Serum carcinoembryonic antigen pre-operative level in colorectal cancer: revisiting risk stratification

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Abstract

Background: Biomarkers may play a role as predictive and prognostic factors in colorectal cancer patients. The aims of the study were to verify the prognostic role of pre-operative serum carcinoembryonic antigen (CEA) level in predicting overall survival and risk of recurrence in a cohort of colorectal cancer patients and to evaluate optimal cut-off values.

Methods: A retrospective cohort analysis was performed on colorectal cancer patients undergoing elective curative surgery between 2004 and 2019 at an Italian Academic Hospital. Main outcomes were overall survival, disease-free survival at 3-years and risk of local, loco-regional and distant recurrence during follow-up. A receiver operating characteristic (ROC) curve analysis was plotted using CEA pre-operative values and follow-up data in order to estimate the optimal cut-off values.

Results: A total of 559 patients were considered. The mean CEA value was 12.1 ± 54.1 ng/mL, and the median 29.3 (0–4995) ng/mL. The ROC curve analysis identified 12.5 ng/mL as the best CEA cut-off value to predict the risk of metastatic development after surgery in stage I–III colorectal cancer patients, and 10 ng/mL as the best CEA cut-off value to predict overall survival and disease-free survival in stage III–IV patients. These data suggest a stratification of colorectal cancer patients in three classes of risk: a low risk class (CEA <10 ng/mL), a moderate risk class (CEA 10–12.5 ng/mL) and a high risk class (CEA >12.5 ng/mL).

Conclusion: In conclusion, pre-operative serum CEA measurements could integrate information to enhance patient risk stratification and tailored therapy.

Introduction

Colorectal cancer (CRC) is the most commonly diagnosed malignancy in Europe and one of the leading causes of cancer-related death worldwide.[1,2] In 2018, nearly 500 000 new cases and 242 500 deaths were estimated to occur in Europe, accounting for 13% of all cancer diagnoses and the second cause of cancer-related death after lung cancer.[1]

Approximately 20–25% of CRC patients are initially diagnosed with stage IV metastatic disease, and 20–50% of stage II and III patients will eventually progress to stage IV, with an overall mortality rate of 40–45%.[3] Thanks to both increased awareness and screening programmes allowing for early tumour detection, as well as to improvements in adjuvant treatments, CRC mortality has significantly declined over the past decades, especially in more developed and high-income countries.[1,4,5] The currently reported 5-year survival rates for stage I, II and III CRC patients are 93%, 72–85% and 44–83%, respectively.[3,6] However, an accurate definition of individual prognosis is still difficult.

In this context, biomarkers can play an important role in the diagnosis and definition of therapeutic strategies of CRC patients and may be used as prognostic and predictive factors. Specifically, carcinoembryonic antigen (CEA) is a circulation glycoprotein that has been widely associated with colon cancer for over half a century.[6–10] Normally produced by the gastrointestinal tract during foetal development, in the adult life it is mostly expressed within epithelial cells of colon and rectum and its circulating levels are increased in 27–70% of CRC patients.[6–8,11,12] In 2000, the Colorectal Working Group of the American Joint Committee on Cancer (AJCC) suggested adding initial CEA levels in the conventional TNM classification of CRC (the 'C-stage'), but its inclusion has yet to take place.[7,11,13] The current guidelines of the National

Comprehensive Cancer Network and the European Society of Medical Oncology suggest routine evaluation of serum CEA values before surgical resection, mainly for subsequent post-operative surveillance. However, the prognostic significance of pre-operative CEA level is still under debate.[11,12,14,15]

The aim of this analysis was to evaluate the role of pre-operative serum CEA value in predicting overall survival (OS), disease-free survival (DFS) and development of metastases in a cohort of CRC patients undergoing curative surgery. We then tried to identify optimal cut-off values for better risk stratification, in order to possibly help clinicians to personalize treatments and follow-up programmes.

