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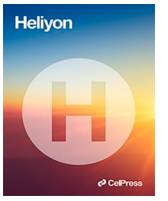

Research article

Association of preoperative and recurrent serum carcinoembryonic antigen and outcome of colorectal cancer patients with metastatic relapse

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ABSTRACT

Background: Seldom have the associations of preoperative CEA (p-CEA) and recurrent CEA (r-CEA) levels as well as changes in p-CEA and r-CEA with survival in patients with stage I–III colorectal cancer (CRC) who have experienced metastatic relapse, been thoroughly examined.
Methods: 241 consecutive patients with stage I–III CRC who experienced metastatic relapse at Fudan University Shanghai Cancer Center (FUSCC) between January 2008 and January 2016 were investigated. The influence of p-CEA, r-CEA and CEA alteration on the overall survival (OS) and relapse-to-death survival (RDS) was evaluated. The restricted cubic spline regression model was employed to explore the optimal cut-off value of CEA.
Results: All 241 patients were categorized into four groups built on their CEA alteration patterns as follows: A, patients presenting elevated p-CEA levels but normal r-CEA levels (P–N); B, patients displaying normal levels of both p-CEA and r-CEA (N–N); C, patients exhibiting elevated levels of both p-CEA and r-CEA (P–P); D, patients with normal p-CEA levels but elevated r-CEA levels (N–P). The correlation between p-CEA and OS ($P = 0.3266$) and RDS ($P = 0.2263$) was insignificant. However, r-CEA exhibited a significant association with both OS ($P = 0.0005$) and RDS ($P = 0.0002$). Group A demonstrated the longest OS and RDS, whereas group D exhibited the poorest OS and RDS outcomes. For both OS and RDS, the CEA alteration groups served as an independent prognostic indicator. The optimal cut-off threshold for CEA was determined to be 5.1 ng/ml via the restricted cubic spline regression model.
Conclusion: r-CEA has a stronger correlation with OS and RDS in individuals with stage I–III CRC who have experienced metastatic relapse.

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The change between p-CEA and r-CEA could further indicate post-relapse survival, thereby facilitating the assessment of mortality risk stratification in stage I-III CRC patients experiencing metastatic relapse.

1. Introduction

Among all types of cancer, colorectal cancer (CRC) ranks as the third most prevalent malignancy and the second leading cause of cancer-related death [1]. The incidence and mortality of CRC are escalating swiftly in developing nations, such as China [2]. After curative treatment, a significant proportion of CRC patients experience local recurrence and distant metastasis within a five-year timeframe [3]. Therefore, further research is necessary to identify prognostic factors that more accurately evaluate the survival and progression of tumors in CRC patients who underwent metastatic relapse.

Carcinoembryonic antigen (CEA) serves as a vital tumor marker that plays an important role in staging, as well as the postoperative follow-up and monitoring, recommended by the current guidelines [4,5]. Most researches have concentrated on investigating the prognostic significance of preoperative and perioperative CEA levels for both relapse-free survival (RFS) and overall survival (OS) [6,7]. Nonetheless, there is a scarcity of studies that have examined the impact of CEA at relapse, especially the dynamic change between p-CEA and r-CEA, on post-recurrence survival and overall survival among individuals with recurrent CRC. CRC exhibits heterogeneity at both the molecular and cellular levels, with significant diversity in the expression of various molecules, including CEA [8]. CRC demonstrates dynamic cellular and genetic heterogeneity during progression and clinical management [9], with CEA levels dynamically changing accordingly. Hence, dynamic changes in CEA levels, such as preoperative CEA levels, hold greater prognostic and clinical value than assessments of CEA levels at a single time point.

Furthermore, although ASCO recommends a threshold of 5.0 ng/ml, a systematic analysis of 52 studies in the Cochrane Library database suggested a threshold of 10.0 ng/ml [10,11]. Thus, the optimal prognostic cutoff point for CEA level continues to be a subject of debate.

Hence, this study retrospectively reviewed patients with stage I-III CRC who experienced metastatic relapse at the Fudan University Shanghai Cancer Center (FUSCC). Our study's principal objective was to investigate the prognostic significance of preoperative CEA (p-CEA) and recurrent CEA (r-CEA) levels, particularly the fluctuation between p-CEA and r-CEA, among individuals with stage I-III CRC who experienced metastatic relapse. Additionally, our study aimed to establish the optimal cutoff value of CEA based on prognosis.

2. Materials and methods

2.1. Study population

We conducted a retrospective review of 7543 consecutive patients diagnosed with CRC at the Department of Colorectal Surgery, FUSCC, spanning from January 2008 to January 2016. The inclusion criteria comprised individuals aged 18–80 years, histologically confirmed with colorectal cancer, staged as I-III, who underwent curative resection and subsequently experienced metastatic relapse. The following patients were excluded: emergent surgery for bleeding, perforation or acute bowel obstruction; preoperative treatment such as neoadjuvant therapy or radiotherapy; evidence of other malignancies; follow-up data missing. Ultimately, 241 patients were included in this study.

