colon cancer. Independent prognostic factors of rectal cancer metastasis included albumin and age. The total number of excision lymph nodes was the only predictor factor of tumor recurrence and death in rectal cancer. The median survival time of colon and rectal cancers were 90 and 110 months, respectively.

**Conclusion:** The size of the tumor and the number of involved lymph nodes were independent prognostic factors for recurrence and metastasis of colon cancer. Also, the number of involved lymph nodes was associated with colon cancer related death. In the case of rectal cancer, albumin levels and age predicted metastases. Only total number of excision lymph nodes had reverse relationship with recurrence and rectal cancer related death.

**Keywords:** Colorectal Neoplasms; Neoplasm Recurrence; Neoplasm Metastasis; Lymphatic Metastasis; Survival

### Abbreviations

NLR: Neutrophil to Lymphocyte Ratio; CEA: Carcinoma Embryonic Antigen

### Introduction

Colorectal cancers are one of the most common cancers [1,2] and about one million new cases occur each year [3-5]. Colorectal

cancers are the third most common cancer and the second leading cause of death from cancers [5-7]. The risk of this disease is estimated at 5% per person throughout life [4]. Surgical treatment is considered as the best treatment of colorectal cancer [6,8]. About 50% of patients were completely treated with surgical and other procedures, but treatment options are more limited in people with

metastases [4]. Metastases and local recurrence were associated with high mortality and morbidity rate [8,9].

Local recurrence occurs in 4 to 30 and even 40 percent of patients [9,10] and greatly reduces the quality of life and the 5-year survival was decrease to about 25% [11,12]. Generally, the 5-year survival in the early stages of colorectal cancers is more than 90%, in an area with lymphatic nodule involvement of up to 65% and in metastatic cases, it reaches less than 10% [4].

In previous studies, different factors such as histologic grade, T stage, the ratio of involved lymph nodes to total excision lymph nodes [2,13], Pre-operative carcinoma-embryonic antigen (CEA) [14,15], neutrophil to lymphocyte ratio (NLR) [3,16], tumor site [5,7,17], obesity [18], genetics [4,19], tumor stage [8,19], male gender, alcohol use [8], surgical quality, pathologic features such as lymphatic invasion, margin positivity or lack of infiltration of lymphocytes [8,11] have been introduced as prognostic factors for recurrence and survival in patients with colorectal cancer. The local and systemic recurrence occurs in about a quarter of patients with colorectal cancer and is considered to be a failure factor of treatment and poor prognosis [6]. So, recognizing the determination factor of prognosis and relapse is very important. Therefore, the present study retrospectively investigated the prognostic factors affecting recurrence and survival of patients with colon and rectal cancers.

## Materials and Methods

In a retrospective study, patients underwent surgery from 21 March 2013 to 20 March, 2016 with diagnosis of colon or rectal cancer at a tertiary colorectal surgery center were evaluated. All of these patients were examined and biopsy by colonoscopy and confirmed the pathological diagnosis before surgery. Patients with metastases, bone and para-aortic lymph nodes involvement and uncertain pathological report were excluded from the study. As routine guide line of our center metastatic patients were discussed in multidisciplinary team which has a combination of colorectal surgeons, radiologist, gastroenterologist and oncologist.

Patient's demographic characteristics including age and sex, Albumin level (for measuring physical and nutritional status), pre-operative data including chemotherapy and radiotherapy were extracted from patients' records. Then, the type of operation, the size of the mass in cm, its degree of differentiation (well, moderately and poorly), proximal, distal and radial, marginal involvement,

total number of excision lymph nodes, number of involved lymph nodes and tumor stage was recorded based on TNM Staging. At the end, the duration of follow up of the patients, recurrence or metastasis of the tumor was investigated and the obtained data entered the analysis process.

## Data analysis

Data were analyzed by SPSS 21 software. The categorized variables by two-sided Pearson or Fisher exact test and quantitative variables by t test were compared. The survival was calculated by Kaplan-Meier test. Also, univariate and multivariate analysis were performed using the Cox proportional hazards regression model. The P value < 0.05 were considered statistically significant.

