Original Paper

Carcinoembryonic Antigen CEA - Prognostic Value in Immediate Post-Operative Mortality in Colorectal Cancer

ANDREEA FIRUT[1], SORIN SCURTU[2], MICHAEL SCHENKER[3], NICOLETA GADEA[3], ANA MARIA PATRASCU[4], VLAD PADUREANU[5], STEFAN PATRASCU[6], VALERIU SURLIN[6]

[1]PhD student, University of Medicine and Pharmacy of Craiova, Romania

[2]Department of Surgery, Clinical Hospital of Filiasi, Romania

[3]Department of Oncology, University of Medicine and Pharmacy of Craiova, Romania

[4]Department of Haematology, University of Medicine and Pharmacy of Craiova, Romania

[5]Department of Internal Medicine, University of Medicine and Pharmacy of Craiova, Romania

[6]Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Introduction: This study investigates the prognostic significance of carcinoembryonic antigen (CEA) levels in predicting early postoperative mortality in patients who have undergone colorectal cancer surgery. Methods: Between 2017 and 2022, total of 325 patients were enrolled in the study, and their preoperative serum CEA levels were measured. Relevant clinical and operative data were extracted and correlations between CEA levels and postoperative mortality was analysed. Results: Among the surgical cases, 180 patients (55.3%) exhibited elevated CEA levels. Within the early postoperative period of 30 days, 14 patients (4.3%) succumbed, comprising 8 cases (2.4%) of colon cancer and 6 cases (1.8%) of rectal cancer. Notably, only 3 cases (0.9%), consisting of 1 (0.3%) colon cancer and 2 (0.6%) rectal cancer cases, were associated with an elevated CEA level. However, no statistically significant correlations were observed between CEA levels and early postoperative mortality. Conclusions: Our findings indicate that increased CEA levels may not serve as a reliable non-invasive marker for identifying patients at high risk of early mortality in the context of colo-rectal cancer surgery.

KEYWORDS: *Postoperative mortality, carcino-embryogenic antigen, colon cancer.*

Introduction

According to official data, colorectal cancer (CRC) has emerged as a predominant form of neoplasia over the past decade, ranking as the third most common neoplastic condition in men, following lung and prostate cancer, and the second most common in women, after breast cancer [1].

Surgical intervention represents the sole curative approach for CRC, yet postoperative mortality persists despite advancements in diagnostic and therapeutic modalities.

Carcinoembryonic antigen (CEA), a glycoprotein initially identified in colon cancer cells by Freedman and Gold [2,3], has been linked to various malignancies, with colorectal cancer expressing CEA in approximately 90% of adenocarcinoma cases [3].

Moreover, CEA elevation is observed in non-malignant conditions such as pulmonary emphysema, liver cirrhosis, cholecystitis, pancreatitis, peptic ulcer, and colitis, thereby limiting its specificity as a marker for a particular cancer type [4,5].

Additionally, smokers typically exhibit raised serum CEA levels beyond 5µg/L [6].

Given its lack of specificity, CEA determination is not recommended for definitive diagnosis or routine screening.

Nevertheless, it holds prognostic value and aids in post-treatment monitoring [7-9].

A normal serum CEA level is considered to be below or equal to 3.0µg/L.

Levels exceeding 5µg/L but below 10µg/L indicate localized disease with a low probability of recurrence, whereas values surpassing 10µg/L suggest advanced disease with a higher likelihood of recurrence.

Serum levels exceeding 20µg/L are typically associated with metastatic disease [10].

Persistent elevation of CEA during or after chemotherapy indicates inadequate response to current treatment, necessitating re-evaluation of therapeutic strategies and portending an unfavorable disease prognosis.

Furthermore, elevated CEA levels following surgery may signify the presence of residual disease or distant metastasis.

10.12865/CHSJ.49.04.14

The primary objective of this investigation is to evaluate the utility of CEA as a prognostic indicator in relation to immediate postoperative mortality.

Material and Methods

Patient selection

Our study included all patients admitted between January 1st 2017 and December 31st 2022 in the Surgery and Oncology Departments of the Emergency County Hospital of Craiova, Romania.

