Prognostic Factors for Survival in Patients with Metastatic Colon Carcinoma

Feride YILMAZ[1], Cevriye Ceyda KARABULUT[2], Feyyaz OZDEMIR[3], Fazil AYDIN[4]

[1] Hacettepe University, Oncology Institute, Department of Medical Oncology
[2] Provincial Health Directorate, Public Health Department
[3] Karadeniz Technical University, Faculty of Medicine, Department of Medical Oncology
[4] Private Imperial Hospital, Department of Medical Oncology

ABSTRACT

Colorectal cancers are the most common cancers of the gastrointestinal system. They rank third after prostate and lung cancer in men and after breast and lung cancer in women. In Turkiye, colon cancer is the third most common among all cancers. In such cancer, beyond the stage of the disease, there are many biological, molecular, genetic, and tissue-related factors that determine the prognosis. Among these, vascular invasion, the number of affected regional lymph nodes, and the levels of preoperative carcinoembryonic antigen (CEA) are prominent factors. In this study, we investigated the personal, clinical, tumoral, metastatic, and treatment characteristics of metastatic colon cancer (MCC) that may be associated with long survival. This study included the data of 103 patients diagnosed with MCC who were followed at the Medical Oncology Department of Karadeniz Technical University Faculty of Medicine between 2010 and 2016. In univariate analyses, primary surgery (p< 0.001), targeted therapy (p= 0.01), being less than 65 years old (p=0.02), having normal CEA levels (p= 0.03), and not having elevated platelet counts (p= 0.001) were significant factors associated with prolonged survival. Multivariate analysis indicated that survival was longer in patients who underwent primary surgery (p= 0.001, 95% CI: 0.07–0.52) and had normal or low platelet levels at the time of diagnosis (p= 0.001, 95% CI: 1.77–9.16), regardless of other factors. In patients diagnosed with MCC, those who had primary tumor surgery and had normal or low platelet levels at the time of diagnosis had a better prognosis regardless of other factors. Therefore, prognostic factors are important in MCC, and more comprehensive studies are needed on this subject.

Keywords: Metastatic colorectal cancer, Survival, Prognostic factors

INTRODUCTION

Colorectal cancers are the most common cancers of the gastrointestinal system. They are the third most frequent cancer in both men (following prostate and lung cancer) and women (following breast and lung cancer).[1] The most critical factor determining the prognosis of colorectal cancers is the stage of the disease. When caught early, it is a malignancy that can be treated with high curative rates through appropriate surgical interventions, which are associated with minimal morbidity and mortality.[2] However, there are numerous other prognostic factors, including biological, molecular, and genetic factors.[3,4]

Each year, there is an increase in the overall survival (OS) duration of colon cancer patients. This is closely related to advancements in diagnostic methods, the widespread implementation of screening programs, the development of new surgical techniques, and the introduction of new methods in radiotherapy and systemic treatments.[5]

The treatment options for colorectal cancers include surgery, chemotherapy, and radiotherapy modalities, which can be modified based on the localization and stage of the primary tumor, and can be applied either alone or in combination. In non-metastatic colorectal cancer, the primary treatment option is surgery.[6]

The 5-year survival rates of patients vary according to the tumor, node, and metastasis (TNM) classification. In this study, we investigated the potential associations between personal, clinical, tumoral, metastatic, and treatment characteristics and long-term survival in metastatic colon cancer (MCC).

PATIENTS AND METHODS

This study analyzed 103 patients diagnosed with MCC at Karadeniz Technical University Faculty of Medicine between 2010 and 2016. Data were obtained from hospital records, laboratory results, and pathology records. Personal information was collected through questionnaires and pathology reports. Tumor staging was performed using the TNM staging system, and performance status (PS) was assessed using the Eastern Cooperative Oncology Group (ECOG) scoring system. Patients with insufficient information, unavailable pathology reports, or follow-up in healthcare institutions outside Karadeniz Technical University were excluded from the study. The reference values for CEA and platelet levels were 0.3–0.3 ng/mL and 100.000–400.000/mm^3, respectively. Descriptive statistics were used for data analysis, and the distribution of variables was checked using the Kolmogorov-Smirnov test, Mann-Whitney U test, chi-square test, Kaplan–Meier method, log-rank test, and Cox regression. Significance was set at $p< 0.05$. Original SPSS 23.0 software was used for the analyses.

