Curr Oncol, Vol. 21, pp. e1-7; doi: http://dx.doi.org/10.3747/co.21.1711

ORIGINAL ARTICLE

Diagnostic value of preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 in colorectal cancer

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ABSTRACT

Background

Since the first introduction of tumour markers, their usefulness for diagnosis has been a challenging question. The aim of the present prospective study was to investigate, in colorectal cancer patients, the relationship between preoperative tumour marker concentrations and various clinical variables.

Methods

The study prospectively enrolled 131 consecutive patients with a confirmed diagnosis of colorectal carcinoma and 131 age- and sex-matched control subjects with no malignancy. The relationships of the tumour markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 with disease stage, tumour differentiation (grade), mucus production, liver function tests, T stage, N stage, M stage were investigated.

Results

Serum concentrations of CEA were significantly higher in the patient group than in the control group ($p = 0.001$); they were also significantly higher in stage III ($p = 0.018$) and IV disease ($p = 0.001$) than in stage I. Serum concentrations of CEA were significantly elevated in the presence of spread to lymph nodes ($p = 0.005$) in the patient group. Levels of both tumour markers were significantly elevated in the presence of distant metastasis in the patient group ($p = 0.005$ for CEA; $p = 0.004$ for CA 19-9).

Conclusions

Preoperative levels of CEA and CA 19-9 might provide an estimate of lymph node invasion and distant metastasis in colorectal cancer patients.

KEY WORDS

Carbohydrate antigen 19-9, carcinoembryonic antigen, colorectal cancer

1. INTRODUCTION

Colorectal cancer is a relatively common malignancy in developed countries. Adequate preoperative staging is important to the management of colorectal cancer patients so that a treatment plan that minimizes the risk after diagnosis can be devised. After completion of treatment, the patient also has to be monitored for development of recurrent cancer or of a new primary[1].

Tumour markers are biologic or biochemical substances that are produced by tumour cells and then secreted into the circulation in detectable amounts. Antigens produced by the body in response to tumour growth or growth markers produced by the tumour itself can both play important roles as detectable markers used for screening and staging[2]. The first tumour markers were described in1965[3]. Most tumour markers are greatly limited for screening the asymptomatic population, being neither sensitive enough nor specific enough to detect early disease, small tumours, or the type of tumour present[4].

Carcinoembryonic antigen (CEA), an oncofetal glycoprotein, is expressed in normal mucosal cells and overexpressed in adenocarcinoma, especially colorectal cancer[5]. The sensitivity of CEA in colorectal cancer increases with advancing tumour stage. Serum concentrations of CEA are elevated in 50% of patients with tumour extension to the lymph nodes and in 75% of patients with distant metastasis[6]. Serum CEA can be used to establish prognosis. A higher preoperative serum CEA might predict a shorter postoperative disease-free period, and the suggestion is that poor prognosis begins at a preoperative CEA of 3.5 ng/mL[7]. Elevation in CEA also occurs in benign conditions such as smoking, peptic ulcer, inflammatory bowel disease, pancreatitis, hypothyroidism,

biliary obstruction, and cirrhosis. Levels exceeding 10 ng/mL are rarely a result of benign disease[8].

The carbohydrate antigen (CA) 19-9 test measures a carbohydrate determinant of a circulating antigen[9]. Elevated serum CA 19-9 has been found in patients with various gastrointestinal malignancies, especially pancreatic cancer[9,10]. Carbohydrate antigen 19-9 might be helpful in the management of colorectal carcinoma[11]. Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations; in those conditions, serum concentrations are usually less than 1000 U/mL[12].

Since the first introduction of tumour markers, their usefulness for diagnosis has been a challenging question. Because the use of tumour markers as a diagnostic tool is not recommended, we have, since 2006, been routinely using preoperative CEA and CA 19-9 measurements in the management of colorectal cancer patients to obtain more clues about spread of the disease. In the present prospective study, we investigated, in colorectal cancer patients, the relationship between serum concentrations of preoperative tumour markers and various clinical variables.

2. METHODS

Our study was approved by the local ethics committee, and written informed consent was obtained from all subjects.