## Results

152 patients from 189 patients with colon cancer and 228 patients from 297 patients with rectal cancer were enrolled to the study. Of the 380 patients in the study, 170 were women (44.7%) and 210 were men (55.3%). The mean age of patients was  $57.11 \pm 14.27$  years (Median = 58). The mean albumin level was  $3.12 \pm 2.00$  (Median = 4.00). The average tumor size was  $3.97 \pm 2.26$  cm (Median = 4 cm). 211 patients (55.5%) had history of radiotherapy. In terms of differentiation, well, moderate and poor differentiation were reported in 209 (55%), 64 (16.84%) and 25 (6.57%) cases, respectively. Also, 82 cases (21.6%) reported as undifferentiated. The mean number of excision lymph nodes was  $8.44 \pm 7.33$  (Median = 7) and the mean number of involved lymph nodes was  $0.99 \pm 3.04$  (S.E = 0.17) (Median = 0) (Rang = 0 - 33). Proximal marginal involvement was not observed in any cases, but in 2 patients (0.5%) there was distal marginal involvement and in 6 patients (1.6%) there was a radial marginal involvement. 174 patients (45.8%) were operated by laparotomy and 206 patients (54.2%) were surgically treated by laparoscopy. Recurrence and metastasis were observed in 21 patients (5.5%) and 38 patients (10%), respectively. The mean follow period was  $34.76 \pm 24.93$  months (Median = 30). At the end of the study, 299 patients (78.7%) were free of disease and 24 patients (6.3%) were alive with cancer. Also, 56 patients (14.7%) were died due to cancer and 1 patient (0.3%) died for other reasons.

## Colon cancer

152 patients (76 males) with an average age of  $57.57 \pm 14.53$  years (range 26 to 87 years, Median=59) were diagnosed with colon cancer. Radiotherapy was performed only in 5 patients (3.3%)

before surgery. The mean albumin level was  $1.98 \pm 2.15$  mg / dl (Standard Error (S.E) =1.17). The mean tumor size was  $4.63 \pm 2.42$ cm (Median = 4.5). Lymphatic invasion was observed in 42 patients (27.6%). The mean number of lymph nodes excision was  $10.04 \pm 8.55$  (Median = 9) and the mean number of involved lymph nodes was  $1.48 \pm 4.32$  (S.E = 0.38). The tumor differentiation was well differentiation in 88 cases (57.9%), moderate differentiation in 26 cases (17.1%), poor differentiation in 10 cases (6.6%), and undifferentiation in 28 cases (18.4%). There was no proximal and distal marginal involvement and only 2 patients (1.3%) had radial marginal involvement. 80 patients (52.6%) under laparotomy and

72 patients (47.4%) were under laparoscopy. Recurrence and metastasis occurred in 2 patients (1.3%) and 5 patients (3.3%), respectively. At the end of the study, 119 patients (78.3%) alive without disease, 14 patients (9.2%) alive with disease and 18 patients (11.8%) died by cancer. Also, a patient died due to other reason.

The average number of involved lymph nodes ( $P < 0.001$ ), relapse rate ( $P < 0.001$ ) and metastasis ( $P = 0.001$ ) were significantly higher in patients who died with colon cancer. The tumor had a worse degree of differentiation in dead patients ( $P = 0.001$ ). Most died patients were undergoing laparotomy surgery ( $P = 0.023$ ).

