



## Prognostic Factors of Disease Recurrence and Overall Survival Following Curative Resection of Colon Cancer: A 10-year Cohort from a Referral Center

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### Abstract

**Background:** The growing incidence of colorectal cancer around the world highlights the significance of tumor recurrence and patient survival as 2 key elements of patient therapy. We aimed to study the factors linked with disease recurrence and survival in colon cancer.

**Methods:** Patients with colon cancer who underwent tumor excision as their primary treatment were enrolled in this prospective cohort and monitored for 10 years. Various demographic and clinicopathologic factors of these patients were studied in association with the 2 primary outcomes of this study, including tumor recurrence and patient survival. Statistical tests and survival analysis were utilized to explore the study aims.

**Results:** An overall number of 113 patients were included in this survey with a mean age of 54.7 ( $\pm$ SD, 14.1), and most of the patients were men (56.6%). The mean follow-up period was 28.3 ( $\pm$ 25.5) months. Tumor recurrence occurred in 32 (28.3%) patients in the study period. The estimated mean survival of patients was 54.9 (95% CI, 45.3-64.4) months. N staging ( $p=0.036$ ), T staging ( $p=0.009$ ), and pathologic staging ( $P=.004$ ) were the significant pathological factors to higher tumor recurrence and lower survival rates.

**Conclusion:** Advanced tumor staging led to increased disease recurrence and lower survival of colon cancer patients in this survey. Further public health screening and education programs are needed to improve the early detection and prognosis of these patients in Iran.

**Keywords:** Colon Cancer; Survival Analyses, Recurrence, Surgery

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### Introduction

According to the most recent worldwide cancer reports from 2020, colorectal cancers (CRC) were the second

most deadly and third most common type of cancer (1). Both in new cases and mortalities, colon cancers rank

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#### ↑What is “already known” in this topic:

The expanding burden of colon cancer globally brings up the importance of tumor recurrence and patient survival as 2 significant factors in the management of patients. A limited number of studies have been done in Iran to evaluate prognostic factors of disease recurrence and the overall survival of these patients.

#### →What this article adds:

This study showed higher recurrence and survival rates of patients with colon cancer with advanced stages of malignancy. Regarding the specific patterns of colorectal cancers in the Iranian population, early screening programs are suggested to improve the prognosis of this major cause of cancer in Iran.

higher than rectal cancers globally and have a more significant burden (1). Developing countries have shown to experience an almost 4-fold higher incidence of CRC compared to developed countries; however, regarding the higher mortality rates in developing countries, the variation among countries is lower globally regarding CRC mortality (1). Iran, as a developing country located in the vulnerable region of the Middle East also follows the global patterns and CRC was the third most common cancer in the last report of the national cancer registry data of 2016 (2). This major cause of cancer had an increasing pattern during the past decades in Iran mainly due to lifestyle and diet changes of the Iranian population and increased cancer screening (3, 4). Therefore, this cancer imposes a substantial economic burden in Iran and regarding the increasing incidence trend, the burden of the disease is estimated to surge in the future (5).

Cancer recurrence and survival of patients are the 2 most important factors that receive special attention in managing these patients. It is shown that about 30% to 50% of patients with colon cancers experience disease recurrence after surgical management of their tumor, and this recurrence happens in the first 5 years in most cases (6). Tumor recurrence and patient survival are in close contact, and the type of local or distant tumor recurrence leads to lower patient survival (7). Therefore, timely tumor recurrence detection and management could lead to higher survival rates in patients with CRC (8). Colon cancer recurrence depends on clinical and demographic factors and varies in different populations and patients (9, 10). Previous evidence shows that among Iranian patients with CRC, women had better survival rates and the statistics were better in colon cancer compared with rectal cancer (11).

Long-term follow-up data on patients with colon cancer after surgical management of the tumors in Iran was missing in the literature. Thus, we aimed to study the tumor recurrence and survival in patients with colon cancer with demographic and clinical details to provide strong evidence for clinicians and policymakers.

