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Original Article

The relationship of preoperative and postoperative serum CEA and CA 19-9 levels with tumor localization, stage and overall survival in patients with colorectal cancer

Fatih Inci, Fatih Karatas

Department of Medical Oncology, Faculty of Medicine, Karabuk University, Karabuk, Turkey

Abstract

Aim: To evaluate the prognostic value of pre/postoperative serum levels of Carcinoembryonic antigen (CEA), Carbohydrate antigen 19-9 (CA 19-9), and their relationship with primary localization and stage of colorectal cancer (CRC) patients.

Materials and Methods: 255 patients who underwent curative or palliative surgery with the diagnosis of CRC between 2015 and 2020 were included in the study. The patients were divided into groups as right colon tumor and left colon tumor based on the region of the primary tumor. Baseline data on age, sex, location of primary tumor, disease stage, histological differentiation, BRAF and RAS mutation situations and serum CEA and CA 19-9 levels were recorded before and after surgery. Individuals were followed for at least sixty months or until they died. Overall survival (OS) and Disease Free Survival (DFS) rates were estimated using the Kaplan–Meier method.

Results: 103 patients had right sided (41.4%) and 152 patients (59.6%) had left sided CRC. Most of the patients were in the early stage (71%). DFS and OS patients with left colon tumors were longer than the right. [(DFS, 32.18 (6-60) vs. 34.25 (6-60) months, p=0.332) and (OS, 41.16 (6-60) vs. 49.05 (11-60) months, p=0.002]. An assessment of the prognosis showed that the OS was significantly worse in the patients with a high CEA level (p=0.001) and in the patients with a high CA 19-9 level (p=0.001). In multivariate analysis, normal serum CA 19-9 levels (p=0.002), RAS wild type tumor (p<0.001), early stage disease (p=0.004) were identified as a good prognostic factors for OS of these patients.

Conclusion: It was determined that left colon tumors had a longer life span than right side. Elevated levels of CEA and CA 19-9 pre and postoperative in CRC have a worst prognosis than those with normal levels of these markers.

Keywords: CA 19-9; CEA; colorectal cancer; tumor localization; stage; survival

INTRODUCTION

Colorectal cancer (CRC) is the second cause of mortality after lung cancer. Two-thirds of CRC develop in the left colon and one-third in the right colon (1). In 40-70% of cases, metastasis is found in regional lymph nodes. Metastases are most common in the liver, peritoneal cavity and lungs (2). Among the treatment options of CRC, surgery, chemotherapy (CT) and radiotherapy (RT) modalities can be modified according to the localization and stage of the primary tumor and can be applied alone or in combination (3). Adjuvant CT decreases recurrence rates when applied in stage III colon cancer and high risk stage II colon cancer without microsatellite instability (4). RT is often used in rectal tumors and is not used except for palliation in colon cancer (5). Palliative surgery, CT and RT options can be applied according to the performance status of the patient, the clinic of the palliation and emergency in advanced stage disease (6).

For early stage CRC, five year survival rate is 90% and 10% for advanced stage patients with distant metastasis (7). In metastatic CRC, curative metastasectomy, age, presence of comorbidity, RAS and BRAF mutation status, and primary tumor localization (in the form of right-left colon) were found to have independent effects on overall survival (OS) (8).

Carcinoembriyonic antigen (CEA) and Carbonhydtrate antigen (CA 19-9) are tumor markers usually expressed by CRC, particularly in advanced cases (9). The preoperative serum CEA and CA 19-9 values are useful for prognostic prediction in CRC (10). However, these markers are not recommended for routine screening. Studies are ongoing to monitor the effectiveness of treatments and to provide information about prognosis (11). CEA is a complex glycoprotein that plays a role as an intercellular adhesion molecule. The carbohydrate determinant of CA 19-9 plays a role in the progression of the tumor. Several authors

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Corresponding Author: Fatih Inci, Department of Medical Oncology, Faculty of Medicine, Karabuk University, Karabuk, Turkey
E-mail: fatihinci65@hotmail.com

propose tumor markers as prognostic factors in different tumors (12). The significance and utility of monitoring the serum CEA and CA 19-9 levels to detect and exclude a recurrence of CRC after potentially curative surgery have been reported in previous studies. However, both tumor markers do not necessarily increase in all cases; sometimes only one of the two tumor markers increases (13).

