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ORIGINAL ARTICLE

The association between post-progression survival and clinical characteristics of patients with metastatic colon cancer: A single center experience

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Summary

Purpose: *In this study, we aimed to determine the factors which affect post-progression survival (PPS) and overall survival (OS) in patients with metastatic colorectal cancer.*

Methods: *87 patients with metastatic colorectal cancer had been followed up with palliative care due to disease progression or ECOG performance status after receiving at least two cycles of chemotherapy. PPS was estimated as the time between the last progression date and last control or death date in patients who were followed up with palliative care.*

Results: *87 patients with metastatic colorectal cancer were included in the study. Evaluation with multivariate analysis of factors affecting PPS revealed a significantly longer PPS (10.8 weeks) in patients with ECOG score 0 or 1 than the PPS of patients with ECOG score 2-5 (3 weeks) (p=0.01). It was also found that PPS was 14.4 weeks in patients with CEA levels <5ng/ml,while it was 6.7 weeks in patients with CEA levels ≥5 ng/ml (p=0.001) and PPS was 13.7 weeks in patients with controlled disease after first-line chemotherapy while it was 8 weeks in patients with progression (p=0.03); both were statistically significant. No significant association was found between PPS and age, gender, tumor location, sites of metastasis, and RAS status.*

Conclusion: *ECOG performance status score of 0-1, CEA levels below 5 ng/ml, and disease control with first-line chemotherapy are related to longer PPS in patients with metastatic colorectal cancer.*

Key words: *colorectal cancer, post-progression survival, overall survival*

Introduction

Colorectal cancer is the second in women and the third most common cancer in men worldwide [1]. While 5-year survival rate is above 90% in patients with stage 1 disease, it is below 10% in patients with stage 4 disease. 22% of the patients are in metastatic stage at the time of diagnosis [2].

Advanced age, male gender, family history, inflammatory bowel disease, diabetes, smoking, alcohol and high consumption of processed meat increase the risk of colorectal cancer. Regular physical activity, consumption of fruits, vegetables, fish, cereals, and fresh foods and use of aspirin are suggested to be associated with decreased risk of colorectal cancers [3].

Most of the tumors (90%) in colon and rectum carcinomas consist of adenocarcinomas [4]. Colorectal cancer generally shows hematogeneous and lymphatic spread along with local invasion and transperitoneal route. The most common sites of metastasis are lymph nodes, liver, lungs,

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and peritoneum. The patients might show signs and symptoms related to these sites of the body. Right upper quadrant pain, abdominal distention, fullness, supraclavicular lymphadenopathy, and periumbilical nodules usually show advanced and metastatic disease [5].

Poor prognostic factors defined for colorectal cancer are advanced stage, high CEA levels at disease onset, right side location, perineural and lymphovascular invasion, and poor performance status score [6-10].

The current approach to first-line therapy of metastatic colorectal cancer includes combinations of targeted agents with dual cytotoxic agents such as fluorouracil, leucovorin, oxaliplatin (FOLFOX), fluorouracil, leucovorin, irinotecan (FOLFIRI) and capecitabine, oxaliplatin (XELOX) [11,12]. Regorafenib and TAS-102 are generally used as second or third-line therapy [14]. Patients who completed and failed all lines of therapy or who are unable to use drugs due to low performance status are usually followed with palliative care.

Overall survival is the combination of progression-free survival (PFS) and PPS. Thus, factors affecting PPS, also affect OS naturally. In this retrospective study we aimed to determine the factors which affect PPS and OS in patients with metastatic colorectal cancer.

Methods

The patients with metastatic colorectal cancer who were followed up and treated between January 2010 and December 2017 were evaluated in this retrospective study. Institutional Review Board approval was obtained (TUTF-BAEK 2018/44). All the procedures performed in studies involving participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Included in this study were the patients who had received at least two lines of chemotherapy and were followed up with palliative care afterward since the treatment options came to an end due to disease progression and low performance status. The file records of 350 patients were evaluated before the study. 87 patients who met the inclusion criteria and whose file data were complete were included in the study. 263 patients were excluded since their file data were missing.

