The Relationship Between Carcinoembryonic Antigen and Prognosis in Colorectal Cancer

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Abstract

Aim: Carcinoembryonic antigen (CEA) serves as a biomarker for gastrointestinal cancers, with high levels often indicating a poor prognosis. Specifically, CEA levels above 10 µg/L are associated with unfavorable outcomes, and those exceeding 20 µg/L are linked to metastatic disease. This investigation aims to explore the relationship between elevated preoperative CEA levels and the survival and prognosis of colon cancer patients at our institution.

Methods: This study was designed as a single-center, retrospective analysis involving colon cancer patients who underwent surgery at CUTF Balcalı Hospital from 2012 to 2022. Patients were stratified based on preoperative CEA levels into three groups: 3-10 µg/L (low-high), 10-20 µg/L (moderately high), and over 20 µg/L (very high). The study compared demographic data, pathological features, and survival outcomes across these groups.

Results: The study included 226 patients, 124 males and 102 females, with an average age of 61 years. Analysis revealed no significant difference in TNM and pathological stages among the groups. Notably, higher CEA levels were significantly correlated with increased instances of venous, perineural and lymphatic invasion. The occurrence of local, para-aortic, and peritoneal recurrences did not significantly differ across the groups, although liver metastasis was more prevalent in the first group.

Conclusions: The findings highlight a significant link between high preoperative CEA levels and an increased risk of lymphovascular and perineural invasion in colon cancer patients. This association underscores the potential for tailoring more intensive treatment regimens for patients with elevated CEA levels, including the possibility of enhanced chemotherapy or radiotherapy.

Keywords: CEA; colon cancer; biomarker; prognosis

1. Introduction

The prevalence of colorectal cancer (CRC) has been showing a global increase in recent years. In 2020, approximately 1.93 million new cases of CRC were diagnosed worldwide, resulting in 0.94 million deaths. According to GLOBOCAN data, colorectal cancers rank as the third most common cancer in men after prostate and lung cancer, and in women after breast and lung cancer [1,2]. Despite advancements in diagnosis and treatment, including surgery, chemotherapy, and radiotherapy, approximately 30% of colorectal cancer patients still experience recurrence. Recent studies have been focused on early detection of recurrent cases and predicting which patients are more likely to experience recurrence [3,4].

Tumor markers, mostly comprised of proteins and glycolipids, are biological substances that emerge due to carcinogenesis at various stages of cell development. Tumor markers not only indicate the presence of cancer but also provide information about the progression of the disease or response to treatment. Serum carcinoembryonic antigen (CEA) has been proposed as a tumor marker for the detection of CRC and for monitoring the response to treatment [5,6]. Various guidelines, such as those from the American Society of Clinical Oncology (ASCO) or the National Comprehensive Cancer Network (NCCN), recommend conducting a CEA test every three to six months for detection [7,8]. Despite these guidelines, the specific prognostic value of preoperative CEA levels in predicting long-term outcomes remains underexplored, especially in the context of localized versus advanced disease.

There are ongoing debates and research regarding the usefulness of CEA level increases in measuring recurrence and the efficacy of the CEA test as a follow-up method based on initial CEA levels [9-11]. Another point of contention is the degree of elevation in CEA levels and what the optimal cut-off value should be [12-16]. In this study, we aimed to investigate the relationship between preoperatively measured CEA values and postoperative survival and prognosis in colon cancer patients.

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2. Materials and Methods

Following approval from the local ethics committee on 08.12.2023, under permit number 139/35, patients who underwent surgical treatment for colon cancer at our clinic between 2012 and 2022 were included in the study. Patients under the age of 18, those with incomplete data, and cases of rectal cancers were excluded. This retrospective cohort study utilized a prospectively maintained database, ensuring the systematic collection of clinical, pathological, and follow-up data.

Patients were divided into three groups based on preoperatively measured carcinoembryonic antigen (CEA) levels: Group 1 (low-high, 3-10 µg/L), Group 2 (moderately high, 10-20 µg/L), and Group 3 (very high, over 20 µg/L). Variables compared among these groups included age, gender, body mass index, tumor localization, pathological stage, T, N, M stages, lymphatic invasion, perineural invasion, venous invasion, and follow-up data such as local recurrence, peritoneal recurrence, para-aortic recurrence, liver metastasis, and average survival.

