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The effect of demographic, biochemical and patholojical parameters on survival in colorectal cancer

Kolorektal kanserde demografik, biyokimyasal ve patolojik parametrelerin sağkalıma etkisi

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Abstract

Aim: Colorectal cancer is one of the most commonly encountered malign tumors. In this study we studied the patients who have been operated for colorectal cancer retrospectively, to determine the parameters if they are prognostic or not.

Materials and Methods: 115 patients who had been operated on because of CRC were evaluated. Gender, age, place of tumor, local invasion, cancer history in first-degree relatives, chemotherapy history, histological grade, T stage, tumor size, total number of resected lymph nodes, metastatic lymph node number, positive lymph node ratio (PLNR),CEA, CA 19-9, albumin, CRP, survival, stage of disease were recorded and those parameters were compared with each other in two groups according to survival during follow-up.

Results: There were not any statistically difference as regard to age, young patients, gender, tumor location and family history between two groups (p=0,411 p=0,545 p=0,656 p=0.177 p=0,659).

However, statistically significant parameters in patients who died during follow-up were histological grade, T stage, the number of metastatic lymph node, stage, PLNR, CEA, CA 19-9 and CRP (p=0.034 for CA 19-9 and p<0.001 for the remaining parameters).

Histological grade and CRP were independent risk factors according to univariate analysis. Gender, age, and total numbers of the resected lymph nodes were parameters very near to significance.

Conclusions: For the patients with colorectal cancer grade, T stage, metastatic lymph node, CEA, CA 19-9 and CRP were found to have poor prognostic values.

Keywords: Cancer; Colorectal; Prognosis; Survival.

Öz

Amac: Kolorektal karsinom en sık rastlanan malign tümörlerdendir. Bu çalışmada hastanemizde kolorektal kanser nedeniyle opere edilen hastaların verileri retrospektif olarak incelenerek elde edilen parametrelerin prognostik olup olmadıklarının araştırılması amaçlanmıştır.

Gerec ve Yöntem: Kolorektal kanser nedeni ile ameliyat ettiğimiz 115 hasta değerlendirildi. Cinsiyet, yaş, tümör yerleşin yeri, lokal invazyon, 1.derece akrabada kanser öyküsü, kemoterapi alıp almadığı, histolojik grade, T evresi, tümör çapı, çıkarılan toplam lenf nodu sayısı, metastatik lenf nodu sayısı, pozitif lenf nodu oranı (PLNR) CEA, CA 19-9, albümin, CRP, takip sırasında sağ kalıp kalmadığı ve evreler kaydedildi.Hastalar takip sırasındaki hayatını kaybetme durumuna göre iki ayrı gruba ayrılarak parametreler kıyaslandı.

Bulgular: BULGULAR: Gruplar arasında yaş ortalamaları, kırk yaş altı hasta oranları, cinsiyet oranları, aile öykülerinde, tümör yerleşim yerlerinde istatistiksel olarak anlamlı fark saptanmadı (sırasıyla p=0,411 p=0,545 p=0,656 p=0,659 p=0,177). Grup 2'de tümör özelliklerinden grade, T, metastatik lenf nodu sayısı, evre, PLNR ortalamaları, CEA, CA 19-9, CRP normal dışı sınır değer oranları Grup 1'e göre istatistiksel olarak anlamlı yüksek saptandı (CA 19-9 için p=0,034 diğer tüm karşılaştırmalar p<0,001). Tek değişkenli analizlerde p<0,100 olan değişkenlerden oluşturulan modelde (uzak metastaz, lokal invazyon, grade, evre, T, toplam lenf nodu sayısı, metastatik lenf nodu sayısı, PLNR, CEA, CA 19-9, CRP) grade ve CRP bağımsız risk faktörü olarak saptandı.

