RESEARCH ARTICLE

CEA and CA 19-9 are Still Valuable Markers for the Prognosis of Colorectal and Gastric Cancer Patients

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Abstract

Background: The purpose of this study was to assess the predictive effect of preoperative CEA and CA 19-9 levels on the prognosis of colorectal and gastric cancer patients. Materials and Methods: CEA and CA 19-9 were evaluated preoperatively in patients undergoing surgery for colorectal cancer (n=116) and gastric cancer (n=49). Patients with CEA levels <5 ng/mL were classified as CEA Group 1, 5-30 ng/mL as CEA Group 2 and >30 ng/mL were classified as CEA Group 3. Similarly the patients with a CA 19-9 level <35 U/mL were classified as CA 19-9 Group 1, with 35-100 U/mL as Group 2 and with >100 U/mL as Group and 3. TNM stages and histologic grades were noted according to histopathological reports. Patients with a TNM grade 0 or 1 were classified as Group A, TNM grade 2 patients constituted Group B and TNM grade 3 and 4 patients constituted Group C. Demographic characteristics, tumor locations and blood types of the patients were all recorded and these data were compared with the preoperative CEA and CA19-9 values. Results: A significant correlation between CA 19-9 levels (>100 U/mL) and TNM stage (in advanced stages) was determined. We also determined a significant correlation between TNM stages and positive vlaues for both CEA and CA 19-9 in colorectal and gastric cancer patients. In comparison between CEA and CA 19-9 levels and age, gender, tumor location, ABO blood group, and tumor histologic grade, no significant correlation was found. Conclusions: Positive levels of both CEA and CA 19-9 can be considered to indicate an advanced stage in colorectal and gastric cancer patients.

Keywords: Colorectal - gastric - tumour markers - CA 19-9 - CEA - prognosis - disease stage

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Introduction

Cancer continues to be an important health problem for both patients and health care workers despite significant advances in medical and technological fields. Colorectal and gastric cancers are the most common cancers of the gastrointestinal system. Colorectal cancer is the third most common cancer type associated with cancer-related mortality after prostate and lung cancers in men. Cancer incidences vary across the world, indicating that environmental factors play a significant role in many cancer types. Gastric cancer is commonly observed particularly in Asia and Eastern Europe, while continuing to be a leading cause of cancer-related deaths. Many studies have proposed that colorectal and gastric cancers show a significant correlation with socioeconomic structure, geographic location, and cultural habits of a population (Mahmoud et al., 2010).

Early diagnosis bears great importance by providing more effective treatment and reduced mortality and morbidity in colorectal and gastric cancer cases. Early diagnosis can be achieved with various screening and laboratory methods.

Tumor markers are the substances that produced by the tumor or secreted by the tissue as a response to the tumor. There may be used in the screening, diagnosis, and classification of tumors, as well as in the prognostic assessment and monitoring of recurrence and metastasis in cancer cases (Hammond, 2002). CEA and CA 19-9 are the most studied serum tumor markers that have been evaluated for the management of gastrointestinal cancers.

Carcinoembriyonik antigen (CEA) is an acknowledged member of immunglobulin superfamily, with a role as an intracellular adhesion molecule. A high serum CEA is associated with a number of malignancies, including colorectal, breast, gastric and pancreatic cancers. Many studies have shown that increased preoperative serum CEA levels are associated with an increased risk of recurrence and a poor prognosis and the prognostic effect of the serum CEA level is independent of the tumor-node-metastasis stage (Park et al., 2006; Huh et al., 2010; Yakabe et al., 2010).

Carbonhydrate antigen 19-9 (CA 19-9) is a ligand for e-selectin that plays an important role in the adhesion of cancer cells to endothelial cells. It has been used as a tumor marker in gastrointestinal cancers. It may also be increase in several benign diseases . In many studies, an increase in CA 19-9 has been found to indicate a poor prognosis and high serum levels of either CEA or CA 19-9 in patients with colorectal cancer are significant,

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independent prognostic factors (McLeod and Murray, 1999; Reiter et al., 2000).

In this study, we aimed to investigate the correlation of preoperative CEA and CA 19-9 tumor marker levels with diagnosis, treatment, and disease stages in patients who received surgery due to gastric or colorectal cancer.