All patients underwent comprehensive clinical and paraclinical investigations, including preoperative abdominal ultrasonography, computed tomography, magnetic resonance imaging (in case of rectal cancer), and extended panel blood test including tumoral markers (CEA, CA19-9).

Patients were operated in different centres, and only patients with scheduled operations were included in the study.

All patients benefited from neoadjuvant treatment, consisting in chemo-and radiation therapy. Serum CEA was determined 2-3 days prior to the surgical procedure.

We included in the study only those values determined preoperatively, since we did not have access to CEA values before the initiation of neoadjuvant therapy.

The patients were followed from the moment of diagnosis until 30 days after the surgical procedure. Two clinical assessments were conducted subsequent to the discharge of patients, with a 7-day interval separating the evaluations.

The inclusion criteria consisted of (*i*) histologically-confirmed colonic or rectal carcinoma, (*ii*) previous preoperative adjuvant treatment, and (*iii*) preoperative serum CEA determination.

Study design and data selection

The study group was stratified into two distinct cohorts based on their serum carcinoembryonic antigen (CEA) levels: a negative cohort with concentrations below 5.0ng/ml, and a positive cohort with concentrations equal to or exceeding 5.0ng/ml.

CEA values of 5ng/dl were considered as cut-off value instead of lesser values due to its superior predictive value in certain categories, such as smokers, patients with benign liver disease, peptic ulcer, etc [11,12].

Immediate mortality, in the context of this study, referred to mortality occurring within the initial 30 days following surgical intervention.

The relevant data was obtained from the medical files and from the institution's electronic database, and was stored as Microsoft Excel documents.

All participants were included in this research after providing informed consent.

The study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ethics Committee of the University of Medicine and Pharmacy of Craiova (protocol no 71/28.04.2022).

Statistical analysis

Statistical comparisons between the groups were conducted using the Fisher exact test for categorical variables and the Student's t-test for assessing normal distribution and homogeneity of variances in continuous variables.

Positive and negative predictive values, along with means and standard deviations, were computed for each parameter.

For nonparametric data, descriptive statistics such as median and range (minimum and maximum) were employed, while parametric data were summarized using the mean and standard deviation.

Statistical significance was determined at a significance level of $p<0.05$.

Correlations between different subgroups were assessed using Pearson correlation coefficient (r), with values ranging from-1 to 1.

An r-value of 1 indicated a perfect positive linear relationship, while an r-value of-1 indicated a perfect negative linear relationship.

An r-value of 0 was representative for a lack of linear relationship between the variables.

Results

A total of 325 patients with colorectal cancers were included in the study, of which 179 with colon cancer (CC) (55.07%) and 146 with rectal cancer (RC) (44.92%).

Notably, the study incorporated 107 patients with rectal cancer (32.92%), in addition to 39 patients diagnosed with cancer at the junction of the rectum and sigmoid colon (12%).

A subset of 14 patients experienced mortality within the initial 30-day postoperative period.

The gender analysis of the 325 patients showed an almost 2:1 ratio in favour of men: 124 (38.15%) were women and 201 (61.84%) men.

10.12865/CHSJ.49.04.14

The distribution of gender within the subset of colon cancer (CC) cases exhibited a relatively equitable pattern.

Thus, of the 179 cases of CC 80 (24.6%) were female and 99 (30.4%) were male.

In contrast, for rectal cancer (CR) cases, there was a distinct male predominance.

Specifically, 44 cases (13.5%) were associated with female patients, while 102 cases (31.3%) were associated with male patients.

Of the 325 cases 180 (55.38%) had positive CEA values before surgery.

The distribution of CEA status by tumor location was as follows: 94 out of 179 patients (28.9%) with colon cancer (CC) and 86 out of 146 patients (26.4%) with rectal cancer (RC) had positive CEA status.

The distribution according to location, CEA and sex groups is represented in Table 1.

Table 1: Groups distribution according to tumor topography, gender, and CEA level.