Between April 2007 and December 2010, the study prospectively enrolled 131 consecutive patients with a confirmed diagnosis of colorectal carcinoma and 131 age- and sex-matched control subjects with no malignancy. The subjects in the control group were selected from the group of patients who had undergone colonoscopy for various reasons and who had no malign or premalignant findings. Exclusion criteria were an operative history of any malignancy, having any malignancy except colorectal cancer, being a smoker, and having pancreatitis. Mean age of the patients (70 men, 61 women) was 61 years (range: 30–83 years). Distribution in the control group was the same because of the age- and sex-matching selection criteria.

In our departments, the routine preoperative evaluation protocol consisted of clinical examination, colonoscopy, abdominal computed tomography, chest radiography, and determination of serum CEA and CA 19-9, but we evaluated only preoperative tumour marker concentrations in relation to various colorectal cancer variables. Of the 131 patients, 36 had an incomplete colonoscopy because of malign obstruction or stricture preventing passage into the proximal segments. Incomplete colonoscopy did not affect the patient population or results, because the cancer diagnosis had been confirmed in all patients by histopathology. Blood samples were obtained 1 week before surgery in the patient group. Serum CEA and CA 19-9 were determined using enzymatic immunoassay kits (Diagnostic Products Corporation, Los Angeles, CA, U.S.A.), with the upper limit of normal defined as 5 ng/mL for CEA and 38 U/mL for CA 19-9 according to the manufacturer's instructions.

The relationships of the tumour markers CEA and CA 19-9 with disease stage (colorectal cancer staging per the American Joint Committee on Cancer), tumour differentiation (grade), mucus production, liver function tests, T stage, N stage, and M stage were investigated.

The IBM SPSS Statistics software (version 20: IBM, Armonk, NY, U.S.A.) was used for data analysis. All values are expressed as medians with minimum–maximum ranges. After homogeneity testing, nonparametric tests (Mann–Whitney and Kruskal–Wallis) were used to evaluate relationships, with $p < 0.05$ being accepted as the level of significance. Receiver operating characteristic (ROC) curves were constructed to determine the sensitivity and specificity of serum CEA and CA 19-9 at several cut-off points for various clinical parameters.

3. RESULTS

Serum CA 19-9 was not significantly different in the control and patient groups; however, serum CEA was significantly higher in the patient group than in the control group ($p = 0.001$). Serum CA 19-9 was not significantly different by disease stage. When we examined serum CEA by disease stage, levels were significantly higher in stages III ($p = 0.018$) and IV ($p = 0.001$) than in stage I. Figure 1 summarizes the tumour marker concentrations in the patient group.

Serum CEA and CA 19-9 showed no significant differences with respect to tumour grade, mucus production, abnormal liver function tests, or T stage ($p > 0.05$). Table I summarizes the results for those variables.

Elevation in serum CEA was significantly associated with spread to lymph nodes (N stage: $p = 0.005$) in the patient group (Figure 1). Serum CA 19-9 had no significant relationship with lymph node status ($p > 0.05$). Levels of both tumour markers were significantly elevated in the presence of distant metastasis (M1) in the patient group ($p = 0.005$ for CEA, $p = 0.004$ for CA 19-9, Figure 1).

The ROC curve analysis for CEA in colorectal cancer patients at all stages showed 51.9% sensitivity at 90% specificity for a cut-off level of 2.41 ng/mL [Figure 2(A)]. The sensitivity of CEA was 38.1% for stage I disease, 36.8% for stage II, 57.1% for stage III, and 78.3% for stage IV.