Data of age, gender, ECOG performance status, location of primary tumor, histopathology of tumor, ras status, location of metastases, CEA levels at the onset of disease, first, second and third-line of chemotherapies, and treatment responses were recorded. OS was estimated as the time between the diagnosis of metastatic disease and death/last control date. PPS was estimated as the time between the last progression date and death/last control date in patients who were followed up with palliative care. Treatment responses were defined according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.

Statistics

Univariate and multivariate analyses were performed. The standard deviation was defined as (±). Comparison of parametric variables between groups was made by the independent t-test. The relationships of nonparametric variables with each other were evaluated using the chi-square test. Kaplan-Meier method and log-rank test were used for survival analyses. Cox regression analysis was performed for multivariate analysis. The confidence interval (CI) was defined as 95% and p value <0.05 was defined as statistically significant.

Results

Patient characteristics

87 patients were included in the study and the median age was 63 years. 36 of the patients were female (41.4%) and 51 (58.6%) male. 34 of the patients were <60 years old (39.1%) while 53 of the

Table 1. Patient demographic data, tumor locations and histopathological characteristics

Characteristics	*n (%)*
Age, years	
Median (IQR)	63 (58-70)
Gender	
Female	36 (41.4)
Male	51 (58.6)
ECOG* performance status	
0-1	77 (88.5)
≥2	10 (11.5)
Histopathology	
Adenocancer	73 (83.9)
Mucinous	14 (16.1)
Tumor location	
Rectum	16 (18.4)
Colon	71 (81.6)
Tumor site	
Right	28 (32.2)
Left	59 (67.8)
Mutations	
ras	41 (47.1)
k-ras	39 (44.8)
n-ras	3 (3.4)
Unknown	9 (10.3)
CEA** ng/ml	
Median (IQR)	9.8

ECOG: Eastern Cooperative Oncology Group; CEA: carcinoembryonic antigen

patients were >60 years old (60.9%). 77 of the patients had an ECOG performance score 0-1 (88.5%) and 10 >2 (11.5%) at the time of diagnosis. Tumor was located on the right side of the colon in 28 patients (32.2%), on the left side of the colon in 43 patients (49.4%), and in the rectum in 16 patients (18.4%). 41 of the patients were with RAS-mutant (47.1%), 39 were K-RAS mutant (44.8%) and 3 of them were n-ras mutant (3.4%). The median CEA levels was 9.8 (3.3-71.4) ng/ml at the time of diagnosis (Table 1).

We found that 69 patients had liver metastasis (79.3%), 20 patients had lung metastasis (22.9%), 7 patients had peritoneal carcinomatosis (8%) and 2 patients had brain metastasis (2.3%). It was seen that 49 of the patients had 2 lines (56.3%), 22 had 3 lines (25.3%), 12 had 4 lines (13.8%) and 4 had 5 lines (4.6%) of chemotherapy during their treatment. The median line of chemotherapy patients received was 2 (least 2, maximum 5).

