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RESEARCH ARTICLE

The Prognostic Value of Preoperative Serum Levels of CEA and CA 19-9 in Patients with Colorectal Cancer

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ABSTRACT

Aim: Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are the most frequently used tumor markers in clinical evaluation of colorectal cancer patients. In this study, we investigated the prognostic significance of CEA and CA 19-9 in colorectal cancer patients without distant metastasis.

Method: We assessed colorectal cancer patients with measured preoperative serum CEA and CA 19-9 levels between 1993 and 2004. Peripheral venous blood samples were taken before surgery. Tumor marker analyses were accomplished with a two-site immuno-radiometric assay. Patients' demographic, clinico-pathological and treatment data were retrieved from the patients files.

Results: A total of 548 patients were included. Mean age was 59.6±12.3 years and 52.5% were male. Serum CEA and CA 19-9 levels were positive (above the cut-off values) in 190 (34.6%) and 97 (17.7%), respectively. In the univariate analyses, CEA and CA 19-9 positive patients showed poorer cancer-specific survival rates than marker negative patients (log-rank x^2=16.935, p<0.001 and log-rank x^2=12.431, p<0.001, respectively). In multivariate Cox analyses, CEA (p=0.003) and CA 19-9 (p=0.001) had independent prognostic significance. When CEA and CA 19-9 were included together in the Cox analysis, CEA (relative risk=1.39, 95% confidence interval (CI)=1.03-1.88, p=0.030) and CA 19-9 (relative risk=1.64, 95% CI=1.15-2.33, p=0.006) maintained their independent prognostic significances.

Conclusion: Preoperative serum CEA and CA 19-9 have prognostic importance independent of clinico-pathological factors in colorectal cancer patients without distant metastasis. These tumor markers can be used in the planning of adjuvant therapy of colorectal cancer patients.

Keywords: CEA, CA 19-9, colorectal carcinoma, survival

Introduction

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are the most frequently used tumor markers in clinical evaluation of colorectal cancer patients. Since both markers have low sensitivity in diagnosis of colorectal cancer, they are not used as diagnostic toll.[1] Although the predominant opinions regarding the prognostic significances of preoperative levels of these markers support that they are beneficial tolls, there are also studies stating that both CEA[2-7] and CA 19-9[6-9] do not have prognostic significance. In some experimental studies, it has been suggested that CEA[10,11] and CA 19-9[12] function as intercellular adhesion molecules and thus they may lead to metastasis. In some clinical reviews[1,13,14] both CEA and CA 19-9 are indicated as intercellular adhesion molecules. It is also stated that CEA induces the release of suppressor lymphokines from healthy human lymphocytes *in vitro*, which may cause immunosuppression in cancer patients.[15] Thus, high preoperative serum levels of CEA and CA 19-9 may be indicators of poor prognosis.

In this study, we investigated the relationship between preoperative serum levels of CEA and CA 19-9 and clinico-pathological features and outcomes, and thus the prognostic significance of CEA and CA 19-9 in colorectal cancer patients without distant metastasis.

Materials and Methods

Patients

The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey,

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İstanbul Training and Research Hospital (approval number: 2840, date: 21.05.2021). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

We retrospectively assessed adult colorectal cancer patients (age >18 years) who underwent curative (R0) resection between January 1993 and December 2004. We collected the serum CEA and CA 19-9 levels of patients measured preoperatively from patient files. Among patients with colorectal cancer, those who received neoadjuvant therapy, patients with synchronous colorectal cancer, and patients with familial adenomatous polyposis coli were excluded. Patient demographic, clinico-pathological (tumor site, tumor size, T-stage, nodal status, histologic grade) and treatment (surgery, adjuvant chemotherapy and radiotherapy) data were retrieved from the patient files.

Patients were categorized into those who had elective or emergency surgery. In histopathological evaluation of the tumors, histologic grade was categorized as low grade (well and moderately differentiated) and high grade (poorly differentiated, undifferentiated, mucinous and signet ring cell). We also recorded whether patients received adjuvant chemotherapy and/or adjuvant radiotherapy.