Sonuçlar: Kolorektal kanserli hastalarda tümör özelliklerinden grade, T evresi, metastatik lenf nodu sayısı, evre, PLNR ortalamaları, CEA, CA 19-9, CRP değerlerinde yükseklik saptanması kötü prognostik belirteç olup hastaların takip ve tedavilerinin planlanmasında göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Kanser; Kolorektal; Prognoz; Sağkalım

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INTRODUCTION

Colorectal carcinoma (CRC) is one of the most common malignant tumors. It comes in third place after prostate and lung cancer in men and after breast and lung cancer in women. In calculations made without considering the gender, 10% of total cancer cases are CRC. It comes in second place after lung cancer in terms of the cause of death (1). However, the minimal morbidity and mortality of surgery and its high curative success rate in CRC are gratifying (2).

Although the new methods used for diagnosis, the initiation of screening programs, the new surgical techniques and the improvements in neoadjuvant and adjuvant radiotherapy and systemic chemotherapy have helped to increase the survival rate, some of the patients are diagnosed with advanced-stage for completely unknown reasons and also the survival rate does not exceed 8% (3,4).

In early stage patients undergoing curative surgery, the development of local and/or distant tumor recurrence leads that 5-year survival rate is respectively reduced to 93%, 78% and 64% for stage 1, 2, and 3 tumors (3). The search for prognostic factors is still continuing to help in making decisions of chemotherapy. It is necessary to diversify the parameters in pathological data. The biochemical parameters should be cheap, standardized and easily accessible, and also the demographic parameters should be developed within their own.

In this study, the data of patients who were operated due to colorectal cancer in our hospital were retrospectively analyzed and then it was aimed to investigate whether the obtained parameters were prognostic.

MATERIALS and METHODS

115 patients who were operated and underwent curative resection due to CRC between January 2008 and December 2009 were included in the study. The patients who had inaccessible data or were not contacted and were presented with the symptoms of ileus and so developed intestinal perforation and had a gastrointestinal stromal tumor showing a different course from other tumors were excluded from the study.

The demographic data of patients, tumor localization, local invasion, the previous operations, the history of cancer in first-degree relatives, the use of chemotherapeutic agents, histological grade, T stage, tumor size, the total number of removing lymph nodes, the number of metastatic lymph nodes, positive lymph node ratio (PLNR), CEA, CA 19-9, albumin, CRP and survival status during the follow-up were recorded. PLNR is calculated by dividing the number of metastatic LAP to the total number of LAP. TNM classification was used in staging. The patients who had 5 years follow-up period were divided into two groups based on mortality event. Alive and dead patients were separated as Group 1 and 2, respectively.

Hypoalbuminemia was considered to be the values below 3.5 gr/dl. The patients with carcinoma in situ were accepted as stage 0. CA 19-9 value was accepted as positive if it was 38 units/mL or above. CEA value was accepted as positive if it was 5ng/dl or above. CRP value was accepted as positive if it was 10 mg/dl or above.

8 distinct tumor localizations were determined: the cecum, the ascending colon, the right flexure, the transverse colon, the left flexure, the descending colon, the sigmoid colon and the rectum.

In our study, the family history of cancer was accepted as the history of cancer including CRC in any organ in first-degree relatives (siblings, parents, grandmothers, grandfathers, aunts, uncles, and first cousins) regardless of colorectal cancer. It did not need to be ethical committee approval because the study was retrospective. The written consent was obtained from the patients included in the study.

Statistical Analysis

SPSS 15.0 (SPSS Inc.; Chicago, IL, ABD) for Windows was used for statistical analysis. The descriptive statistics were given as number and percentage for the categorical variables and as mean, standard deviation, the median for the numerical variables. In the comparison of the numerical variables between two independent groups, the Student t test was used if a normal distribution was achieved and the Mann-Whitney U test was used if a normal distribution was not achieved. In the comparison of all the variables between more than two independent groups, the Kruskal-Wallis test was used if a normal distribution was not achieved. A Bonferroni-corrected Mann-Whitney U test was used in subgroup analyses. Because the relationship of the numerical variables did not show a normal distribution, the spearman correlation analysis was used. The Chi-square test was used to analyze the categorical variables in independent groups. P values of less than 0.05 were regarded as statistically significant.