Karadeniz Technical University Ethics Committee approved the study protocol (Date: September 2015, Approval number: 2015/151).

RESULTS

The study included 103 patients diagnosed with MCC. Among them, 34 (33%) were female and 69 (67%) were male. The median follow-up period

Table 1. General clinical and sociodemographic characteristics of the patients

Characteristic	n	%
Age (mean ± SD)	61.9±11.3	
Gender (n= 103)		
Female	34	33
Male	69	67
Family history of cancer (n= 91)		
Yes	41	45
No	50	55
Smoking status (n= 98)		%
Yes	53	54.1
No	45	45.9
Comorbid disease (n= 103)		
Yes	70	68
No	33	32
Aspirin use (n= 103)		
Yes	22	21.4
No	81	78.6
Primary surgery (n= 103)		
Yes	85	82.5
No	18	17.5
Metastasectomy (n= 103)		
Yes	36	35
No	67	65
PS at diagnosis (n= 103)		
0	63	61.2
1	36	35
2	4	3.9
Tumor localization (n= 97)		
Rectosigmoid	41	42
Descending colon	26	27
Ascending colon	25	26
Transverse colon	5	5
CEA level at diagnosis (n= 98)		
High	58	59.2
Normal	40	40.8
Platelet count at diagnosis (n= 102)		
Normal	69	67.6
High	30	29.4
Low	3	3
KRAS (n= 44)		
Positive	28	64
Negative	16	36
Targeted therapy (n= 103)		
Received	75	72.8
Not received	28	27.2
Survival status (n= 103)		
Alive	70	68
Deceased	33	32

SD= standard deviation; PS= performance status; CEA= carcinoembryonic antigen; KRAS= Kirsten rat sarcoma virus

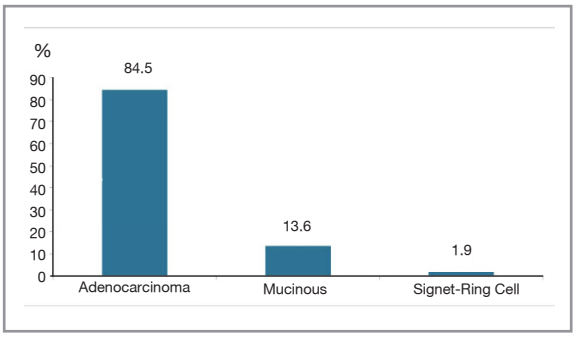

Figure 1. Percentage distribution of tumor histological types in patients diagnosed with metastatic colon cancer

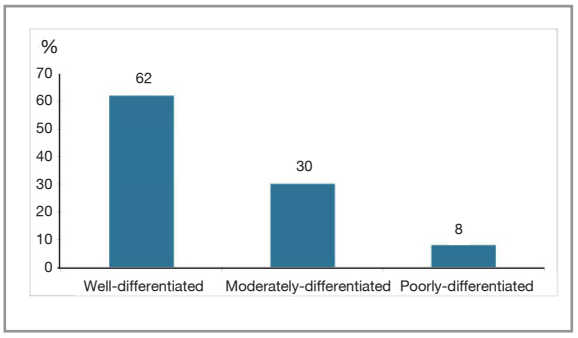

Figure 2. Percentage distribution of histological grades in patients diagnosed with metastatic colon cancer

Table 2. Distribution of metastasis by site

	n	%
Liver metastasis (n= 103)		
Yes	81	78.6
No	22	21.4
Lung metastasis (n= 103)		
Yes	57	55.3
No	46	44.7
Soft tissue/Other metastasis (n= 103)		
Yes	64	62.1
No	39	37.9
Bone metastasis (n=103)		
Yes	13	12.6
No	90	87.4

was 19 months, ranging from 2 to 66 months. Of the patients, 62 (60.2%) were under the age of 65 and 41 (39.8%) were over the age of 65 (Table 1).

The tumor localization was known in 97 of 103 patients and unknown in 6 because they had not undergone primary surgery and sampling was performed via colonoscopic biopsy. Regarding the histological distribution of tumors, 87 patients (84.5%) were diagnosed with adenocarcinoma, 14 (13.6%) had mucinous adenocarcinoma, and 2 (1.9%) had signet-ring cell carcinoma (Figure 1).