Methods

A retrospective cohort analysis was performed on all patients undergoing elective potentially curative surgery for CRC between 2004 and 2019 at an Italian Academic Hospital. Baseline demographics, tumour characteristics, adjuvant therapies and outcomes were documented for all patients. Patients requiring emergency procedures (i.e. bowel obstruction and/or perforation), those undergoing neoadjuvant therapy, those undergoing palliative surgery and those missing pre-operative CEA data were excluded from the analysis. The institutional laboratory CEA level range of normality was 0–4.5 ng/mL.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent by the institutional research committee is not required in Italy. Informed consent was obtained from all the participants included.

All patients were routinely studied pre-operatively with complete blood count comprehensive of liver function tests and tumour markers (i.e. CEA and CA 19-9), colonoscopy with biopsy, contrast-enhanced computed tomography of abdomen and chest, and pelvic magnetic resonance imaging in case of rectal cancer. All cases were reviewed by a multidisciplinary team, including general surgeons, colorectal surgeons, hepatobiliary surgeons, oncologists, radiotherapists, radiologists and pathologists. Definitive treatment was carried out in accordance with interdisciplinary assessment, depending on patients' performance status and tumour staging based on the seventh edition of the *AJCC Cancer Manual*.[16] All patients undergoing surgical treatment underwent a laparoscopic approach except for those presenting with substantial medical and/or local contraindications (e.g. severe cardiovascular or pulmonary dysfunction, previous significant abdominal surgery, cT4 tumours potentially requiring technically challenging resections).

Patients were compared in terms of: demographic parameters (i.e. age, gender, smoking habit, American Society of Anesthesiologists (ASA) score); tumour characteristics (i.e. location, dimension, positive lymph nodes, staging, grading, histopathology, adjuvant treatment); clinical, pathological and oncological outcomes (i.e. operation performed, major post-operative complications, length of hospital stay, number of harvested lymph nodes, resection margin status, local and/or regional and/or distant recurrence, OS and DFS). Quality of radical surgery was classified according to the AJCC residual tumour definition.[16] Post-operative mortality was defined as death occurring within 30 days from surgery.

As recommended by international protocols,[3,14] all patients entered a 5-year post-operative follow-up assessment consisting of: regular clinical evaluation and laboratory assay including dosage of CEA, abdominal ultrasound and/or thoraco-abdominal computed tomography scan every 6–12 months and complete colonoscopy at 1, 3 and 5 years from surgery. Positron emission tomography scanning was performed in selected cases on the basis of specific suspicious evidence.

Diagnosis of recurrence was defined by clinical, radiological, endoscopic and/or histological findings. According to the site of recurrence, patients were classified as having local recurrence (i.e. at the same place the cancer first started), regional recurrence (i.e. in the lymph nodes near the place the cancer first started) or distant recurrence (i.e. in another part of the body from where the cancer first started).

Main outcomes measured were OS, DFS at 3 years and risk of recurrence. OS and risk of recurrence were calculated from the date of surgery to either the last visit recorded or the date of death. DFS was calculated from the date of surgery to either the last follow-up assessment or disease recurrence, whichever came first.

Statistical analysis

Quantitative values were expressed in terms of mean and standard deviation (SD) for normal distributions and median and interquartile range for non-parametric distributions, and analysis was performed using analysis of variance or Kruskal–Wallis test, where appropriate. Qualitative variables were reported in terms of absolute frequencies and percentages and analysed using Fisher's exact test or chi-squared test, where appropriate.

As regards CEA values, a time-dependent ROC curve analysis was performed for determining the prognostic accuracy of CEA in predicting survival and recurrence. Specifically, a ROC curve analysis was plotted using CEA pre-operative values and follow-up data for recurrence and metastases in order to estimate cut-off values to distribute the cohort into 'high CEA' and 'low CEA' patients. Kaplan–Meyer curves were used for OS and DFS for the two groups and compared using log-rank test. General linear model multivariate analysis, Fisher's scoring iteration tests and correlation tests were performed to verify iterations between explanatory variables.

Statistical analysis was performed using R software (version 3.5.0). A P-value of less than 0.05 was considered to be statistically significant.

Results

Between 2004 and 2019, a total of 941 patients underwent surgery with curative intent for CRC at our Institution. Of these, 382 were excluded because of missing pre-operative CEA values ($n = 203$), emergency surgery ($n = 90$) and neoadjuvant therapy ($n = 89$). Overall, a total of 559 were considered for the analysis. Summary data are reported in Table 1.