This retrospective study received approval from the Institutional Review Board of FUSCC (2006219-13). The need for obtaining informed written consent was waived.

2.2. Serum CEA assessment

Serum was acquired from the most recent peripheral blood samples collected from CRC patients <1 week prior to surgery (p-CEA) and <1 week after relapse (r-CEA) following standard operating procedures and the manufacturer's recommendations. Serum concentrations of CEA were detected by electro-chemiluminescent (immunoassay, using Roche Modular E170 automatic system (Roche Diagnostics, Shanghai, China). All the serum samples were independently analyzed at the Laboratory Medicine, FUSCC. The normal reference range was CEA <5 ng/ml. The results are presented according to the REMARK guideline [12].

2.3. Follow-up

This study was designed to ensure that all patients were not harmed. Patients or their legal guardians provided informed consent. Retrospective clinical data were retrieved from the medical records database of FUSCC.

Following the CSCO guideline [13], all patients with colorectal cancer (CRC) underwent routine follow-up. Serum levels of CEA and CA19-9 were monitored every three months for the initial two years, and then every six months for the next three. The patient additionally underwent radiological scans every six months for a duration of five years, along with colonoscopy examinations in the first and third years.

Relapse-to-death survival (RDS) was characterized as the duration between the onset of relapse and the date of death due to any

cause. Overall survival (OS) was delineated as the duration from the date of radical resection to the date of death due to any cause. All follow-up information was acquired by calling or emailing patients directly, or through FUSCC medical records follow-up platform, which is registered in the Clinical Statistics Center of FUSCC. Patients who were alive at the time of the last visit or were lost to follow-up were censored for the analysis.

2.4. Statistical analysis

Statistical analysis was conducted using SPSS version 24 (IBM SPSS Inc., Chicago, IL, USA), GraphPad Prism version 8 (La Jolla, CA, USA) and R 4.1.1 program (http://www.r-project.org/). Categorical variables were assessed using the two-sided Pearson chi-square test or Fisher's exact test when applicable. The *t*-test or Wilcoxon rank test were used to analyze the CEA level, which was regarded a continuous variable. The log-rank test and Cox regression model were utilized in the Kaplan-Meier method's survival analysis. P values (all two-sided) less than 0.05 were deemed statistically significant.

Moreover, with the use of the R package "rms", the associations between CEA levels and RDS or OS were depicted on a continuous scale using restricted cubic splines (RCSs), constructed through a multivariable Cox model with four nodes positioned at the 5th, 35th, 65th, and 95th percentiles of CEA. The use of restricted cubic splines (RCSs) has been extensively recognized as a reliable approach for examining the association between survival and independent variables [14,15]. As a smoothly connected combination of polynomial functions, the RCS does not presuppose linearity in the relationship between variables and the response, such as survival [16]. Moreover, the application of the RCS allows for the identification of the inflection point in the risk function, such as the threshold [17].

3. Results

3.1. Baseline characteristics

In total, 241 CRC patients who experienced metastatic relapse were consecutively enrolled at FUSCC from January 2008 to January 2016. The patient enrollment process is illustrated in Fig. 1.

The patients had a median age of 56 years, with a range of 20–80 years. The interquartile range (IQR) for age was 46–64 years. The median follow-up time for the patients was 40 months, with a range of 9.2–109.8 months. The IQR for follow-up time was 27.5–56.9 months. All patients underwent relapse with distant metastases and 63(26.1 %) patients experienced mortality. The 3-year OS rate was 82.3 % and the 3-year RDS rate was 63.3 %. The 5-year RFS rate was 63.9 % and the 5-year OS rates was 56.1 %. Table 1 presents the following details: age, gender, histology, smoking history, tumor location, AJCC stage, T stage, N stage, pathological grading, presence of venous/perineural invasion, receipt of adjuvant chemotherapy/radiation, number of dissected lymph nodes, and sites of metastasis.