## Methods

### Study Design and Population

We created a prospective cohort to include colon cancer patients who had undergone surgical tumor excision during a 10-year period (2005-2015). The ethical committee approved this study at Tehran University of Medical Sciences (Ethics No. IR.TUMS.IKHC.REC.1395.903). All patients were selected from the patients referred to a colorectal referral clinic at Tehran University of Medical Sciences. Patients with histologically established colon cancer without any distant metastases and a prior history of curative cancer resection met the inclusion criteria. Patients with tumor metastasis and those who were not operated on for metastasectomy were excluded from the study. Demographic and clinical data of patients were stored on our CRC data registry. Patients were monitored every 3 months for 2 years, every 6 months for 3 years, and once a year for 3 years.

### Study Variables

Age, sex, tobacco use, type of surgery, location of the tumor, pathology of tumor, the initial presentation of the tumor, location of tumor recurrence, ostomy presence, adjuvant chemotherapy, adjuvant radiotherapy, TNM tumor staging, perineural tumor invasion, and perivascular tumor invasion were the demographic and clinical variables included in this study. Also, blood carcinoembryonic antigen (CEA) level (ng/mL) was the only laboratory variable in the study analysis. Study variables were selected using a literature review and expert opinion.

### Statistical Analysis

Various quantitative and qualitative variables were analyzed using descriptive statistics. Patients' survival was assessed using the Kaplan Meier method for survival rate, and differences between groups were analyzed by the Log-rank test. Significance level was considered as  $P > .05$  in this study. All analyses were made by the SPSS statistical package Version 16 (IBM Inc).

## Results

A total of 113 colon cancer patients who underwent surgery at our center were included in this survey. The mean age of patients was 54.7 years ( $\pm$ SD, 14.1), and 56.6% of the patients were men. Patients were followed for a mean period of 28.3 ( $\pm$ 25.5) months. At the endpoint of the cohort, 38 (33.6%) patients had died, and 32 (28.3%) patients had tumor recurrence. Fourteen (12.4%) patients had metastasis diagnoses at the start point of the study and underwent metastasectomy. Adjuvant chemotherapy and radiotherapy were done for 53 (46.9%) and 11 (9.7%) patients, respectively. The mean CEA level was 12.6 ( $\pm$ 14.4) ng/mL.

In nearly half of the patients (42.5%), colon tumors were in the sigmoid. Cecum (16.8%) and ascending colon (9.7%) were the second and third common places for tumor location at diagnosis. The most tumor pathology diagnosis was moderately differentiated colon adenocarcinoma (51.9%). Most patients were in N0 (56.8%) and T3 (53.2%) staging classification. Perivascular (44.1%) and perineural tumor invasion were positive in less than half of the patients. Pathologic staging was stage 2 (40.9%) and stage 3 (37.3%) in most of the patients. Comprehensive details of the demographic and clinical information of patients are presented in Table 1.

Tumor recurrence varies based on various demographic and clinical characteristics. The highest recurrence rate was in tumors located in ascending colon (45.5%), followed by the transverse colon (42.4%) and splenic flexure (33.3%). In contrast, the lowest recurrence rate was in tumors located in the cecum (9.5%). Poorly differentiated tumors had the highest recurrence rate (50%), followed by moderately (29.1%) and well (25%) differentiated tumors. Patients undergoing sigmoid resection (39.33%), extended left hemicolectomy (33.3%), and right hemicolectomy (30%) experienced the highest tumor recurrence based on the type of surgery. The presence of tumor metastasis at the cancer diagnosis and higher CEA levels were significant contributors to recurrence in included patients ( $p =$

Table 1. Demographic and clinical information of the patients included in this survey