Materials and Methods

In this study, we prospectively evaluated colorectal and gastric cancer patients who were diagnosed and operated between January 1st 2009 and March 1st 2012 in the Surgical Department of Umraniye Training and Research Hospital. The patients who were operated due to tumor recurrence, unresectable tumor and patients diagnosed as GIST were excluded from the study.

The CEA and CA 19-9 levels of patients were evaluated preoperatively. CEA value lower than 5 ng/mL was recognized as negative and classified as CEA Group 1. The patients with a CEA level between 5-30 ng/mL classified as CEA Group 2 and CEA level >30 ng/mL classified as CEA Group 3.

A CA 19-9 value lower than 35 U/mL was recognized as negative and these patients constituted CA 19-9 Group 1. The patients with a CA 19-9 value between 35-100 U/mL and those with a value >100 U/mL were considered as CA 19-9 Group 2 and 3, respectively.

TNM stages and histologic grades were noted according to histopathological reports. Patients with a TNM grade 0 or 1 classified as Group A (early stage group), TNM grade 2 patients constituted Group B and TNM grade 3 and 4 patients constituted Group C (advanced stage group).

Demographic characteristics, tumor locations and blood types of the patients were all recorded and these data were compared with the preoperative CEA and CA19-9 values.

Statistical analyses were done with NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program. The evaluation of the study data was performed using Oneway ANOVA test for intergroup comparisons of normally distributed parameters and Mann-Whitney U test for comparing two independent samples, in addition to using descriptive statistical methods (mean, standard deviation, median, frequency, percentage). Qualitative data were compared with Pearson's chi-squared test. The $p<0.05$ was recognized as statistically significant.

Results

A total of 165 patients were included in the study. 153 patients were operated because of colorectal cancer. Thirty-seven of the colorectal cancer patients were excluded from the study because of unmesaured preoperative tumor marker levels, unresectable tumor, tumor recurrence and the GIST diagnosis. Seventy-two patients were operated because of gastric cancer. Twenty-three of the gastric cancer patients were excluded from the study because of unmeasured preoperative tumor marker levels, unresectable tumor andGIST diagnosis. Eventually 116 patients with colorectal cancer and 49 patients with gastric cancer were included in the study.

Colorectal cancer patients

The mean age of the study group was 63.15 (31-105); 67 (58.7%) patients were female and 49 (42.2%) were male. The tumor location in colorectal cancer patients was rectum in 31 (26.7%) patients, sigmoid colon in 48 (41.4%) patients, ascending colon in 12 (10.3%) patients, transverse colon in 7 (6%) patients , descending colon in 8 (6.9%) patients, and caecum in 10 (8.6%) patients. While 17 (14.7%) patients received emergency surgery, 99 (85.3%) patients received elective surgery. Four patients (3.4%) had synchronous tumor. The blood types were Type A in 51 (44%) patients, Type 0 in 41 (35.3%) patients, Type B in 19 (16.4%) patients and Type AB in 5 (4.3%) patients respectively. The histologic tumor grade was poorly differentiated in 10 (8.6%) patients, moderately differentiated in 93 (80.2%) patients, and well differentiated in 9 (7.8) patients. The distribution of the patients according to pathological evaluation was as follows: invasive adenocarcinoma was detected in 102 (87.9%) patients, mucinous carcinoma in 9 (7.8%) patients, and carcinoma in situ in 5 (4.3%) patients. Regarding to the TNM classification, 5 (4.3%) patients were in stage 0, 8 (6.9%) were in stage I, 48 (41.4%) were in stage II, 44 (37.9%) were in stage III, and 11 (9.5%) were in stage IV (Table 1).

