The relationship between preoperative CEA and CA19-9 status and patient characteristics and lymph node involvement in early-stage colon cancer

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Abstract. – **OBJECTIVE:** Colon cancer is a primary human cancer that accounts for approximately one-tenth of all cancers and is one of the three most common cancers in incidence and mortality. This study investigated the relationship between serum preoperative carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), patient characteristics and lymph node (LND) involvement in early-stage colon cancer.

PATIENTS AND METHODS: A total of 154 patients who had undergone surgery for early-stage colon cancer were included in this study. Patient demographics regarding age and gender, laboratory parameters, tumor size, and tumor laterality were recorded. CEA and CA19-9 positivity was defined as patients whose tumor markers were above the cut-off values, and patients were grouped according to CEA and CA19-9 positivity. Patients were compared according to the CEA and CA19-9 status and pathological LND involvement.

RESULTS: We found that patients in the CEA (+) and CA19-9 (+) groups were significantly older than the others. Our study detected LND involvement in histopathological examination in 25% of patients. LND pathological participation was significantly higher in the CEA (+) CA19-9 (+) group, and being age 65 years or older was found to be a risk factor for pathological LND involvement.

CONCLUSIONS: Clinicians should pay more attention to LND involvement when both CEA and CA19-9 are elevated preoperatively in early-stage colon cancer patients. Preoperative CEA and CA19-9 status of patients is important in predicting LND involvement and, as a result, the prognosis of these patients.

Key Words:
   Colon cancer, Lymph nodes, CEA, CA19-9.

Introduction

Colon cancer is one of the most common cancers in humans, approximately one-tenth of all causes of cancer, making it one of the top three cancers in incidence and mortality[1]. The incidence of colon cancer in humans is 10.2%, and the mortality rate is 9.2%, according to the American Cancer Society[2,3]. It is the third most common cancer seen in men and women in the United States[4]. Surgical resection of the invaded colon is the first treatment for colon cancer, and tumor resection is usually performed in the early stages of colon cancer. Early-stage colon cancer is highly curable and is generally treated with surgery. Serum markers are universally used in the treatment of cancer patients. Several biomarkers are used for early diagnosis, staging, treatment, and prognosis of colon cancer. Carcinoembryonic antigen (CEA) is one of the oncofetal antigens usually produced in the fetus and is present at low levels in adults. CEA is a long-established tumor marker associated with colon cancer[5]. In 1965, Gold and Freedman[6] first discovered CEA, a glycoprotein in 90% of patients with colorectal carcinoma. Studies[5,7] showed that high CEA serum levels in the preoperative period are associated with a worse prognosis in cancer patients. Thirunavukarasu et al[8] suggested that patients with high CEA levels but node-negative early colon cancer have a worse prognosis than node-positive patients.

Carbohydrate antigen 19-9 (CA19-9), a monoclonal antibody, has been a known serum marker for many diseases since 1979. In malignant diseases, elevated serum CA19-9 levels can also be present in benign conditions[9]. It is a tumor marker for many cancers, such as pancreatic, gastric, lung, and biliary tract[10,11]. It has also been found to be elevated in colon cancer and associated with prognosis and metastasis of the disease. Serum level CA19-9 is elevated in 35-40% of patients with metastatic colon malignancy[12]. We aimed to evaluate the role of preoperative CEA and CA19-9 serum markers in characteristics of patients with early-stage colon cancer and the role of these markers in pathological lymph node involvement (LND) in these patients.

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Patients and Methods

The local Ethics Committee of Giresun Training and Research Hospital approved the study, which was conducted according to the ethical principles of the Declaration of Helsinki, revised in 2013. Because of the study's retrospective design, written informed consent was not obtained from the patients. A total of 154 patients who underwent surgery for colon cancer between January 2019 and December 2022 were included in the study. Patients in the study population were staged using preoperative abdominal tomography and abdominal magnetic resonance imaging. Early-stage patients (no LND involvement, no distant metastases) were classified as stage I-II and these patients underwent surgery. Patients at stage III-IV, age < 18 years, and patients with missing data were excluded from the study. Patient demographics regarding age and sex, preoperative serum CEA and CA19-9 levels, laboratory parameters, tumor size, tumor laterality, and pathologic LND involvement were recorded. Information about patient smoking history could not be obtained, therefore, demographic data of the patients were not included. Clinical conditions such as fatty liver, active inflammation, liver cirrhosis, and hepatitis affecting serum CA19-9 levels were absent for the patients.