Survival analysis

Mean PPS was 8 weeks for the patients below 60 years of age and 10.8 weeks for the patients ≥60 years of age; nevertheless, the difference was not statistically significant (p=0.10). The mean PPS for women was 9.8 weeks and the mean PPS for men was 10 weeks which means gender did not have a statistically significant role on PPS (p=0.24). The patients were divided into two groups as "ECOG score 0-1" and "ECOG score 2-4" according to ECOG performance status at the time of diagnosis. The PPS of the "ECOG score 0-1" group was 10.8 weeks while the PPS of the "ECOG score 2-4" was 3 weeks and this difference is statistically significant (p=0.03) (Table 2). PPS of the patients with right-sided colon tumor was 11.8 weeks whereas PPS of the patients with left-sided colon tumor was 9.2 weeks (p=0.64). PPS of RAS mutant patients was 11.4 weeks and PPS of the patients with RAS-wild type cancer was 9.4 weeks (p=0.72). PPS was 14.4 weeks in patients with CEA levels ≤ to 5 ng/ml at the time of diagnosis while PPS of the patients with CEA levels above 5 ng/ml was 6.7 weeks. Low CEA levels at the time of diagnosis were shown to have a positive effect on PPS (p=0.005). In addition, the OS of the patients with CEA levels ≤ to 5 ng/ml was 26.4 months whereas the OS of the patients with CEA level above 5 ng/ml was 19.1 months (p=0.004). It was found that PPS of the patients with liver metastasis was 9.2 weeks while PPS of the patients without liver metastasis was 28.5 weeks. Liver metastasis was found to be associated with shorter PPS (p=0.003). Nonetheless, post-metastasis overall survival (PMOS) of the patients with liver metastasis was 19.7 months compared with the PMOS of the patients without liver metastasis (29.8 months, p=0.05). Liver metastasis was found to be related to shorter PMOS. The PPS of the patients with controlled disease after first-line chemotherapy was 13.7 weeks while PPS of the patients with advanced disease after first line chemotherapy was 8 weeks. It was determined that controlled disease after first-line chemotherapy associated with longer PPS (p<0.001). PPS of the patients with controlled disease after second-line chemotherapy was 13.7 weeks whereas PPS of the patients with advanced disease after second-line

Table 2. Factors affecting post progression survival time

	Univariate analysis		*Multivariate analysis*	
	HR (95% CI)	*p value*	*HR (95% CI)*	*p value*
Age,years ≥60	0.69 (0.44-1.08)	0.10	0.40 (0.22-0.72)	0.002
Gender, Male	0.77 (0.49-1.20)	0.25	0.91 (0.53-1.54)	0.73
ECOG-2 and above	2.05 (1.02-4.14)	0.04	2.98 (1.21-7.33)	0.01
Tumor location site				
Right	0.98 (0.56-1.43)	0.65		
Liver metastasis				
(+)	1.77 (1.02-3.11)	0.04	1.37 (0.69-2.72)	0.36
Lung metastasis				
(+)	0.74 (0.44-1.24)	0.26		
ras mutation	0.92 (0.59-1.43)	0.72		
ras mutant				
CEA High (>5 ng/mL)	1.98 (1.21-3.24)	0.006	2.46 (1.43-4.25)	0.001
Disease control status after 1st line therapy				
(+)	0.39 (0.23-0.66)	<0.001	0.51 (0.27-0.96)	0.03