Variable	Frequency (%)	Variable	Frequency (%)
Initial tumor presentation	Pain	N staging	N0
	Rectorrhagia		N1
	Other		N2
Tumor location	Sigmoid	T staging	T in-situ
	Cecum		T0
	Ascending colon		T1
	Descending colon		T2
	Transvers colon		T3
	Splenic flexure		T4
	Other		Perivascular invasion
	Adenocarcinoma pathology		Well differentiated
Moderately differentiated	Negative		
Poorly differentiated	Pathologic staging	Stage 0	
Undifferentiated	Stage 1		
Ostomy	Negative	Stage 2	
	Colostomy	Stage 3	
	Ileostomy	Stage 4	
Tobacco use	Missing	Perineural invasion	Positive
	Negative		Negative
	Tobacco		Primary anastomosis
Type of surgery	Cigarette or opium	Positive	
	Right hemicolectomy	Negative	
	Extended right hemicolectomy	Missing	
	Left hemicolectomy		
	Extended left hemicolectomy		
	Total colectomy		
	Sigmoid resection		
	Other		

0.003 and  $p = 0.005$ , respectively). The tumor recurrence was significantly higher in tumors with N2 staging (53.8%) compared with  $N \leq 1$  (24.7%) ( $p = 0.036$ ; odds ratio, 3.54). Also, tumors with T3 (22.4%) and T4 (46.9%) had significantly higher recurrence rates compared with  $T \leq 2$  tumors (15%) ( $p = 0.009$ ). Pathologic staging  $\geq 2$  had significantly higher recurrence compared with lower-stage tumors ( $p = 0.004$ ). The distribution of tumor recurrence based on different variables is presented in Table 2.

Survival analysis based on different tumor features showed colon cancer survival patterns. The overall estimated mean survival of patients was 54.9 (95% CI, 45.3-64.4) months. The mean number of months for survival in the T2 stage, T3 stage, and T4 stage were 74.1 (56.9-91.3), 54.5 (42.3-66.7), and 41.1 (25.6-56.5), respectively. Patients with N1 staging had an estimated mean survival of 59.6 (49.1-70.1) months compared with the N2 stage, with a mean survival of 29.3 (14.9-43.7) months, which was significantly lower. When compared to moderately differentiated (44.5 [32.4-56.6]) and poorly differentiated cancers, well-differentiated tumors have a mean survival of 67.5 (53.1-81.8) months, while the latter 2 have a much lower mean survival (36.1 [24.6-47.6]). Patients with M0 tumor staging had a significantly higher mean survival of 59 (48.8-69.2) months compared with M1 stage patients, with a mean survival of 26.3 (9.5-43.2). More details of the survival analysis are presented in Figure 1.

## Discussion

The main findings of this cohort were colon cancer recurrence in nearly one-third of the patients, and higher

tumor recurrence in patients with higher stages of colon cancer, leading to lower survival rates in the advanced stages of the disease.

The overall recurrence rate in this cohort was 28.3%. This finding was consistent with the literature. A previous study on 107 Iranian patients with CRC during a 9-year follow-up showed that the recurrence rate 5 years after surgery was 5.7% (12). With a median follow-up of 26 months, another large cohort of 442 CRC patients (294 cases of rectal cancer and 148 cases of colon cancer) discovered a tumor recurrence rate of about 19.6% in colon cancer patients, which was very similar to our finding. As a result, the cohort was stratified for colon malignancy (13). Significant clinicopathologic and epidemiologic differences between rectal and colon cancers, as suggested to be due to basic variations in their etiology and pathogenesis, propose stratified analyses for each cause of cancer (14). Studies of CRC in other countries found a recurrence rate of between 20% to 40% in different reports (15-20). Therefore, our results are reliable as it relies on previous evidence.

Colon cancer recurrence was significantly associated with N staging, T staging, and the pathologic staging of patients' tumors. This finding was consistent with similar evidence and highlights the importance of tumor pathology in disease recurrence (16, 21-23). In our study, the recurrence rate increased with decreasing tumor differentiation; however, the difference was not statistically significant, the same as similar studies on CRC patients (23-25). Also, the literature showed that higher tumor grades are associated with local recurrence in CRC patients (13).