CEA was measured in 114 of the 116 colorectal cancer patient's. Sixty-six (57.9%) patients were in CEA group 1, 35 (30.7%) patients were in CEA group 2 and 13 (11.4%)

Table 1. Identifying Informations of Patients with Colorectal Cancer

		n	%
Age (Years)	Min-Max/Ort±SD	31-105/63.15±12.27	
Gender	Female	67	58.7
	Male	49	42.2
Tumor location	Rectum	31	26.7
	Sigmoid colon	48	41.4
	Ascending colon	12	10.3
	Transverse colon	7	6
	Descending colon	8	6.9
	Caecum	10	8.6
Elective/Emergency	Emergency surgery	17	14.7
	Elective surgery	99	85.3
Blood types	A	51	44
	B	19	16.4
	AB	5	4.3
	O	41	35.3
Histologic tumor grade	Unknown	4	3.4
	Poorly differentiated	10	8.6
	Moderately differantiated	93	80.2
	Well differentiated	9	7.8
Pathological diagnose	Invasive adenocarcinoma	102	87.9
	Mucinous carcinoma	9	7.8
	Carcinoma in situ	5	4.3
Synchronous tumor	No	112	96.6
	Yes	4	3.4
TNM Stage	0	5	4.3
	1	8	6.9
	2	48	41.4
	3	44	37.9
	4	11	9.5

Table 2. Comparison of CA 19-9 Groups and Stage Groups in Colorectal Cancer Patients

		CA19-9 Group			
		Group 1 (n=74) n (%)	Group 2 (n=10) n (%)	Group 3 (n=10) n (%)	p
Stage	0-1 (Group A)	10 (13.5)	0	0	0.025
	2 (Group B)	36 (48.6)	5 (50.0)	1 (10.0)	
	3-4 (Group C)	28 (37.8)	5 (50.0)	9 (90.0)	

Table 3. Comparison of Positivitiy for Both Markers and Stage Groups

		CEA>5, CA 19-9 >35		Others*		p
		n	(%)	n	(%)	
Stage	0-1 (Group A)	-	-	10	12.3	0.035
	2 (Group B)	3	23.1	39	48.1	
	3-4 (Group C)	10	76.9	32	39.5	
Total		13	100	81	100	

*CEA positive and CA 19-9 negative patients, CEA negative and CA 19-9 positive patients, both markers are negative patients

Table 4. Identifying Informations of Patients with Gastric Cancer

		n	%
Age (Years)	Min-Max/Ort±SD	21-83/63.08±12.48	
Gender	Female	32	65.3
	Male	17	34.7
Tumor location	Corpus	15	30.6
	Cardia	12	24.5
	Antrum	18	36.7
	Linitis plastica	2	4.1
	Remnant stomach	2	4.1
	Adenocarcinoma	29	59.2
Pathological diagnose	Mucinous adenocarcinoma	3	6.1
	Signet ring cell adenocarcinoma	15	30.6
	Adenosquamous carcinoma	1	2
	Undifferentiated carcinoma	1	2
Stage	1	6	12.2
	2	9	18.4
	3	27	55.1
	4	7	14.3

Table 5. Comparison of CA 19-9 Groups and Stage Groups in Gastric Cancer Patients

		CA19-9 Group			
		Group 1 (n=19) n (%)	Group 2 (n=9) n (%)	Group 3 (n=15) n (%)	p
Stage	0-1 (Group A)	4 (21.1)	0	0	0.124
	2 (Group B)	5 (26.3)	2 (22.2)	2 (13.3)	
	3-4 (Group C)	10 (52.6)	7 (77.8)	13 (86.7)	
TNM	1	4 (21.1)	0	0	0.06
Stage	2	5 (26.3)	2 (22.2)	2 (13.3)	0.649
	3	7 (36.8)	6 (66.7)	12 (80)	0.034
	4	3 (15.8)	1 (11.1)	1 (6.7)	0.711

Table 6. Comparison of Positivitiy for Both Markers and Stage Groups

		CEA>5, CA 19-9 >35		Others*		p
		n	(%)	n	(%)	
Stage	0-1 (Group A)	0	0	6	15.8	0.044
	2 (Group B)	0	0	9	23.7	
	3-4 (Group C)	11	100	23	60.5	
Total		11	100	38	100	

*CEA positive and CA 19-9 negative patients, CEA negative and CA 19-9 positive patients, both markers are negative patients

patients were in CEA group 3. The evaluation of CEA groups with the colorectal cancer stage groups didn't show any statistically significant correlation (p>0.05).

