Clinical research

Effects of prognostic factors on overall and disease-free survival in patients with stage I–III colorectal cancer

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Abstract

Introduction: The aim of this study was to retrospectively analyze predictive factors for overall survival (OS) and disease-free survival (DFS) rates in patients with stage I, II, or III colorectal cancer who underwent surgical treatment.

Material and methods: Files and electronic data of 120 patients with stage I, II, or III colorectal cancer who underwent surgery between 2008 and 2012 in the Department of General Surgery of Izmir Bozyaka Research and Training Hospital were retrospectively analyzed. The effects of several prognostic factors for DFS and OS were investigated.

Results: There were 45 (37.5%) female and 75 (62.5%) male patients; mean age was 65.51 ±11.29 years. In univariate analysis, length of DFS was found to be associated with presence of perforation, lymphovascular invasion, preoperative carcinoembryonic antigen (CEA) value and positive surgical margin. Presence of comorbidities, American Society of Anesthesiologists (ASA) score, histological grade of tumor, presence of lymphovascular invasion, preoperative CEA value, preoperative albumin value, number of metastatic lymph nodes and positive surgical margin were found to be independent prognostic factors for DFS. Cox regression analysis indicated radial surgical margin and presence of perforation had statistical significance for DFS (p value of 0.008 and 0.025, respectively).

Conclusions: There are numerous prognostic parameters affecting postoperative survival in colorectal cancers. Prospective studies and studies on a larger scale are necessary in order to more accurately designate clinical prognostic factors that have an effect on survival time and to identify new biological and molecular markers.

Key words: colorectal cancer, disease-free survival, overall survival, prognostic factors.

Introduction

Colon adenocarcinoma is the most frequently encountered cancer of the gastrointestinal tract. It is an important cause of mortality and morbidity worldwide. More than 1 million people worldwide are estimated to develop this disease annually. Rectal cancer is the third most commonly seen cancer in men after prostate and lung cancers, and it is third in women after breast and lung cancers. Colorectal cancer constitutes approximately 10% of all cancers seen in men and women. In the United

States, colorectal cancer is the third most common cause of cancer-related death [1]. In 2007, 112 340 new cases of colon cancer and 41 420 new cases of rectum cancer were detected in the United States, and it was predicted that 52 180 individuals would die due to colorectal cancer [1]. When caught in the early stages, colon cancer is a malignancy that can be curatively treated with appropriate surgical intervention with minimal morbidity and mortality [2]. However, for cases in advanced stages, the 5-year survival rate is only 8% [3]. Overall survival (OS) in colon cancer is prolonged with every passing year, a situation associated with advances in diagnostic methods, increase in prevalence of use of scanning programs, development of new surgical techniques, and usage of new methods in radiotherapy and systemic chemotherapy [4]. Local or distal tumor recurrences develop in time in some patients curatively treated as a result of diagnosis at an early stage; 5-year survival rates for stage I, II, and III tumors are 93%, 78% and 64% respectively [3]. Prognostic factors for development of recurrences in operated colon cancer are depth of colon wall involvement, lymph node involvement, presence of vascular and perineural invasion, presence of obstruction or perforation at time of diagnosis, and tumor grade [4–6]. This retrospective study analyzed prognostic factors affecting disease-free survival (DFS) and OS in patients with stage I, II or III colorectal cancer who were surgically treated in the clinic.

Material and methods

In this study, data of patients with stage I, II or III colorectal cancer who underwent surgery in the General Surgery Department of Izmir Bozyaka Research and Training Hospital between 2008 and 2012 were retrospectively reviewed. Patients who were stage IV at the time of diagnosis were excluded from the study. Files and electronic data of 120 patients who met the criteria were taken under review. Age, gender, comorbidities, family history, weight loss, emergency/elective application, presence of obstruction on presentation, state of perforation, blood replacement, stage, ASA score, tumor localization, tumor type, tumor size, invasion depth of tumor, tumor differentiation, presence of lymphovascular and perineural invasion, positivity of surgical margin, number of lymph nodes removed and number of those that were positive, operation type, presence of postoperative morbidity or mortality, presence of local relapse or distal metastasis during postoperative follow-up and laboratory tests (hemogram, biochemical parameters, tumor markers) were analyzed. Latest status of surviving patients was determined according to the last follow-up findings. Patients whose last follow-up visit was more than 6 months earlier were reached by phone and asked about their status. Overall survival time was defined as the time between diagnosis and date of death. Disease-free survival time was defined as the time between diagnosis and the date when the first recurrence was detected.