In the presence of lymph node metastasis in the patient group, serum CEA had 28.4% sensitivity at 90% specificity for a cut-off level of 7.67 ng/mL [Figure 2(B)]. The ROC curve analysis of CEA and CA 19-9 in the presence of distant metastasis in the patient group showed 30.4% and 34.8% sensitivity respectively at 90% specificity [Figure 2(C,D)]. At 90% specificity, the cut-off values of CEA and CA 19-9

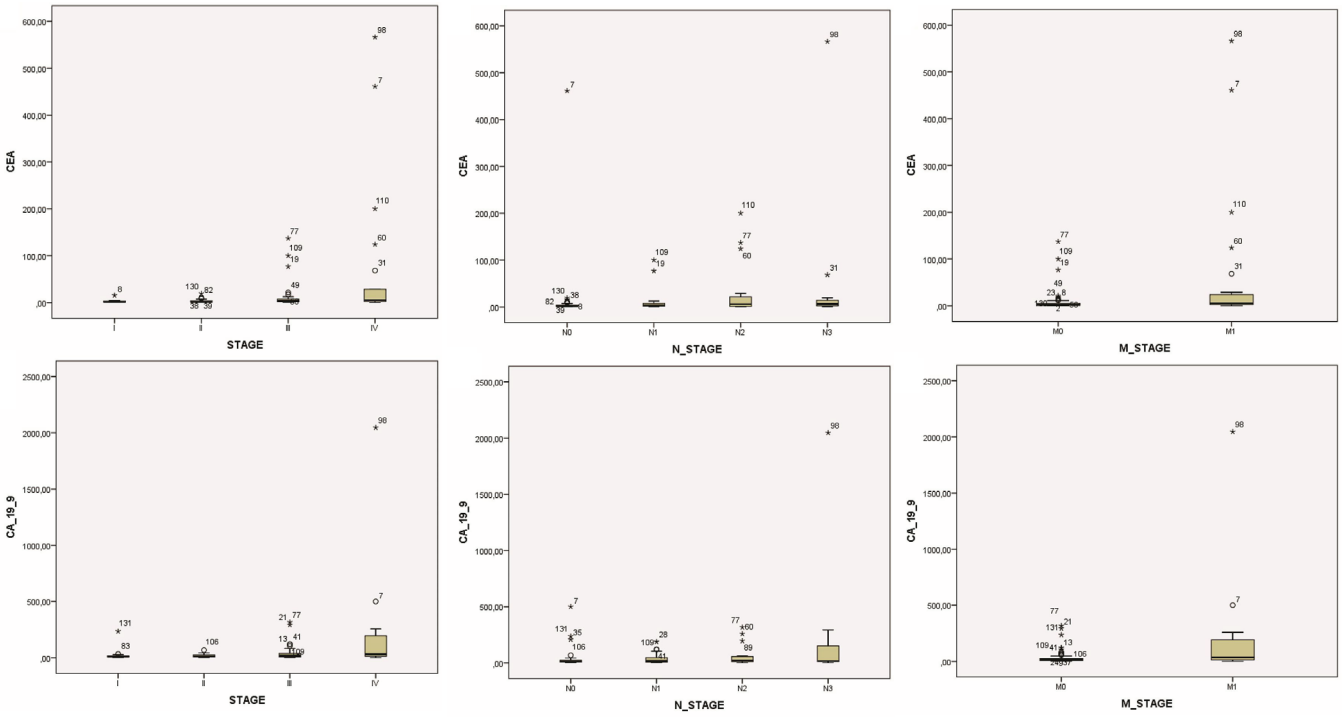

FIGURE 1 Levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 according to tumour stage, lymphatic spread (N stage), and distant metastasis (M stage) in the patient cohort. Circles mark outlier subjects, and stars mark far outliers.

TABLE I Summary of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels by tumour grade, T stage, mucus production, and liver function

Variable	*Pts (n)*	*Antigen level [median (minimum–maximum)]*[a]	
		CEA (ng/mL)	*CA 19-9 (U/mL)*
Grade			
1	5	1.29 (0.77–2.04)	17 (5.58–18)
2	110	2.73 (0.12–461)	13.74 (0.36–500)
3	16	2.74 (0.1–566.23)	24.7 (0.5–2046)
T stage			
1	3	0.77 (0.73–1.5)	17.8 (0.36–18)
2	27	1.99 (0.12–76.8)	9.7 (0.8–235.5)
3	86	3.04 (0.1–200)	16.38 (0.5–316)
4	15	3.5 (0.91–566.23)	20.51 (6.2–2046)
Mucus production			
Yes	19	4.83 (0.1–533.23)	13.7 (0.5–2046)
No	112	2.36 (0.12–200)	16.33 (0.36–316)
Liver function			
Normal	123	2.42 (0.1–566.23)	14.53 (0.36–2046)
Abnormal	8	5.18 (0.91–461)	32.4 (0.8–500)

[a] $p > 0.05$.
Pts = patients.

were set at 10.75 ng/mL and 60 U/mL respectively for the presence of distant metastasis. Table II summarizes the performance analysis of tumour markers for control subjects compared with patients.