The pathological diagnosis was invasive adenocarcinoma in all three CEA groups mostly and there was no statistical significance in comparison of CEA groups and pathological diagnosis. Most common tumor location in all three CEA groups was sigmoid colon, followed by rectum. No statistical significance was determined in this result, as well. Most of the patients in the CEA groups were found to have tumors with moderately differentiated histology. 50% (n=2) of the patients with a synchronous tumor (n=4) were in the CEA group 1, 1 patient was in CEA group 2 and 1 was in CEA group 3. CEA values did not exhibit a statistically significant relationship with presence of synchronous tumor or histologic grade. The mean age was 61.8 years in the CEA group 1, 66.4 years in the CEA group 2, and 60.5 years in the CEA group 3; no statistically significant correlation was detected between the CEA groups relative to mean age (p>0.05).

CA 19-9 was evaluated in 94 of the 116 patients. According to CA 19-9 levels 74 (82.8%) patients were in CA 19-9 group 1, 10 (8.6%) patient were in CA 19-9 group 2, and 10 (8.6%) patient were in CA 19-9 group 3. In the comparison between CA 19-9 groups and stage groups, 90% (n=9) of the CA 19-9 group 3 patients (n=10) were in stage group C. This was also statistically significant (p<0.05) (Table 2). Accordingly, a CA 19-9 value >100 U/mL was concluded to be an indicator of advanced stage.

The pathological diagnosis was invasive adenocarcinoma in all three CA 19-9 groups mostly and there was no statistical significance in comparison of CA 19-9 groups and pathological diagnosis. In all the CA 19-9 groups, most common tumor location was sigmoid colon, followed by rectum. There was no statistically significant correlation in this regard, as well. Moderately differentiated tumor was the most common histologic grade in all the CA 19-9 groups. Of the patients with a synchronous tumor, 75% were in the CA 19-9 group 1 and 1 patient was in CA 19-9 group 3. CA 19-9 values were not found to be correlated with histologic grade or presence of a synchronous tumor. The mean age was 63.31 years in the CA 19-9 group 1, 61 years in the CA 19-9 group 2, and 58 years in the CA 19-9 group 3; there was no statistically significant relationship between mean age and CA 19-9 groups (p>0.05).

Among patients who underwent surgery due to colorectal cancer and demonstrated positivity for both markers (CEA>5 and CA 19-9 >35) (n=13), 76.9% (n=10) were in the stage group C. Positivity for both markers was observed to be more common in advanced stage tumors and the difference was statistically significant (p<0.05) (Table 3). Accordingly, positivity for both markers may be an indicator of advanced stage colorectal cancer.

Gastric cancer patients

While 32 (65.3%) of the gastric cancer patients were female, 17 (34.7%) were male, and the mean age of the study population was 63.08 years.

The tumor location in gastric cancer patients was

corpus in 15 (30.6%), cardia in 12 (24.5%), and antrum in 18 (36.7%) patients. Two (2.1%) patients had a tumor in the remnant stomach and 2 (4.1%) patients had a tumor of linitis plastica. The pathological diagnosis was adenocarcinoma in 29 (59.2%) patients, mucinous adenocarcinoma in 3 (6.1%) patients, signet ring cell carcinoma in 15 (30.6%) patients, adenosquamous carcinoma in 1 (2%), and undifferentiated carcinoma in 1 (2%) patient. Regarding the distribution of TNM stages, 6 (12.2%) cases were stage 1, 9 (18.4%) were stage 2, 27 cases (55.1%) were stage 3, and 7 cases (14.3%) were stage 4 (Table 4).

CEA was measured in all 49 patients. Thirty-three (67.3%)patients were in CEA group 1, 7 (14.3%) patients were in CEA group 2 and 9 (18.4%) patients were in CEA group 3. The evaluation of CEA groups with the gastric cancer stage groups didn't show any statistically significant correlation ($p>0.05$).

The pathological diagnosis was adenocarcinoma in 22 (66.7%) patients in the CEA group 1 and 5 patients in the CEA group 3. Signet ring cell carcinoma was the pathological diagnose of 4 (57.1%) patients in the CEA group 2; no statistical significance between CEA groups and pathological diagnoses was found. Tumor location was similar in all three CEA groups and there was no statistical significance. The mean age was 63.64 years in the CEA group 1, 58.71 years in the CEA group 2, and 64.44 years in CEA group 3. There was no statistical significance between CEA groups and mean age ($p>0.05$).