Regarding the histological grade, 44 of 103 patients (42.7%) were well-differentiated (grade 1), 21 patients (20.4%) were moderately differentiated (grade 2), and 6 patients (5.8%) were poorly differentiated (grade 3). The grade information for 32 patients was unavailable. Among the patients with known grades, 62% were well-differentiated, 29.6% were moderately differentiated, and 8.5% were poorly differentiated (Figure 2).

CEA levels were found to be elevated in 59 patients (approximately 60% among those whose CEA levels were measured), while 40 patients (approximately 40%) had normal levels. CEA was not initially measured in 4 patients. The average CEA level was 135.96 ng/mL (ranging from a minimum of 0.67 to a maximum of 1123). The metastatic sites of the patients are detailed in Table 2.

In the 103 patients evaluated, the median OS was 37 months (95% CI: 29.32–44.68), with a follow-up period ranging from a minimum of 2 months to a maximum of 66 months. By age, the median was 52 months for patients aged 65 and under and 29 months for those over 65 years old. This difference was statistically significant (p= 0.024) (see Table 3 for more data).

The median OS for patients who underwent primary surgery was 37 months, which showed a statistically significant difference compared to patients who did not undergo surgery (median of 16 months) (p< 0.001) (Figure 3).

Survival was evaluated based on the PS at the time of diagnosis. Accordingly, the median survival time for patients with a PS of 0 was 54 months (95% CI: 38.98–69.02), for those with a PS of 1, it was 23 months (95% CI: 9.92–36.08), and for those with a PS of 2 at the time of diagnosis, the median survival time was 7 months (95% CI: 3.80–17.20). These findings were statistically significant (p= 0.001).

Table 3. Survival analyses

		Median (Months)	95% CI	p
Age	≥ 65	29	22.99–35.01	0.02
	< 65	52	30.80–73.19	
Gender	Female	37	16.12–57.88	0.854
	Male	36	26.05–45.95	
Family history of cancer	Yes	37	17.87–90.12	0.636
	No	54	33.86–40.14	
Body Mass Index	25 ≥	30	20.12–39.88	0.141
	26 <	50	34.70–65.29	
Smoking status	Yes	50	15.46–84.54	0.210
	No	37	35.35–38.64	
Comorbid disease	Yes	35	24.83–45.17	0.145
	No	52	38.21–65.78	
Aspirin use	Yes	54	23.18–46.52	0.340
	No	36	28.96–43.03	
Tumor localization	Rectosigmoid	37.00	16.65–57.35	
	Descending colon	54.00	5.54–102.46	0.440
	Ascending colon	35.00	11.67–58.33	
	Transverse colon	27.20	11.83–42.57	
Tumor histology	Adenocarcinoma	37.00	34.36–39.64	
	Mucinous	26.00	0.00–53.44	0.560
	Signet-ring cell	21	21.00–21.00	
Tumor grade	Grade 1	37	24.74–49.26	
	Grade 2	36	33.96–38.04	0.542
	Grade 3	52	48.80–55.20	
Targeted therapy	Received	37	34.35–39.65	0.01
	Not Received	26	10.53–41.47	
CEA level at diagnosis	High	29.00	20.60–37.40	0.03
	Normal	48.27	37.33–59.22	
Platelet level at diagnosis	Low and normal	37	17.98–56.02	
	High	15	5.69–24.30	0.00
KRAS	Positive	37	31.08–42.92	
	Negative	23	18.66–37.62	0.418
Liver metastasis	Yes	36.00	28.06–43.93	
	No	46.28	32.85–59.72	0.119
Lung metastasis	Yes	37	29.03–44.97	
	No	36	7.87–64.12	0.547
Soft tissue/Other metastasis	Yes	35	24.62–45.38	
	No	54	35.28–53.02	0.097
Bone metastasis	Yes	37.00	32.89–41.11	
	No	36.00	25.97–46.03	0.763
Metastasectomy	Yes	37	27.56–46.44	
	No	35	17.85–52.14	0.445
Primary surgery	Yes	37	19.73–54.27	
	No	16	5.05–26.95	<0.001

CI= confidence interval; CEA= carcinoembryonic antigen; KRAS= Kirsten rat sarcoma virus