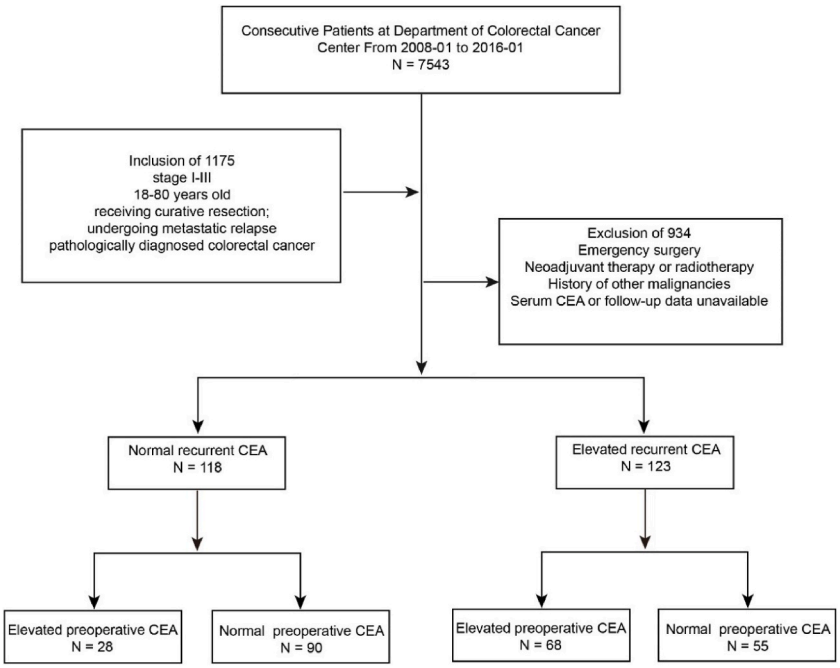

Fig. 1. Flow diagram illustrating the process of enrollment, inclusion, exclusion, and grouping.

Table 1
The baseline clinicopathological characteristics of the consecutively enrolled CRC patients.

Characteristic	Cases	Preoperative to Recurrent CEA				
	N (%)	P–N	N–N	P–P	N–P	P
No. of patients	241(100)	28(11.6)	90(37.3)	68(28.2)	55(22.8)	
Age						0.001
<60	151(62.7)	12(7.9)	69(45.7)	34(22.5)	36(23.8)	
≥60	90(37.3)	16(17.8)	21(23.3)	34(37.8)	19(21.1)	
Sex						0.378
Male	141(58.5)	18(12.8)	54(38.3)	34(24.1)	35(24.8)	
Female	100(41.5)	10(10.0)	36(36.0)	34(34.0)	20(20.0)	
Histology						0.762
Adenocarcinoma	195(80.9)	23(11.8)	71(39.4)	58(29.7)	43(22.1)	
Mucinous tumors	42(17.4)	4(9.5)	17(40.5)	10(23.8)	11(26.2)	
Unknown	4(1.7)	1(25.0)	2(50.0)	0(0)	1(25.0)	
Smoking history						0.774
No	196(81.3)	23(11.7)	76(38.8)	54(27.6)	43(21.9)	
Yes	45(18.7)	5(11.1)	14(31.1)	14(31.1)	12(26.7)	
Tumor location						0.013
Colon	78(32.4)	5(6.4)	27(34.6)	32(41.0)	14(17.9)	
Rectum	163(67.6)	23(14.1)	63(38.7)	36(22.1)	41(25.2)	
AJCC stage						0.045
I	21(8.7)	1(4.8)	5(23.8)	3(14.3)	12(57.1)	
II	56(23.2)	8(14.3)	23(41.1)	15(26.8)	10(17.9)	
III	160(66.4)	19(11.9)	59(36.9)	50(31.3)	32(20.0)	
Unknown	4(1.7)	0(0)	3(75.0)	0(0)	1(25.0)	
T stage						0.025
Tis-T2	36(14.9)	2(5.6)	13(36.1)	6(16.7)	15(41.7)	
T3	80(33.2)	11(13.8)	27(33.8)	23(28.7)	19(11.0)	
T4	117(48.5)	15(12.8)	43(36.8)	39(33.3)	20(17.1)	
Unknown	8(3.3)	5(0)	7(87.5)	0(0)	1(12.5)	
N stage						0.749
N0	93(38.6)	11(11.8)	34(36.6)	23(24.7)	25(26.9)	
N1	78(32.4)	10(12.8)	32(41.0)	23(29.5)	13(16.7)	
N2	70(29.0)	7(10.0)	24(34.3)	22(31.4)	17(24.3)	
Pathological grading						0.849
Well & moderate	162(67.2)	18(11.1)	64(39.5)	46(28.4)	34(21.0)	
Poo & anaplastic	54(22.4)	7(13.0)	19(35.2)	13(24.1)	15(27.8)	
Unknown	25(10.40	3(12.0)	7(28.0)	9(36.0)	6(24.0)	
Venous invasion						0.079
	163(67.6)	16(9.8)	65(39.9)	49(30.1)	33(20.2)	
+	72(29.9)	9(12.5)	23(31.9)	18(25.0)	22(30.6)	
Unknown	6(2.5)	3(50.0)	2(33.3)	1(16.7)	0(0)	
Perineural invasion						0.425
	151(62.7)	18(11.9)	59(39.1)	39(25.8)	35(23.2)	
+	85(35.3)	8(9.4)	29(34.1)	29(34.1)	19(22.4)	
Unknown	5(2.1)	2(40.0)	2(40.0)	0(0)	1(20.0)	
Adjuvant chemotherapy						0.056
No	3(1.2)	0(0)	1(33.3)	0(0)	2(66.7)	
Yes	215(89.2)	28(13.0)	81((37.7)	63(29.3)	43(20.0)	
Unknown	23(9.5)	0(0)	8(34.8)	5(21.7)	10(43.5)	
Adjuvant radiotherapy						0.319
No	159(66.0)	17(10.7)	56(35.2)	51(32.1)	35(22.0)	
Yes	82(34.0)	11(13.4)	34(41.5)	17(20.7)	20(24.4)	
No. of LNs dissected						0.107
<12	75(31.1)	11(14.7)	25(33.3)	16(21.3)	23(30.7)	
≥12	166(68.9)	17(10.2)	65(39.2)	52(31.3)	32(19.3)	
Metastatic site						0.792
Liver	42(17.4)	3(7.1)	15(35.7)	16(38.1)	8(19.0)	
Lung	76(31.5)	6(7.9)	30(39.5)	23(30.3)	17(22.4)	
Bone	11(4.6)	2(18.2)	3(27.3)	4(36.4)	2(18.2)	
Abdominopelvic	81(33.6)	11(13.6)	31(38.3)	18(22.2)	21(25.9)	
Others	4(1.7)	1(25.0)	2(50.0)	0(0)	1(25.0)	
Multiple metastasis	27(11.2)	5(18.5)	9(33.3)	7(25.9)	6(22.2)	