Patients who died due to postoperative complications were not included in survival analysis. Survival data were obtained from the patient files in the oncology department and from the phone calls with patients or patients' relatives. The endpoint of the study was patient death. Cancer-specific survival (CSS) time was identified as the time interval between surgery and death due to disease recurrence. In patients who developed a secondary malignancy, the date of the diagnosis of second malignancy was considered as the last follow-up date. In patients who died due to a cause other than cancer, the date of death was considered as the last follow-up date.

Tumor Marker Measurements

Peripheral venous blood samples were taken from the patients before surgery, centrifuged and serum samples were stored at -20 °C until analyzed. A commercial kit, IRMA-coat CEA kit (Byke Sangtec Diagnostica GmbH, Dietzenbach, Germany) was used for CEA analysis, which had a recommended cut-off value of 5 ng/mL. Two different kits were used for CA 19-9 measurements: the IRMA-mat CA 19-9 (Byke Sangtec Diagnostica GmbH. Dietzenbach, Germany) with a recommended cut-off value of 37 U/mL and the GI-MA IRMA (EURO/DPC Ltd., Glyn Rhonwy, United Kingdom) with a lower recommended cut-off value of 29 U/mL. All analyses were accomplished with a two-site immuno-radiometric assay.

Statistical Analysis

Chi-square test was used to assess the relationship between tumor marker positivity and clinico-pathological features. Student's t-test was used to compare the mean ages of the patient groups. The Kaplan-Meier method was used to calculate CSS, and the two-sided log-rank test was used for comparison of the survival curves. The relative importance of the prognostic features was investigated using the Cox proportional hazards model. A p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Among 620 patients with colorectal cancer whose data were retrieved, 42 (6.8%) who received neoadjuvant therapy, 16 (2.6%) with synchronous colorectal cancer, and 14 (2.3%) with familial adenomatous polyposis coli were excluded. Thus, a total of 548 patients were eligible for this study. In these 548 the mean age was 59.6±12.3 years (median: 61, range: 19-91) and 52.5% of patients were male. Of the patients, 329 (60%) patients were younger and 219 (40%) were older than 65 years.

Demographic, clinico-pathologic and treatment features of patients are summarized in Table 1. Most of the patients had negative preoperative CEA and CA 19-9 serum levels. Almost all patients underwent elective surgery rather than urgent surgery. We found that the number of patients with tumors located in the colon and rectum were the same. Almost two-thirds of patients had tumors >5 cm in diameter and more than three-quarters had tumor T stage T3-T4. However, the rate of nodal involvement was just below 40%. Most of the tumors were low grade. While most of the patients received adjuvant chemotherapy, fewer patients were irradiated. A 5-fluorouracyl based chemotherapy regimen was used in patients who received adjuvant chemotherapy.

Thirty-seven patients died due to postoperative complications and were not included in survival analysis. Of the patients, 13 developed a secondary malignancy and 73 patients died from a cause other than cancer.

Relationship between Clinico-Pathological Features and CEA and CA 19-9 Positivity

Among the 548 patients, preoperative serum CEA of 190 patients (34.6%) and CA 19-9 levels of 97 patients (17.7%) were positive (above the cut-off values). As seen in Table 2, there was no correlation between CEA or CA 19-9 positivity and gender and age. There was no correlation between CEA positivity and tumor location. Patients who

Table 1. Demographic, clinico-pathologic and treatment characteristics of patients

Variable	Category	n (%)
Age	All	548 (100)
Age group	<65	329 (60)
	≥65	219 (40)
Gender	Male	288 (52.5)
	Female	260 (47.5)
CEA	Positive	190 (34.6)
	Negative	358 (65.3)
Ca 19-9	Positive	97 (17.7)
	Negative	451 (82.2)
Surgery	Elective	525 (95.8)
	Urgent	23 (4.1)
Tumor site	Colon	273 (49.8)
	Rectum	275 (50.2)
Tumor size, cm	≤5	192 (35)
	>5	256 (65)
T-stage	T1-T2	123 (22.4)
	T3-T4	425 (77.5)
Nodal status	Negative	330 (60.2)
	Positive	218 (39.8)
Histologic grade	Low grade	464 (84.7)
	High grade	84 (15.3)
Adjuvant chemotherapy	Yes	388 (70.8)
Adjuvant radiotherapy	Yes	193 (35.2)