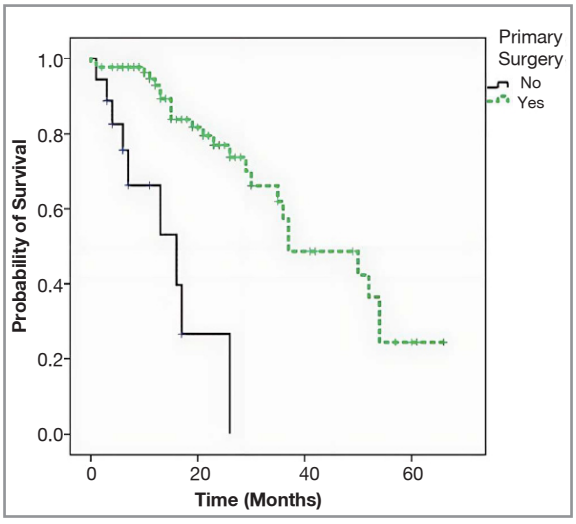

Figure 3. Survival curve based on primary surgery status (p<0.001)

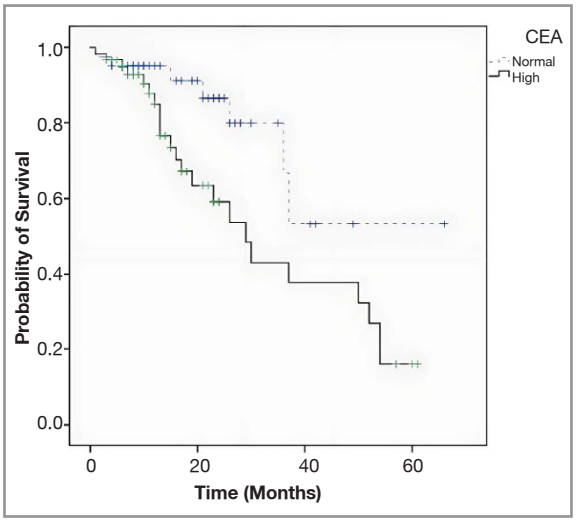

Figure 4. Relationship between CEA levels and survival

The increased variability in survival times is attributed to the differences between patients with a PS of 0 and 1, and between those with a PS of 0 and 2 (p= 0.007).

For patients with elevated CEA levels, the median survival time was 29 months (95% CI: 20.60–37.40), whereas for those with normal CEA levels, the median survival time was 48.27 months (95% CI: 37.33–59.22). This difference was statistically significant (p= 0.03) (Figure 4).

The median survival time was 15 (95% CI: 5.69–24.30) months for patients with elevated platelet counts at the time of diagnosis and 37 (95% CI: 17.98-56.02) months for those with normal and low platelet counts (p= 0.00).

In univariate analyses, age at diagnosis, CEA levels at diagnosis, targeted therapy, primary surgery, and elevated platelet counts showed significant associations with overall survival. These factors were included in multivariate analysis (Table 4).

According to Cox regression, patients who did not undergo primary surgery were at higher risk for mortality compared to those who did, and this difference was statistically significant (p= 0.001). In addition, patients with elevated initial platelet counts were at 4.02 times higher risk for death compared to those with normal and low platelet counts, and this difference was statistically significant (p= 0.001).

Table 4. Multivariate analysis of factors affecting overall survival

	95% CI	HR	p
Age	0.63–3.13	1.40	0.40
CEA level	0.79–5.62	2.11	0.13
Targeted therapy	0.21–1.19	0.50	0.11
Primary surgery	0.07–0.52	0.19	0.001
Elevated platelet level	1.77–9.16	4.02	0.001

CEA= carcinoembryonic antigen; CI= confidence interval; HR= hazard ratio

DISCUSSION

It is crucial to evaluate the prognostic factors in colorectal cancer to be able to determine both metastasis and recurrence as well as to plan treatment strategies.[7] Furthermore, numerous studies[8-10] have demonstrated a substantial positive correlation between a favorable PS at the time of diagnosis and improved survival rates in individuals diagnosed with such cancer. In our study, the median survival time was 54 months for patients with a PS of 0 at diagnosis, 23 months for those with a PS of 1, and 7 months for those with a PS of 2; all of these findings were statistically significant.

A multivariate analysis comparing age, CEA levels, receipt of targeted therapy, primary surgery, and elevated platelet levels at diagnosis indicated that patients who did not undergo primary surgery were at higher risk for death compared to those who did undergo surgery. In addition, patients with high platelet counts were at higher risk for mortality than those with normal and low platelet counts. Cook et al.,[11] found that survival rates were significantly higher in patients with advanced colorectal cancer who underwent primary surgery across all age groups (11 months vs. 2 months for colon cancer; 16 months vs. 6 months for rectal cancer). Consistent with the literature, our univariate analysis showed that the median OS for patients who underwent primary surgery was 37 months, which was statistically significantly different compared to 16 months for those who did not undergo surgery.