An electrochemiluminescence immunoassay (ECLIA) was used for quantitative *in vitro* determination of CEA and CA19-9 and were measured at the initial diagnosis of the disease before surgery. CEA levels of 5 ng/ml or more were defined as elevated and grouped as CEA (+). For CA19-9, a value of 37 U/mL or more was described as an elevated value and grouped as CA19-9 (+). These cut-off values were derived from the reference values used by the laboratory of the Giresun Training and Research Hospital. The histopathological results of the patients were evaluated.

The patients were divided into four groups: CEA (-) CA19-9 (-) (n = 76), CEA (+) CA19-9 (-) (n = 45), CEA (-) CA19-9 (+) (n = 7), CEA (+) CA19-9 (+) (n = 26) according to the marker status. The patients were then divided into two groups according to LND involvement, those with positive or negative LND involvement. Data were compared between the groups.

Statistical Analysis

Statistical analyses in our study were performed with the program Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY, USA). The normality of data

distribution was assessed using the Kolmogorov-Smirnov test. Normally distributed numeric data were expressed as mean ± standard deviation (SD), and non-normally distributed numeric data were described as median (minimum-maximum value). Categorical variables were expressed as numbers (n) and percentages (%) and compared with the Chi-square test. One-way analysis of variance (ANOVA) was used to analyze differences between the means of the groups. In contrast, the Kruskal-Wallis test analysed significant differences in median values. When the results of the one-way ANOVA and Kruskal-Wallis tests were effective, post-hoc Tukey's or non-parametric multiple comparison tests were used to determine the reasons for the difference. Risk factors for pathologic lymph node involvement were determined by multivariate logistic regression analysis. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each variable. Hypotheses were two-sided, and a *p*-value of < 0.05 was considered statistically significant.

Results

The mean age of patients in the study population was 68.58 ± 11.91, with 92 (60%) males. The distribution of the study population according to marker status is presented in Figure 1.

It was found that the mean age of the CEA (+) CA19-9 (+) group was significantly higher when compared with the other groups (*p* < 0.05). Albumin level was significantly lower in the CEA (+) CA19-9 (+) group than in the CEA (-) CA19.9 (-) and CEA (+) CA19.9 (-) groups. There was no significant difference in terms of tumor size between groups. While 62% of patients in the study had left colon involvement, tumor location did not change between groups. The distribution of demographic data and laboratory tests between groups is shown in Table I. Pathological LND involvement was observed in 25% (n = 39) of patients enrolled in our study. While no pathological LND involvement was detected in the CEA (-) CA19-9 (+) group, 15 (20%) patients in the CEA (-) CA19-9 (-) group, 6 (13%) patients in the CEA (+) CA19-9 (-) group, and 18 (69%) patients in the CEA (+) CA19-9 (+) group showed LND involvement on histopathological examination. It was found that LND involvement was significantly increased in the CEA (+) CA19-9 (+) group compared to the other groups. Histopathology of all patients was reported as adeno-

Figure 1. Distribution of patients according to CEA and CA19-9 status.
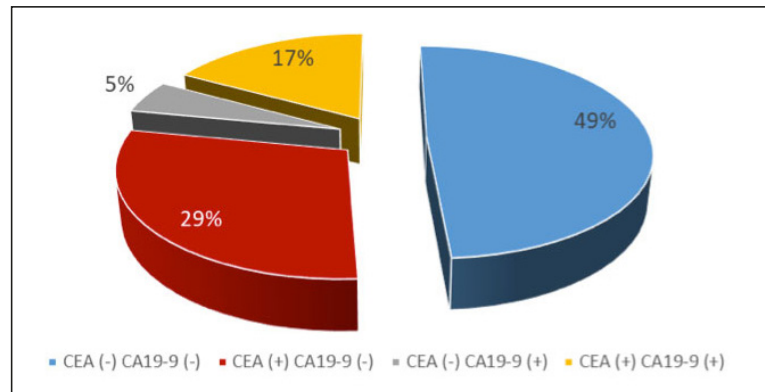
Table I. Demographic and laboratory characteristics of study groups according to CEA and CA19-9.