CEA: Carcinoembryonic antigen, Ca 19-9: Carbohydrate antigen 19-9

had positive CA 19-9 levels tended to have colon located tumors (p=0.052). The proportions of tumors larger than 5 cm were significantly higher in CEA and CA 19-9 positive patients than tumor-marker negative patients (p<0.001 and p=0.003, respectively). While CEA positive patients had significantly more T3 and T4 tumors than negative patients (p=0.001), the rate of T3-T4 tumors was slightly higher in the CA 19-9 positive group and the difference approached significance (p=0.051). The ratio of lymph node positive patients was significantly higher in CA 19-9 positive patients than negative patients (p=0.001), whereas in the CEA positive patients, the ratio of lymph node positive patients was slightly higher, but the difference was not significant (p=0.084). Patients who had positive CEA and CA 19-9 levels had significantly more high-grade tumors compared to patients who had negative markers (p=0.007 and p=0.018, respectively).

Cancer-Specific Survival in the Patient Groups

Two hundred and three patients died because of colorectal cancer. Mean follow-up period for the surviving patients was 137.3 months. CEA and CA 19-9 positive patients showed poorer CSS rates than marker negative patients (log-rank x^2=16.935, p<0.001 and log-rank x^2=12.431, p<0.001, respectively) (Figure 1, 2). In multivariate Cox analyses, CEA (p=0.003) (Table 3) and CA 19-9 (p=0.001) (Table 4) had independent prognostic significance. When both CEA and CA 19-9 were included in the Cox analysis, both CEA [relative risk=1.39, 95% confidence interval (CI)=1.03-1.88, p=0.030] and CA 19-9 (relative risk=1.64, 95% CI=1.15-2.33, p=0.006) maintained their independent prognostic significances.

Discussion

In this study the preoperative serum CEA and CA19-9 levels of non-metastatic colorectal cancer patients were measured and the prognostic significance of CEA and CA 19-9 positivity in colorectal cancer patients was investigated. We found that 190 (34.6%) patients were CEA positive and 97 (17.7%) patients were CA 19-9 positive. CEA and CA 19-9 positive patients showed poorer CSS rates than marker negative patients. CEA and CA 19-9 had independent prognostic significance.

In some studies, CSS rate has been reported as 25.0-42.3% in non-metastatic colorectal cancer patients.[6,16-19] CA 19-9 positive rates are reported to vary between 13.5-25.1% in some studies.[3,16,17] We found CA 19-9 positive rates compatible with the literature. These low positivity rates confirm that serum CEA and CA 19-9 have no significance in diagnosis of colorectal cancer.

In our study, there was no correlation between CEA positivity and tumor location but CA 19-9 positivity rate was higher in colon tumors compared with rectal tumors. Recent studies stated no correlation between tumor location and CEA[6,18,20-23] or CA 19-9[6,24] positivity. In addition, the number of patients who have tumors >5 cm was more in both the tumor marker positive groups than tumor-marker negative patients. Some studies[21,25,26] reported significantly larger tumor size in CEA positive patients, and only one study[25] found significantly larger tumor size in CA 19-9 patients. On the contrary, some studies found no correlation between tumor size and high CEA[21] or CA 19-9[24] levels.

Some studies have found significantly higher CEA[18,25] and CA 19-9[24] positivity in T3-T4 tumors. There is only one study that reported no correlation between the depth of wall invasion and CA 19-9 positivity.[25] We found that the rate of T3-T4 tumors invading the muscularis propria was

Table 2. The relation between clinicopathological features and serum CEA and CA 19-9

