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An investigation on the relationship of preoperative CEA/CA 19-9 levels with clinicopathological features and recurrence in colorectal cancer

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Abstract

Aim: The clinical benefits of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9) levels for diagnosis and prognosis in colorectal cancer are controversial, and studies on this subject have reported various results. This study aimed to reveal whether the preoperative CEA and CA 19-9 levels were correlated with clinicopathological features, recurrence, and overall survival and investigate the tumor marker with more predictive characteristics.

Material and Methods: An analysis was performed of on the records of 142 patients who were hospitalized due to colorectal cancer and underwent surgery was performed. The demographic, biochemical, and pathological characteristics of patients were investigated retrospectively.

Results: A significant difference was observed in the CRP level measured in the preoperative period. In multivariate analyses, only age (HR=1.19, 95% CI 1.05-1.34, p=0.004) and recurrence (HR=20.65, 95% CI 3.14-135.62, p=0.002) were found to affect overall survival. Nevertheless, CEA and CA19-9 elevations were not predictive of overall survival. CEA and CA 19-9 elevations did not have a superiority over each other in predicting the clinicopathological pattern of the disease. Nonetheless, it was determined that the elevated CEA+CA 19-9 indicated a more aggressive pathology in terms of clinicopathological pattern. It was not found predictive of recurrence and overall survival, which are significant markers in the prognosis of the disease.

Discussion: It was concluded that the preoperative serum tumor marker elevation, which was the subject of our study, should be considered in decisions related to neoadjuvant/adjuvant chemoradiotherapy (CRT) and more aggressive treatment in advanced cancer.

Keywords

Colorectal Cancer, Carcinoembryonic Antigen (CEA), Cancer Antigen 19-9 (CA 19-9), Neoadjuvant Therapy

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Introduction

Colorectal cancers rank third among the most common cancers in the world and fourth in deaths due to cancer. Colorectal cancers are most commonly localized in the rectum, and the second most common location is the sigmoid colon [1]. Colorectal cancers can be treated with surgery, chemotherapy, and/or radiotherapy, and adjuvant treatment can be administered as an alternative. Various tumor markers can be used in cancer diagnosis and postoperative patient follow-up [2]. Carcinoembryonic antigen (CEA) is an oncofetal tumor marker and is essential in the diagnosis process in 70% of patients. Similarly, cancer antigen 19-9 (CA 19-9) level is one of the most common tumor markers used in colorectal cancers [3, 4].

A relationship between elevated preoperative serum CA 19-9 levels and poor prognosis was determined depending on the stage of the disease, and this relationship may be more effective than CEA; however, the effect of CA 19-9 was found to be limited in studies proving the contrary. In addition, the 5-year survival rate was reported to be lower in patients with elevated CEA and CA 19-9 [5]. It is not recommended to use the preoperative tumor marker level as a screening test or for diagnostic purposes; however, it can be used to give an idea about the spread of the disease. This study aimed to reveal whether the preoperative CEA and CA 19-9 levels were correlated with clinicopathological features, recurrence, and overall survival and investigate the more predictive tumor marker.

Material and Methods

This study investigated patients who were hospitalized and underwent surgery due to colorectal cancer between November 2016 and June 2021 in the General Surgery Clinic of University of Health Sciences Gülhane Training and Research Hospital based on their file records. Our study was approved by the decision of the University of Health Sciences Gülhane Training and Research Hospital Local Ethics Committee dated 23.09.2021 and numbered 46418926. Patients with unknown tumor marker values in the preoperative period, patients with inflammatory bowel disease such as ulcerative colitis and Crohn's disease, patients who underwent surgery due to benign pathologies such as diverticular diseases of the colon, patients undergoing surgery under emergency conditions, and patients under the age of 18 were excluded from the study.

The study included 142 patients who met the determined criteria. Data including CEA/CA 19-9 as preoperative biomarkers, biochemical parameters, computed tomography reports, and histopathological reports (tumor diameter, histopathological features of the tumor, length of the removed intestinal segment, the distance of the tumor to the proximal and distal surgical margins, number of metastatic and reactive lymph nodes, tumor budding level, histopathological pattern of the tumor, tumor diameter, and tumor stage), recurrence, colorectal obstruction, and follow-up periods of the patients were collected retrospectively. The patients were classified into four groups according to their tumor marker levels. The study was conducted by analyzing patients in four groups where one group consisted of patients with elevated serum CEA (CA 19-9 normal), one group consisted of patients with elevated serum CA 19-9 (CEA normal), one group consisted of patients with elevated levels in both tumor markers, and the last group consisted of patients with tumor markers within normal limits. Demographic, biochemical, clinical, and entire pathological data of the patients in the four groups were examined by comparing them with each other, and the effects of tumor marker levels on the clinicopathological characteristics of the patients were investigated.