Variables	All Patients (n = 154)	CEA (-) CA19-9 (-) (n = 76)	CEA (+) CA19-9 (-) (n = 45)	CEA (-) CA19-9 (+) (n = 7)	CEA (+) CA19-9 (+) (n = 26)
Age	68.58 ± 11.91	65.64 ± 11.31[a]	67.44 ± 11.42[b]	70.57 ± 4.27	78.58 ± 10.83
Gender, n (%)					
Male	92 (60%)	40 (53%)	33 (73%)	4 (57%)	15 (58%)
Female	62 (40%)	36 (47%)	12 (27%)	3 (43%)	11 (42%)
WBC	7.60 ± 2.60	7.36 ± 2.46	8.01 ± 2.95	7.55 ± 1.96	7.61 ± 2.52
Hgb	11.83 ± 2.36	12.23 ± 2.40	11.89 ± 2.20	10.33 ± 1.80	10.94 ± 2.35
Plt (10^9/L)	326 (31 - 958)	338 (184 - 958)	308 (31 - 958)	360 (184 - 513)	312 (160 - 958)
RDW (fL)	45.44 ± 8.81	44.11 ± 6.31[c]	48.99 ± 7.20	44.60 ± 1.27	43.42 ± 4.02[b]
INR	1.02 ± 0.14	1.04 ± 0.18	0.99 ± 0.09	1.01 ± 0.06	0.99 ± 0.08
Fibrinogen (mg/dL)	443.52 ± 107.45	424.03 ± 116.10[d]	456.94 ± 100.31	510.14 ± 28.16	454.14 ± 101.29
Urea (mg/dL)	36.41 ± 9.52	35.11 ± 11.18	37.15 ± 9.31	26.28 ± 8.67	41.69 ± 9.93
Creatinine (mg/dL)	0.66 ± 0.27	0.64 ± 0.29	0.71 ± 0.27	0.61 ± 0.24	0.60 ± 0.17
ALT (u/L)	13.49 ± 3.97	15.13 ± 4.30	12.20 ± 4.42	11.86 ± 5.30	11.35 ± 3.63[a]
AST (u/L)	18.21 ± 4.57	18.47 ± 3.90	18.24 ± 5.99	16.29 ± 3.88	17.88 ± 4.48
D. Bilirubin (mg/dL)	0.16 ± 0.07	0.18 ± 0.06	0.14 ± 0.07	0.09 ± 0.02[d,e]	0.17 ± 0.08
I. Bilirubin (mg/dL)	0.27 ± 0.07	0.29 ± 0.08	0.27 ± 0.06	0.27 ± 0.07	0.23 ± 0.06
Total Protein (g/L)	68.43 ± 4.97	68.29 ± 4.18	70.58 ± 5.97	66.65 ± 4.65	65.82 ± 3.68
Albumin (g/L)	40.17 ± 4.77	40.85 ± 4.39	41.41 ± 4.38	36.60 ± 5.58	37.39 ± 4.82[a,b]
CRP (mg/dL)	25 (0.29 - 201)	22 (0.72 - 160)	20 (0.72 - 201)	46 (9 - 94)	37 (0.29 - 201)
Sodium (mmol/L)	139.07 ± 4.15	137.50 ± 4.51[a,c,d]	139.67 ± 3.29[f]	144.50 ± 4.54	141.27 ± 2.23
Glucose (mg/dL)	110.99 ± 27.94	121.34 ± 92.59	99.67 ± 24.77	91.86 ± 19.75	105.50 ± 25.82
BUN	16.99 ± 9.11	16.38 ± 9.35	17.33 ± 7.61	12.26 ± 5.91	19.45 ± 7.90
Potassium (mmol/L)	6.38 ± 1.29	4.40 ± 0.55	6.59 ± 1.64	4.20 ± 0.65	4.13 ± 0.75
Calcium (mg/dL)	9.26 ± 0.50	9.20 ± 0.50	9.40 ± 0.45	8.70 ± 0.43[e,f]	9.39 ± 0.46
CEA (ng/ml)	22.71± 4.91	2.38 ± 1.15	39.22 ± 5.17	2.08 ± 0.48	59.12 ± 9.42
CA19-9 (U/mL)	116.73 ± 38.80	10.50 ± 3.85	11.03 ± 4.55	70.18 ± 13.44	622.75 ± 174.44
Tumor size (cm)	5.63 ± 2.36	4.96 ± 2.01[c]	6.53 ± 2.60	4.64 ± 2.39	6.19 ± 2.09
Tumor localization, n (%)					
Left colon	96 (62%)	50 (66%)	28 (62%)	6 (86%)	12 (46%)
Right colon	58 (38%)	26 (34%)	17 (38%)	1 (14%)	14 (54%)
Pathologic lymph node involvement	39 (25%)	15 (20%)[a]	6 (13%)[b]	0[e]	18 (69%)