LNs, lymph nodes; pMMR, proficient Mismatch Repair; dMMR, deficient Mismatch Repair.

4. Associations between CEA changes and clinicopathologic characteristics

Patients were categorized into four groups based on the threshold value of 5.0 ng/ml: A, patients presenting elevated p-CEA levels but normal r-CEA levels (P–N); B, patients displaying normal levels of both p-CEA and r-CEA (N–N); C, patients exhibiting elevated

levels of both p-CEA and r-CEA (P–P); D, patients with normal p-CEA levels but elevated r-CEA levels (N–P). Significant associations were observed between changes in p-CEA and r-CEA levels and various factors including age (P = 0.001), tumor location (P = 0.013), AJCC stage (P = 0.045), and T stage (P = 0.025) (Table 2). Nevertheless, no significant associations were found between changes in p-CEA and r-CEA levels and factors such as sex, histology, smoking history, N stage, pathologic grading, venous/perineural invasion, adjuvant chemotherapy/radiotherapy, number of LNs dissected, or metastatic sites (Table 2).

Table 2
Univariate Cox regression analysis for OS and RDS.

Variables	Overall survival			Relapse to death survival		
	Hazard ratio	95%CI	P	Hazard ratio	95%CI	P
Age			0.566			0.642
<60	1.00			1.00		
≥60	1.160	0.698–1.928		1.128	0.679–1.874	
Sex			0.668			0.652
Male	1.00			1.00		
Female	0.894	0.536–1.491		0.889	0.533–1.482	
Histology			0.327			0.153
Adenocarcinoma	1.00			1.00		
Mucinous tumors	1.398	0.744–2.627		1.586	0.842–2.986	
Smoking history			0.954			0.991
No	1.00			1.00		
Yes	1.018	0.561–1.846		0.997	0.549–1.809	
Tumor location			0.995			0.587
Colon	1.00			1.00		
Rectum	1.002	0.573–1.751		1.167	0.668–2.040	
AJCC stage			0.308			0.523
I	1.00			1.00		
II	1.409	0.464–4.284		1.113	0.365–3.395	
III	1.938	0.696–5.397		1.488	0.534–4.151	
T stage			0.740			0.847
Tis-T2	1.00			1.00		
T3	1.357	0.624–2.950		1.203	0.553–2.613	
T4	1.270	0.604–2.668		1.046	0.498–2.199	
N stage			0.204			0.307
N0	1.00			1.00		
N1	1.705	0.942–3.084		1.590	0.879–2.875	
N2	1.422	0.757–2.670		1.307	0.696–2.454	
Pathological grading			0.778			0.815
Well and moderate	1.00			1.00		
Poor and anaplastic	0.914	0.487–1.713		0.928	0.495–1.739	
Venous invasion			0.412			0.482
	1.00			1.00		
+	1.250	0.733–2.132		1.210	0.710–2.063	
Perineural invasion			0.665			0.937
	1.00			1.00		
+	1.120	0.671–1.868		1.021	0.612–1.703	
Adjuvant chemotherapy			0.935			0.491
No	1.00			1.00		
Yes	0.921	0.127–6.676		0.498	0.068–3.622	
Adjuvant radiotherapy			0.286			0.123
No	1.00			1.00		
Yes	1.314	0.796–2.171		1.482	0.899–2.441	
No. of LNs dissected			0.454			0.387
<12	1.00			1.00		
≥12	0.823	0.493–1.372		0.798	0.478–1.331	
Metastatic site			0.330			0.366
Liver	1.00			1.00		
Lung	1.194	0.599–2.379		1.171	0.588–2.331	
Bone	1.191	0.335–4.231		1.741	0.488–6.209	
Abdominopelvic	0.871	0.423–1.797		0.837	0.406–1.724	
Others	<0.0001	<0.0001–8.340e267		<0.0001	<0.0001–2.368e70	
Multiple metastasis	0.291	0.082–1.032		0.349	0.098–1.237	
CEA group			0.002			<0.0001
P–N	1.00			1.00		
N–N	5.204	0.696–38.893		5.839	0.781–43.649	
P–P	8.353	1.118–62.413		9.439	1.263–70.553	
N–P	14.049	1.896–104.120		17.633	2.378–130.751	