Statistical Analysis

Statistical analysis was performed using the SPSS version 22.0 software. Descriptive statistics were expressed as numbers, percentages, mean and standard deviation, and median (min-max). The compliance of variables with Whether the variables conformed to normal distribution was evaluated using visual and analytical methods. Normally distributed continuous variables were analyzed within the group using the "Student's T-test and One Way ANOVA", and the variables with non-normal distribution were analyzed using the "Mann-Whitney U test and Kruskal-Wallis Test". Nominal values were compared using the "Chi-square analysis" and the "Fisher's Exact Test". The effect of elevated CEA and CA19.9 on survival was tested using the "Kaplan-Meier analysis" . The variables assumed to be associated with survival after univariant analyses and clinical evaluation were evaluated by multivariant analyses using the "Cox proportional hazards model." The regression model was expressed as Hazard Ratio (HR), a 95% confidence interval (CI). Comparisons with a p-value below 0.05 were considered statistically significant in the statistical analyses of the study.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The CEA and CA19-9 groups were compared in terms of tumor-related characteristics. Significant differences were observed in terms of tumor diameter (p=0.009), budding score (p=0.025), lymphovascular invasion (p=0.001), and number of metastatic lymph nodes (p=0.006). Paired analyses concluded that patients with elevated levels of both tumor markers had a greater tumor diameter compared to patients with only elevated CA19-9 levels (p=0.001), and patients with elevated CA19-9 levels had greater tumor diameter compared to patients with both tumor markers at normal levels (p=0.031). In terms of elevated CEA+CA, the tumor budding score was moderate or high in 56.5% of patients with elevated CEA only, 15% of patients with elevated CA19-9 only, 36.4% of patients with both tumor markers at elevated levels, and 48.1% of patients with both tumor markers at normal levels. The rate of lymphovascular invasion was 77.3% in patients with elevated CEA+CA19-9 levels and 40.3% in patients with both tumor markers at normal levels. The number of metastatic lymph nodes in patients with elevated CEA+CA19-9 was higher compared to patients with only elevated CEA levels (p=0.007), patients with only elevated CA19-9 levels (p=0.002), and patients with both tumor markers at normal levels (p=0.023). On the other hand, no difference was observed between the groups in terms of recurrence and mortality (Table 1).

The survival period was 46.4 months for patients with only

elevated CEA, 46.2 months for patients with only elevated CA19-9, 50.1 months for patients with CEA+CA19-9 elevation, and 48.2 months for patients with both tumor markers at normal levels. No difference was observed between the groups according to survival periods (Table 2).

The effect of elevated CEA and CA19-9 levels on survival was evaluated using the Cox proportional hazards model. The multivariant model included factors that were associated with mortality in univariant analyses and considered clinically significant. Factors in the model were tested for collinearity. The final version of the model included age, gender, budding score, recurrence, and CEA and CA19-9 elevations (-2 log likelihood= 45.418, X2=42.637, p<0.001). According to the multivariant analyses, only age (HR=1.19, 95% CI 1.05-1.34, p=0.004) and recurrence (HR=20.65, 95% CI 3.14-135.62, p=0.002) were determined to affect survival. Nevertheless, the CEA and CA19-9 elevations did not predict survival (Table 3).

Table 1. Comparison of tumor-related characteristics in patients classified according to CEA and CA19-9 elevation

