

Research Article

Prognostic Role of Pre-Treatment Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 in Metastatic Colorectal Cancer

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Abstract

Objectives: Carcinoembryonic Antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are the most commonly used tumor-associated antigens in the colorectal cancer. Several contradictory studies reported that patients with metastatic colorectal cancer (mCRC) with normal serum CEA and CA 19-9 levels survived significantly longer than patients with higher serum CEA and CA19-9 levels.

Methods: 240 patients with mCRC were enrolled. The parameters evaluated were age, gender, tumor location, metastatic organs, resection of the primary tumor, metastasectomy, pretreatment serum concentrations of CEA and CA19-9, first line chemotherapy regimens and overall survival (OS). CEA and CA19-9 were divided into three groups as normal (CEA ≤ 5 ng/mL, CA 19-9 ≤ 35 U/mL) elevated (CEA: 5–50 ng/mL, CA19-9: 35–350 U/mL) and high (CEA > 50 ng/mL, and CA 19-9 > 350 U/mL). Primary study endpoint was overall survival (OS).

Results: Serum CA 19-9 level ($p=0.040$), primary tumor resection ($p<0.001$), metastasectomy ($p=0.042$) and tumor location ($p=0.029$) were independent predictors of survival in multivariate analysis. The survival was 29.5, 21.2 and 15.4 months for the patients with normal, elevated and high CA 19-9 levels.

Conclusion: High pretreatment serum CA19-9 may be a useful predictive factor of survival rather than CEA in patients with stage IV CRC.

Keywords: Carbohydrate antigen (CA) 19-9, carcinoembryonic antigen, metastatic colorectal cancer, survival

Cite This Article: Urvay S, Karagoz H. Prognostic Role of Pre-Treatment Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 in Metastatic Colorectal Cancer. EJMI 2021;5(1):73–80.

Colorectal cancer (CRC), is one of the most common cancer types in the world and^[1] and ranked third in cancer-related mortality.^[2] To estimate the survival results of metastatic colorectal cancer (mCRC) and to develop prognostic markers are crucial for choosing appropriate

preventive and therapeutic regimens. Gold and Freedman first isolated Carcinoembryonic antigen (CEA), a fetal glycoprotein from human CRC tissue in 1965 and usually this antigen is not produced in significant quantity after birth.^[3,4] Although the most common clinical use of serum CEA

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Submitted Date: January 18, 2021 **Accepted Date:** March 22, 2021 **Available Online Date:** April 01, 2021

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concentration is surveillance for CRC recurrence, it still remains unclear whether it can be used as a marker for survival in patients with mCRC.^[5]

Serum CA 19-9 level has been reported as a predictive factor for survival in colorectal cancer patients and studies also have shown that CA 19-9 level is a better prognostic indicator than CEA level. A few articles have stated that mCRC patients with normal serum CA 19-9 levels survived significantly longer than those with higher serum CA 19-9 levels.^[6,7] However, the results of these reports are controversial and do not contain definite conclusions.

In this retrospective study, we aimed to analyze the relationship between pretreatment serum levels of CEA and CA 19-9 and survival in mCRC patients.

Methods

240 mCRC patients who received chemotherapy from medical oncology department of Acibadem Kayseri Hospital between January 2010 and June 2018 were included in this study. The clinical and pathological features of the patients were examined retrospectively. The patient data were as follows: Age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking status, tumor location site, metastatic organs, resection of the primary tumor, metastasectomy, pretreatment serum concentrations of CEA and CA19-9, first line chemotherapy regimens, and OS. The right-sided colon cancer (RCC) included the patients whose cancer localization was in cecum, ascending colon, and proximal two-thirds of the transversum and left-sided colon cancer (LCC) included the patients with cancer localization in distal one-third of the transversum, descending colon, sigmoid colon and rectum. We categorized the patients into 3 groups as normal, elevated and high according to pretreatment serum concentrations of CEA and CA 19-9. The cutoff values for normal, elevated and high CEA were as follows ≤ 5 ng/mL, 5–50 ng/mL, and >50 ng/mL and the cutoff values for normal, elevated and high CA 19-9 were as follows, respectively: ≤ 35 U/mL, 35–350 U/mL, and >350 U/mL. Non-mCRC causes that cause CA 19-9 or CEA elevation (e.g cirrhosis, cholangitis, hepatitis, pancreatitis) were excluded from study. OS was defined as the interval from the date of metastatic diagnosis to the date of death or last follow-up. M1a group consisted the patients with only liver metastasis, M1b consisted the patients with any organ metastasis among with liver metastasis and M1c consisted the patients with peritoneum metastasis.