5. The prognostic significance of CEA groups for OS and RDS

The p-CEA did not exhibit a significant correlation with OS (P = 0.3266) or RDS (P = 0.2263) (Fig. 2 A and D). Conversely, the r-CEA demonstrated a notable association with both OS (P = 0.0005) and RDS (P = 0.0002) (Fig. 2 B and E). Fig. 2C and F demonstrate OS and RDS curves for CEA groups (OS: P = 0.0004; RDS: P < 0.0001). For Group A (n = 28), the 5-year OS and RDS rates stood at 91.7 % and 93.3 %, respectively. In Group B (n = 90), these rates were 74.5 % for OS and 65.2 % for RDS. Group C (n = 68) exhibited rates of 55.0 % for OS and 49.0 % for RDS, while Group D (n = 55) showed rates of 43.8 % for OS and 29.5 % for RDS. In addition, patients with normal r-CEA (groups A and B) had better OS and RDS than did those with elevated r-CEA (groups C and D) regardless of whether preoperative CEA was normal (Fig. 2C and F).

5.1. CEA groups as an independent factor for OS and RDS

Cox regression analysis was conducted to assess OS and RDS. The univariate analysis unveiled a significant correlation between CEA groups and both OS and RDS (P = 0.002 and P < 0.0001, respectively; see Table 3). Furthermore, the multivariate analysis underscored that CEA groups remained an independent factor for both OS and RDS (P = 0.008 and 0.001, respectively; refer to Table 3). After multivariate adjustment, Group C(OS: HR:9.793, 95 % CI, 1.201–79.845; RDS: HR:11.337,95 % CI, 1.401–91.720) and Group D (OS: HR:16.664, 95 % CI, 2.016–137.735; RDS: HR:23.599,95 % CI, 2.854–195.141) had worse OS and RDS than did group A. RDS was worse in group B (HR:5.061, 95 % CI, 0.643–39.810) compared with group A, which was the same case for OS, although not significantly (HR: 5.354, 95%CI, 0.682–42.056).

6. The optimal cut-off value of CEA

We utilized a four-knot restricted cubic spline model to illustrate the relationship between the hazard ratio (HR) and r-CEA concerning both OS and RDS. The knots were strategically positioned at the 5th, 35th, 65th, and 95th percentiles of r-CEA values, which corresponded to 1.08, 3.17, 9.38, and 123.55, respectively. When the r-CEA level was <5.1 ng/ml, an increase in the r-CEA level increased the risk of death, but the HRs was <1. When the r-CEA concentration was above 5.1 ng/ml, the curve remained largely stable, but all HRs were greater than 1(Fig. 3). Hence, the optimal cutoff value for CEA in predicting prognosis for stage I-III CRC patients with metastatic relapse was determined to be 5.1 ng/ml, closely aligned with the threshold of 5.0 ng/ml.

7. Discussion

We retrospectively reviewed a large cohort of consecutive stage I-III CRC patients with metastatic relapse according to p-CEA and r-CEA levels. We demonstrated that r-CEA had better prognostic value than p-CEA in terms of OS and RDS. Additionally, the dynamic