Median (range) age at the time of diagnosis was 72 (28–100) years. Overall, there were 341 (61.0%) males and 218 (39.0%) females. According to cancer staging, 228 (40.8%) patients presented with stage I CRC, 177 (31.7%) with stage II CRC, 121 (21.6%) with stage III CRC, and 33 (5.9%) with stage IV CRC. The mean ± SD pre-operative CEA value was 12.1 ± 54.1 ng/mL, and the median (range) pre-operative CEA value was 29.3 (0–4995) ng/mL. Median (range) follow-up was 64.8 (0.3–121.4) months. Patients' characteristics are displayed in Table 2.

First of all, we considered stage I, II and III CRC patients (n = 526) in accordance with metachronous metastatic development at any moment during the post-operative follow-up. In this set, 137 (26.1%) patients developed regional and/or distant metastases. When comparing mean ± SD pre-operative CEA values between non-metastatic (n = 389) and metastatic (n = 137) patients, we found significantly lower pre-operative values in the non-metastatic group (i.e. 7.6 ± 31.57 ng/mL versus 73.44 ± 165.02 ng/mL, respectively; P = 0.0004). Median (range) pre-operative CEA level was 3 (0–723) ng/mL in non-metastatic patients and 5 (1–4995) ng/mL in metastatic patients, respectively. Considering the non-homogenous distribution of pre-operative CEA values among the two groups, a trim-mean function was performed to help eliminate the influence of outliers that may have unfairly affected the results. Ruling the 5% of highest and lowest values out, the mean CEA values remained considerably lower in non-metastatic patients compared to metastatic patients (i.e. 4.7 ng/mL versus 22.3 ng/mL, respectively; P = 0.03).

Table 1 Total population characteristics

	Available CEA (n = 559)
Sex, n (%)	
M	341 (61)
F	218 (39)
Age (years), median (range)	72 (28–100)
Smoking habit, n (%)	170 (30)
American Society of Anesthesiologists score ≥3, n (%)	179 (32)
Site of primary tumour, n (%)	
Colon	425 (76)
Rectum	134 (24)
Surgical approach, n (%)	
Open	235 (42)
Laparoscopy	324 (58)
Length of hospital stay (days), median (range)	9 (3–90)
Major post-operative complications (Clavien-Dindo ≥3), n (%)	73 (13)
30-day reoperation, n (%)	56 (10%)
30-day mortality, n (%)	12 (2)
Histopathological features, n (%)	
Adenocarcinoma	475 (85)
Others	84 (15)
American Joint Committee on Cancer stage, n (%)	
Stage I	228 (40.8)
Stage II	177 (31.7)
Stage III	121 (21.6)
Stage IV	33 (5.9)
Adjuvant treatment, n (%)	196 (35)
Loco-regional recurrence, n (%)	101 (18.1)
Distant recurrence, n (%)	136 (24.3)

CEA, carcinoembryonic antigen.

In this subset of patients, the ROC curve analysis identified 12.5 ng/mL as the best cut-off CEA pre-operative level (sensitivity 89%, specificity 96%, area under the curve (AUC) 0.74) to predict the risk of recurrence (local recurrence, loco-regional recurrence and distant metastases) after surgical resection in stage I, II and III CRC (Fig. 1). This cut-off value was then applied to distribute patients into 'high CEA' (n = 167) and 'low CEA' (n = 359). Subgroups analysis did not find any significant difference in terms of age, sex, smoking habit, ASA score, tumour site, histopathological characteristics and post-operative short-term outcomes. However, a higher proportion of 'low CEA' patients presented with lower cancer stage (P = 0.01), underwent laparoscopic surgery (P = 0.04) and presented a longer length of in-hospital stay (P = 0.01). Subgroup patients' characteristics are summarized in Table 3.