		CEA (+) CA19-9 (-) (n=23)	CEA (-) CA19-9 (+) (n=20)	CEA (+) CA19-9 (+) (n=22)	CEA (-) CA19-9 (-) (n=77)	p value
		N (%)	N (%)	N (%)	N (%)	
Tumor location	Right colon	5 (21.7)	6 (30.0)	8 (36.4)	19 (24.7)	0.704†
	Left colon	3 (13.0)	3 (15.0)	4 (18.2)	19 (24.7)	
	Rectum	15 (65.2)	11 (55.0)	10 (45.5)	39 (50.6)	
Length of resected segment (cm)*		19 (13-32)	19.5 (11-42)	20.5 (11-45)	20.5 (9-55)	0.833†††
Proximal Length from the tumor (cm)*		10 (3.5-17)	9.5 (4-27)	9.2 (4-15)	9 (1.5-30)	0.273†††
Distal length from the tumor (cm)*		5 (1.5-14)	5.5 (3-12)	6.2 (3-28)	6 (1.5-20)	0.715†††
Tumor diameter (cm)*		4 (1.5-9.0)	3 (2-5)	4.7 (2-11)	4 (1.5-10)	0.009†††
Tumor macroscopy	Ulcerovegetan	20 (87.0)	18 (90.0)	16 (72.7)	65 (84.4)	0.487†
	Polypoid	1 (4.3)	0	0	2 (2.6)	
	Infiltrative	2 (8.7)	2 (10.0)	6 (27.3)	10 (13.0)	
Differentiation	Poor	0	3 (15.0)	1 (4.5)	6 (7.8)	0.413†
	Moderate	22 (95.7)	17 (85.0)	21 (95.5)	67 (87.0)	
	Good	1 (4.3)	0	0	4 (5.2)	
Budding	Low score	10 (43.5)	17 (85.0)	14 (63.6)	40 (51.9)	0.025†
	Medium-high score	13 (56.5)	3 (15.0)	8 (36.4)	37 (48.1)	
Lymphovascular invasion		10 (43.5)	3 (15.0)	17 (77.3)	31 (40.3)	0.001†
Perineural Invasion		9 (39.1)	4 (20.0)	7 (31.8)	14 (18.2)	0.155†
Number of reactive lymph nodes		16 (6-46)	22.5 (2-37)	19 (9-46)	18 (6-65)	0.186†††
Number of metastatic lymph nodes		0 (0-10)	0 (0-3)	1 (0-8)	0 (0-12)	0.006†††
MSS/ MSI	MSS	20 (87.0)	20 (100)	21 (95.5)	74 (96.1)	0.217†
	MSI	3 (13.0)	0	1 (4.5)	3 (3.9)	
Postoperative complication (+)		1 (4.3)	3 (15.0)	2 (9.1)	5 (6.5)	0.558†
Tumor obstruction (+)		3 (13.0)	4 (20.0)	4 (18.2)	9 (11.7)	0.736†
Length of hospital stay (days)*		8 (5-15)	8 (6-12)	9.5 (6-30)	7 (4-20)	0.202†††
Clavien Dindo Classification		1.27 ± 0.46	1.88 ± 0.35	1.86 ± 0.66	1.70 ± 0.64	0.079††
Recurrence (+)		1 (4.3)	1 (5.0)	3 (13.6)	11 (14.3)	0.438†
Follow-up period (months)*		40 (14-47)	30 (13-48)	42 (12-52)	41 (12-50)	0.142†††
Mortality (+)		1 (4.3)	1 (5.0)	2 (9.1)	6 (7.8)	0.899†

†Chi-square, ††One-Way ANOVA, †††Kruskal Wallis
*Median (min-max)
** CEA: carcinoembryonic antigen, CA 19-9: Cancer antigen 19-9, MSS: Microsatellite stable, MSI: Microsatellite instabilityle
*** A p-value below 0.05 was considered significant; significant values were typed in bold.

Discussion

Colorectal cancers rank second in the world after lung cancer among deaths due to cancer and are the most common cancer of the gastrointestinal system [6, 7]. Knowing the prognostic factors affecting the course of the disease, accurate staging, and selection of selecting the best treatment for the patient and the disease are quite important in colorectal cancers.

The literature on the tumor markers used more effectively used in the diagnosis and follow-up of colorectal cancer, alone or in combination, contains controversial and different outcomes. CEA is an oncofetal protein used in diagnosing colorectal cancer; however, it has been listed as an independent prognostic criterion concerning colorectal cancer in some consensus treatment guidelines [8, 9]. The literature also contains studied arguing that CEA is an independent variable in predicting the prognostic outcome [10, 11]. Chen et al. suggested including the CEA level in the staging system [12].

Chronic inflammation has a significant role in the pathogenesis of colorectal cancer. It has been reported that especially

Table 2. The relationship of CEA and CA19-9 levels with survival

		n	Survival period (months)	95% CI	p value
CEA (ng/ml)	<3	97	48.2	47.0-49.5	0.602
	≥3	45	49.9	48.1-51.8	
CA19-9 (U/ml)	<37	104	48.2	47.1-49.4	0.456
	≥37-200	38	50.2	48.2-52.2	
Coexistence of CEA and CA19-9	CEA (+) CA19-9 (-)	23	46.4	45.4-47.4	0.964
	CEA (-) CA19-9 (+)	20	46.2	42.9-49.5	
	CEA (+) CA19-9 (+)	22	50.1	48.1-52.1	
	CEA (-) CA19-9 (-)	77	48.2	46.8-49.6	

†The Kaplan-Meier Survival analysis; p- value was obtained by the log rank test.
* CEA: carcinoembryonic antigen, CA 19-9: Cancer antigen 19-9
** A p-value below 0.05 was considered significant; significant values were typed in bold.