Colon Cancer				**Rectal cancer**			
Women (80 pts)		**Men (99 pts)**		**Women**		**Men**	
Total	CEA(+)	Total	CEA(+)	Total	CEA(+)	Total	CEA(+)
80 (24.6%)	36 (11.0%)	99 (30.4%)	58 (17.8%)	44 (13.5%)	32 (9.8%)	102 (31.3%)	54 (16.6%)
Total cases: 179 (55.07%)				Total cases: 146 (44.9%)			
Total CEA(+) cases: 94 (28.9%)				Total CEA(+) cases: 86 (26.4%)			
Total cases: 325 (100%)							
Total CEA(+) cases: 180 (55.38%)							

No statistical differences were observed between CEA (-) and CEA (+) groups in term of tumor grading, size, age, and haemoglobin (Hb) level.

No correlations were found between the above-mentioned variables and CEA level (Table 2).

Table 2. CEA status in relation to tumor size, grading, age, and haemoglobin level in colorectal cancer patients.

Variable Mean (±Std Dev)	***CEA (-)***	***CEA (+)***	***r (Pearson)***	***p (t-test)***
Mean tumor size (cm)	5.61 (±2.90)	5.37 (±2.46)	0.04	0.04
Tumor grading	2.18 (±0.48)	2.13 (±0.50)	0.04	0.42
Age (y)	67.90 (±12.46)	67.64 (±9.87)	0.01	0.83
Haemoglobin (g/dl)	11.52 (±2.18)	11.67 (±2.23)	0.06	0.55

Among the cohort of 325 cases subjected to a surgical intervention, a total of 14 cases (4.3% of the sample), experienced mortality within the initial postoperative month.

Of these fatalities, 8 patients (2.4%) presented with colonic carcinoma, while the remaining 6 cases exhibited rectal carcinoma, amounting to 1.8% of the overall population.

Notably, only 3 cases (0.9%) of the 8 colon cancer cases, exhibited elevated preoperative carcinoembryonic antigen (CEA) levels.

The distribution according to location, CEA and sex is presented in Table 3.

Table 3. Distribution of mortality according to tumor location, gender, and CEA level.

Colon cancer				**Rectal cancer**			
Women		**Men**		**Women**		**Men**	
Total	CEA+	total	CEA+	Total	CEA+	Total	CEA+
3 (0.9%)	0	5 (1.5%)	1 (0.3%)	0	0	6 (1.8%)	2 (0.6%)
Total cases: 8 (2.4%)				Total cases: 6 (1.8%)			
Total CEA+ cases: 1 (0.3%)				Total CEA+ cases: 2 (0.6%)			
Total cases: 14 (4.3%)							
Total CEA+: 3 (0.9%)							

In all 14 (100%) cases adenocarcinoma was identified as the pathological form.

Of the 14 cases, 9 (64.2%) presented a form of anemia, with mean Hb level of 10.6g/dl in patients with colon cancer and 9.9g/dl in rectal cancer patients.

Only 3 cases with anemia had increased CEA level (one patient with colon cancer and 2 with rectal cancer).

Concerning the TNM staging, it was observed that all cases with mortality in the first month were stage IIIB and IV, as noted in Table 4.

Table no 4. Distribution of cases based on mortality and TNM stage.

Total cases	Colon cancer (8 cases; 2.4%)		Rectal cancer (6; 1.8%)	
14 (100%)	Std III B	Std IV	Std III B	Std IV
CEA +	0	1 (0,3%)	0	2 (0,6%)

The examination of the surgical procedures revealed a consistent pattern in all patients diagnosed with colon cancer, wherein tumor resection was carried out as the initial stage procedure, irrespective of the TNM staging.

Conversely, in patients with rectal cancer, resection was solely conducted in those with stage IIIB, while in stage IV a consistent approach of supratumoral anus was maintained in all cases.

Discussions

Colorectal cancer ranks among the most prevalent malignancies worldwide, necessitating the continuous exploration of reliable markers for early detection, treatment response assessment, and patient prognosis.

CEA, a glycoprotein expressed in a variety of cancers, is notably upregulated in approximately 90% of colorectal adenocarcinomas.

Given its widespread occurrence, CEA has emerged as an attractive candidate for clinical application in CRC management.

On the other hand, mortality in the first postoperative month following colorectal cancer surgery remains high, although in recent years, with advances in diagnostic and treatment methods, a certain decrease has been noted. International studies report a mortality rate between 0 and 8%, therefore the mortality identified in our study is within the international average [13-15].

The utility of CEA as a perioperative marker of prognosis and oncologic monitoring in colorectal cancer is well established since its first description in 1965 by Gold and Freedman, which first extracted it from colon cancer and embryonic tissues.