We then analysed OS and DFS for all CRC patients according to the stage of disease. In this context, pre-operative CEA values showed a low accuracy in predicting OS and DFS for stage I and II CRC patients (AUC 0.64 and 0.54 and threshold values of 1.5 ng/mL and 2.9 ng/mL, respectively). However, when analysing only stage III and IV CRC patients, the ROC curve analysis showed a high accuracy to predict OS and DFS (sensitivity 100%, specificity 63.87%, AUC 0.92) for a threshold value of 10 ng/mL (Fig. 2). Therefore, we further analysed this subset of patients, who were divided into 'high CEA' (n = 52) and 'low CEA' (n = 102) groups. Subgroups analysis did not find any significant difference in terms of age, sex, smoking habit, ASA score, tumour site, histopathological characteristics and post-operative short-term outcomes. However, a higher proportion of 'low CEA' patients presented with lower cancer stage (P = 0.05) and underwent laparoscopic surgery (P = 0.003). The higher rate of laparoscopic surgery in both 'low CEA' groups can be easily explained considering that cT4 tumours seldom received a laparoscopic approach *per se*, thus determining that the laparoscopic group accounted for a higher number of lower stage CRCs. Subgroup patients' characteristics are summarized in Table 4.

As far as oncological outcomes are concerned, when excluding from the aforementioned analysis stage IV CRC patients, 3-year OS of patients with pre-operative CEA >10 ng/mL was 36.2% versus 61.6% of patients with pre-operative CEA <10 ng/mL (P = 0.01). Similarly, 3-year DFS of 'high CEA' patients was 35.6% compared to 66.2% of 'low CEA' patients (P = 0.03). When considering for analysis also stage IV CRC cases, DFS was still significantly worse in 'high CEA' patients (23.9% versus 54.9%, P = 0.004). Relative Kaplan–Meyer curves are shown in Figures 3, 4 and 5.

Correlation tests confirmed a correlation only between pre-operative CEA and CA 19-9 testing (0.53), and no correlation between any of the others explanatory variables. The general linear model multivariate analysis suggested as possible interaction variables age for OS (P = 0.04), pT and pN for metastatic development (P = 0.03 and P = 0.04, respectively), and tumour grading for local and loco-regional recurrence (P = 0.02).

Table 2 Study population characteristics

	CRC patients (*n* = 559)	Stage I (*n* = 228)	Stage II (*n* = 177)	Stage III (*n* = 121)	Stage IV (*n* = 33)
Sex, *n* (%)					
M	341 (61)	137 (60)	110 (62)	73 (60)	21 (64)
F	218 (39)	91 (40)	67 (38)	48 (40)	12 (36)
Age (years), median (range)	72 (28–100)	71 (28–89)	73 (42–93)	78 (41–88)	72 (49–100)
Smoking habit, *n* (%)	170 (30)	74 (32)	49 (28)	36 (30)	11 (33)
American Society of Anesthesiologists score ≥3, *n* (%)	171 (31)	41 (18)	67 (38)	50 (41)	13 (39)
Site of primary tumour, *n* (%)					
Colon	410 (73)	162 (71)	129 (73)	93 (77)	26 (79)
Rectum	149 (27)	66 (29)	48 (27)	28 (23)	7 (21)
Surgical approach, *n* (%)					
Open	211 (38)	61 (27)	71 (40)	54 (45)	25 (76)
Laparoscopy	348 (62)	167 (73)	106 (60)	67 (55)	8 (24)
Length of hospital stay (days), median (range)	9 (3–90)	6 (3–28)	8 (5–25)	9 (5–35)	11 (4–90)
Major post-operative complications (Clavien-Dindo ≥3), *n* (%)	78 (14)	21 (9)	27 (15)	21 (17)	9 (28)
30-day re-operation, *n* (%)	57 (10)	11 (5)	21 (12)	19 (16)	6 (18)
30-day mortality, *n* (%)	11 (2)	2 (0.9)	3 (2)	4 (3)	2 (6)
Histopathological features, *n* (%)					
Adenocarcinoma	474 (85)	196 (86)	149 (84)	99 (82)	30 (91)
Others	85 (15)	32 (14)	28 (16)	22 (18)	3 (9)
Adjuvant treatment, *n* (%)	196 (35)	21 (9)	69 (39)	82 (68)	24 (73)
Loco-regional recurrence, *n* (%)	101 (18)	20 (9)	42 (24)	31 (26)	8 (24)
Distant recurrence, *n* (%)	136 (24)	35 (15)	53 (30)	37 (31)	11 (33)
Pre-operative mean CEA level (ng/mL)	12.1 ± 54.1	4.3 ± 8.3	12.5 ± 51.9	22.9 ± 85.2	66.5 ± 176

CEA, carcinoembryonic antigen; CRC, colorectal cancer.