Table 3. Multivariate analysis for overall survival as the Cox proportional hazards model

		n	HR	95% CI	p value
Age			1.19	1.05-1.34	0.004
Gender	Female	59	1	0.27-6.69	0.713
	Male	83	1.35		
Budding	Low score	81	1		
	Moderate-high score	61	1.71	0.36-8.01	0.495
Recurrence	Yes	16	20.65	3.14-135.62	0.002
	None	126	1		
Tumor stage	Stage I, II	90	1		
	Stage III, IV	52	2.78	0.26-29.18	0.393
Coexistence of CEA and CA19-9	CEA (-) CA19-9 (-)	77	1		
	CEA (+) CA19-9 (-)	23	0.65	0.05-8.04	0.741
	CEA (-) CA19-9 (+)	20	0.2	0.01-16.30	0.481
	CEA (+) CA19-9 (+)	22	2.46	0.12-50.5	0.559

* CEA: carcinoembryonic antigen, CA 19-9: Cancer antigen 19-9
** A p-value below 0.05 was considered significant; significant values were typed in bold.

patients who develop colorectal cancer have higher CRP levels, and the development of colorectal cancer increased 1.88 times in patients with a CRP level higher than 1.19 mcg/mL [13]. Our study concluded that the CRP level measured in the preoperative period was significantly higher in groups with elevated CA 19-9 and CEA+CA 19-9 levels compared to the group with normal CEA+CA 19-9 levels (p=0.014). In their study, Zhou et al. found that the CRP level measured in the preoperative period was higher in patients with elevated serum CEA and CA 19-9 levels compared to patients with normal serum tumor marker levels [14]. We think that the preoperative CRP elevation is associated with advanced clinicopathological characteristics.

According to our study data, tumor diameter (p=0.009), lymphovascular invasion (p=0.001), and number of metastatic lymph nodes (p=0.006) were found to be significant. Our results indicated that elevation of both tumor markers led to more metastatic lymph node involvement, it was associated with larger tumor diameter and greater lymphovascular invasion, and there was no significant difference between CEA and CA 19-9.

In some studies on the relationship between tumor marker elevation and tumor pathology, tumor diameter, lymphovascular invasion, and the number of metastatic lymph nodes were reported to be significantly higher in patients with elevated serum CEA and CA 19-9 levels [15-17].

In their study, Lakemayer et al. recommended thatusing only CEA be used with other screening methods to determine colorectal cancer prognosis, predict neoadjuvant chemoradiotherapy decisions, and predict and monitor chemotherapy or radiotherapy after curative resection. It was not recommended to use the CA 19-9 alone for detecting colorectal cancer prognosis, monitoring ongoing therapy, or follow-up due to its poor sensitivity [18]. On the other hand, our study and the study of Lakemayer revealed that patients with elevated serum CEA levels received neoadjuvant therapy at a higher rate, and serum CEA elevation emerged as a parameter to be considered when deciding on neoadjuvant therapy. We can recommend neoadjuvant chemotherapy/CRT for patients with both tumor markers at elevated levels of both tumor markers. In the study by Partyka et al., it was recommended to monitor the CEA level when CEA and CA 19-9 levels were used to diagnose the disease and monitor prognosis [19]. In another study by Gao et al., it was demonstrated that measuring serum tumor markers in combination rather than using CEA alone had a better sensitivity in diagnosing colorectal cancer and predicting the prognosis [20]. When groups with only elevated CEA or CA 19-9 levels were compared, this study showed that they were not superior to each other concerning the clinicopathological results.

Study Limitations

The limitations of our study included the retrospective design and the lack of analysis of zing both tumor marker levels of in all patients in the preoperative period. Moreover, most patients with rectal colorectal cancer underwent neoadjuvant CRT; however, the heterogeneity caused by the fact that most patients with colon cancer did not receive neoadjuvant CRT also affected the results of our study.

Conclusion

The elevated CEA or CA 19-9 levels do not have a significant advantage over each other in predicting the clinicopathological pattern of the disease. Nevertheless, the elevated CEA+CA 19-9 levels indicate a more aggressive pathology in terms of clinicopathological pattern. Despite all, they have no predictive effect on recurrence and overall survival in predicting the prognosis of the disease. Multicentered, multilayered, and prospective studies, including postoperative treatments, are needed to confirm the clinical significance of combining tumor markers, homogeneous stage, and tumor localization. The analysis of these markers in combination canould provide significant data for clinical evaluation and patient management.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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