Feature	CEA (-)		CEA (+)		p	CA 19-9 (-)		CA 19-9 (+)		p
	n	%	n	%		n	%	n	%	
Gender	-				**0.456**	-				**0.373**
Female	174	48.6	86	45.3		210	46.6	50	51.5	
Male	184	51.4	104	54.7		241	53.4	47	48.5	
Age, years	-				**0.291**	-				**0.339**
Mean	60.1		58.8			59.5		60.2		
Median	61.0		61.0			61.0		62.0		
Range	19.0-91.0		22.0-85.0			19.0-91.0		22.0-83.0		
Age, years	-				**0.204**	-				**0.460**
<65	208	58.1	121	63.7		274	60.8	55	56.7	
≥65	150	41.9	69	36.3		177	39.4	42	43.3	
Tumor site	-				**0.767**	-				**0.052**
Colon	180	50.3	93	48.9		216	47.9	57	58.8	
Rectum	178	49.7	97	51.1		235	52.1	40	41.2	
Tumor size, cm	-				**<0.001**	-				**0.003**
≤5	150	41.9	42	22.1		171	37.9	21	21.6	
>5	208	58.1	148	77.9		280	62.1	76	78.4	
T-stage	-				**0.001**	-				**0.051**
T1-T2	96	26.8	27	14.2		109	24.2	14	14.4	
T3-T4	262	73.2	163	85.8		342	75.8	83	85.6	
Nodal status	-				**0.084**	-				**0.001**
Negative	225	62.8	105	55.3		286	63.4	44	45.4	
Positive	133	37.2	85	44.7		165	36.6	53	54.6	
Histologic grade	-				**0.007**	-				**0.018**
Low grade	314	87.7	150	78.9		390	86.5	74	76.3	
High grade	44	12.3	40	21.1		61	13.5	23	23.7	

CEA: Carcinoembryonic antigen, Ca 19-9: Carbohydrate antigen 19-9

significantly higher in patients in the CEA positive group and approached significance in those with CA 19-9 positivity compared to those patients in the marker negative groups.

Lymph node positivity was significantly higher in CEA[18,25] and CA 19-9[24,25] positive patients in some studies. In our series, the rate of lymph node positive patients was significantly higher in CA 19-9 positive patients compared with CA 19-9 negative patients and this rate was slightly higher in CEA positive patients, although not significant. We also found that the rate of high histologic grade tumors was significantly higher in CEA and CA 19-9 positive patients compared with marker negative patients. However, many studies found no significant correlation between histologic type and CEA[6,18,21,22,25] or CA 19-9[6,24,25] positivity.

In this study, univariate analysis showed significantly poorer CSS in CEA and CA 19-9 positive patients compared with marker negative patients. In multivariate Cox regression analysis, CEA and CA 19-9 both had prognostic significance, independent of clinico-pathological features, separately and together. Some studies have found no significant correlation between survival of colorectal cancer patients and CEA[5,7] or CA 19-9[6,8,9]. In other studies, although CEA[8,23,25-27] and CA 19-9[25,27] positive patients had significantly poorer survival than marker negative patients in the univariate analysis, in multivariate analysis no independent prognostic significance was found. On the other hand, various studies showed poorer survival in CEA positive patients[9,18,21,22,28] and some other studies showed poorer survival in CA 19-9

Table 3. Cox proportional hazards model analysis of the clinicopathological and treatment features, and CEA

Feature	Relative risk	95% CI	p
Gender			**0.376**
Female	1.00	-	
Male	0.88	0.66-1.16	
Age, years			**0.017**
<65	1.00	-	
≥65	1.45	1.06-1.96	
Tumor site			**0.048**
Colon	1.00	-	
Rectum	1.34	1.01-1.79	
Tumor size, cm			**0.342**
≤5	1.00	-	
>5	0.86	0.62-1.17	
T-stage			**0.002**
T1-T2	1.00	-	
T3-T4	2.06	1.31-3.26	
Nodal status			**<0.001**
Negative	1.00	-	
Positive	2.93	2.19-3.91	
Histologic grade			**0.085**
Low grade	1.00	-	
High grade	1.37	0.95-1.97	
CEA			**0.003**
Negative	1.00	-	
Positive	1.54	1.15-2.05	
Surgery			**0.522**
Elective	1.00	-	
Urgent	0.78	0.36-1.67	
Adjuvant chemotherapy			**0.603**
Yes	1.00	-	
No	1.11	0.75-1.64	

CI: Confidence interval, CEA: Carcinoembryonic antigen

positive patients[19,20,26] compared with marker negative ones, and independent prognostic significance of these markers was maintained in multivariate analysis.

Study Limitations

Our study has some limitations. Since it is a retrospective study there may be some missing data. Some survival data were not available because of the lack of hospital visits.