We evaluated separately the cohort of patients with colon cancer ($n = 447$) and the cohort of patients with rectal cancer ($n = 112$), but we did not find any statistical differences in any of the outcomes analysed ($P = 0.8$ and $P = 0.4$ for differences in CEA cut-offs, $P = 0.1$ and $P = 0.5$ for differences in oncological outcomes).

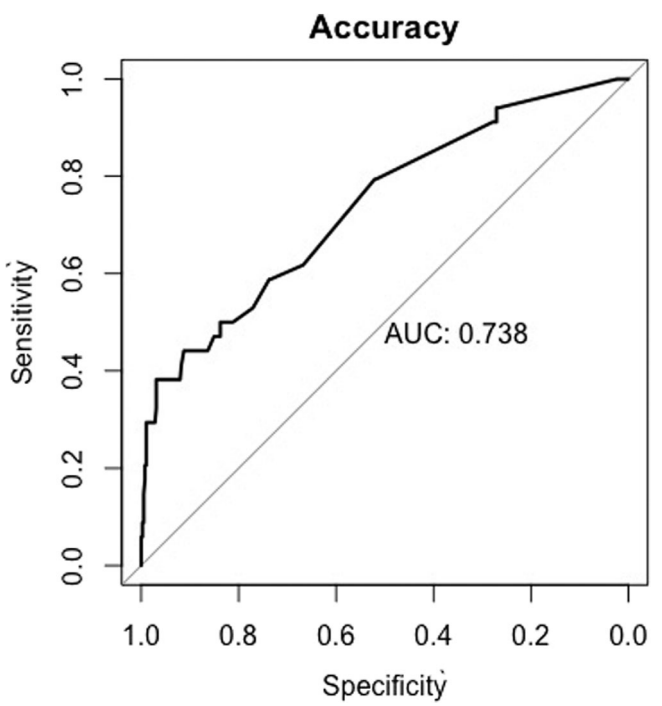

Fig 1. ROC curve analysis for risk of developing metastases in stage I–III CRC. AUC, area under the curve.

Discussion

The aim of this analysis was to define the value of pre-operative CEA measurement as prognostic factor in a cohort of CRC patients undergoing elective potentially curative surgery. Although most literature data usually define 4.5 ng/mL as the best CEA cut-off level, this might not adequately reflect the outcomes when uniformly applied to different stages.[7–9,17–20] In the present study, a ROC curve analysis confirmed that a pre-operative serum CEA value >12.5 ng/mL correlated with a higher risk of developing regional and/or distant recurrence in stage I, II and III CRC patients. Moreover, a pre-operative serum CEA level >10 ng/mL was found to be considerably predictive of all-cause mortality and poor DFS in patients with stage III and IV CRC undergoing potentially curative surgical resection.

Although the accuracy of ROC curve analysis for stage I, II and III CRC patients was not extremely high (AUC 0.74), the cut-off value of 12.5 ng/mL is consistent with literature data. Park *et al.*[18] performed a retrospective analysis of 989 CRC patients who were distributed into four subgroups depending on pre-operative serum CEA level (cut-off values set at 3, 6 and 17 ng/mL). The authors found that 5-year DFS was significantly different among the four subgroups, and that higher pre-operative serum CEA values (i.e. >17 ng/mL) were strongly correlated to higher risk of metastases or recurrence. Moreover, a CEA level above 3 ng/mL seemed associated

Table 3 Stage I–III colorectal cancer patients' characteristics according to carcinoembryonic antigen (CEA) level (cut-off: 12.5 ng/mL)