Differences between groups were evaluated with the post-hoc Tukey test; a *p*-value < 0.05 indicates statistically significant. [a]*p*-value is < 0.05 for differences between CEA (-) CA19-9 (-) and CEA (+) CA19-9 (+). [b]*p*-value is < 0.05 for differences between CEA (+) CA19-9 (-) and CEA (+) CA19-9 (+). [c]*p*-value is < 0.05 for differences between CEA (+) CA19-9 (-) and CEA (-) CA19-9 (-). [d]*p*-value is < 0.05 for differences between CEA (-) CA19-9 (-) and CEA (-) CA19-9 (+). [e]*p*-value is < 0.05 for differences between CEA (-) CA19-9 (+) and CEA (+) CA19-9 (+). [f]*p*-value is < 0.05 for differences between CEA (-) CA19-9 (+) and CEA (+) CA19-9 (-).
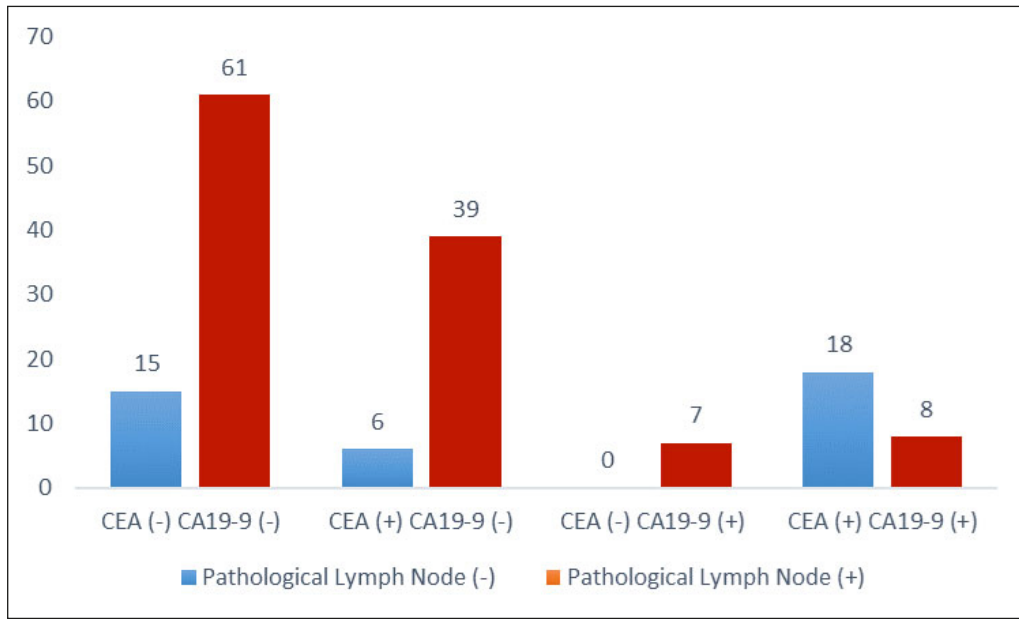
Figure 2. Pathological lymph node involvement according to the groups.

carcinoma without lymphatic and neural invasion in our study population. The pathological LND involvement in each group is shown in Figure 2.

When comparing patients by pathologic LND involvement, LND involvement was significantly higher in patients > 65 years old. Being over 65 years was found to be a risk factor for pathologic

LND involvement. CEA and CA19-9 positivity were risk factors, whereas gender and right or left colon tumor involvement were not risk factors for pathologic LND involvement. The distribution of demographic data and laboratory tests between LND (+) and LND (-) patients and the risk factors for LND involvement are presented in Table II.

Table II. Demographic and laboratory characteristics of study population according to LND involvement.

Variables	Pathological Lymph Node (+) (n = 39)	Pathological Lymph Node (-) (n = 115)	Pearson Chi-Square (*p*-value)	OR (95% CI), (*p*-value)
Age				
< 65 years	9 (23%)	50 (43%)	5.129	0
≥ 65 years	30 (77%)	65 (57%)	(*p* = 0.024)	2.564 (1.117 - 5.887)
				(***p* = 0.026**)
Gender				
Female	18 (46%)	44 (38%)	0.754	0.723 (0.347 - 1.505)
Male	21 (54%)	71 (62%)	(*p* = 0.385)	(***p* = 0.386**)
Laterality				
Right Colon	15 (38%)	43 (37%)	0.014	0.956 (0.452 - 2.018)
Left Colon	24 (62%)	72 (63%)	(*p* = 0.905)	(*p* = 0.905)
CEA (-) CA19-9 (-)	15 (39%)	61 (53%)	33.554	0
CEA (+) CA19-9 (-)	6 (15%)	39 (34%)	(*p* < 0.001)	0.626 (0.224 - 1.750)
				(*p* = 0.371)
CEA (-) CA19-9 (+)	0	7 (6%)		0
CEA (+) CA19-9 (+)	18 (46%)	8 (7%)		9.150 (3.345 - 25.03)
				(***p* < 0.001**)

OR: Odds Ratio, CI: Confidence Interval. A *p*-value < 0.05 indicates statistically significant.