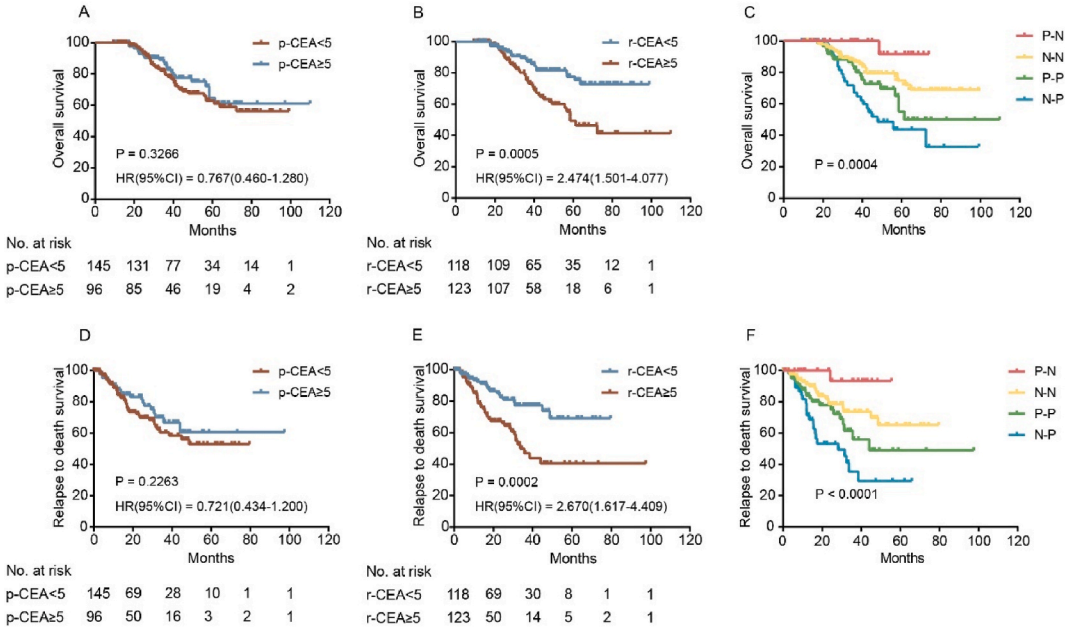

Fig. 2. Kaplan-Meier curves of OS and RDS according to p-CEA, r-CEA and CEA changes. OS and RDS according to p-CEA (A, D); OS and RDS according to r-CEA (B, E); OS and RDS according to changes of p-CEA and r-CEA (C, F). The log-rank test was utilized to calculate P-values, and GraphPad Prism was utilized to produce hazard ratios (HRs).

Table 3
Multivariate Cox regression analysis for OS and RDS.

Variables	Overall survival			Relapse to death survival		
	Hazard ratio	95%CI	P	Hazard ratio	95%CI	P
Age			0.450			0.698
<60	1.00			1.00		
≥60	1.276	0.677–2.406		1.133	0.602–2.135	
Sex			0.494			0.528
Male	1.00			1.00		
Female	1.278	0.633–2.581		1.257	0.617–2.559	
Histology			0.100			0.024
Adenocarcinoma	1.00			1.00		
Mucinous tumors	2.142	0.864–5.312		2.960	0.617–2.559	
Smoking history			0.510			0.762
No	1.00			1.00		
Yes	1.378	0.530–3.582		1.156	0.453–2.948	
Tumor location			0.697			0.351
Colon	1.00			1.00		
Rectum	1.167	0.535–2.544		1.444	0.667–3.126	
AJCC stage			0.512			0.253
I	1.00			1.00		
II	1.751	0.444–6.915		2.725	0.671–11.076	
III	2.081	0.572–7.564		3.107	0.811–11.902	
Pathological grading			0.643			0.399
Well and moderate	1.00			1.00		
Poor and anaplastic	0.838	0.398–1.766		0.723	0.340–1.537	
Venous invasion			0.317			0.413
	1.00			1.00		
+	1.432	0.708–2.897		1.334	0.669–2.657	
Perineural invasion			0.257			0.339
	1.00			1.00		
+	0.667	0.331–1.343		0.711	0.354–1.430	
Adjuvant chemotherapy			0.991			0.993
No	1.00			1.00		
Yes	6.183e5	<0.0001->e1000		1.961e5	<0.0001->e1000	
Adjuvant radiotherapy			0.192			0.301
No	1.00			1.00		
Yes	1.559	0.800–3.035		1.417	0.732–2.745	
No. of LNs dissected			0.549			0.377
<12	1.00			1.00		
≥12	0.818	0.425–1.576		0.734	0.369–1.460	
Metastatic site			0.436			0.559
Liver	1.00			1.00		
Lung	0.896	0.393–2.043		0.875	0.381–2.007	
Bone	0.433	0.076–2.460		1.123	0.193–6.546	
Abdominopelvic	1.010	0.408–2.503		1.484	0.588–3.744	
others	<0.0001	<0.0001->e1000		<0.0001	<0.0001–4.519e276	
Multiple metastasis	0.248	0.061–1.010		0.388	0.096–1.561	
CEA group			0.008			0.001
P–N	1.00			1.00		
N–N	5.061	0.643–39.810		5.354	0.682–42.056	
P–P	9.793	1.201–79.845		11.337	1.401–91.720	
N–P	16.664	2.016–137.735		23.599	2.854–195.141	