Ethics committee approval

Since it is a retrospective study, we did not apply for ethical committee approval.

Statistical analysis

Homogeneity comparisons between groups were made with Fisher's exact test, and analyses of GS and DFS as well as creation of survival curves were done with the Kaplan-Meier method. The log-rank test was used to compare survival curves. Multivariate analysis using the Cox regression test was conducted for prognostic factors with a p-value < 0.15. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using Statistica software (StatSoft, Tulsa, OK, USA).

Results

There were 45 (37.5%) female and 75 (62.5%) male patients in the study; mean age was 65.51 ±11.29 years. Demographic characteristics and clinical features of patients are given in Table I. Mean follow-up period of patients was 25 months (range: 1–65 months). Mean survival value was 57 months for DFS and 55 months for OS. Eighteen (15.0%) of the patients included in the review were diagnosed as stage I, 48 (40.0%) were stage II and 54 (45.0%) were stage III. Median tumor diameter of the 120 cases examined was 4.9 cm (range: 1–11 cm). Median number of lymph nodes removed was 30 (range: 3–117). Median number of positive lymph nodes was 2.4 (range: 0–35). Clinical and histopathological characteristics of the tumors are provided in Table II. Locoregional recurrence and distant metastases were not detected in the stage I patient group. Locoregional recurrence and distant metastases were detected in 2 (4.2%) patients in the stage II group: Locoregional recurrence was found at the 24th postoperative month in 1 (50%) case and liver metastasis was observed at the 36th postoperative month in 1 (50%) case. Locoregional recurrence and distant metastases were detected in 10 (18.5%) patients in the stage III patient group. Locoregional recurrence was seen in 3 (30%) cases at the postoperative 6th month, in 1 (10%) case at the postoperative 7th month, and in 1 (10%) case at the postoperative 12th month. Liver metastasis was detected in 1 (10%) case at the postoperative

Table I. Demographic characteristics and clinical features

Parameter		Value, *n* (%)
Age	Aged 55 and under	27 (22.5)
	Aged 55 and over	93 (77.5)
Gender	Male	75 (62.5)
	Female	45 (37.5)
Comorbidities	Present	88 (73.3)
	None	32 (26.7)
Family history	Present	4 (3.3)
	None	116 (97.7)
Weight loss	Present	25 (20.8)
	None	95 (79.2)
Emergent or elective application	Emergent	17 (14.2)
	Elective	103 (85.8)
Perforation	Present	2 (1.7)
	None	118 (98.3)
Obstruction	Present	17 (14.2)
	None	103 (85.8)
Preoperative blood replacement	None	76 (63.3)
	1 pRBC	15 (12.5)
	2 pRBC	19 (15.8)
	3 pRBC	6 (5.0)
	4 pRBC	4 (3.3)
ASA score	ASA 1	31 (25.8)
	ASA 2	52 (43.3)
	ASA 3	34 (28.3)
	ASA 4	3 (2.5)
Operation type	Right hemicolectomy	26 (21.7)
	Left hemicolectomy	16 (13.3)
	Subtotal colectomy	4 (3.3)
	Total colectomy	5 (4.2)
	AR	19 (15.8)
	LAR	20 (16.7)
	APR	20 (16.7)
	Sigmoid resection	2 (1.7)
	Laparoscopic AR	2 (1.7)
	Hartmann	6 (5.0)

pRBC – packed red blood cells, ASA – American Society of Anesthesiologists, AR – anterior resection, LAR – low anterior resection, APR – abdominoperineal resection.