Tumor localization is important in the pathogenesis of CRC. This distinction between right-sided and left-sided colon is based on their embryological origins (14). Right-sided CRC tumors involve the intestinal segment up to a distal one-third of the transverse colon. The left colon tumor includes the portion of the intestine up to the anus (15).

Mutations of KRAS are seen 35-45% of CRC (16). KRAS mutational status is predictive factor for anti- epidermal growth factor receptor (EGFR) therapy (17). CRC mortality decreased with the addition of anti-VEGF and anti-EGFR antibodies to CT (18). Anti-EGFR therapies improved the OS in patients with left-sided RAS wild (and also BRAF wild) type tumors but not in wild type RCRC (19). The bevacizumab and CT decreased the mortality in both right side and left side tumors. The cetuximab and chemotherapy was effective only in left side tumors (20). Mutant BRAF in CRC is associated with worse OS (21). While RCRC are frequently togetherness with BRAF mutation and high microsatellite instability (22), p53 and KRAS mutations are often seen in left sided tumors (23).

In this study, we aimed to demonstrate the prognostic value of CEA, CA 19-9 pre/postoperative serum levels and their relationship with the primary localization and stage of CRC patients.

MATERIALS and METHODS

Two hundred and fifty five patients who underwent curative or palliative surgery with the diagnosis of CRC between 2015 and 2020 were included in the study. Baseline data on age, sex, location of primary tumor, disease stage, histological differentiation, BRAF and RAS mutation situations and pre/postoperative CEA and CA 19-9 levels were recorded. Patients were divided in two groups as RCRC and LCRC. Right colon; cecum, ascending colon and hepatic flexure, the right half of the transverse colon, left colon; defined by including the left half of the transverse colon, splenic flexure, descending colon, sigmoid colon and rectum.

DFS was determined as the time from curative surgery to recurrence, and OS as the time from diagnosis to death or the last follow-up date. In our laboratory, the normal ranges of markers are 0-5 ng / mL for CEA and 0-37 U / mL for CA 19-9 and are measured by the enzyme-linked immunosorbent assay (ELISA) method. The upper limit of Ca 19-9 can be measured as 700 U / mL and the upper limit of CEA as 100 ng / mL. When the values exceed these limits, the measurement is repeated automatically by the device dilution method. Individuals were followed for at least sixty months or until they died. The relationship with correlations between the preoperative CEA/CA 19-9 and the clinicopathological characteristics was analyzed using the chi-square test. All statistical analyses were performed using SPSS software, version 22. Values with p <0.05 were considered statistically significant.

The required approval was obtained from Local Ethics Committee for this study (decision number: 2020/232, 28.05.2020).

RESULTS

Mean ages of RCRC and LCRC groups were not different (67.1 vs. 66.2 years, p=0.481). Gender, age, T (tumor), N (node) involvement, stage, type of surgery, type of chemotherapy, BRAF status, RAS status, metastasis locations were similar for the right and left colon. DFS and OS was longer in LCRC patients according to RCRC [DFS, 32.18 (6-60) vs. 34.25 (6-60) months, p=0.332 and OS, 41.16 (6-60) vs. 49.05 (11-60) month, p=0.002] (Table 1) (Figure 1). During the median 28.33 (6-60) months follow-up, 111 patients developed progression and recurrent disease and 78 patients died. In early stages disease, OS was longer than in advanced stages (55.66 vs 22.04 months p <0.001).