Factors		Alive patients	Dead patients	P value
Age		57.18 ± 14.11	60.44 ± 17.55	0.37
Sex	Male	65 (48.5%)	11 (61.1%)	0.31
	Female	69 (51.5%)	7 (38.9%)	
Radiotherapy (yes)		4 (3%)	1 (5.6%)	0.56
Albumin		2.05 ± 2.10 (S.E:0.18)	1.48 ± 2.49 (S.E:0.60)	0.30
Tumor Size		4.60 ± 2.41	4.90 ± 2.58	0.66
Total lymph node excision		10.27 ± 8.38	8.33 ± 9.81 (S.E:2.31)	0.36
involved lymph node	Mean ± SD	1.01 ± 2.25 (S.E:0.21)	5.21 ± 10.89 (S.E:2.91)	<0.001
	Yes	37 (27.6%)	5 (27.8%)	0.98
	No	97 (72.4%)	13 (72.2%)	
Differentiation	Well	81 (60.4%)	7 (38.9%)	0.001
	Moderate	24 (17.9%)	2 (11 %)	
	Poor	5 (3.7%)	5 (27.8%)	
	Undifferentiated	24 (17.9%)	4 (22.2%)	
Margin involvement	Proximal	0	0	-
	Distal	0	0	-
	Radial	2 (1.5%)	0	0.60
Type of Surgery	Laparotomy	66 (49.3%)	14 (77.8%)	0.023
	Laparoscopy	68 (50.7%)	4 (22.2%)	
Tumor recurrence (yes)		0	2 (11.1%)	<0.001
Tumor Metastasis (yes)		2 (1.5%)	3 (16.7%)	0.001
Time of follow-up		36.78 ± 23.94	21.17 ± 14.99	0.008

**Table 1:** Data comparison of patients with colon cancer on based of clinical outcome.

**Rectal cancer**

228 patients (134 men) with a mean age of  $56.81 \pm 14.11$  years (range 25 to 94 years, median = 57) had rectal cancer. Radiotherapy was performed in 164 patients (71.9%) before surgery. The mean albumin level was  $4.31 \pm 0.76$  mg/dl (median = 4.30). The mean rectum mass size was  $3.48 \pm 2.00$ cm (Median = 3.5). Lymphatic invasion was observed in 41 patients (18%). The mean number of lymph nodes removed was  $5.85 \pm 5.99$  (S.E: 0.39, Median = 5) and the average number of involved nodes was  $0.65 \pm 1.58$  (S.E = 0.11), respectively. The tumor differentiation was well differentiation in 121 cases (53.1%), moderate differentiation in 38 cases (16.7%),

poorly differentiation in 15 cases (6.6%) and undifferentiated in 54 cases (23.7%), respectively. There was no proximal marginal involvement. However, distal and radial marginal involvement were observed in 2 (0.9%) and 4 (1.8%) cases, respectively. 94 patients (41.2%) were under laparotomy and 134 patients (58.8%) were under laparoscopy. Recurrence was seen in 19 patients (8.3%) and metastasis in 33 patients (14.5%). At the end of the study, 180 patients (78.9%) alive without disease, 10 patients (4.4%) alive with disease and 38 patients (16.7%) died by cancer. The incidence of recurrence and metastasis in the patient who died was significantly higher ( $P < 0.001$ ).

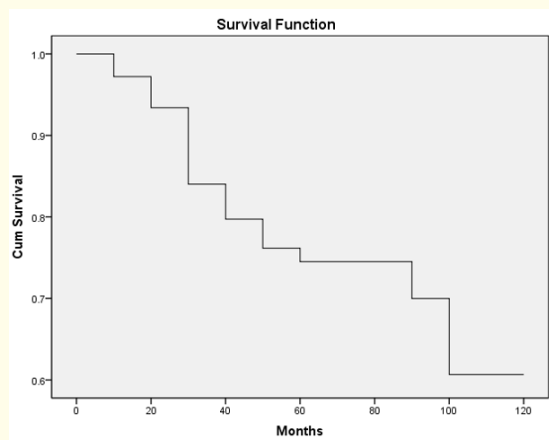
Factors		Alive patients	Dead patients	P value
Age		$56.54 \pm 14.02$	$58.16 \pm 14.65$	0.51
Sex	Male	81 (42.6%)	13 (34.2%)	0.33
	Female	109 (57.4%)	25 (65.8%)	
Radiotherapy (yes)		135 (71.1%)	29 (76.3%)	0.51
Albumin		$4.32 \pm 0.78$	$4.28 \pm 0.68$	0.84
Tumor Size		$3.35 \pm 1.96$	$4.21 \pm 2.09$	0.037
Total lymph node excision		$6.07 \pm 5.95$	$4.76 \pm 6.17$ (S.E:1.00)	0.22
involved lymph node	Mean $\pm$ SD	$0.63 \pm 1.62$ (S.E: 0.13)	$0.76 \pm 1.43$ (S.E: 0.26)	0.70
	Yes	33 (17.4%)	8 (21.1%)	0.58
	No	157 (82.6%)	30 (78.9%)	
Differentiation	Well	103 (54.2%)	18 (47.4%)	0.29
	Moderate	33 (17.4%)	5 (13.2%)	
	Poor	10 (5.3%)	5 (13.2%)	
	Undifferentiation	44 (23.2%)	10 (26.3%)	
Margin involvement	Proximal	0	0	-
	Distal	2 (1.1%)	0	0.52
	Radial	4 (2.1%)	0	0.36
Type of Surgery	Laparotomy	76 (40%)	18 (47.4%)	0.40
	Laparoscopy	114 (60%)	20 (52.6%)	
Tumor recurrence (yes)		10 (5.3%)	9 (23.7%)	<0.001
Tumor Metastasis (yes)		15 (7.9%)	18 (47.4%)	<0.001
Time of follow-up		$36.12 \pm 26.68$	$27.24 \pm 34.64$	0.053