Table 2. Frequency of tumor recurrence based on different demographic and clinical variables

Variable	Frequency of tumor recurrence (%)	P-value	Variable	Frequency of tumor recurrence (%)	P-value		
Initial tumor presentation	Pain	6 (17.6%)	N staging	N ≤1	24 (24.7%)		
	Rectorrhagia	6 (28.6%)		N2	8 (53.8%)		
	Other	21 (36.8%)					
Tumor location	Sigmoid	15 (31.4%)	T staging	T ≤2	3 (15%)		
	Cecum	2 (9.5%)		T3	13 (22.4%)		
	Ascending colon	5 (45.5%)		T4	15 (46.9%)		
	Descending colon	1 (16.7%)		Perivascular invasion	Positive	16 (31.8%)	
	Transvers colon	3 (42.4%)			Negative	15 (24.6%)	
	Splenic flexure	2 (33.3%)			Pathologic staging	Stage 0,1	1 (6.7%)
	Other	5 (33.3%)				Stage 2	12 (26.7%)
	Adenocarcinoma pathology	Well differentiated		12 (25%)	Stage 3	12 (27.5%)	
Moderately differentiated		17 (29.1%)	Stage 4	7 (77.8%)			
Poorly differentiated		4 (50%)	Perineural invasion	Positive	14 (37.5%)		
		Negative		18 (24.2%)			
Ostomy	Negative	21 (24.4%)	Sex	Male (64)	18 (28.6%)		
	Colostomy	6 (54.5%)		Female (49)	14 (29.2%)		
	Ileostomy	1 (20%)		Adjuvant chemotherapy	Positive (53)	20 (36.9%)	
		Negative (60)	10 (16.7%)				
Tobacco use	Negative	22 (27.6%)	Adjuvant radiotherapy	Positive (11)	6 (54.5%)		
	Tobacco	5 (29.4%)		Negative (102)	31 (30%)		
	Cigarette or opium	4 (28.6%)					
Type of surgery	Right hemicolectomy	6 (30%)	Other		4 (20%)		
	Extended right hemicolectomy	3 (27.3%)					
	Left hemicolectomy	4 (26.7%)					
	Extended left hemicolectomy	1 (33.3%)					
	Total colectomy	2 (15.4%)					
	Sigmoid resection	11 (39.3%)					