	High CEA (n = 167)	Low CEA (n = 359)	P-value
Sex, n (%)			
M	89 (53)	219 (61)	0.11
F	78 (47)	140 (39)	
Age (years), median (range)	74 (36–92)	70 (29–100)	0.12
Smoking habit, n (%)	53 (32)	106 (30)	0.58
American Society of Anesthesiologists score ≥3, n (%)	50 (30)	126 (35)	0.69
Site of primary tumour, n (%)			
Colon	125 (75)	262 (73)	0.78
Rectum	42 (25)	97 (27)	
Surgical approach, n (%)			
Open	72 (43)	104 (29)	**0.04**
Laparoscopy	95 (57)	255 (71)	
Length of hospital stay (days), median (range)	9 (3–90)	14 (3–75)	**0.02**
Major post-operative complications (Clavien-Dindo ≥3), n (%)	22 (13)	32 (9)	0.55
30-day reoperation, n (%)	17 (10)	21 (6)	0.41
30-day mortality, n (%)	3 (2)	4 (1)	0.89
American Joint Committee on Cancer stage, n (%)			
Stage I	86 (52)	142 (40)	**0.01**
Stage II	69 (41)	108 (30)	
Stage III	12 (7)	109 (30)	
Histopathological features, n (%)			
Adenocarcinoma	149 (89)	337 (94)	0.67
Others	18 (11)	22 (6)	
Adjuvant treatment, n (%)	52 (31)	101 (28)	0.78
Loco-regional recurrence, n (%)	39 (23)	54 (15)	**0.05**
Distant recurrence, n (%)	51 (31)	74 (21)	**0.04**

with reduced OS in stage III CRC patients. Comparable results were more recently reported by Kim *et al.*,[7] who demonstrated that pre-operative CEA >3 ng/mL represented a poor independent prognostic factor for all outcomes in stage III colon cancer. Similarly, Gunawardene *et al.*[11] evaluated 138 CRC patients and established a pre-operative CEA level of 3.3 ng/mL as prognostic cut-off for poorer OS and DFS, independently from stage disease. Jeon *et al.*[20] performing a ROC curve on 520 patients determined that optimal cut-off values of pre-operative CEA were 7.4, 5.5 and 4.5 ng/mL for CRC stage I, II and III. The authors concluded that individualized cut-offs would be more accurate in predicting the prognosis according to TNM stages.

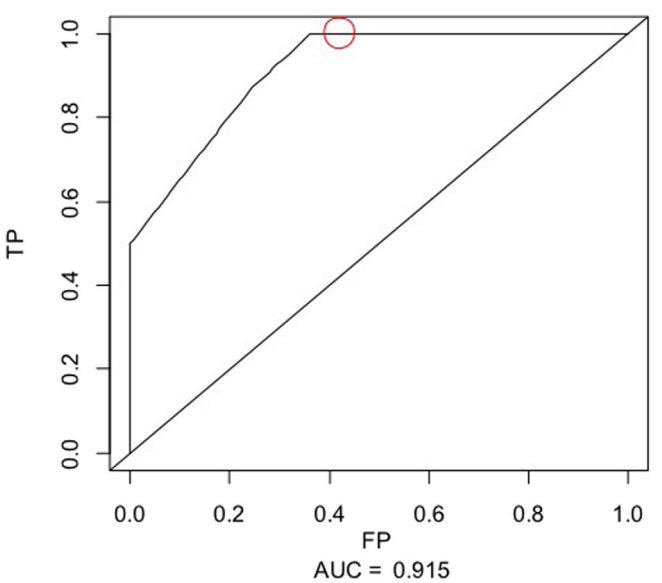

Fig 2. ROC curve analysis for DSF in stage III–IV colorectal cancer. AUC, area under the curve. FP, False positive; TP, True positive.

When evaluating OS and DFS of patients at higher risk of developing disease recurrence (i.e. stage III and IV CRC), the ideal cut-off was identified at 10 ng/mL. Although the values were probably influenced by an already advanced stage of disease, pre-operative CEA levels >10 ng/mL were correlated to a significantly worse 3-year OS and DFS, when compared to CEA <10 ng/mL. Moreover, the incidence of disease recurrence was significantly higher in 'high CEA' patients compared to 'low CEA' patients even when stage IV patients were excluded from the analysis (48.7% versus 20.9%, P = 0.002), over a median follow-up of 64.8 months.