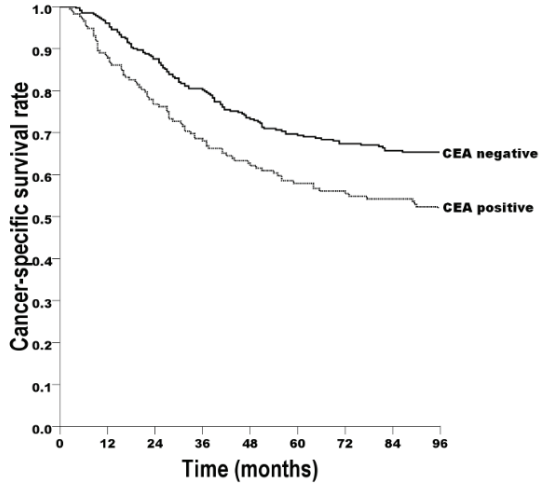

Figure 1. Cancer-specific survival rates of the CEA negative (336 patients) and positive (175 patients) colorectal cancer patients (log-rank x^2=16.935, p<0.001)

Number at risk									
Months	0	12	24	36	48	60	72	84	96
CEA negative	336	316	288	257	230	214	204	196	186
CEA positive	175	152	132	117	106	94	91	86	82
CEA: Carcinoembryonic antigen									

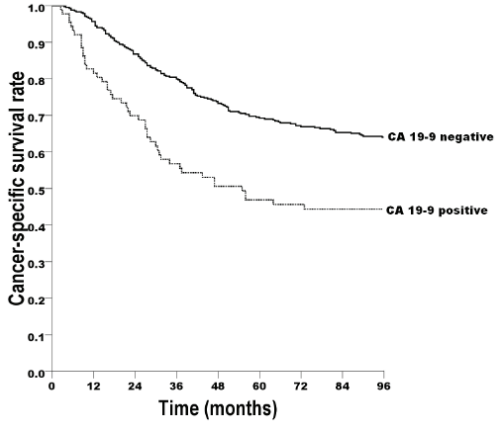

Figure 2. Cancer-specific survival rates of the CA 19-9 negative (421 patients) and positive (90 patients) colorectal cancer patients (log-rank x^2=12.431, p<0.001)

Number at risk									
Months	0	12	24	36	48	60	72	84	96
CA 19-9 negative	421	397	360	328	295	271	259	248	234
CA 19-9 positive	90	71	60	46	41	37	36	34	34
CA 19-9: Carbohydrate antigen 19-9									

Table 4. Cox proportional hazards model analysis of the clinicopathological and treatment features, and CA 19-9

Feature	Relative risk	95% CI	p
Gender			0.462
Female	1.00	-	
Male	0.90	0.68-1.19	
Age, years			0.039
<65	1.00	-	
≥65	1.37	1.01-1.86	
Tumor site			0.012
Colon	1.00	-	
Rectum	1.45	1.08-1.94	
Tumor size, cm			0.364
≤5	1.00	-	
>5	0.86	0.63-1.18	
T-stage			0.001
T1-T2	1.00	-	
T3-T4	2.23	1.41-3.52	
Nodal status			<0.001
Negative	1.00	-	
Positive	2.89	2.16-3.87	
Histologic grade			0.132
Low grade	1.00	-	
High grade	1.32	0.92-1.90	
CA 19-9			0.001
Negative	1.00	-	
Positive	1.82	1.29-2.55	
Surgery			0.617
Elective	1.00	-	
Urgent	0.82	0.38-1.76	
Adjuvant chemotherapy			0.372
Yes	1.00	-	
No	1.20	0.80-1.78	

CI: Confidence interval, Ca 19-9: Carbohydrate antigen 19-9

Conclusion

Preoperative serum CEA and CA 19-9 have prognostic importance, independent of clinico-pathological factors, in colorectal cancer patients with no distant metastasis and who did not receive neoadjuvant therapy. These tumor markers can be used to estimate prognosis and schedule adjuvant therapies for the colorectal cancer patients at high risk.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2840, date: 21.05.2021). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: D.C.T., N.D., Z.C.Ç., Concept: D.C.T., N.D., Design: D.C.T., N.D., Data Collection or Processing: D.C.T., N.D., Z.C.Ç., Analysis or Interpretation: D.C.T., N.D., Z.C.Ç., Literature Search: D.C.T., N.D., Z.C.Ç., Writing: D.C.T., N.D.

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