Serum CEA levels were measured preoperatively. The normal range for serum CEA at our clinic is defined as 0–3.0 ng/mL. Pathological staging was conducted according to the seventh and eighth editions of the TNM Classification [17,18].

Typically, in general practice, patients were subjected to regular follow-ups every 3-6 months during the first two years post-surgery. In the first year, clinical, colonoscopic, and radiological examinations (chest, abdominal, and pelvic CT) were conducted, along with serial CEA measurements. Subsequently, follow-ups to detect local recurrence and metachronous disease typically involved annual CT scans, CEA tests, and colonoscopies. The diagnosis of recurrence was determined through clinical, radiological, endoscopic, and/or histological findings.

Statistical analysis was performed using SPSS 22.0 (IBM Corp). The suitability of numerical data for normal distribution was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Numerical parameters that conformed to normal distribution were presented as mean±standard deviation, while categorical data were expressed as number (percentage). The Kruskal-Wallis test was used for the comparison of numerical data. The chi-square test was applied for the comparison of categorical data. A p-value of less than 0.05 was considered statistically significant. For examining the cumulative survival data of the groups, the Kaplan-Meier analysis was utilized.

Table 1

Demographic and Clinical Data

CEA Value			Group 1 (3-10 ng/mL)	Group 2 (10-20 ng/mL)	Group 3 (>20 ng/mL)	P
Age			61.02±13.15	64.28±10.64	59.77±12.91	0.594
Gender		Male Female	54.2%(n=91) 45.8%(n=77)	61.1%(n=11) 38.9%(n=7)	53.8%(n=21) 46.2%(n=18)	0.848
BMI			26.46±4.3	24.75±3.37	26.64±4.94	0.195
Tumor Localization	Right	n %	76 45.2%	12 66.7%	18 46.2%	0.66
	Left	n %	69 41.1%	5 27.8%	16 41.0%	
	Multiple	n %	13 7.7%	0 0.0%	2 5.1%	
	Transverse	n %	10 6.0%	1 5.6%	3 7.7%	

Figure 1

Survival analysis.