Statistical Analysis

The Statistical Package for the Social Sciences 22.0 (SPSS22.0) statistical software were used for all statistical

analyses. OS was calculated via the Kaplan-Meier method, and log-rank tests were used for comparison. The Cox regression model was used to determine the impact of selected factors on OS. A Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals for both univariate and multivariate analyses. P values <0.05 were considered statistically significant.

Results

The median age of the 240 patients was 61.5 (27-86). 98 (40.8%) of the patients were females and 142 (59.2%) were males. 55(22.9%) were smokers, 115 (47.9%) were non-smokers and 70 (29.2) ex-smokers. 188 (78.4) of the patients had ECOG PS 0-1 and 52 (21.7) patients had ECOG PS 2.

The number of RCC and LCC patients was 51 (21.3%) and 189 (78.8%), respectively. Primary tumor resection was performed in 180 patients (75%), while 24 patients (10%) underwent metastasectomy. 78 (32.5%) of the patients were in group M1a, 123 (51.2%) were in group M1b and 39 (16.3%) were in group M1c. 143 patients (59.6%) received Folfiri/Folfox/xelox+ Bevacizumab, 52 patients (21.7%) received Folfiri/Folfox/xelox + Cetuximab/Panitumumab and 45 patients (18.8%) received Folfiri/Folfox/xelox regimen (Table 1).

The number of patients with normal, elevated and high pretreatment serum CEA concentrations was 106 (44.2%), 88 (36.7%) and 46 (19.2%) and the number of patients with normal, elevated and high pretreatment serum CA19-9 concentrations was 155 (64.6%), 50 (20.8%) and 35 (14.6%), respectively. In the univariate analyses for overall survival; resection of the primary tumor, metastasectomy, serum CEA and CA19-9 levels were found to predict survival ($p<0.001$, 0.001, 0.001, <0.001 , respectively) (Table 2). The median survival for all patients was 22.2 (2.3-103.5) months. The median survival was 29.5, 24.2 and 17.6 months for the patients with normal, elevated and high CEA levels; while it was 29.5, 21.2 and 15.4 months for the patients with normal, elevated and high CA 19-9 levels. First line chemotherapy regimens did not have any statistically significant effect on OS both in univariate and multivariate analyses. The location of the primary tumor (RCC or LCC) did not make any difference on OS in the univariate analyses; but in the multivariate analyses, LCC patients showed a significant superiority of prognosis compared to the RCC patients ($p=0.029$; HR: 0.675). Similarly, resection of the primary tumor, resection of metastatic tumor and CA 19-9 were found to be a significant predictor of survival also in multivariate analyses ($p<0.001$, $p=0.042$; respectively) (Table 3). In multivariate analyses, the survival difference between those with elevated CA 19-9 levels and normal ones was statistically significant, while it did not show any statistically sig-

Table 1. Characteristics of the patients

Parameters	n (%)
Age (years)	61.50 (27-86)
Gender	
Male	142 (59.2)
Female	98 (40.8)
ECOG PS	
0-1	188 (78.4)
2	52 (21.7)
Smoking status	
Smoker	55 (22.9)
Non-smoker	115 (47.9)
Ex-smoker	70 (29.2)
Primary tumor location	
Right	51 (21.3)
Left	189 (78.8)
Metastasis stage	
M1a	78 (32.5)
M1b	123 (51.2)
M1c	39 (16.3)
Resection of the primary tumor	
Yes	180 (75)
No	60 (25)
Metastasectomy	
Yes	24 (10)
No	216 (90)
Pretreatment serum CEA level	
≤5 ng/ml	106 (44.2)
5-50 ng/ml	88 (36.7)
>50 ng/ml	46 (19.2)
Pretreatment serum CA 19-9 level	
≤35 U/ml	155 (64.6)
35-350 U/ml	50 (20.8)
>350 U/ml	35 (14.6)
First line chemotherapy regimen	
Foliri/Folfox/xelox+Bevacizumab	143 (59.6)
Foliri/Folfox/xelox+Cetuximab/Panitumumab	52 (21.7)
Foliri/Folfox/xelox	45 (18.8)

ECOG PS: Eastern Cooperative Group Performance score, M1a: only liver metastasis, M1b: any organ metastasis with liver metastasis, M1c: peritoneal metastasis.

nificant difference between the patients with elevated and high CA 19-9 levels (even it was clinically significant, 21.2 vs 15.4 months). We thought that the low number of cases in CA 19-9 high patient group might be effective in this result. After that, we analyzed the patients again by dividing into two groups as normal and high (cut off value was 5 and 35 for CEA and CA 19-9, respectively). In this analysis, it was seen that high levels of serum CA 19-9 affected prognosis as an independent factor ($p < 0.001$), but this did not apply to high CEA levels.