Table 1. Demographic and clinical characteristics of the patients

Variables	Right sided (n=103)	Left sided (n=152)	p
Gender			0.835*
Female	42 (41.2)	60 (58.8)	
Male	61 (39.9)	92 (60.1)	
Age (years), median (min-max)	67.1 (42-86)	66.2 (40-90)	0.481**
T stage			0.156*
I	0	0	
II	4 (1.6)	11 (4.3)	
III	66 (25.9)	107 (42)	
IV	33 (12.9)	34 (13.3)	
N stage			0.430*
0	30 (11.8)	52 (20.4)	
I	38 (14.9)	60 (23.5)	
II	30 (11.8)	17 (14.5)	
III	5 (2)	3 (1.2)	
Histopathological grade			0.041*
I	0 (0.0)	9 (3.5)	
II	38 (14.9)	55 (21.6)	
III	65 (25.5)	88 (34.5)	
Surgery Type			0.092*
Curative	70 (27.5)	116 (45.5)	
Palliative	33 (12.9)	36 (14.1)	
BRAF status			0.616*
Unknown	79 (31)	124 (48.6)	
Wild	12 (4.7)	15 (5.9)	
Mutant	12 (4.7)	13 (5.1)	

Stage			0.155*
Early	69 (21.1)	112 (43.9)	
Advanced	34 (13.3)	40 (15.7)	
RAS status			0.582*
Unknown	58 (22.7)	95 (37.3)	
Wild	16 (6.3)	22 (8.6)	
Mutant	29 (11.4)	35 (13.7)	
Chemotherapy type			0.130*
No	14 (5.5)	9 (3.5)	
Neoadjuvant	4 (1.6)	9 (3.5)	
Adjuvant	53 (20.8)	92 (36.1)	
Palliative	32 (12.5)	42 (16.5)	
Chemotherapy Regimen			0.005*
Folfox/Xelox	64 (25.1)	84 (32.9)	
Beva+ Folfox/Folfiri/Xelox	30 (11.8)	29 (11.4)	
Cetux/pani +(Folfox/Folfiri/Xelox)	4 (1.6)	12 (4.7)	
No	5 (2)	27 (10.6)	
Latest Status			0.049*
Died	38 (14.9)	40 (15.7)	
Alive	65 (25.5)	112 (43.9)	
Survival (month)(mean)(min-max)			
DFS	32.18 (6-60)	34.25 (6-60)	0.332**
OS	39.81 (6-60)	46.73 (11-60)	0.002**

p*, Chi-square test; p**, Independent sample t-test; n, Number

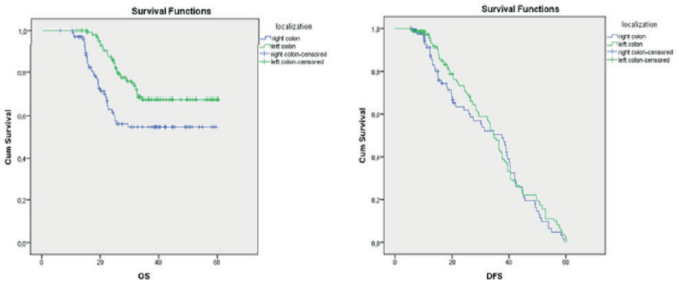

Figure 1. Overall Survival and Disease-Free Survival Curves by Localization

In the whole patient group, the preoperative CA 19-9 value of 59 (23.1%) patients was higher than normal and the median CA 19-9 value was 42.95 (range; 0-1542 U/mL). 98 patients (38.4%) had pre CEA values higher than normal and the median CEA value was 17.32 (Range; 0-380 ng/mL). There were 30 (11.8%) patients with a post CA 19-9 higher than normal and a median of 31.5 (0-1105) U/mL, 50 (19.6%) patients with a post CEA value higher than normal, and a median of 11.24 (0-456) ng/mL. The rate of patients with normal or high pre-post surgery CEA and CA 19-9 values were similar in RCRC and LCRC patients. In early stages, pre CEA, pre CA 19-9, post CEA and post CA 19-9 levels were found significantly lower compared to in advanced stage (p <0.001, all) (Table 2). OS was found longer in group with normal levels of pre CEA, pre CA 19-9, post CEA and post CA 19-9 compared to the group with high levels (p <0.001, all) (Table 3) (Figure 2).