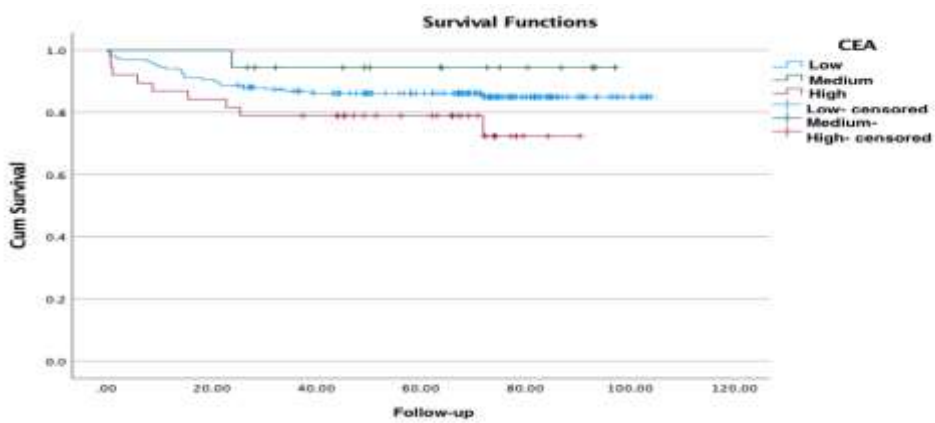

Table 2

Pathological outcomes

CEA Value		Group 1 (3-10 ng/mL)	Group 2 (10-20 ng/mL)	Group 3 (>20 ng/mL)	p
Pathological Grade	0	5.4% (n=9)	0.0% (n=0)	0.0% (n=0)	0.304
	1	16.2% (n=27)	22.2% (n=4)	10.5% (n=4)	
	2	32.3% (n=54)	55.6% (n=10)	36.8% (n=14)	
	3	34.1% (n=57)	16.7% (n=3)	36.8% (n=14)	
	4	12.0% (n=20)	5.6% (n=1)	15.8% (n=6)	
T Stage	0	0.6% (n=1)	0.0% (n=0)	0.0% (n=0)	0.384
	Tis	7.1% (n=12)	0.0% (n=0)	0.0% (n=0)	
	T1	5.4% (n=9)	11.1% (n=2)	7.7% (n=3)	
	T2	11.9% (n=20)	22.2% (n=4)	7.7% (n=3)	
	T3	19.0% (n=32)	16.7% (n=3)	20.5% (n=8)	
	T4	56.0% (n=94)	50.0% (n=9)	61.5% (n=24)	
N Stage	N0	57.1% (n=96)	83.3% (n=15)	51.3% (n=20)	0.419
	N1	26.8% (n=45)	11.1% (n=2)	33.3% (n=13)	
	N2	15.5% (n=26)	5.6% (n=1)	15.4% (n=6)	
	N4	0.6% (n=1)	0.0% (n=0)	0.0% (n=0)	
M Stage	M0	89.3% (n=150)	94.4% (n=17)	84.6% (n=33)	0.52
	M1	10.7% (n=18)	5.6% (n=1)	15.4% (n=6)	
Vascular Invasion	No	25.6% (n=43)	16.7% (n=3)	2.6% (n=1)	0.006*
	Yes	74.4% (n=125)	83.3% (n=15)	97.4% (n=38)	
Perineural Invasion	No	47.6% (n=80)	66.7% (n=12)	28.2% (n=11)	0.016*
	Yes	52.4% (n=88)	33.3% (n=6)	71.8% (n=28)	
Lymphatic Invasion	No	25.6% (n=43)	11.1% (n=2)	2.6% (n=1)	0.003*
	Yes	74.4% (n=125)	88.9% (n=16)	97.4% (n=38)	

Table 3

Follow-Up Data

CEA Value		Group 1 (3-10 ng/mL)	Group 2 (10-20 ng/mL)	Group 3 (>20 ng/mL)	p
Local Recurrence	No	96.4% (n=133)	100.0% (n=15)	100.0% (n=28)	0.449
	Yes	3.6% (n=5)	0.0% (n=0)	0.0% (n=0)	
Para-aortic Recurrence	No	97.8% (n=135)	100.0% (n=15)	100.0% (n=30)	0.608
	Yes	2.2% (n=3)	0.0% (n=0)	0.0% (n=0)	
Peritoneal Recurrence	No	94.0% (n=158)	100.0% (n=18)	100.0% (n=39)	0.169
	Yes	6.0% (n=10)	0.0% (n=0)	0.0% (n=0)	
Liver Metastasis	No	94.0% (n=158)	100.0% (n=18)	100.0% (n=39)	<0.001*
	Yes	6.0% (n=10)	0.0% (n=0)	0.0% (n=0)	

3. Results

A total of 226 patients were included in the study, with 168 in Group 1, 18 in Group 2, and 39 in Group 3. The male gender was predominant across all groups (p=0.848). Body mass index (BMI) was similar across the groups. A dominance of tumors located in the right colon was observed in all groups (45% vs 66.7% vs 46.2%, p=0.66). Demographic and clinical characteristics are presented in Table 1.

Pathological stage (p=0.304), T stage (p=0.384), N stage (p=0.419), and M stage (p=0.52) were similar across the groups. Venous invasion (74.4% vs 83.3% vs 97.4%, p=0.006), perineural invasion (52.4% vs 33% vs 71.8%, p=0.016), and lymphatic invasion (74.4% vs 88.9% vs 97.4%, p=0.003) were found to be higher in Group 3. Pathological data are shown in Table 2.

The presence of local recurrence (p=0.449), para-aortic recurrence (p=0.608), and peritoneal recurrence (p=0.169) were similar across the groups, while liver metastasis was more frequent in Group 1. Follow-up data are presented in Table 3.

The average survival time according to CEA groups was 91.23 for Group 1, 92.99 for Group 2, and 72.24 for Group 3 (p=0.153), as shown in Figure 1.