Subsequently, extensive efforts have been undertaken to identify additional functions for this biomarker, beyond its conventional roles in diagnosis, prognosis assessment, recurrence detection, metastasis monitoring, and the evaluation of chemotherapy efficacy. [16-18].

Despite a multitude of published studies illustrating the prognostic significance of carcinoembryonic antigen (CEA) in colorectal cancer (CRC) patients, a consensus on the specific cutoff values has yet to be reached.

While the serum level of carcinoembryonic antigen (CEA) is frequently elevated in cancer patients, it can also be raised in various benign conditions, including cirrhosis, inflammatory bowel disease, pancreatitis, and among heavy smokers.

In an effort to enhance the specificity and sensitivity of CEA as a diagnostic marker for malignancies, the decision was made to raise its threshold value.

Taking into account these considerations and recognizing the heterogeneity of the study population, a higher CEA threshold of 5ng/dl was adopted for this research.

Our study indicated no correlations between increased CEA levels and certain clinical and biological variables, such as tumor grading and size, age, or haemoglobin level.

These findings seem to at least partially contradict previous research indicating a direct connection between CEA level and these variables [19].

Recently, the role of CEA as a marker for mortality risk assessment was analysed, with encouraging results.

A multicentric longitudinal cohort study of Li et al indicated that the dynamic measurements of CEA, alongside CA 19-9 and CA 125, were recommended to monitor the prognosis of colorectal cancer patients [17].

Another study of Zhang et al showed that postoperative CEA levels seem to predict outcomes after resection of colorectal cancer in patients with normal preoperative CEA levels [20].

However, to our knowledge, no study specifically identifying a relationship between CEA values and early postoperative mortality in colorectal cancer has been published.

While CEA has demonstrated considerable clinical utility, certain limitations warrant consideration.

Based on our analysis, no link between CEA+cases and mortality have been identified.

On the contrary, the percentage of CEA-cases with nefarious outcomes was higher than CEA+cases.

Based on these findings, it seems safe to assume that its clinical and prognostic application must be interpreted judiciously in conjunction with other diagnostic tools.

10.12865/CHSJ.49.04.14

Further research and advancements in biomarker discovery may hold promise for improving CRC patient care, ultimately contributing to enhanced treatment outcomes and overall survival.

Conclusion

Serum CEA should not be used as a prognostic marker for early mortality in colorectal cancer surgery.

Integrating CEA with other emerging biomarkers and advanced imaging techniques may enhance its diagnostic and prognostic value in clinical practice.

Conflict of interests

None to declare.