RESULTS

A total of 115 patients with the average age 61.93±13.12 including 62 (53.9%) men and 53 (46.1%) women were included in the study. 5 (4.3%) patients were under the age of 40 and 33 (28.7%) patients had a family history. The tumor was located in the rectum in 43 (37.4%) patients and in the sigmoid colon in 33 (28.7%) patients and in the cecum in 13 (11.3%) patients. Distant metastasis was found in the liver in 4 (3.5%) patients and local invasion was found in 14 (12.2%) patients. 82 (71.3%) patients had received chemotherapy. In the patients, the median value of T was 2, the median value of S was 3 and also the average tumor size was 5.2±1.9 cm. Tumor size was above 5 cm in 44 (38.3%) patients. The average number of removing lymph nodes was 15.14±9.31, the average number of metastatic LN was 3.01±3.97 and the average value of PLNR was 0.19±0.24. 102 (88.7) patients had hypoalbuminemia, 17 (14.8%) patients had a high level of CEA, 7 (6.1%) patients had a high level of CA19-9 and 38 (33.3%) patients had a high level of CRP (Graphic 1,2).

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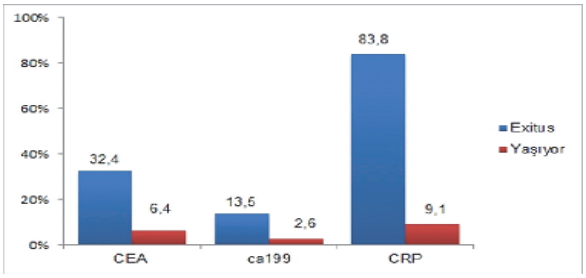

Figure 1. The distribution of the groups according to CEA, CRP, CA 19-9

Figure2. 95% confidence interval for PLNR

At the end of 5-year follow-up, 78 (67.8%) patients continued to live and these patients constituted group 1. 37 (32.2%) patients lost their lives and these patients constituted group 2.

There was no statistically significant difference between the groups in terms of average age, the rate of the patients under the age of 40, gender ratio, family history and tumor localization (respectively, p=0.411, p=0.545, p=0.656, p=0.659, p=0.177).

The high values for grade, T, the number of metastatic lymph nodes, stage, the average PLNR, CEA, CA 19-9, CRP from the characteristics of tumor were statistically significantly higher in the Group 2 compared to the Group 1 (p=0.034 for CA 19-9, p<0,001 for all other comparisons) (Table 1). In univariate analyses, grade and CRP were found to be an independent risk factor in the model formed from the variables with p<0.100 (distant metastasis, local invasion, grade, stage, T, the total number of lymph nodes, the number of metastatic lymph nodes, PLNR, CEA, CA 19-9, CRP) (Table 2).

Table 1. The comparison of the parameters according to the groups

		Grup 1 n(%)	Grup 2 n(%)	P
Gender	Male	40 (51.3)	22 (59.5)	0.411
	Female	38 (48.7)	15 (40.5)	
Age of 40	<age of 40	3 (3.8)	2 (5.4)	0.656
	>age of 40	75 (96.2)	35 (94.6)	
Family history		21 (26.9)	12 (32.4)	0.659
Tumor localization	Rectum	30 (38.5)	13 (35.1)	0.177
	Sigmoid	20 (25.6)	13 (35.1)	
	Cecum	8 (10.3)	5 (13.5)	
	Right flexure	5 (6.4)	2 (5.4)	
	Left flexure	6 (7.7)	0 (0.0)	
	Descending col	2 (2.6)	4 (10.8)	
	Ascending col	5 (6.4)	0 (0.0)	
	Transvers col	2 (2.6)	0 (0.0)	
Distant metastasis	Liver metastasis	1 (1.3)	3 (8.1)	0.097
Local invasion		6 (7.7)	8 (21.6)	0,063
Chemotherapy		52 (66.7)	30 (81.1)	0.110
Grade	0	1 (1.3)	0 (0.0)	**<0.001**
	1	5 (6.4)	0 (0.0)	
	2	69 (88.5)	23 (62.2)	
	3	3 (3.8)	14 (37.8)	
T	0	2 (2.6)	0 (0.0)	**<0.001**
	2	61 (78.2)	16 (43.2)	
	3	11 (14.1)	9 (24.3)	
	4	4 (5.1)	12 (32.4)	
Metastatic	>3 LAP	13 (16.7)	26 (70.3)	**<0.001**
	>7 LAP	61 (78.2)	32 (86.5)	0.292
	>11 LAP	46 (59.0)	25 (67.6)	0.376
Stage	0	2 (2.6)	0 (0.0)	**<0.001**
	1	36 (46.2)	5 (13.5)	
	2	7 (9.0)	1 (2.7)	
	3	32 (41.0)	28 (75.7)	
	4	1 (1.3)	3 (8.1)	
Tumor diameter	>5	27 (34.6)	17 (45.9)	0,243
PLNR Ort.±SD (median)		0.12±0.20 (0)	0.35±0.25 (0.4)	**<0.001**
Elevation in albumin level		68 (87.2)	34 (91.9)	0.544
Elevation in CEA level		5 (6.4)	12 (32.4)	**<0.001**
Elevation in CA 19-9 level		2 (2.6)	5 (13.5)	**0.034**
Elevation in CRP level		7 (9.1)	31 (83.8)	**<0.001**