Table 2. Relationship of CEA and CA 19-9 with localization and stage of disease

	Localization			Stage					
	Right n=103(%)	Left n=152(%)	p*	Early (n=181) n, (%)	Advanced (n=74) n, (%)	p**	Early (mean±SD)	Advanced (mean±SD)	p***
Pre CA19-9									
Normal	77 (30.2)	119(46.7)	0.306	160 (62.7)	36 (14.1)	0.001	22.26 ± 3.198	93.54 ± 25.024	0.001
High	26 (10.2)	33 (12.9)		21 (8.2)	38 (14.9)				
Post CA19-9									
Normal	90 (52.9)	135 (35.3)	0.436	171 (67.1)	54 (21.2)	0.001	13.66 ± 1.957	73.92 ± 19.935	0.001
High	13 (5.1)	17 (6.7)		10 (3.9)	20 (7.8)				
Pre CEA									
Normal	61 (23.9)	96(37.6)	0.307	132 (51.8)	25 (9.8)	0.001	7.66 ± 2.081	40.95 ± 10.306	0.001
High	42 (16.5)	56(22.0)		49 (19.2)	49 (19.2)				
Post CEA									
Normal	82 (32.2)	123(48.2)	0.459	163 (63.9)	42 (13.5)	0.001	4.38 ± 1.365	28.03 ± 8.771	0.001
High	21 (8.2)	29(11.4)		18 (7.1)	32 (12.5)				

p*, p**, Chi-square test; p***, Independent sample t- test; n, Number

Table 3. Pre-Post Surgery OS data in all groups according to tumor marker levels

Variables	n	Overall survival (95% CI)	p
Pre CA 19-9			0.000
Normal	196	51.454 (48.923-53.984)	
High	59	26.003 (23.186-28.189)	
Post CA 19-9			0.000
Normal	225	48.455 (45.882-51.028)	
High	30	24.134 (20.691-27.578)	
Pre CEA			0.000
Normal	157	52.295 (49.580-55.010)	
High	98	34.656 (30.816-38.495)	
Post CEA			0.000
Normal	205	49.872 (47.271-52.474)	
High	50	29.152 (24.693-33.611)	

Kaplan- Meier test; n, Number; CI, Confidence Interval

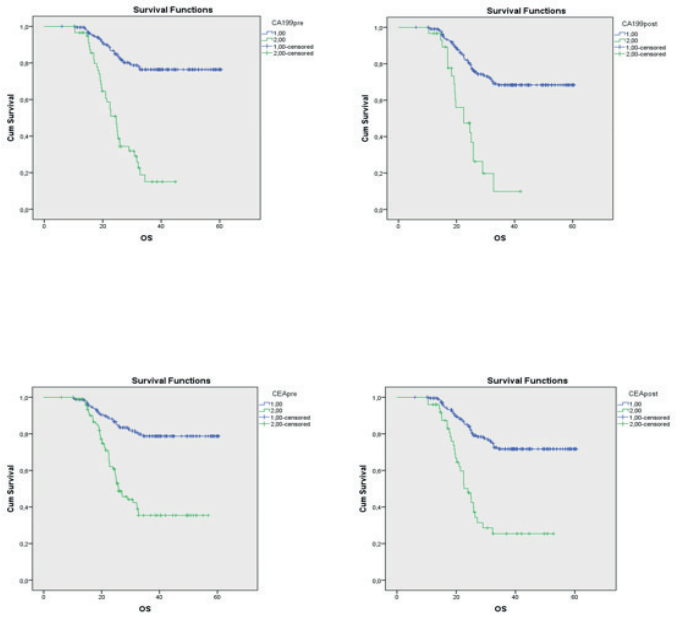

Figure 2. Survival graphics according to pre-post CEA, CA 19-9 levels

Table 4. Predictive factors affecting survival among tumor characteristics

Variables	OR	%95 CI	p
Stage (early)	4.225	1.581-11.287	0.004
RAS (wild)	23.224	7.061-76.380	0.000
Pre CA 19-9 (normal)	5.428	1.837-16.036	0.002

p value, Logistic regression test; OR, Odds Ratio; CI, Confidence Interval

In logistic regression analysis; stage (early) (OR, 4.225; 95% CI: 1.581-11.287, p=0.004), RAS (wild) status (OR, 23.224; 95% CI: 7.061-76.380, p <0.001), Pre CA 19-9 (normal level) (OR, 5.428; 95% CI: 1.837-16.036, p=0.002) variables were found to be predictive factors for OS (Table 4). A statistically significant decrease was observed in CEA and CA 19-9 values with surgery in all groups (p=0.006, p=0.001, respectively) (Table 5).