Discussion

With the recent advances in systemic treatments, unresectable colon cancer has made remarkable progress. Identifying of poor prognostic factors is important to determine the most correct approach to the patient. The presence of <3 tumors, presence of extrahepatic metastasis (especially peritoneal metastasis), tumor location^[6-10] and genetic variants of RAS, BRAF and UGT1A1^[11-13] are determined as factors affecting prognosis. Also, circulating tumor cells (CTCs) can be regarded as a prognostic factor^[14,15], but its complex protocol and high cost make it impossible to use it in routine practice. Serum CEA and CA 19-9 levels are the most general, inexpensive and easy-to-access prognostic markers used in colorectal cancer.

A correlation between CEA levels and prognosis was determined in CRC.^[16-18] Many studies showed association of preoperative high CEA levels (>5 ng/mL) with disease-related mortality and a higher recurrence rate.^[17-21] CEA decrease in the postoperative period was found to be a prognostic indicator for to predict the OS^[22,23] and disease-free survival.^[24] This also applies to patients undergoing liver surgery with mCRC.^[25] The correlation of CEA level with the presence of circulating cancer cells was also shown.^[21] Despite many current studies, it is still unclear whether serum CEA levels can be used as a marker to predict response to chemotherapy or radiotherapy. Although, there are studies which show the association of an elevated pre-treatment CEA (>9 ng/mL) with a poor response to long-course chemoradiotherapy compared to CEA <3 ng/mL^[26], there are also studies showing no correlation.^[27] Perez et al. showed that the decreases in CEA values after neoadjuvant chemoradiotherapy had a prognostic significance in rectal cancer patients and also CEA ≤5 ng/mL was also correlated with increased complete clinical and pathological response and better overall and disease-free survivals.^[28]

CA 19-9 is also another tumor marker widely used in CRC. Takakura et al. stated that serum CA 19-9 elevation in the preoperative period in colorectal cancer is an important determinant of both peritoneal dissemination and poor survival.^[29] Katoh et al. showed that a high value of preoperative CA 19-9 was one of the most robust univariate predictors of poor prognosis in stage IV CRC with noncurable resection.^[30] Hidaka et al. reported that a serum CA 19-9 concentration >370 U/mL was a significant independent prognostic factor for OS in stage IV elderly CRC patients, the median OS was quite poor at 8.5 months for these patients.^[7] Also a meta-analysis involving 6434 patients from seventeen studies with CRC revealed that pre-treatment high serum CA 19-9 levels were significant predictors of poor OS.^[31] In some studies, preoperative serum CA 19-9

Table 2. Univariate analysis for overall survival

Variables	Months-median Estimate (SE)	95% CI	p
Age			
≤70	23.819 (1.886)	20.122-27.517	0.579
>70	23.655 (3.777)	20.015-25.413	
Gender			
Male	21.158 (1.325)	18.561-23.755	0.108
Female	27.762 (3.174)	21.541-33.982	
ECOG PS			
0-1	24.509 (2.001)	20.587-28.432	0.099
2	21.158 (2.055)	17.131-25.186	
Smoking status			
Smoker	20.764 (3.191)	14.510-27.018	0.232
Non-smoker	25.853 (2.480)	20.963-30.684	
Ex-smoker	21.421 (1.408)	18.661-24.181	
Primary tumor location			
Right	18.628 (2.264)	14.191-23.066	0.191
Left	24.641 (1.910)	20.897-28.384	
Metastasis stage			
M1a	27.828 (3.533)	20.902-34.753	0.155
M1b	24.181 (1.648)	20.952-27.410	
M1c	17.1 (1.313)	14.577-19.723	
Resection of the primay tumor			
Yes	27.828 (2.425)	23.074-32.581	<0.001
No	14.259 (1.564)	11.194-17.324	
Metastasectomy			
Yes	56.016 (14.006)	28.566-83.467	0.001
No	21.454 (1.580)	18.356-24.551	
First line chemotherapy regimen			
Foliri/Folfox/xelox+Bevacizumab	21.454 (1.683)	18.156-24.752	0.095
Foliri/Folfox/xelox+anti EGFR	18.858 (2.259)	14.431-23.286	
Foliri/Folfox/xelox	35.220 (1.247)	32.776-37.664	
Pretreatment serum CEA level			
≤5 ng/ml	29.536 (4.645)	20.432-38.640	0.001
5-50 ng/ml	24.279 (1.922)	20.512-28.046	
>50 ng/ml	17.676 (1.947)	13.859-21.492	
Pretreatment serum CA19-9 level			
≤35 U/ml	29.536 (3.581)	22.516-36.556	<0.001
35-350 U/ml	21.290 (2.420)	16.546-26.033	
>350 U/ml	15.474 (2.157)	11.247-19.701	

ECOG PS: Eastern Cooperative Group Performance score, M1a: only liver metastasis, M1b: any organ metastasis with liver metastasis, M1c: peritoneal metastasis.