PLNR: positive lymph node rate
T: Tumor size

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Table 2. The independent risk factors

	p	OR	(%95 CI)	
			Min	Max
Grade	0.004	14.1	2.3	85.3
CRP	0.000	48.2	13.2	176.1

DISCUSSION

CRC is slightly more common in men according to the literature (5,6). There are some studies indicating that male gender is a poor prognostic factor (7,8). In our study, there was no statistically significant difference in terms of gender (p<0.411).

Colon cancer incidence rates increase after the age of 40 and reach the highest value after the age of 60. Therefore, patients younger than 40 years of age are considered as a separate patient group. There are some studies indicating that young age is a poor prognostic criteria. The factors such as the presence of hereditary cancer in young people, the existence of less prominent symptoms in young people and the emergence of the symptoms in late life support that tumors are more aggressive in young patients (5,9-11).

In our study, the number of patients under 40 years of age was 5 (4.3%). Although their prognosis was not statistically significant compared to the others (p<0.656), the prognosis was worse in the patients under 40 years of age.

Many studies have emphasized that the localization of primary tumor had no the effect on prognosis (11-14). In our study, there was no statistically significant difference in terms of the localization of the tumor (p<0.177).

There are serious evidence for that tumor grade has a significant impact on prognosis (4,14-18). Although tumor grade is a significant prognostic factor in almost all studies, there was no any correlation between the grade and prognosis in some studies (17).

In our study, tumor grade was statistically significantly higher (p<0.001). In univariate analyses, grade and CRP were found to be an independent risk factor in the model formed from the variables with p<0.100 (distant metastasis, local invasion, grade, stage, tumor invasion, the total number of lymph nodes, the number of metastatic lymph nodes, PLNR, CEA, CA 19-9, CRP).

T stage is the depth of the tumor in the bowel wall and has been found to be effective in prognosis. Especially, even T4 tumors are in stage 2, it has been emphasized that T stage is a poor prognostic parameter (4). In our study, there was a statistically significant difference between groups in terms of T stage (p<0.001).

The types of signet ring cell within mucinous cancers are more aggressive (7,15). A statistical study could not be performed because the number of signet ring cell carcinoma was few in the distribution of histological types in our study. Therefore, a comment could not be made about its effect on the prognosis.

In the literature, there are many studies indicating that there is no a significant relationship between tumor size and prognosis (4,15,19). In a study made in 2230 patients by Park et al. (13), they reported that tumor size was not related to the prognosis. In our study, there was no statistically significant difference between the groups in terms of tumor size.

There are some studies indicating that high CEA serum levels in the preoperative period had a negative impact on survival regardless of tumor stage (11,13,20,21), and it was reported that CEA monitoring can be performed to evaluate the response to treatment and to detect the recurrence in colon cancers (16,22-24).