4. Discussion

In this study investigating the prognostic significance of elevated carcinoembryonic antigen (CEA) levels in colorectal cancer, we categorized the elevation of CEA into groups. While the highest levels of CEA were associated with adverse pathological

parameters, such as lymphovascular invasion or poorly differentiated tumors, this association did not significantly affect overall survival or recurrence rates.

CEA, a glycoprotein oncofetal antigen, is expressed in many epithelial tumors. First described by Gold and Freedman in 1965, this relatively inexpensive blood test has become an important marker in follow-up care. CEA, which is produced by cells in the colon, is elevated in approximately seventy percent of patients with CRC at diagnosis, making it an excellent marker for post-resection disease management and monitoring. [19]

Previous literature on extensive patient series has found significant associations between high preoperative CEA levels and age ($p<0.001$), lymphovascular invasion (LVI) ($p=0.002$), and stage ($p<0.001$). There were no significant differences between groups in terms of gender ($p=0.103$), BMI ($p=0.397$), and tumor localization ($p=0.327$) [18] Another comprehensive series showed that high CEA levels at presentation were associated with advanced TNM stage (stage 4, $p<0.001$ for each), increased perineural invasion ($p=0.023$), high metastatic lymph node count ($p<0.001$), tumor localization (left colon, transverse colon, and synchronous, $p=0.016$), advanced T stage (T3-4, $p<0.001$), intramural venous ($p=0.019$), presence of lymphatic invasion ($p=0.003$), and larger tumor volume ($p=0.02$). [20] The common theme in these studies was the comparison between normal and high preoperative CEA levels. The distinct feature of our cohort was that all patients had elevated CEA levels. Our study not only demonstrated the association between high CEA levels and adverse histological features but also showed that the presence of cellular-level invasion is correlated with the elevation of CEA levels.

In patients with colorectal cancer (CRC), most studies have identified preoperative carcinoembryonic antigen (CEA) level as a significant prognostic factor. Based on its clinical significance, a threshold value of 5 ng/mL is now commonly accepted, with values at or above this level representing high CEA [6]. In a multicenter study in the literature, high preoperative CEA (≥5 ng/ml) was an independent predictor of overall survival, disease-free survival, and recurrence, and was associated with a higher risk of death across the entire cohort.[21] Iacuzzo et al.'s series confirmed that a preoperative serum CEA level >12.5 ng/mL was associated with a higher risk of regional and/or distant recurrence in stage I, II, and III CRC patients. Additionally, they demonstrated that a preoperative serum CEA level >10 ng/mL was a significant predictor of all-cause mortality and poor disease-free survival (DFS) in stage III and IV CRC patients undergoing potentially curative surgical resection.[22] In our study, we could not demonstrate a relationship between the degree of CEA elevation and survival or local recurrences. We found an association only between CEA and liver metastasis, more pronounced in the group with lower levels of high CEA. We attribute this to the fact that all patients in our study had elevated CEA levels. If we had compared with patients with normal CEA levels, we might have been able to demonstrate its prognostic importance.

The most significant limitation of our study is its retrospective nature; additionally, our patient number was limited.

5. Conclusion

In conclusion, considering the association between preoperative high CEA levels and recurrence, clinicians may consider recommending more aggressive imaging modalities such as endoscopy or CT scans during postoperative follow-up, particularly for patients with very high preoperative CEA levels. Our findings underscore the potential utility of preoperative CEA levels in identifying high-risk patients who may benefit from more intensive monitoring or adjunct therapies. This approach could allow for a more personalized follow-up protocol. To validate our analyses and further investigate the appropriate threshold values necessary for the classification and individualization of treatment and follow-up procedures, additional studies with different populations are needed.

Statement of ethics

This study is approved by the Ethical Committee of Çukurova University Faculty of Medicine dated December 2023 (Approval No. 139/35).

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

İshak Aydın – Conception and Design, Drafting the article, Final Approval

Uğur Topal – Conception, Analysis and interpretation of data, Drafting the article, Final Approval

Burak Yavuz – Data Analysis, Revising the article, Final Approval

Orçun Yalav – Design, Revising the article, Final Approval

İsmail Cem Eray – Conception, Acquistion of Data, Drafting the article, Supervision, Final Approval

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