Table 5. Change in CEA and CA 19-9 with surgery in all groups

Variables	Pre (mean±SD)	Post (mean±SD)	Mean difference	%95 CI	p
Ca19-9	42.9 ± 7.8	31.1 ± 6.1	11.8	4.6-18.9	0.001
CEA	17.3 ± 3.4	11.2 ± 2.7	6.1	1.7-10.4	0.006

p value, paired samples test; SD, Standart Deviation; CI, Confidence Interval

When the effects of pre/postoperative normal and high CEA and Ca 19-9 levels on OS for the right and left colon were examined, it was observed that survival was longer in left colon tumors regardless of the marker level. For DFS, this difference was only seen in favor of the left colon at pre/postoperative normal CA 19-9 levels (p=0.010, p=0.004, respectively) (Table 6).

Table 6. Relationship of CEA and CA 19-9 with localization and stage of disease

	Side	OS	p	DFS	p		OS	p	DFS	p
Normal pre-op Ca19-9	right	46.69	0.010	33.34	0.435	**Normal post-op Ca19-9**	43.03	0.002	32.81	0.349
	left	53.87		34.93			51.41		34.97	
High pre-op Ca19-9	right	21.45	0.004	22.41	0.298	**High post-op Ca19-9**	23.15	0.621	23.26	0.887
	left	28.90		28.20			24.09		20.64	
Normal pre-op CEA	right	47.40	0.018	33.66	0.570	**Normal post-op CEA**	44.97	0.007	32.96	0.450
	left	54.72		35.20			52.42		34.52	
High pre-op CEA	right	30.60	0.027	28.81	0.295	**High post-op CEA**	22.95	0.027	24.92	0.249
	left	37.03		32.03			32.27		31.79	

p value, Kaplan- Meier test

DISCUSSION

In our study, it was found that pre CEA, pre CA 19-9, post CEA and post CA 19-9 levels were statistically significantly lower in early stage disease compared to advanced stage disease (p=0.001, all) (Table 2). Elevated CEA and CA19-9 in CRC have a poorer prognosis than those with normal (24). In our study, it was found that pre CEA, pre CA 19-9, post CEA and post CA 19-9 levels had statistically significantly longer OS durations in the group with normal levels compared to the groups with high levels (p <0.001) (Table 3). In a study the DFS and OS were worse with both a high CEA level and high CA 19-9 level. The combination of this marker levels were useful for relapse after curative surgery for stage II CRC (13). Another study found that the elevated CEA and CA 19-9 levels always represent heavy tumor load which can partly explain the relationship with pathological changes. Patients with elevated CA 19-9 had significantly worse OS and DFS. In our study, a statistically significant decrease was observed in CEA and CA 19-9 values with surgery in all groups (p=0.006, p <0.001) (Table 5). Significant OS difference was found in patients with tumor marker reduction after surgery (p <0.001) (Table 5) (Figure 2). Several studies reported that the preoperative CEA and CA 19-9 levels was useful for predicting the prognosis after surgery (12). The data from our study indicate that the variable preoperative CA 19-9 (normal level) (OR, 5.428; 95% CI: 1.837-16.036, p=0.002) is the significant prognostic indicator of patients with metastatic CRC. In a study, patients whose initial CA 19-9 level was higher than 37 U/ml had a 4.32-fold greater risk of death due to the cancer (95% CI: 1.72-10.84) (p <0.001) than patients with lower values. Another study show that CA 19-9 is an independent prognostic factor of survival in CRC (25). A few articles have reported that patients with metastatic CRC who have normal (≤37 U/mL) serum CA 19-9 levels survived significantly longer than those with higher serum CA 19-9 levels (26). In the present study, when right and left colon tumors were divided into normal and high levels according to pre-postoperative CA 19-9 and CEA levels, a statistically significant long survival difference was found in favor of the left colon in all subgroups for OS. For DFS, this difference was only seen in favor of the left colon at pre/postoperative normal CA 19-9 levels. The effects of pre/postoperative levels of tumor markers on survival have been examined in the literature, but the difference in survival of these markers for the right colon and left colon has not been investigated in studies. Several researchers have suggested that perioperative serum CEA changes in the preoperative and early postoperative periods are predictive of recurrence and prognosis in patients with colorectal cancer (27). Qin et al. reported in their study that preoperative CA 19-9 levels were higher in right colon tumors and survival was lower in right colon tumors (28). Several studies suggested that CA 19-9 level was prognostic indicators in advanced colorectal carcinoma. According a study high preoperative serum levels of CA 19-9 may useful marker in patients with node negative CRC at high risk for relapse after surgery (12).