Table II. Clinical and histopathological features of the tumors

Features		Value, *n* (%)
Tumor localization	Cecum	19 (15.8)
	Ascending colon	7 (5.8)
	Hepatic flexure	3 (2.5)
	Transverse colon	5 (4.2)
	Splenic flexure	5 (4.2)
	Descending colon	6 (5.0)
	Sigmoid colon	24 (20.0)
	Rectosigmoid	11 (9.2)
	Rectum	40 (33.3)
Tumor stage	Stage 1	18 (15.0)
	Stage 2	48 (40.0)
	Stage 3	54 (45.0)
Tumor histological type	Adenocarcinoma	108 (90.0)
	Mucinous	7 (5.8)
	Signet-ring cell	2 (1.7)
	Malignant epithelial tumor	1 (0.8)
	Adenoneuroendocrine tumor	1 (0.8)
	Carcinoma	1 (0.8)
Tumor size	Smaller than 5 cm	54 (45.0)
	5 cm and over	66 (55.0)
Tumor invasion depth	T1	4 (3.3)
	T2	16 (13.3)
	T3	74 (61.7)
	T4	26 (21.7)
Number of lymph nodes removed	Under 12	18 (15.0)
	Over 12	102 (85.0)
Number of positive lymph nodes	Under 4	92 (76.7)
	4 and over	28 (23.3)
Histological grade	Good	6 (5.0)
	Medium	100 (83.3)
	Bad	14 (11.7)
Lymphovascular invasion	Present	40 (33.3)
	None	80 (66.7)
Perineural invasion	Present	31 (25.8)
	None	89 (74.2)
Surgical margin positivity	Positive	3 (2.5)
	Negative	117 (97.5)

16th month, in 1 (10%) case at the postoperative 18th month, in 1 (10%) case at the postoperative 20th month, and in 1 (10%) case at the postoperative 24th month. Bone metastasis was detected in 1 case at the postoperative 6th month. Table III illustrates local relapse, distant metastases and postoperative morbidity and mortality distribution of the cases. The preoperative median hemoglobin value of the 120 study participants was 11.8 g/dl (range: 6.7–16.8 g/dl). The preoperative median albumin value was 3.8 g/dl (range: 2–4.7 g/dl). The preoperative median CEA value was 9.9 ng/ml (range: 0.58–111.2 ng/ml). The preoperative median carbohydrate antigen 19-9 (CA 19-9) value was 26.8 ng/ml (range: 0.8–619.9 ng/ml). Distribution of laboratory findings can be seen in Table IV.

Effective prognostic factors for survival time

Factors considered effective for DFS and for which *p*-value was < 0.15 with univariate analysis were analyzed with multivariate analysis: perforation, tumor stage, presence of lymphovascular invasion, preoperative CEA value and radial surgical margin. Cox regression analysis indicated that radial surgical margin and presence of perforation had statistical significance for DFS (*p*-value of 0.008 and 0.025, respectively). Similar analysis was conducted for OS factors: presence of comorbidities, ASA score, tumor differentiation, lymphovascular invasion, preoperative CEA value, preoperative albumin value, number of metastatic lymph nodes, and radial surgical margin. Variables considered for the model were not found to have statistical significance for OS. Results of univariate and multivariate analyses carried out to determine the effect of demographic characteristics and clinical features on DFS and OS are provided in Table V.

Table III. Local recurrence, distal metastasis and postoperative morbidity and mortality distributions

Variable		Value, *n* (%)
Locoregional recurrence	None	113 (94.2)
	Present	7 (5.8)
Distal metastasis	None	114 (95.0)
	Present	6 (5.0)
Postoperative morbidity	Surgical site infection	10 (8.3)
	Evisceration	6 (5.0)
	Gastrointestinal fistula	3 (2.5)
	Anastomosis leak	3 (2.5)
	Colostomy necrosis	3 (2.5)
	Pulmonary embolism	2 (1.7)
	Anastomosis hemorrhage	2 (1.7)
	Pneumothorax	1 (0.8)
Postoperative mortality	None	110 (91.7)
	Present	10 (8.3)

Discussion

Colon adenocarcinoma is the most frequently encountered cancer of the gastrointestinal tract. When caught in early stages, colon cancer is a malignancy that can be curatively treated with appropriate surgical intervention with minimal morbidity and mortality. Tumor stage and other prognostic factors are indispensable in order to manage and predict the probable course of the disease [2].