References

1. Planul Național de Combatere și Control al Cancerului [National Plan for the Prevention and Control of Cancer] [Online]. Available at: https://ms.ro/media/documents/Planul_Na%C8%9Bional_de_Combatere_%C8%99i_Control_al_Cancerului_RIQiTXG.pdf [Accessed 07. 09. 2023].
2. Gold P, Freedman SO. Specific carcinoembryonic antigens of the human digestive system. J Exp Med, 1965,122(3):467-81.
3. Forones NM, Tanaka M, Falcão JB. CEA as a prognostic index in colorectal cancer. São Paulo Med J, 1997,115(6):1589-1592.
4. Lázaro-Gorines R, Ruiz-de-la-Herrán J, Navarro R, Sanz L, Álvarez-Vallina L, Martínez-Del-Pozo A, Gavilanes JG, Lacadena J. A novel Carcinoembryonic Antigen (CEA)-Targeted Trimeric Immunotoxin shows significantly enhanced Antitumor Activity in Human Colorectal Cancer Xenografts. Sci Rep, 2019, 9(1):11680.
5. Wang H, Meng AM, Li SH, Zhou XL. A nanobody targeting carcinoembryonic antigen as a promising molecular probe for non-small cell lung cancer. Mol Med Rep, 2017, 16(1):625-630.
6. Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, Perera R, Primrose JN, Mant D. Blood CEA levels for detecting recurrent colorectal cancer. Cochrane Database Syst Rev, 2015, 2015(12):CD011134.
7. Fenqi D, Yupeng L, Qiuju Z, Chao Y, Wenjie S, Tianyi X, Junnan G, Weinan X, Xiufeng J, Junge B, Chenyang J, Hua X, Yien L, Xuefeng B, Yanlong L. Early Postoperative Serum Carcinoembryonic Antigen Is a Stronger Independent Prognostic Factor for Stage II Colorectal Cancer Patients Than T4 Stage and Preoperative CEA. Front Oncol, 2022, 11:758509.
8. Shinmi D, Nakano R, Mitamura K, Suzuki-Imaizumi M, Iwano J, Isoda Y, Enokizono J, Shiraishi Y, Arakawa E, Tomizuka K, Masuda K. Novel anticarcinoembryonic antigen antibody-drug conjugate has antitumor activity in the existence of soluble antigen. Cancer Med, 2017, 6(4):798-808.
9. Hall C, Clarke L, Pal A, Buchwald P, Eglinton T, Wakeman C, Frizelle F. A Review of the Role of Carcinoembryonic Antigen in Clinical Practice. Ann Coloproctol, 2019, 35(6):294-305.
10. Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, Perera R, Primrose JN, Mant D. Blood CEA levels for detecting recurrent colorectal cancer. Cochrane Database Syst Rev, 2015, 2015(12):CD011134.
11. Fukuda I, Yamakado M, Kiyose H. Influence of smoking on serum carcinoembryonic antigen levels in subjects who underwent multiphasic health testing and services. J Med Syst, 1998, 22(2):89-93.
12. Fletcher RH. Carcinoembryonic antigen. Ann Intern Med. 1986 Jan;104(1):66-73.
13. Morris EJ, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, Rachet B, Forman D. Thirty-day postoperative mortality after colorectal cancer surgery in England. Gut, 2011, 60(6):806-13.
14. Valenti V, Hernandez-Lizoain JL, Baixauli J, Pastor C, Aristu J, Diaz-Gonzalez J, Beunza JJ, Alvarez-Cienfuegos JA. Analysis of Early Postoperative Morbidity Among Patients with Rectal Cancer Treated with and without Neoadjuvant Chemoradiotherapy. Ann Surg Oncol, 2007, 14:1744-1751.
15. Van Eeghen EE, Den Boer FC, Loffeld RJLF. Thirty days post-operative mortality after surgery for colorectal cancer: a descriptive study. J Gastrointest Oncol, 2015, 6(6):E127-E132.
16. Gao Y, Wang J, Zhou Y, Sheng S, Qian SY, Huo X. Evaluation of Serum CEA, CA19-9, CA72-4, CA125 and Ferritin as Diagnostic Markers and Factors of Clinical Parameters for Colorectal Cancer. Sci Rep, 2018, 8(1):2732.
17. Li C, Zhang D, Pang X, Pu H, Lei M, Fan B, Lv J, You D, Li Z, Zhang T. Trajectories of Perioperative Serum Tumor Markers and Colorectal Cancer Outcomes: A Retrospective, Multicenter Longitudinal Cohort Study. EbioMedicine, 2021, 74:103706.
18. Cai D, Huang ZH, Yu HC, Wang XL, Bai LL, Tang GN, Peng SY, Li YJ, Huang MJ, Cao GW, Wang JP, Luo YX. Prognostic value of preoperative carcinoembryonic antigen/tumor size in rectal cancer. World J Gastroenterol, 2019, 25(33):4945-4958.
19. Zhang C, Zheng W, Lv Y, Shan L, Xu D, Pan Y, Zhu H, Qi H. Postoperative carcinoembryonic antigen (CEA) levels predict outcomes after resection of colorectal cancer in patients with normal preoperative CEA levels. Transl Cancer Res, 2020, 9(1):111-118.
20. Cai D, Huang ZH, Yu HC, Wang XL, Bai LL, Tang GN, Peng SY, Li YJ, Huang MJ, Cao GW, Wang JP, Luo YX. Prognostic value of preoperative carcinoembryonic antigen/tumor size in rectal cancer. World J Gastroenterol, 2019, 25(33):4945-4958

Corresponding Authors: Stefan Patrascu, Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania, e-mail: stef.patrascu@gmail.com

Sorin Scurtu, Department of Surgery, Clinical Hosptal of Filiasi, Romania, e-mail: scurtusorin78@yahoo.com