**Table 2:** Data comparison of patients with rectal cancer on based of clinical outcome.

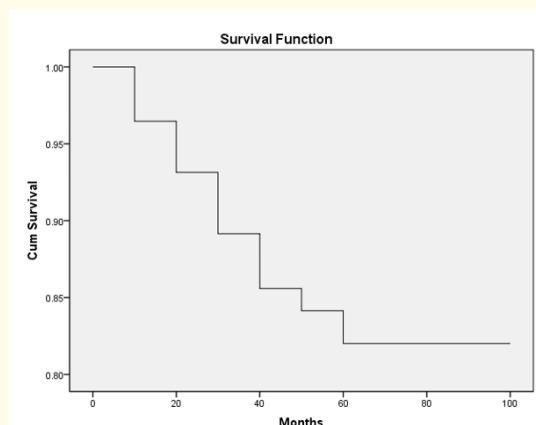
**Factors affecting recurrence, metastasis and survival**

Cox analysis showed that Tumor size (Chi-square= 4.86, P = 0.027) and Involved lymph nodes (Chi-square= 8.22, P = 0.016) were independent factors of prognosis recurrence of colon cancer. Prognostic factors for colon metastases included Tumor size (Chi-square = 25,986, P = 0.009) and Involved lymph nodes (Chi-square= 29.52, P = 0.003). Only involved lymph nodes were associated with death due to colon malignancy (Chi-square = 4.82, P = 0.028). Independent prognostic factors of rectal cancer metastasis included albumin (Chi-square = 7.97, P = 0.005) and age (Chi-square = 5.20, P = 0.023). The total number of excision lymph nodes was the only predictor factor of tumor recurrence (Chi-square = 6.74, P = 0.009) and death (Chi-square= 5.48, P = 0.008) in rectal cancer.

The median survival time of colon and rectal cancers were 90 and 110 months, respectively (Figure 1 and 2).



**Figure 1:** Overall survival of rectal cancer.



**Figure 2:** Overall survival of colon cancer.

**Discussion**

The present study was conducted to determine the prognostic factors in recurrence and survival of patients with colon and rectal cancer. Based on the results, the average age of patients with both malignancies was reported to be 57 years, indicating that the sixth decade of life has the highest prevalence rate for individuals. About one quarter of patients with colon cancer and one fifth of patients with rectal cancer experienced regional lymph node involvement, and with very little difference between the two, their radical margins were reported in about 2% of the cases. 8.3% of patients with rectal cancer and 1.3% of patients with colon cancer experienced localized relapses. The results showed that the tumor size and number of involved lymph nodes were associated with poor prognosis of colon cancer and considered as a risk factor for recurrence and metastasis. Other factors such as age, sex, marginal involvement, tumor location, cell differentiation, and metastasis were not associated with recurrence and metastasis. Also, the number of involved lymph nodes was associated with colon cancer related death.