shifts between plasma carcinoembryonic antigen (p-CEA) and resected carcinoembryonic antigen (r-CEA) levels could offer further categorization of patients into four distinct groups: A, patients presenting elevated p-CEA levels but normal r-CEA levels (P–N); B, patients displaying normal levels of both p-CEA and r-CEA (N–N); C, patients exhibiting elevated levels of both p-CEA and r-CEA (P–P); D, patients with normal p-CEA levels but elevated r-CEA levels (N–P). RDS and OS were increasingly worse in groups A-D. Cox regression analysis demonstrated that dynamic changes between p-CEA and r-CEA level independently serve as prognostic indicators for CRC patients experiencing metastatic relapse.

Several studies have underscored the significance of preoperative CEA levels in evaluating the prognosis of CRC patients [18–21], whereas others have highlighted the prognostic value of postoperative CEA [22–24] or perioperative changes of CEA [6,7,25,26]. However, in stage I-III CRC patients experiencing metastatic relapse, our data demonstrated that the r-CEA had greater prognostic value in terms of OS and RDS than the p-CEA, which highlighted the importance of postoperative CEA. Furthermore, dynamic changes in p-CEA and r-CEA could provide a more informative prognostic reference for post-relapse survival in stage I-III CRC individuals.

Despite receiving curative treatment, the majority of patients experience relapse within a span of three years [27]. Managing and treating colorectal cancer (CRC) following metastatic recurrence poses significant challenges. However, to date, limited research has focused on the surveillance and treatment strategies for CRC following relapse [27,28]. No comprehensive study has thoroughly

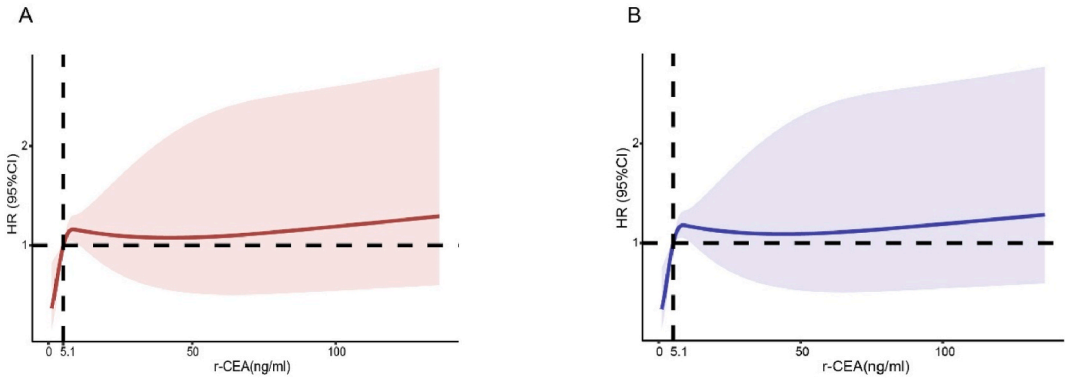

Fig. 3. Association of r-CEA and mortality risk. r-CEA and HRs of OS (A); r-CEA and HRs of RDS(B). Hazard ratios are represented by solid lines, while shaded areas indicate 95 % CIs.

explored the association between p-CEA, r-CEA, and CEA alterations and survival outcomes in stage I-III CRC patients experiencing metastatic relapse.

Significantly, our research uncovered that patients exhibiting positive CEA levels both at the onset and upon relapse, as well as those testing negative, experienced the shortest durations of RDS and OS. Therefore, in clinical practice, it's imperative to closely monitor not only patients presenting with positive p-CEA and r-CEA levels, but also those initially negative who later test positive upon relapse. Tailoring post-recurrence follow-up strategies is essential, alongside potential therapeutic interventions like adjuvant chemotherapy, radiotherapy, or other treatments, aimed at enhancing their long-term outcomes following recurrence.

Several studies have suggested that patients with negative p-CEA levels demonstrate superior RFS or OS compared to those with positive p-CEA levels.

Nevertheless, within the cohort of patients with initially negative p-CEA levels, our findings revealed that those who transitioned to positive CEA levels at the time of relapse exhibited worse outcomes compared to those who consistently maintained negativity upon recurrence. At present, there is a lack of pertinent research investigating the underlying mechanism behind the shift in CEA concentration from negative to positive. However, these findings underscore the significant heterogeneity of CRC. In clinical practice, it is imperative to develop personalized management and treatment plans for patients with CRC. This may entail additional diagnostic procedures such as CT/MRI scans or more frequent follow-up appointments, especially for those deemed at higher risk of recurrence and mortality.