Of the 49 patients, CA 19-9 was evaluated in 43. 19 (44.2%) patients were in CA 19-9 group 1, 9 (20.9%) patients were in CA 19-9 group 2, and 15 (34.9%) patients were in CA 19-9 group 3. In the comparison between CA 19-9 groups and stage groups, when they were grouped as group A (Stage 0-I), group B (Stage II), group C (Stage III-IV), no statistically significant correlation was determined between CA 19-9 values and advanced stages, however, 77.8% of the patients in the CA 19-9 group 2 and 86.7% of the patients in the CA 19-9 group 3 were in the stage group C. When the stages were not grouped and evaluated as in TNM staging, 80% (n=12) of the cases (n=15) in the CA 19-9 group 3 (>100 U/mL) observed to be stage III ($p<0.05$) (Table 5). In light of this result, further studies including larger series may be helpful in showing a significant relationship between advanced stage and positivity for CA 19-9.

Regarding the pathological diagnoses, adenocarcinoma was detected in 13 (68.4%) patients in the CA 19-9 group 1, 5 (55.6%) patients in the CA 19-9 group 2, and 7 (46.7%) patients in the CA 19-9 group 3; no statistical significance was found between CA 19-9 groups and pathological diagnoses. Furthermore, there was no statistical significance between the three CA 19-9 groups and tumor location. The mean age was 63.47 years in group 1, 63.67 years in group 2, and 60.80 years in group 3; no statistically significant difference was found between the CA 19-9 groups with regard to mean age.

All the patients who received surgery due to gastric cancer and were positive for both markers (CEA>5 and CA 19-9>35) (n=11), were in the stage group C (n=11). Positivity for both markers was statistically significantly more common in cases of advanced stage ($p<0.05$) (Table 6). Accordingly, positivity for both tumor markers was thought to be an indicator of advanced stage gastric cancer.

Discussion

Since early diagnosis raises the success rate of cancer treatment significantly, it is of utmost importance to investigate tumor markers. Recently, many studies have been performed relative to the location of tumor markers in colorectal and gastric cancer patients. One of the most freqently studied subjects in these efforts is to define new parameters that may be predict the prognosis of the cancers (Jass, 2000, Redstone, 2004).

Many studies have been performed on the prognostic value of parameters such as lymphatic involvement, preoperative CEA levels, histologic type and grade of the tumor, radial surgical margin, pattern of tumor spread. Most of those parameters have been shown to have a prognostic value, while studies on some are yet to be completed. Nonetheless, pathologic stage is the most important prognostic indicator of colorectal cancer (Dalton and Chandrosoma, 1999; Hamilton et al., 2000; Harpaz and Saxena, 2003; Cooper, 2004). In the present study, we evaluated the preoperative CEA and CA 19-9 values along with disease stages in colorectal and gastric cancer patients.

Zheng et al. (2001) investigated the prognostic value of CEA, CA 19-9, and CA 72-4 in colorectal cancer patients by evaluating Dukes stages and tumor marker values, and found that patients with advanced stage had significantly increased levels of CEA, CA 19-9, and CA 72-4. Wanebo et al. (1978) compared preoperative CEA values and Dukes stages in colorectal cancer patients and determined an association between tumor marker values and disease stage. In our study 42.1% of the colorectal cancer patients had high preoperative CEA values, however, no significance was found in term of the disease stages. In the same patient group, 17.2% of the patients were found to be high level of CA 19-9 and it was found to have a statistically significant correlation with advanced stages ($p=0.025$).

Basbug et al. (2011) evaluated the prognostic value of CEA and CA 19-9 in colorectal cancer patients and found a statistically significant relationship between positivity for both tumor markers and advanced TNM stage. Similarly, Xue-Qin Yang et al. (2001) investigated the prognostic importance of preoperative CEA, CA 19-9, and CA 125 values in colorectal cancer patients and found a correlation between increased preoperative values of these parameters and advanced stage. Most of these studies appear to indicate a significant correlation between CEA and advanced stage, while only some of them show a relationship between CA 19-9 and advanced stage.