In the case of rectal cancer, according to the present study, no risk factors for recurrence were found. But the interesting point is that the total number of lymph nodes removed during the operation had inverse relationship with recurrence. This finding show removing more lymph nodes in the area indicates better quality of surgery and its accuracy. The total number of lymph nodes removed has also been a predictor of rectal cancer related death. Additionally, age and albumin level were prognostic factors for rectal cancer metastasis. After an average follow-up of three years, about 85% of the patients were alive. There is a low rate of mesorectal involvement that might be due to neoadjuvant therapy that was done for nearly all rectal cancers.

Trivedi and colleagues conducted a study to determine the effective factors in the survival of patients with stage 2 colon cancer. They concluded the age is the only factor that is completely relevant to survival. In their study, postoperative chemotherapy reduced the chance of death by up to 42 percent, and the number of lymph nodes removed was poor relatively, but not statistically significant [20]. In our study, age did not relate to relapse but was related to metastasis of rectal cancer. Also, there was a significant relationship between the number of positive lymph nodes with relapse. Compton in his review study, stated that the tumor stage is the most accurate determinant of the prognosis of survival. The quality of surgery, resection of mesentery and the proximity of the mass with margin were the most promising factor in recurrence of disease in patients without metastasis. He argued that other pathological factors such as tumor grade, histology, vascular, neurological and lymphatic invasion could be helpful in determining the risk

of unpleasant complications of the disease [11]. In our study, the positive effects of margins did not have an effect on recurrence. But, considering the effect of total number of lymph nodes excision on decrease recurrence of rectal cancer, and the impact of involved lymph nodes on colon cancer recurrence, it seems that proper quality of surgery and complete lymph nodes dissociation are very important. Various factors have been introduced as a prognostic factor in various studies. For example, Hao, *et al.* reported histology grade, T stage, number of positive lymph nodes, total number of excision lymph nodes, carcinoembryonic antigen (CEA) and neutrophil to lymphocyte ratio (NLR) as prognostic factors of colonic cancer. In their study, the histology grade, preoperative CEA and NLR were determined as independent factors [3]. Patel and his colleagues named male sex, alcohol use, and wounded mass as risk factors for recurrent rectal cancer [8]. Zhao, *et al.* Described T stage, vascular invasion and topical relapses as three important factors in determining the 5-year survival prognosis in patients with rectal concertation [13]. Pacelli, *et al.* expressed the availability of surgical facilities and radical mass removal as positive prognostic factors of rectal cancer. They also acknowledged that increasing preoperative CEA, back pain, and adhesion of the mass to the pelvic wall based on CT scan were significantly related to survival. Also, preoperative chemoradiotherapy and radical removal of the tumor is independently associated with localized mass control [21]. Parnaby and colleagues also concluded that LNR and extramural vascular invasion independently predicted overall survival and disease free survival of colon cancer [16].

In the study of Sinicrope, *et al.* the body mass index (BMI) of patients with colon cancer was associated with prognosis. They found that obesity was an independent factor of prognosis and survival of colon cancer. Men with colon cancer and stage 2 and 3 of obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) had less survival than men of normal weight. Women with stage 1 of obesity (BMI = 30 -34 Kg/m<sup>2</sup>) also had a lower survival than normal women. Furthermore, weight gain (BMI = 25 - 30 kg/m<sup>2</sup>) without obesity improved survival and weight loss associated with worsening survival [18]. Our study also looked at the patient's nutritional status by reviewing the pre-operative albumin level. Our results showed higher albumin level decrease the risk of rectal cancer metastasis.

## Conclusion

As a final result, it can be argued that in the present study, the recurrence of colon cancer with mass size as well as the number of

involved lymph nodes has a direct relationship. In other words, the larger size of the mass and the increase in the number of involved lymph nodes around the mass can be associated with an increased chance of recurrence in colon cancer. Also, it has been shown that the removal of regional lymph nodes can play a role in protecting against recurrence of rectal cancer.

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## Conflict of Interest

There is no conflict of interest.

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