Performing a retrospective analysis of 395 CRC patients, Li Destri *et al.*[21] defined 5 ng/mL as the optimal cut-off level to identify a higher risk of recurrence (P = 0.004). Likewise, Cai *et al.*[12] categorized pre-operative CEA values into quintiles and observed increasingly worse OS and DFS in increasing quintiles of pre-operative CEA. Thirunavukarasu *et al.*[22] retrospectively analysed 16 000 CRC patients from the National Cancer Institute's Surveillance, Epidemiology and End Results database and divided the patients

Table 4 Stage III–IV colorectal cancer patients' characteristics according to carcinoembryonic antigen (CEA) level (cut-off: 10 ng/mL)

	High CEA (n = 52)	Low CEA (n = 102)	P-value
Sex, n (%)			
M	35 (67)	61 (60)	0.38
F	17 (33)	41 (40)	
Age (years), median (range)	74 (41–92)	71 (28–93)	0.16
Smoking habit, n (%)	17 (33)	30 (29)	0.65
American Society of Anesthesiologists score ≥3, n (%)	17 (33)	36 (35)	0.85
Site of primary tumour, n (%)			
Colon	40 (77)	79 (77)	0.9
Rectum	12 (23)	23 (23)	
Surgical approach, n (%)			
Open	33 (63)	39 (38)	**0.003**
Laparoscopy	19 (37)	63 (62)	
Length of hospital stay (days) median (range)	9 (5–59)	8 (4–75)	0.18
Major post-operative complications (Clavien-Dindo ≥3), n (%)	8 (15)	13 (13)	0.9
30-day reoperation, n (%)	3 (6)	12 (12)	0.38
30-day mortality, n (%)	1 (2)	3 (3)	0.9
American Joint Committee on Cancer stage, n (%)			
Stage III	35 (67)	86 (84)	**0.02**
Stage IV	17 (33)	16 (16)	
Histopathological features, n (%)			
Adenocarcinoma	45 (87)	94 (92)	0.26
Others	7 (13)	8 (8)	
Adjuvant treatment, n (%)	31 (60)	57 (56)	0.73
Loco-regional recurrence, n (%)	19 (37)	20 (20)	**0.05**
Distant recurrence, n (%)	23 (44)	25 (25)	**0.04**

into two groups (C0, normal, or C1, elevated) according to pre-operative CEA value. The authors defined that pre-operative value of 5 ng/mL was associated with a 60% increased risk of mortality. Furthermore, the study reported that higher CEA levels in lower AJCC stages were correlated with comparable or worse prognosis than lower CEA levels in higher AJCC stages.

The present study has several limitations. First of all, the limited sample size and the retrospective nature may prevent generalization of results and appropriate identification of individualized cut-off values. Second, non-cancer related causes of increased serum CEA levels were not considered (with the exception for smoking habit), thus possibly affecting the accuracy of our analysis.

Furthermore, patients undergoing neoadjuvant therapy, those undergoing emergency surgery and those missing pre-operative CEA data were not included the analysis. Although allowing for a more homogeneous group of analysis, it may have prevented the evaluation for potential bias.

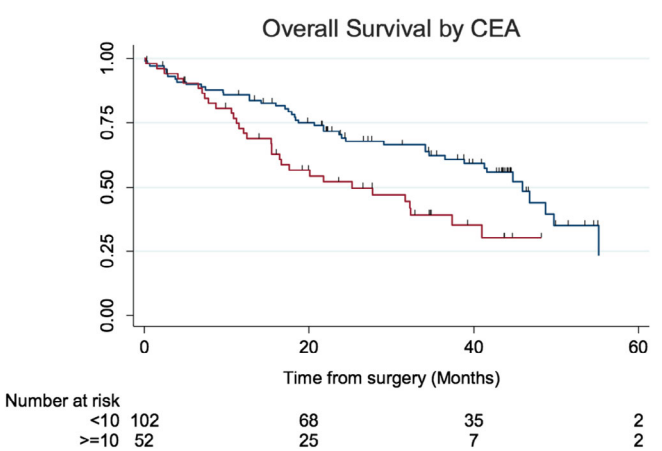

Fig 3. Overall survival of 'high carcinoembryonic antigen (CEA)' patients versus 'low CEA' patients (stage III–IV). (——) CEA <10; (——) CEA ≥10.