Studies have shown the importance of tumor location in survival (29). In a study, it was revealed that the primary tumor on the right side in metastatic CRC is a factor that reduces OS independent of all other possible negative prognostic factors (30). According to a meta-analysis that pooled studies based on localization on metastatic CRC, OS durations of patients with right-sided metastatic CRC were found to be significantly shorter than the left-sided. OS [HR=2.03 right (95% CI: 1.69-2.42) and 1.38 left (1.17-1.63)], PS [HR=1.59 right (1.34-1.88) and 1.25 left (1.06-1.47)]. In our study, we obtained results consistent with the literature. DFS and OS of LCRC patients were longer than RCRC patients [(DFS, 32.18 (6-60) vs. 34.25 (6-60) months, p=0.332) and (OS, 41.16 (6-60) vs. 49.05 (11-60) months, p=0.002] (Table 1) (Figure1).

In our study, according to logistic regression analysis, RAS (wild) status (OR, 23.224) was seen to be one of the independent predictive factors for OS. Adding anti EGFR therapy to chemotherapy was more effective than adding anti VEGF in left sided wild type tumors (HR=0.71; 95% CI: 0.58-0.85; p=0.0003) (7). KRAS mutational status is a predictive factor for anti-EGFR therapy (17).

In present study, disease stage (early) (OR, 4.225; 95% CI: 1.581-11.287, p=0.004) was found to be a predictive factor among the independent variables on OS. Significant difference was seen in OS between early and metastatic stages (55.66 vs 22.04 months p <0.001). In a study for early stage CRC, five year survival rate is 90% and 10% for advanced stage patients with distant metastasis (7).

In our study, KRAS results of 102 (40%) patients could be obtained. Mutations of KRAS are seen 35-45% of CRC (16). Of these, 38 (14.9%) were wild type and 64 (25.1%) were mutant type. In the present study there was no statistically significant difference in OS between the two groups, but numerically, wild type tumor (25.29 vs 22.04 month) was found to have longer OS. Due to the retrospective nature of our study and the limited samples for re-analysis, we could not reach sufficient conclusions about how the RAS mutation status affects survival. RAS mutation has been reported to be associated with aggressive tumor biology and RAS mutation status is an independent predictor of OS (31). When the BRAF mutation status was evaluated, the BRAF result of 52 (20.4%) patients was obtained. 27 patients (10.6%) were wild type, and 25 (9.8%) patients were mutant type. BRAF mutations are seen in 5-15% of CRC (32). No statistically significant OS difference was found between the two groups, but numerically, it was seen that the wild type tumor (29.3 vs 23.7 month) had a longer OS. The fact that there was no statistically significant difference in these two patient groups may have been due to the low number of patients whose data on RAS and BRAF states could be obtained.

CONCLUSION

In conclusion, all survival patterns in right-sided was lower than left-sided. Elevated CEA and CA 19-9 in CRC have a poorer prognosis than those with normal. The predictive information provided by early stage disease, RAS wild type

disease and preoperative normal serum CA 19-9 levels are independent from that obtained by the other factors investigated.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Karabuk University (decision number: 2020/153, 27.02.2020).

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