Discussion

This study found that pathologic LND involvement was significantly higher in patients with CEA (+) and CA19-9 (+) preoperatively defined as early-stage colon cancer who underwent surgery. In addition, age was found to be a significant risk factor for pathological LND involvement. Commonly, LNDs form the center of the immune system. When an infection occurs or a person is vaccinated, immune cells assemble, activate, and proliferate to mobilize an effective immune response at LND sites[13]. LND metastasis is used in all current cancer staging systems, especially in the tumor node metastasis system developed by the Union for International Cancer Control and the American Joint Committee on Cancer (AJCC)[14]. LND involvement is an important factor in predicting disease-free survival (DFS) and overall survival (OS) in patients with early-stage colorectal cancer[15]. In this study, pathologic LND involvement was found in 25% of patients with colon cancer. Similarly, in a study by Bostanci et al[16], LND involvement was found in 21.9% of patients with colon cancer.

Age is a significant and independent risk factor for LND involvement in many cancers, and Wildiers et al[17] found that axillary LND involvement increases in breast cancer patients after age 70. In contrast, Xie et al[18] suggested that the risk of LND metastasis was higher in younger patients with early-stage colon cancer. In another study[19], young age was related to LND involvement in colorectal cancer. In a population-based study, Khan et al[20] observed a negative correlation between age and LND positivity in colon cancer patients. Unlike the previous studies[18-20], in our study, age was found to be a risk factor for developing LND involvement. This study found that LND involvement was significantly higher in patients ≥ 65 years old. We think the difference between studies may be related to patient selection and methodology to determine LND involvement.

In moleculer studies[21], new possible markers have been examined in colon cancer for diagnosis and prediction of prognosis, however only a few markers are recommended in practical use in the clinic. CEA and CA19-9 are the most used and studied serum tumor biomarkers for colon cancer. Elevated preoperative CEA level was found to be correlated with poor prognosis and CEA is used as a prognostic factor and for monitoring the disease during systemic therapy also

with metastatic disease[22]. Topdagi and Timuroglu[23] reported that an average CEA level does not mean that the patient does not have colorectal carcinoma and suggested that these patients should be investigated in detail. In a study by Xu et al[24], LND metastasis was related to preoperative CEA level. Bandara et al[25] compared the efficacy of CEA and IL-8 in colorectal cancer patients and showed that most of the colorectal cancers were diagnosed at a moderately differentiated stage in their study with increased CEA levels and that CEA can be used as a diagnostic marker in favor of IL-8. However, to date data is insufficient for the use of CA-19.9 in the management of all stages of colon cancer patients[22].

Our study found pathologic LND involvement in 25.32% (n = 39) of patients. CEA (+) was found in 61.5% (n = 24) and CA-19-9 was found in 54.5% (n = 18) of LND (+) patients. LND involvement was highest in patients with CEA (+) and CA19-9 (+) preoperatively, suggesting that concurrent preoperative CEA and CA19-9 positivity may be a more valuable parameter for predicting LND involvement in colorectal cancer.

Limitations

Our study had several limitations. First, the number of patients was relatively small, and the study was retrospective in a single center. Second, tumor size could not be included in the analysis of LND involvement. However, regarding our knowledge, this is the first study in the literature that evaluates the relationships between CEA, CA19-9 status and demographic and laboratory characteristics and LND involvement in patients with colon cancer. Further comprehensive multicenter studies with more significant numbers of patients are needed to understand the role of tumor markers in the early stage of colon cancer.

Conclusions

We demonstrated that pathological LND involvement was significantly increased in colon cancer patients when both preoperative CEA and CA19-9 were elevated. In addition, being older than 65 years of age was found to be a significant risk factor for the development of LND involvement. Clinicians should pay more attention to LND involvement when CEA and CA19-9 are elevated preoperatively in colon cancer patients.

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