It has been claimed that in some studies that an increase in CA 19-9 levels is a poor prognostic factor (20,25-27). However, high CA 19-9 level has not been found in the majority of patients with colon cancer. Therefore, it has been reported that it can be a safe monitoring tool to follow only patients with high CA 19-9 level in the preoperative period (23). Nozoe et al. (20) have supported that the combination of elevated of CEA and CA 19-9 is a poor prognosis factor. In our study, both CEA and CA 19-9 values were statistically significantly higher (p<0.001 and p<0.034).

The American Joint Committee on Cancer (AJCC) and The American Institute for Cancer Research (AICR) have emphasized that LAP must be removed at least 12 in colon cancer (28).

In a study made with 35787 patients by Swanson et al. (29), they found that an increase in the number of benign lymph node (N0) removed in patients with T3N0 has a positive impact on prognosis. In our study, the number of lymph nodes removed has ranged from 3 to 69. In our study, while 12 and more lymph nodes were removed in 71 of 115 patients, less than 12 lymph nodes were removed in 44 of 115 patients. 8-12 lymph nodes were removed in 22 patients. While the number of lymph nodes was increased, it was found to have a significant effect on survival. When all patients in our study were examined, the number of lymph nodes removed was 15.14 ± 9.31, and this has shown that we made adequately dissection. In our study, the total number of lymph nodes was nearly statistically significant (p<0.077). In a study of 174 patients with stage 2 according to TNM classification by Asaad et al., they found that the prognosis was worse in patients with 7 and fewer lymph nodes removed (8).

Prandi et al. (30) showed in 3648 patients that the group with 8-12 lymph nodes removed had a better prognosis compared to the group with 7 and fewer lymph nodes. In the same study, they have stated that patients with stage II with inadequate lymph nodes resection can not be actually considered stage II and also adjuvant

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chemotherapy is essential due to low life expectancy in these patients. In our study, it was found that the patients with inadequate lymph nodes resection were treated as stage III.

Chang et al. (31) sought to answer this question with meta-analysis. Meta-analysis was applied to 17 reliable studies from 9 countries by them. While the number of lymph nodes removed was increased in stage II and III colon cancer, it was found that survival rate was increased.

In a study made with 20702 patients, it was reported that an increase in the number of negative lymph nodes removed in patients with stage III B and stage III C increased survival rate (32).

It has been suggested in many studies that lymph node positivity is the most important prognostic indicator in terms of both survival and recurrence (4,11-14,16,33-35). Cohen et al. (36) reported that while the 5-year survival was 66% in patients with 1-3 positive lymph nodes, it was decreased to 37% in patients with more than 3 positive lymph nodes. Burton et al. (14) and Suzuki et al. (34) have stated that 4 and more positive lymph nodes are a poor prognostic factor. In our study, the number of metastatic lymph nodes was significantly higher in the Group 1 ($p<0.001$).

Although there is an association between histology and stage of the disease and cancer cachexia, directly related parameters have not been revealed. In today, the most important indicators of cachexia are weight loss and hypoproteinemia. Significant weight loss is a poor indicator of the response to treatment and survival in patients with cancer. Protein and amino acid metabolism in the cancerous organism are damaged. In these patients, protein turnover is increased in both in the cancerous tissue and in the organism. There are studies investigating that serum albumin levels in the preoperative period have the effects on prognosis and the values above and below 3.5 g/dl are taken as the cut-off value in general (24). Low albumin level means lower survival. The prognosis is worse in patients with the combination of low albumin level and high CRP level compared to patients with only low albumin level.

In our study, there was no statistically significant difference between the groups in terms of hypoalbuminemia. Albumin levels were within normal limits in 68 (87.2%) patients in the Group 1 and 34 (91.9%) patients in the Group 2.

The high values for the grade, T, the number of metastatic lymph nodes, stage, the average PLNR, CEA, CA 19-9, CRP from the characteristics of the tumor are poor prognostic indicators in patients with colorectal cancer. It should be considered in the planning of follow-up and treatment of patients.

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