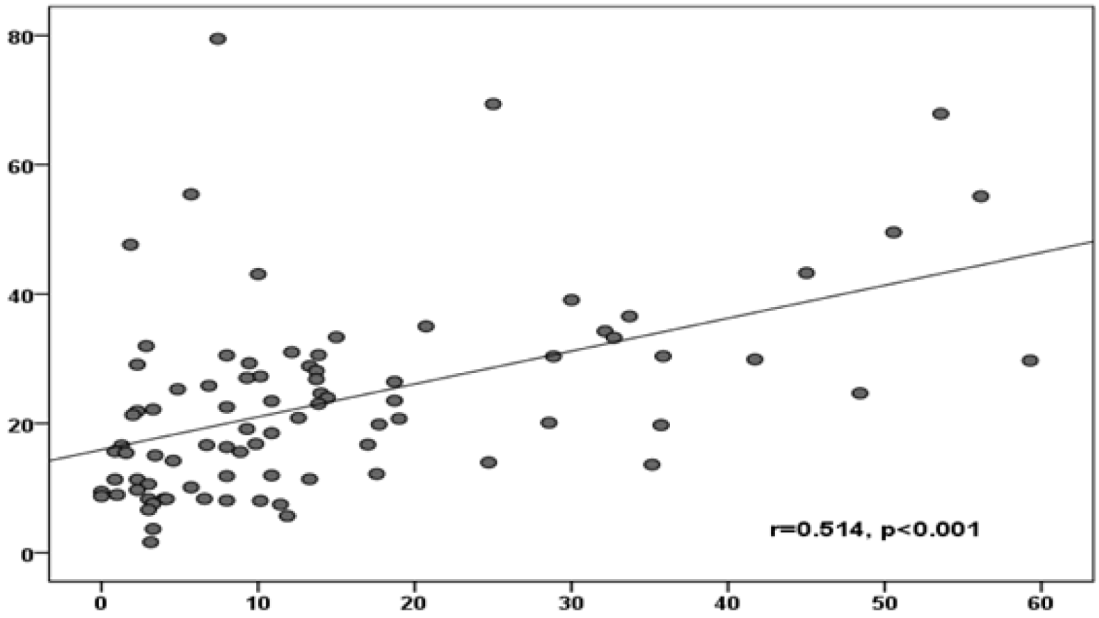

Figure 1. Graphic of correlation between post progression survival and overall survival.

chemotherapy was 8.8 weeks (p=0.44). Multivariate analyses, showed that the ECOG performance status score of 0-1, CEA levels ≤ to 5ng/ml, and controlled disease after first-line chemotherapy were associated with longer PPS (Table 2).

OS time was highly correlated with post progression survival time (r=0.514 p<0.001). Median OS was 21.3 months (confidence interval (CI): 95%, min-max: 18.1-24.6 months). Median PPS time was 10 weeks (CI: 95% min-max: 8.1-11.8) (Figure 1).

Discussion

In this study, we aimed to search the contribution of PPS to OS by presenting the factors related to patient and tumor which affect PPS in patients with metastatic colorectal cancer. According to the literature it is apparent that there are very few studies investigating PPS separately. Thus, our study is one of the leading studies about PPS in patients with metastatic colorectal cancer. As a result of this study, a strong correlation was found between PPS and OS.

Although colorectal cancer is more frequently seen in men, no significant difference between males and females was found in terms of prognosis in studies [15]. In line with this, we also found no PPS difference among genders. Colorectal cancer prevalence increases with age. In a study in which Fietkau et al. analyzed 6016 patients, it was shown that colon cancer prevalence increases with advanced age while no significant relationship could be demonstrated with survival rates [16]. In a single-center study, Kucukoner et al revealed that OS in patients ≤ 60 years is longer than the ones above the age of 60 [17]. In our study, although OS dis not change with age, PPS was significantly associated with age in multivariate analyses. We think that this is because the older patients were withdrawn from chemotherapy and followed up with palliative care in early phases since physicians worry more about chemotherapy toxicity in these patients. Determination of stable OS but longer PPS in these patients lets us think that this approach is correct. In a study in which patients with gastric cancer were evaluated in terms of PPS, Turkmen et al showed that higher ECOG performance status is related to longer PPS [18]. This result is in line with our study. In a meta-analysis in which location-based clinical studies were analyzed, the survival of the patients with right-sided colon tumor was shorter [19]. No significant association was shown between PPS and tumor location in our study and this can be explained by the small patient population of our study. The liver is the most common site of metastasis and recurrence during the clinical course of colorectal cancers [20]. PPS of the patients with liver metastasis was numerically shorter but this result was not statistically significant. We can speculate that the small population of patients without liver metastasis could affect this result. In a study by Harrison et al it was revealed that high levels of CEA are a poor prognostic factor for colon cancer and affect survival [21]. In line with this, CEA levels below 5 ng/ml were found as an independent risk factor for both PPS and OS in

our study. These findings show that patients with CEA-expressing tumors have shorter PPS also in the palliative stage. It is well known that establishing tumor regression or showing better treatment response with first-line chemotherapy in the early phase prolong PPS and OS [22] and in the present study we demonstrated that tumor control with first-line therapy prolongs the survival of the patients even in the palliative phase.

The limitations of this study comprise its retrospective nature and the small patient population. Long follow-up time and complete extraction of patient parameters from the files are positive sides of the study.

Results of univariate and multivariate analyses have shown that the ECOG score of 0-1, CEA levels below 5 ng/ml, and controlled disease after first-line chemotherapy are independent factors related to long PPS. Moreover, liver metastasis, CEA levels above 5 ng/ml, and advanced disease after second-line chemotherapy were found as independent factors related to short OS.

Informed consent

Written informed consent form was obtained from all subjects (patients) in this study.

Conflict of interests

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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