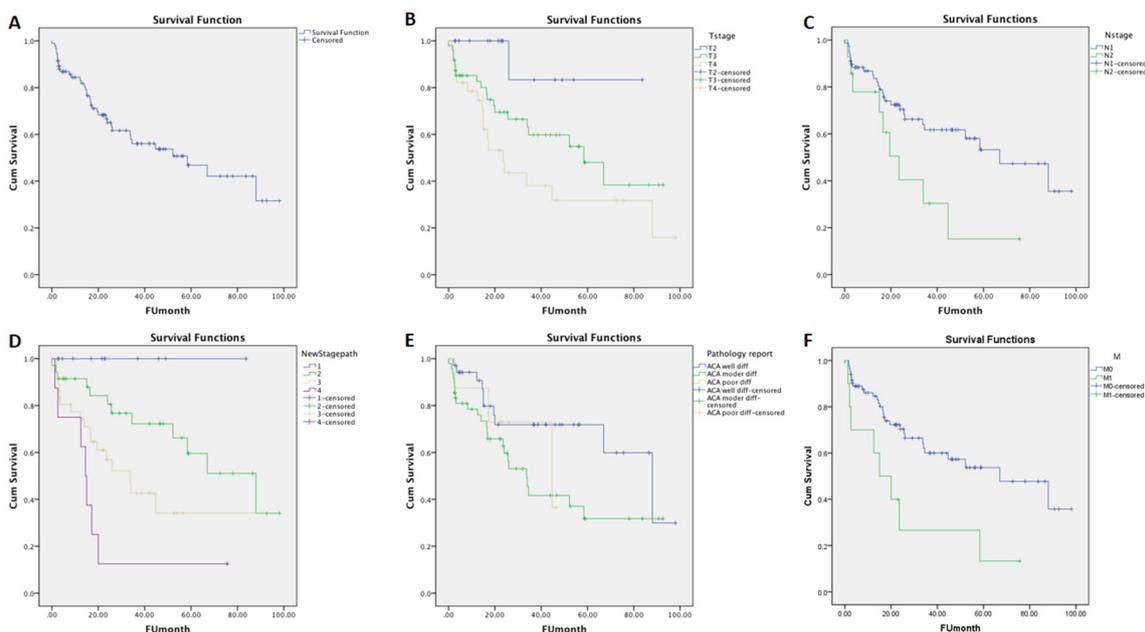


Fig. 1. Survival analysis based on different pathologic characteristics of patients with colon cancer in this survey

Perivascular and perineural invasion of colon cancer was no significant predictor of tumor recurrence. This issue also remains controversial in the literature. Contrary

to other studies that contradict this theory, other investigations indicated perivascular invasion as a predictive marker of cancer recurrence (26-31). Perineural invasion of

tumors is suggested to be associated with higher recurrence rates and as an aiding factor in the decision to start adjuvant chemotherapy in CRC patients (26-29).

Surprisingly, adjuvant chemotherapy and radiotherapy increased tumor recurrence rate; however, both results were not statistically significant. This finding was consistent with previous evidence that proposed adjuvant chemotherapy does not necessarily improve the survival of patients, especially those with lower stages of the disease (30-32). Microsatellite instability and inadequate chemotherapy dosages provided to patients have been proposed as potential explanations for this condition (33, 34).

Our cohort found a mean survival rate of 54.9 months in colon cancer patients. A previous study on Iranian patients with CRC found a 5-year survival rate of 61% (35). A systematic review and meta-analysis on CRC in Iran found that the 5-year survival rate of colon cancer was 0.6 (0.49-0.75), with better survival rates in women compared with men and better statistics in women compared with men (11). Another study revealed that while CRC survival rates in Iran are comparable to those in certain developed countries, they still lag behind countries with highly developed health care systems that offer world-class care for CRC patients (36).

In addition to growing CRC incidence and prevalence in Iran, it is shown that this influential group of cancers tends to be presented with locally advanced stages leading to poor prognosis for these patients (37). This phenomenon could be due to the noticeable poor and moderate levels of knowledge, attitude, and behaviors regarding CRC in Iran (38). Strengthening public health strategies and public knowledge about different aspects of CRC, specifically cancer screening programs, would be beneficial in curbing the burden of CRC in Iran (37). This is alongside the fact that CRC tends to manifest in lower ages in the Iranian population compared with other countries, and implementing proper strategies and programs is necessary in this regard (39).

This study provided updated data about colon cancer recurrence and survival in Iran. However, it has some limitations. The study's shortcomings include the lack of information on tumor grade and several important patient background factors, such as comorbidities and a family history of CRC. The other limitation of this study is the short follow-up of patients included in the survey. Another study restriction that prevents us from extending the findings to all colon cancer patients in Iran is that our facility serves as a referral center for CRC surgery. To supplement the current evidence on CRC in Iran, further cohorts with larger samples and more comprehensive follow-up data are needed.

### Conclusion

This study showed higher recurrence and survival rates of patients with colon cancer with advanced stages of malignancy. Regarding the specific patterns of CRC in the Iranian population, early screening programs are suggested to improve the prognosis of this major cause of cancer in Iran.

### Acknowledgment

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### Ethical Considerations

The ethical committee of Tehran University of Medical Sciences approved this study (Ethics No.: IR.TUMS.IKHC.REC.1395.903).

### Conflict of Interests

The authors declare that they have no competing interests.

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