4. DISCUSSION

It remains unclear whether monitoring tumour markers has any clinical benefit in the management of colorectal cancer patients[13]. Serum CEA is not recommended as a screening test, but it might be ordered preoperatively if it can assist in staging and in planning treatment strategies. Elevated serum CEA (>5 ng/mL) suggests that the patient has a poor prognosis[14]; however, data are insufficient to support the use of CEA to determine whether to treat the patient with adjuvant therapy[15]. We have been using preoperative CEA and CA 19-9 measurements routinely in the management of colorectal cancer patients to obtain more clues about spread of the disease. We therefore aimed to evaluate the feasibility of using preoperative levels of these tumour markers to estimate either local or distant spread of disease.

Previous reports showed a significant association between elevated serum CA 19-9 and poor prognosis related to disease stage in the preoperative setting. The association of CA 19-9 with prognosis was found to be better than that of CEA[16–18]. In contrast, other publications have reported that the use of CA 19-9 is limited. The antigen was found to have no value in

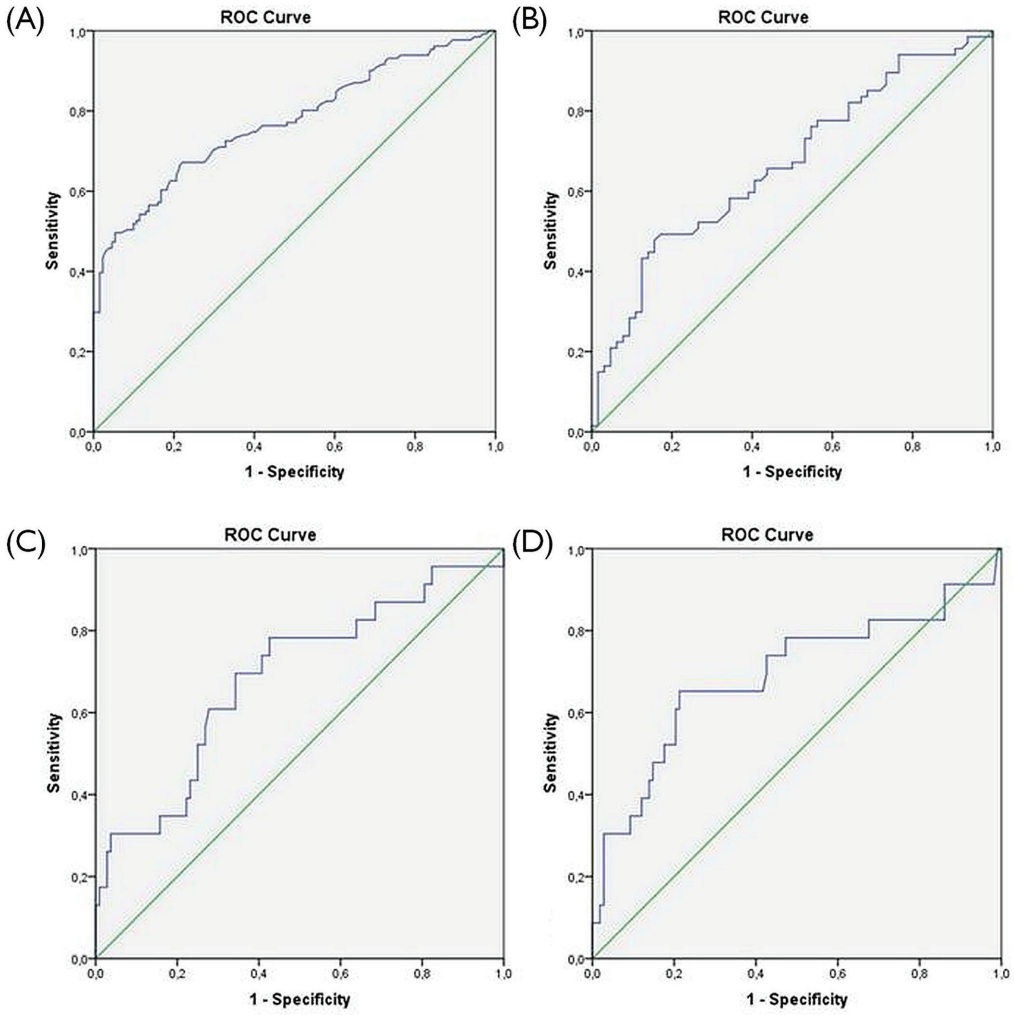

FIGURE 2 (A) Receiver operating characteristic (ROC) curve for carcinoembryonic antigen (CEA) in patients and controls [area under the curve (AUC): 0.773; p = *0.001]. (B) ROC curve for CEA in patient groups with spread to lymph nodes (AUC: 0.666;* p = *0.005). (C) ROC curve for CEA in patient groups with distant metastasis (AUC: 0.686;* p = *0.005). (D) ROC curve for carbohydrate antigen (CA) 19-9 in patient groups with distant metastasis (AUC: 0.691;* p = *0.004). Diagonal segments are produced by ties.*

screening because its positive predictive value was less than 1%[12,19]. In our study, CA 19-9 did not significantly differ between the control group and the patient group; however, serum CEA was significantly higher in the patient group than in the control group ($p = 0.001$). Those results suggest that elevated levels of CEA might signal a need for more complicated diagnostic interventions during preoperative staging.

Serum CEA was significantly higher in stage III ($p = 0.018$) and IV ($p = 0.001$) than in stage I disease, a result that accords with findings in previous reports. Elevated serum CEA predicted a more advanced stage in earlier reports[20,21]. Some studies have also demonstrated that serum CEA has significant prognostic value in some stages[14,20,22].