In the present study, positivity for both CEA and CA 19-9 tumor markers was observed to be a valuable prognostic indicator, since 76.9% of the patients positive for both markers were in the advanced stage group and 23.1% were in the moderate stage group ($p=0.035$).

In a study from Katmandu Valley they found that the serum levels of AFP, CEA, CA19-9, and CA50 were

significantly correlated with survival rate in patients with gastric cancer and these correlations indicated that patients with positive values of tumor markers have worse prognosis (Mittal, 2013).

Our study did not reveal statistically significant results between CEA and CA 19-9 values of colorectal cancer patients and the age, histologic grade, pathological diagnosis, tumor location, and presence of synchronous tumor. In their study, Zheng et al. (2001) did not find a statistically significant correlation of CEA and CA 19-9 positivity with histologic grade and tumor size.

In the literature, 15.9-57.6% of gastric cancer patients show a positivity for serum CEA , while 16-44% show a positivity for serum CA 19-9 (Gonzales et al., 1996; Ychou et al., 2000; Duraker and Celik, 2001; Carpelan-Holmstrom et al., 2002; Yamashita et al., 2007). In the current study, 67.3% of the gastric cancer patients were preoperatively negative for CEA and 32.7% were positive. No correlation was determined between CEA and disease stage. The positivity range for CA 19-9 was 55.8%. No correlation was detected between CA 19-9 and disease stage groups in our study, however, there was a significant relationship between disease stage III and the group with a CA 19-9 value >100 U/mL (p=0.03). Ucar et al. (2008) conducted a study to reveal the prognostic value of preoperative CEA, CA 19-9, AFP, and CA 72-4. Similar to our study, they did not find a correlation between increased CEA value and advanced TNM stage, however, there was a statistically significant correlation between increased CA 19-9 value and advanced stage. In another study Hang Dong et al. (2013) suggested that the CA 19-9 might be a potential valuable indicator for liver metastasis of colorectal carcinom in the clinic.This shows the correlation between advaned stage colorectal cancer and high values of CA 19-9.

Harada et al. (1994) studied tumor markers in 52 gastric cancer patients and found the following positivity rates: 9.6% for CEA, 2.3% for AFP, 25% for CA 19–9, and 8.1% for CA 125.

Uehara et al. (1985) conducted a study focusing on the importance of CEA in gastric and colorectal cancer cases and determined that CEA was important in colorectal cancer, but was not important in gastric cancer. A study from Italy evaluated CA 19-9, CA 72-4, and CEA levels in 59 gastric cancer, 47 gastritis, and 40 healthy individuals, revealing that CEA and CA 19-9 had insignificant diagnostic value and significant prognostic value (Tocchi et al., 1998). Mihmanli et al. (2004) reported CEA and CA 19-9 as parameters that should be evaluated in gastric cancer patients.

In the present study, CEA and CA 19-9 values were found to have no significant correlation with pathological diagnosis, tumor location, and mean age. In their study, Ucar et al. (2008) did not observe a significant correlation between tumor marker positivity and tumor location, as well.

In the present study, all 11 gastric cancer patients positive for both tumor markers were in the advanced stage gastric cancer group and there was a statistically significant correlation, similar to that in colorectal patients, between positivity for both tumor markers and advanced stage (p=0.04). CEA and CA 19-9 are not only tumor markers, but also intercellular adhesion molecules. The cells expressing these molecules may have higher invasive potential (Ychou et al., 2000). This may be the reason why both colorectal and gastric cancer patients positive for both tumor markers had tumors with advanced stages.

In conclusion, in the present study, the comparison of CEA and CA 19-9 levels with TNM stages in colorectal and gastric cancer patients revealed that increased CA 19-9 level was an indicator of advanced stage (3-4) in both patient groups. Also, positivity for both tumor markers was found to be an important indicator of advanced stage. There was no significant correlation of CEA and CA 19-9 values with the histologic grade, tumor location, pathological diagnosis, presence of synchronous tumor and mean age. Different results available in the literature suggest that further studies including larger populations are required.

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