Mucinous type carcinomas tend to be more aggressive[12] and associated with worse prognosis than non-mucinous types.[13] However, in our study, an effect of tumor histological type on survival was not demonstrated statistically.

Many previous studies have demonstrated the survival benefit of metastasectomy, reporting that hepatic and pulmonary metastasectomies significantly improve survival in colorectal cancer.[14-16] However, we did not find a significant difference in survival between patients who did and not undergo metastasectomy. This result may have been due to the limited number of patients included in our study.

This study had some limitations. First, due to its retrospective nature, selection bias is likely to have occurred, which could affect the results. Second, the acquired data were from only one single tertiary care facility, which makes it difficult to interpret the analyses relative to the general population due to the small sample size.

Patients who underwent primary surgical intervention had better OS compared to those who did not, identifying primary surgery as an independent prognostic factor for OS. Similarly, shorter survival durations were significantly associated with initially elevated platelet counts at diagnosis compared to normal or low platelet counts. However, future comprehensive studies are still needed to further elucidate the importance of prognostic factors in colon cancer.

REFERENCES

1. Karaca H, Berk V, Inanç M, et al. Erciyes Universitesi Tip Fakültesi Tibbi Onkoloji Bilim Dali'na 2006-2009 yillari arasinda basvuran kanser hastalarinin epidemiyolojik degerlendirmesi. JHS ((Journal of Health Sciences), 20: 1-8, 2011.
2. Compton CC. Colorectal carcinoma: diagnostic, prognostic, and molecular features. Mod Pathol 16: 376-388, 2003.
3. Chapuis P, Dent O, Fisher R, et al. A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. Br J Surg 72: 698-702, 1985.
4. Ryan R, Gibbons D, Hyland J, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 47: 141-146, 2005.
5. Sökmen S. Kolorektal Kanserde Prognoz. Turkiye Klinikleri J Surg 9: 57-64, 2004.
6. Nordlinger B, Van Cutsem E, Gruenberger T, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol 20: 985-992, 2009.
7. Altekruse S, Kosary C, Krapcho M, et al. SEER cancer statistics review, 1975-2007. Bethesda, MD: National Cancer Institute 7: 2010.
8. Galizia G, Lieto E, Orditura M, et al. First-line chemotherapy vs bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. Arch Surg 143: 352-358, 2008.
9. Tebbutt N, Norman A, Cunningham D, et al. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. Gut 52: 568-573, 2003.

10. Bajwa A, Blunt N, Vyas S, et al. Primary tumour resection and survival in the palliative management of metastatic colorectal cancer. Eur J Surg Oncol (EJSO) 35: 164-167, 2009.

11. Cook AD, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. Annals of surgical oncology 12: 637-645, 2005.

12. Kupelioglu AA. Kolorektal Kanserde Histopatoloji. Turkiye Klinikleri J Surg 9: 25-27, 2004.

13. Han-Shiang C. Curative resection of colorectal adenocarcinoma: multivariate analysis of 5-year follow-up. World J Surg 23: 1301-1306, 1999.

14. Inoue M, Ohta M, Iuchi K, et al. Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. Ann Thorac Surg 78: 238-244, 2004.

15. López-Gómez M, Cejas P, Merino M, et al. Management of colorectal cancer patients after resection of liver metastases: can we offer a tailored treatment? Clin Transl Oncol 14: 641-658, 2012.

16. Scheele J, Altendorf-Hofmann A. Resection of colorectal liver metastases. Langenbecks Arch Surg 384: 313-327, 1999.

Correspondence:

Dr. Feride YILMAZ

Hacettepe Universitesi, Onkoloji Enstitusu

Tibbi Onkoloji Bolumu,

Sihhiye, ANKARA / TURKIYE

Tel: (+90-507) 524 28 05

e-mail: doktorferide@gmail.com

ORCIDs:

Feride Yilmaz	0000-0001-5848-3381
Cevriye Ceyda Karabulut	0000-0001-7734-8206
Feyyaz Ozdemir	0000-0001-6980-2800
Fazil Aydin	0000-0001-7215-8809