The frequency of colorectal cancer is quite low under the age of 40, but it starts to increase after the age of 50; two-thirds of cases are diagnosed after the age of 50 [7, 8]. Mehrkhani *et al.* [9] established in a study that age was a prognostic factor. In that study, 65 years of age was regarded as the differentiation point. Moghimi-Dehkordi *et al.* [10] stated that age was not a significant prognostic factor. Age 50 has been regarded as the differentiation point; however, Mitry *et al.* [11] indicated that young age is not a poor prognostic factor. In the present study, patients under the age of 55 represented 22.5% of all patients, and patients over the age of 55 represented 77.5% of all patients. Age was not found to be statistically significant for DFS and OS time in univariate and multivariate analyses.

Colon cancer occurs slightly more frequently in men [7]. Han-Shiang [12] established in a study that male gender was a poor prognostic factor. Assad *et al.* [13] also reported in a study conducted on patients with stage II colon cancer that male

Table IV. Distribution of laboratory findings of the patients

Parameter		Value, *n* (%)
Preoperative hemoglobin	< 10 g/dl	43 (35.8)
	10 g/dl and over	77 (64.2)
Preoperative albumin	< 3.5 g/dl	27 (22.5)
	3.5 g/dl and over	93 (77.5)
Preoperative CEA	< 4 ng/ml	74 (61.7)
	4 ng/ml and over	46 (38.3)
Preoperative CA 19-9	< 35 ng/ml	104 (86.7)
	35 ng/ml and over	16 (13.3)

CEA – carcinoembryonic antigen, CA 19-9 – carbohydrate antigen 19-9.

Table V. Results of univariate and multivariate analyses conducted to determine the effect of demographic characteristics and clinical features of the cases on disease-free survival and general survival

Parameter	DFS		OS	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	P-value	*P*-value	*P*-value	*P*-value
Age	0.800		0.395	
Gender	0.680		0.617	
Comorbidity	0.204		**0.018***	0.955
Family history	0.404		0.341	
Weight loss	0.668		0.077	
Emergent/elective application	0.705		0.941	
Perforation	**0.047***	**0.025***	0.082	
Obstruction	0.705		0.941	
Preoperative pRBC replacement	0.955		0.073	
ASA score	0.141		**0.006***	0.487
Tumor stage	**0.007***	0.272	0.153	
Tumor size	0.474		0.196	
Tumor invasion	0.443		0.788	
Differentiation	0.058		**0.021***	0.661
Perineural invasion	0.052		0.282	
Lymphovascular invasion	**0.004***	0.129	**0.036***	0.211
Preoperative hemoglobin value	0.976		0.060	
Preoperative CEA value	**0.005***	0.109	**0.032***	0.820
Preoperative CA19-9 value	0.184		0.096	
Preoperative albumin value	0.620		**0.012***	0.062
Number of lymph nodes removed	0.509		0.619	
Number of metastatic lymph nodes	0.105		**0.034***	0.721
Surgical margin [cm]	**< 0.001***	**0.008***	**0.001***	0.583

**Statistically significant. ASA – American Society of Anesthesiologists, CEA – carcinoembryonic antigen, DFS – disease-free survival, pRBC – packed red blood cells, OS – overall survival.*

gender was a poor prognostic factor. It has been observed in most of the studies that there is no statistically significant difference based on gender. In the present study, 62.5% of the patients were male and 37.5% were female. Gender was not found to be statistically significant for DFS and OS time in univariate and multivariate analyses.

Various studies have investigated the effect of primary localization of tumor on prognosis. Park *et al.* [14] revealed that localization of the tumor was not associated with prognosis. Sjo *et al.* [15] found in a study of 627 patients that survival time is much shorter in tumors with left colon localization and that this type of localization has a negative effect on prognosis. A clear result regarding the effect of tumor localization on prognosis could not be reached in our study due to an insufficient number of patients.

It is known that the risk of suffering from colorectal cancer is higher in individuals with a family history of colorectal cancer. However, the effect of the presence of family history on survival of patients with colorectal cancer is controversial. Bass *et al.* [16] reported in a study of 1001 patients with colorectal cancer that survival is significantly worse in patients with a family history of colorectal cancer in first-degree relatives. Slattery *et al.* [17] reported in their study that family history did not have an effect on survival. However, when subgroups were analyzed, it was determined that presence of family history in male patients with colorectal cancer aged 55 and under has a significant association with poor prognosis. In the present study, history of colorectal cancer was present in 3.3% of patients, but presence of family history was not found to be statistically significantly related to DFS or OS time in univariate or multivariate analysis.