In the patient group, serum CEA and CA 19-9 were not significantly different by T stage ($p > 0.05$), but serum CEA was significantly elevated with spread to lymph nodes (N stage: $p = 0.005$). Serum CA 19-9 was not significantly associated with lymph node status ($p > 0.05$). An earlier study had suggested that preoperative serum CEA might be correlated with survival only in patients with stage III tumours, and not in those with stage I or II disease[23]. The same study also reported that N stage but not T stage was correlated with serum CEA.

As in previous reports, our results concerning the relations of preoperative tumour marker levels with T and N stage suggest that a preoperative increase in the serum concentrations of these biomarkers might be a clue to lymphatic invasion. If the results of preoperative imaging studies are negative for lymphatic invasion, but elevated serum concentrations of tumour markers are present in a colorectal cancer patient, the physician might want to manage the patient as suspected for lymphatic invasion.

TABLE II Analysis of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 as tumour markers in control subjects compared with patients, at 90% specificity

Marker	*Value [median (minimum–maximum)]*		*Cut-off*	*Sensitivity (%)*
	Control subjects	*Patients*		
CEA (ng/mL)	1.12 (0.03–5.43)	2.6 (0.1–566.23)	2.41	51.9
CA 19-9 (U/mL)	12.91 (0.17–429.58)	15.3 (0.36–2046)	32.14	25.2

Several studies showed that more CEA per gram of total protein was produced by well-differentiated colorectal cancers than by poorly differentiated specimens[24,25]. Serum CEA has also been reported to trend higher in patients with well-differentiated tumours than in those with poorly differentiated tumours[26]. A review by Duffy[27] suggested that a lack of differentiation or poor differentiation may explain why some patients with advanced colorectal cancer don't show increased serum concentrations of CEA. On the other hand, our results showed that serum concentrations of tumour markers were not significantly different by tumour grade ($p > 0.05$). Those results have to be confirmed in molecular studies targeting the mechanisms of tumour marker production. Patients with aneuploid colorectal cancers have been shown to have higher serum concentrations of CEA than are seen in patients with tumours having a near diploid pattern[28].