Generally, 5.0 ng/ml is referred to as the cut-off point for CEA. However, some studies have reported multiple optimal cut-off values for CEA, but only three thresholds (2.5, 5, and 10 ng/ml) had sufficient data for meta-analysis [10,11]. In this study, we utilized a restricted cubic splines model to assess the correlation between recurrent CEA levels and hazard ratio (HR). The model revealed that the optimal prognostic threshold value for CRC patients with metastatic relapse was determined to be 5.1 ng/ml, which closely aligns with 5.0 ng/ml. This minor difference may have been caused by measurement and process errors. This may also be attributed to that the fairly small number of patients distributed around 5.0 ng/ml. Survival analysis further indicated that setting the CEA cutoff value at 5.0 ng/ml resulted in a more pronounced association with both OS and RDS compared to cutoff values of 2.5 ng/ml or 10.0 ng/ml, particularly concerning the dynamic change between p-CEA and r-CEA levels.

Notably, within our study, solely the CEA level exhibited statistical significance in both univariate and multivariate Cox regression analyses. None of the other variables, such as AJCC stages, venous invasion, or adjuvant chemotherapy, were significantly different. First, this may be partly because we focused on CRC patients who experienced metastatic relapse, a subgroup of all CRC patients. Second, this study was retrospective in nature, characterized by a limited sample size, resulting in lower statistical power [29]. Although not significant, the trends for other clinicopathological factors correlated with OS or RDS in both univariate and multivariate analyses remained in line with findings reported in existing literature. In addition, the association between CEA levels and OS or RDS was statistically significant, despite a relatively small sample size. We are confident that the CEA level would have prognostic value in a wider population.

Although our study has provided new findings and real-world evidence, we are aware that our research has several limitations. First, the retrospective design of this study renders it vulnerable to missing data. In our study, some clinical information, such as histological, T stage, and pathological grade, was missing. Given the close relationship between CEA levels and the aim of our study, a few patients with missing p-CEA or r-CEA values were excluded. However, the small proportion of missing data minimizes attrition. Second, this study was conducted as a single-center cohort study, featuring a relatively modest sample size, and included exclusively Chinese patients diagnosed with CRC. We recommend conducting a prospective multicenter cohort study to validate the reproducibility of our study's findings. Third, a large proportion of subjects are with rectal cancer and in stage III, which may cause potential selection bias. Moreover, we didn't control after-recurrence treatment regiments that may influence OS and RDS. Generally, certain scholars have investigated solely the association between baseline CEA levels and patient prognosis, while others have concentrated on CEA levels both pre- and post-treatment. However, few have delved into the prognostic significance of CEA levels upon recurrence. Our team has pioneered a systematic exploration into the correlation between CEA levels from initial diagnosis to relapse and subsequent

post-recurrence survival, offering valuable insights to inform clinical practice. The positive p-CEA does not uniformly indicate a poor prognosis, nor does the negative p-CEA consistently denote a favorable prognosis among patients. Therefore, the management and follow-up of patients with CRC should be based on p-CEA and subsequent CEA levels upon relapse. Patients with negative p-CEA levels require regular monitoring, while those with positive r-CEA levels necessitate comprehensive treatment regardless of their p-CEA status.

For instance, in the N–P and P–P groups, it is advisable to reduce the post-treatment follow-up interval from six months to three months, along with administering adjuvant therapy as deemed necessary to enhance patient prognosis. In summary, we can foresee post-treatment recurrence by assessing p-CEA levels and forecast long-term survival following recurrence through evaluating r-CEA and CEA alterations.

8. Conclusion

This study demonstrated that r-CEA was more important in assessing post-recurrence survival than p-CEA in stage I-III CRC patients experiencing metastatic relapse. Dynamic changes in p-CEA and r-CEA could help to stratify stage I-III CRC individuals into different mortality risk groups.

Data availability statement

The data associated with our study has not been deposited into a publicly available repository. Data will be made available on request.

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Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Board of Fudan University Shanghai Cancer Center, with the approval number: 2006219-13. Due to the retrospective study, the requirement to obtain informed written consent was waived. All methods were carried out in compliance with relevant guidelines and regulations.

CRediT authorship contribution statement

Shanyou Tong: Writing – original draft, Methodology, Investigation, Data curation. **Renping Wu:** Writing – original draft, Investigation, Project administration. **Long Zhang:** Writing – review & editing, Project administration, Investigation. **Ping Lu:** Writing – review & editing, Resources, Project administration. **Xiang Hu:** Supervision, Resources, Funding acquisition, Conceptualization. **Yaqi Li:** Supervision, Resources, Funding acquisition, Conceptualization. **Junjie Peng:** Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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