It has been reported that survival rate is worse in patients with obstruction or perforation findings. The most important reason for this is the fact that limited lymphadenectomy is performed

under urgent conditions. Kruschewski *et al.* [18] reported that extended lymphadenectomy can be more safely performed in patients with obstruction findings and that survival is better. Biondo *et al.* [19] stated that there was no difference in terms of 5-year survival between patients who underwent surgery for obstruction and perforation. In the current study, no statistical significance was found in univariate or multivariate analysis with regard to DFS and OS time in patients for whom emergency surgery was necessary due to obstruction. However, presence of perforation was found to be a statistically significant prognostic factor in univariate and multivariate analyses in terms of DFS time in patients on whom emergency surgery was performed due to perforation. Statistical significance was not found in univariate or multivariate analysis for OS time. Moreover, emergent/elective quality was not found to be statistically significant for either DFS or OS.

Tumor grade has an important effect on prognosis [2, 4, 20]. In a study by Mekele *et al.* [20] investigating prognostic factors in patients under the age of 50, histological grade was found to be a significant, independent prognostic factor for local recurrence and OS. In the evaluation of histological grade made in the present study, no significant difference was found for DFS, according to differentiation. However, a significant statistical value was detected in univariate analysis for OS. Multivariate analysis did not reveal statistical significance for OS time.

The presence of lymphovascular invasion is an important prognostic factor that must be included in the pathology report [4]. Burton *et al.* [21] found that presence of vessel invasion was a poor prognostic factor. Mekele *et al.* [20] determined that presence of vessel invasion was a significant prognostic factor for local recurrence and OS time. The American Joint Committee on Cancer has stated that presence of vessel invasion is a poor prognostic factor [22]. In the current study, DFS and OS rates were better in the patient group with no vessel invasion compared to the group with invasion. Presence of vessel invasion was statistically significant in univariate analysis. However, presence of vessel invasion was not found to have statistical significance for DFS and OS. Presence of lymphovascular invasion was determined to be statistically significant in local recurrence and metastasis rates.

The presence of perineural invasion usually indicates advanced disease and is associated with a low survival rate. Presence of perineural invasion is typically seen with other poor prognostic findings [4]. Enker *et al.* [23] demonstrated that presence of perineural invasion is a risk factor for local recurrence. In the present study, DFS and OS rates were better in the patient group with no perineural invasion compared to the group with perineural invasion; however, a statistical significance was not detected in univariate and multivariate analyses.

In most studies, tumor stage has been reported to be the most important independent prognostic factor. Anticipated length of survival worsens as tumor stage advances. While the 5-year survival rate is over 90% for early stage tumors, this rate drops to 10% and below for advanced stage tumors [24].

The TNM staging system accepts each of the following three basic factors as independent prognostic factors: depth of colon wall penetration, lymph node involvement, and distal organ metastasis. Hermanek *et al.* [25] also reported that depth of colon wall penetration was an independent prognostic factor. Accordingly, as the T stage increases, reflecting the size of the primary tumor and invasion of nearby tissue, survival expectancy worsens. Gill *et al.* [26] found in a study conducted on 3302 chemotherapy patients with stage II and III colon cancer that depth of tumor penetration of the colon wall was a prognostic factor associated with DFS and OS time. In the present study, tumor stage was found to be statistically significant in predicting development of local recurrence and metastases. Local recurrence and metastases developed in 0 (0%) stage I patients, in 2 (4.2%) stage II patients and in 10 (18.5%) stage III patients. In univariate analysis, tumor stage was found to be a prognostic factor for DFS time, but not a statistically significant factor for OS time. However, results of multivariate analysis did not indicate that tumor stage was statistically significant for DFS or OS. Depth of tumor invasion was not found to be statistically significant in univariate or multivariate analysis in the present study.