Benign liver disease can impair liver function and, thus, clearance of CEA, potentially resulting in increased serum CEA in colorectal cancer patients with non-malignant liver disease[29]. In contrast, our results showed no significant relation between serum concentrations of tumour markers and liver function in our patient group.

Levy *et al.*[30] also stated that CEA and CA 19-9 are statistically significantly different in early and metastatic colorectal cancer. The gene encoding CEA is classified as a member of the immunoglobulin supergene family, which includes intercellular adhesion molecule 1. The structural similarity of CEA to intercellular adhesion molecule 1 might alter cell adhesion, which might in turn have a role in cancer invasion and metastasis. Thus, CEA might play a role in the metastatic process[31–34]. Evidence for the role of CEA in cancer dissemination was revealed in a study by Hostetter *et al.*[35], who showed that the rate of liver metastasis in mice transplanted with colorectal tumours increased to 48% from 2% after CEA injection. In our study, serum CEA and CA 19-9 were found to be significantly elevated in the presence of distant metastasis, confirming that earlier report. In previous studies, elevated serum CA 19-9 was found to be related to distant metastasis[36] and elevated serum CEA and CA 19-9 were both found to be related to poor prognosis[37].

Previous reports showed different overall rates of positivity for tumour markers. In a review that used an upper limit of normal of 2.5 ng/mL for CEA, a sensitivity of 36% and a specificity of 87% was reported in screening for Dukes A and B colorectal cancer; a more recent study using cut-off values of 3.56 ng/mL for serum CEA and 28 U/mL for CA 19-9 in a limited patient population revealed sensitivities of 56.2% and 36.4% and specificities of 100% and 88.9% respectively for those markers[8,27,38].

Our ROC curve analysis for CEA in the diagnosis of colorectal cancer patients at all disease stages had 51.9% sensitivity at 90% specificity for a cut-off level of 2.41 ng/mL. We also found that the sensitivity of CEA was 38.1% for stage I disease, 36.8% for stage II, 57.1% for stage III, and 78.3% for stage IV. Wild *et al.*[39] reported that the sensitivity of serum CEA increased to 88.2% from 13.2% with increasing disease stage (I to IV respectively). In the same study, the authors noted that, at all disease stages, CEA had a sensitivity of 43.9% at a specificity of 95% for a cut-off level of 4.8 ng/mL. In our patients with a diagnosis of lymph node metastasis, serum CEA had a 28.4% sensitivity at 90% specificity using a cut-off level of 7.67 ng/mL. The ROC curve analysis of CEA and CA 19-9 in the presence of distant metastasis in the patient group showed sensitivities of 30.4% and 34.8% respectively at 90% specificity. At 90% specificity, cut-off values of serum CEA and CA 19-9 were set at 10.75 ng/mL and 60 U/mL respectively for the presence of distant metastasis. Table II summarizes our tumour marker performance analysis in the control and patient groups.

5. CONCLUSIONS

Given that colorectal cancer is a common cause of death worldwide, an effort either to achieve early diagnosis or to identify patients with poor prognosis in the preoperative period is needed to support patient management. Despite the significant difference found between the patient and control groups in the present study ($p = 0.001$), tumour markers are known not to be feasible in population screening, and our results confirmed that understanding, given the low sensitivity of the markers studied. The main goal in the preoperative management of colorectal cancer patients, after localization of the primary tumour, is to determine lymph node invasion and distant metastasis. In the present study, we found that preoperative serum CEA and CA 19-9 might suggest when lymph node invasion and distant metastasis are present. We therefore recommend routine preoperative tests to evaluate especially serum CEA in colorectal cancer. Further studies into the molecular basis of tumour

biology might contribute the current understanding of the nature of these tumours and tumour markers.

6. ACKNOWLEDGMENTS

This study was presented as a poster at the 18th National Surgical Congress; Izmir, Turkey; May 23–27, 2012; and as an oral presentation at the Annual Meeting of the European Society of Surgery; Istanbul, Turkey; November 22–24, 2012.

7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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