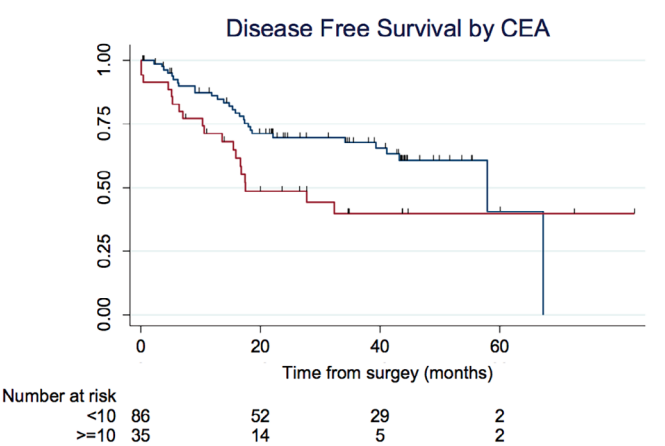

Fig 4. Disease-free survival of 'high carcinoembryonic antigen (CEA)' patients versus 'low CEA' patients (stage IV excluded). (——) CEA <10; (——) CEA ≥10.

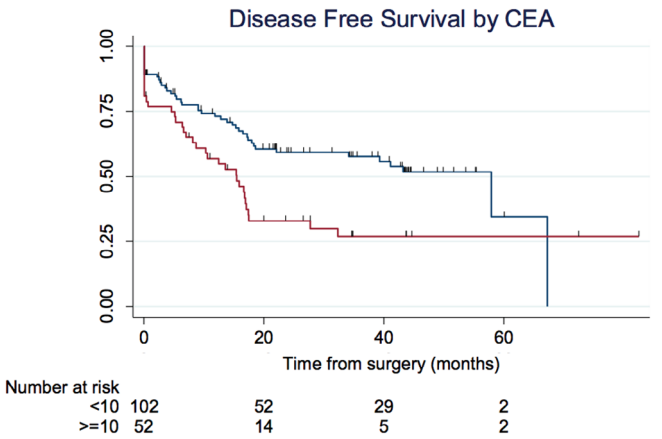

Fig 5. Disease-free survival of 'high carcinoembryonic antigen (CEA)' patients versus 'low CEA' patients (stage IV included). (——) CEA <10; (——) CEA ≥10.

Conclusion

The study managed to confirm that pre-operative measurement of CEA is an independent negative prognostic factor for CRC patients undergoing curative surgery. Pre-operative measurements could be used to integrate information given by TNM staging in order to enhance patient risk stratification and possible tailored multimodality therapy. With regard to our findings, we suggest a stratification of CRC patients in three classes of risk: a low risk class (CEA <10 ng/mL), a moderate risk class (CEA 10–12.5 ng/mL), burdened by a high risk of shorter OS, and a high risk class (CEA >12.5 ng/mL), burdened by a high risk of both metastatic development and shorter OS. However, further studies with different populations are required to validate our analysis, and eventually investigate other accurate cut-off values needed for stratification and individualization of treatment and follow-up procedures.

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Author contributions

Cristiana Iacuzzo: Conceptualization; data curation; formal analysis; writing-original draft. **Paola Germani:** Conceptualization; data curation; formal analysis; supervision. **Marina Troian:** Conceptualization; data curation; formal analysis; supervision; writing-review & editing. **Tommaso Cipolat Mis:** Conceptualization; data curation; formal analysis. **Fabiola Giudici:** Data curation; formal analysis; supervision. **Edoardo Osenda:** Conceptualization; data curation. **Marina Bortul:** Supervision; validation. **Nicolò de Manzini:** Supervision; validation; writing-review & editing.

Data availability statement

The data sets generated and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Conflicts of interest

None declared.

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