Lymph node involvement has been found to be closely associated with survival in colorectal cancers. Chang *et al.* [27] found in a systematic review of 61 371 patients that lymph node involvement was a poor prognostic factor and that the number of involved lymph nodes also affects survival. Uribarrena-Amezaga *et al.* [28] reported that presence of micrometastases in regional lymph nodes was not associated with poor prognosis. In the current study, lymph node involvement was found to be closely associated with both DFS and OS in univariate analysis. However, it was not found to be an independent prognostic factor for DFS and OS time in multivariate analysis.

Though a limited number of studies have reported an association between tumor diameter and survival, it is mostly accepted that there is no association between tumor diameter and prognosis [29, 30]. In the present study, tumor diameter was not found to be significant for either DFS or OS time.

Positive surgical margin has been shown to be a poor prognostic factor in most studies regarding survival [31]. Goldstein *et al.* [32] reported in a study conducted on 418 colorectal cancer patients that DFS and OS time worsen in patients with a positive surgical margin. In the present study, positivity of the surgical margin was found to be an independent prognostic factor in terms of both DFS and OS time in univariate and multivariate analyses.

Serum CEA level is used in patient postoperative follow-up. It has been reported that preoperative serum CEA level has prognostic significance independent of tumor stage [4, 22, 33]. In a study that included 2230 patients, Park *et al.* [29] found that CEA elevation was a poor prognostic factor. Harrison *et al.* [34] reported in a study conducted on 572 patients that preoperative CEA level was associated with survival in patients without lymph node involvement. In the present study, preoperative CEA level was found to be statistically significant in terms of DFS and OS in univariate analysis. Survival was significantly lower in patients with a serum CEA limit value of 4 ng/ml or more. However, preoperative CEA level was not found to be an independent prognostic factor in multivariate analysis. In many studies, CA 19-9 elevation has been found to be a poor prognostic factor [33, 35]. CA 19-9 elevation is not encountered in most patients with colon cancer, but it has been reported that CA 19-9 levels are beneficial in postoperative follow-up. Nozoe *et al.* [36] suggested in a study conducted on 103 patients that preoperative simultaneous CEA and CA 19-9 elevation is associated with poor prognosis. Reiter *et al.* [37] demonstrated in a study of 495 cases that preoperative CA 19-9 levels are prognostic factors. In the current study, CA 19-9 levels were not found to be significant with respect to DFS or OS.

Several studies have been conducted on the effect of preoperative albumin level on prognosis, one of which was carried out by Boonpipattanapong and Chewatanakornkul [35] It was established in their study that prognosis was worse for patients with a preoperative albumin level under 3.5 g/dl. In the present study, no statistically significant difference in DFS rate was observed in univariate analysis of the patient group with a preoperative albumin level over 3.5 g/dl. Overall survival time was found to be statistically significantly longer in the group with a high albumin level when OS rates were examined in univariate analysis; however, a statistically significant difference was not found in multivariate analysis. Asaad *et al.* [38] found in a study of 174 stage II patients that prognosis was worse for patients with preoperative anemia. Liang *et al.* [39] demonstrated in a study of young patients with colon cancer that prognosis was worse for those requiring blood transfusion preoperatively. In the present study, a statistically significant difference was not found in terms of DFS and OS time in the patient group with a preoperative hemoglobin level over 10 g/dl, nor was a statistically significant difference found with regard to preoperative blood transfusion.

In conclusion, there are numerous prognostic parameters affecting post-operative survival in colorectal cancers. Expected survival and recurrence times are important in terms of designating frequency of postoperative follow-up with patients and carrying out the necessary scans on patients with risk of early recurrence. Depth of colon wall involvement, lymph node involvement, presence of vascular or perineural invasion, presence of obstruction or perforation at the time of diagnosis, and tumor grade are among the useful postoperative prognostic factors regarding development of recurrence and survival time for patients with colon cancers. In the current study, presence of perforation and positive surgical margin were found to be independent prognostic factors for DFS in multivariate analysis conducted on the effect of demographic, clinical, and pathological features with respect to DFS and OS time. Prospective studies and studies on a larger scale are necessary to more accurately designate both clinical prognostic factors that affect survival time and new biological and molecular markers.

Conflict of interest

The authors declare no conflict of interest.

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