concentration has been shown to be a reliable marker of tumor recurrence and prognosis in stage IV CRC patients undergoing curative resection.^[32,33] The relationship between high levels of CA 19-9 after chemotherapy and poor prognosis has also been shown.^[34] CA 19-9 values, which were examined in the 3rd month after curative resection in stage IV CRC patients, had a strong prognostic significance for recurrence.^[35] Stojkovic Lalosevic et al. showed that CEA and CA 19-9 can be used as diagnostic

factors to suggest metastatic disease in CRC.^[36] Serum CA 19-9 levels of ≥ 100 U/ml and CEA levels of ≥ 100 ng/ml before chemotherapy in patients with colon cancer and unresectable liver metastasis were found as poor prognostic factors in the study of Mitsuyama et al.^[37] Although many studies have shown the importance of CA 19-9 in mCRC prognosis, CEA is recommended to be used in clinical guidelines but not CA 19-9.^[38,39] In the present study, we have showed that serum CEA and CA 19-9 levels are poor

Table 3. Cox regression analysis for OS in multivariate model

Variables	Beta	p	HR	95% CI for Exp (B) Lower
Gender				
≤70	-0.244	0.208	0.784	0.537
>70				
Gender				
Male	-0.168	0.397	0.845	0.573
Female				
ECOG PS				
0-1	-0.025	0.900	0.975	0.661
2				
Smoking status				
Smoker	0.277	0.211	1.319	0.855
Non-smoker	-0.117	0.577	1.124	0.745
Ex-smoker				
Primary tumor location				
Right	-0.394	0.029	0.675	0.474
Left				
Metastasis stage				
M1a	0.198	0.229	1.219	0.883
M1b	0.261	0.255	1.298	0.828
M1c				
Resection of the primary tumor				
Yes	-0.831	<0.001	0.436	0.311
No				
Metastasectomy				
Yes	-0.577	0.042	0.561	0.322
No				
First line chemotherapy regimen				
Folfiri/Folfox/xelox+Bevacizumab	-0.041	0.831	0.960	0.657
Folfiri/Folfox/xelox+anti EGFR	-0.127	0.527	0.881	0.594
Folfiri/Folfox/xelox				
Pretreatment serum CEA level				
≤5	-0.320	0.242	0.726	0.425
5-50 arası	-0.282	0.275	0.754	0.454
>50				
Pretreatment serum CA 19-9 level				
≤35	-0.611	0.040	0.543	0.303
35-350 arası	-0.054	0.849	0.947	0.543
>350				
Pretreatment serum CEA level				
≤5	0.099	0.560	1.104	0.792
>5				
Pretreatment serum CA 19-9 level				
≤35	0.696	<0.001	0,498	1.432
>35				

ECOG PS: Eastern Cooperative Group Performance score, M1a: only liver metastasis, M1b: any organ metastasis with liver metastasis, M1c: peritoneal metastasis.

prognostic indicators and the survival time decreases as their blood levels increase and CA 19-9 levels were statistically more significant than CEA.

Serum CA 19-9 level, primary tumor resection, metastasectomy and tumor location were found to be significant in multivariate analyses of this study. Many studies

have shown that metastasectomy for colorectal liver and lung metastasis in patients undergoing surgery increases survival and even cure is possible in this population.^[40-43] Although, primary tumor resection in patients with asymptomatic colorectal cancer and unresectable synchronous metastasis not recommended by clinical guidelines, prolonged OS in these patients has been shown in the literature reviews and large population-based studies.^[44-46] Differential biological features have been described for RCC and LCC^[47] and in several retrospective studies and meta-analyses, primary tumor location has been suggested to play a relevant prognostic role with RCC being associated with an inferior outcome.^[48-50] In the current study, we showed increased survival in LCC patients consistent with the literature.

This study had some limitations because of its retrospective nature and single-center design. Also the relatively small number of patients analyzed was another limitation of this study.

Conclusion

High pretreatment serum CA 19-9 level may be a useful predictive factor of survival rather than CEA level in patients with stage IV CRC. Primary tumor resection, metastasectomy and tumor location were the other prognostic factors affecting survival. Randomised and large-scale clinical trials based on serum CA 19-9 levels should be carried out for patients with mCRC.

Disclosures

Ethics Committee Approval: This is a retrospective study and approved by the Acibadem University Ethics Committee (2020-05/17 - 09.04.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Authorship Contributions: Concept – S.U., H.K.; Design – S.U., H.K.; Supervision – S.U., H.K.; Materials – S.U., H.K.; Data collection &/or processing – S.U.; Analysis and/or interpretation – S.U., H.K.; Literature search – S.U.; Writing – S.U., H.K.; Critical review – S.U.

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