



Postoperative carcinoembryonic antigen (CEA) levels predict outcomes after resection of colorectal cancer in patients with normal preoperative CEA levels

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Background: Carcinoembryonic antigen (CEA) is a cancer biomarker used in colorectal cancer (CRC) for tumor screening and outcome prediction. However it is still lack of sensitivity and specificity in general population. The present study aimed to investigate the clinical significance of CEA in patients with normal preoperative CEA levels.

Methods: Ninety-four patients were included who received surgery and developed an elevated CEA level postoperatively. They were divided into group A1 and A2 according to the peak CEA level (whether more than 10 ng/mL); group B1 and B2 according to CEA variation (whether reached a normal level at least once). The association between postoperative CEA and overall survival (OS), and disease-free survival (DFS) were analyzed using Kaplan-Meier method and Cox's proportional hazards regression model.

Results: The median follow-up time was 38 months. Patients in Group A2 and Group B2 had greater opportunities for recurrence and metastasis ($P < 0.05$) compared to Group A1 and Group B1. Cox regression analysis revealed that high CEA levels and consistently elevated CEA levels were significantly associated with worse OS and DFS. Furthermore, patients with p-stage II in group A2 had worse OS than patients with p-stage III in group A1. The same result was detected when comparing group B2 and B1.

Conclusions: Among patients with an initially normal CEA level, postoperative CEA level and variation could be effective markers for tumor progression assessment. TNM stage, combined with CEA level might be more accurate in prognostic prediction.

Keywords: Colorectal cancer (CRC); carcinoembryonic antigen (CEA); postoperative follow up; prognosis

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Introduction

Colorectal cancer (CRC) is currently the third most common cancer and one of the major causes of cancer-related deaths worldwide (1). In recent years, the prevalence of CRC has increased rapidly in China (2). Despite extensive advances in adjuvant therapies and biomarker

target drugs, the 5-year overall survival (OS) of CRC patients is still poor. Currently, resection of the primary tumors is the cornerstone of CRC management and is the only available treatment choice that offers the opportunity for a cure. Unfortunately, almost half of the CRC patients who underwent surgical resection died due to recurrences

or metastatic diseases (3). Numerous studies have indicated that prognostic assessment mainly relies on clinical or pathological stages. Practically, however, the outcome of the same stage patients can be considerably different (4). Patients with other aggressive prognostic factors, e.g., elevated expression of CEA, vascular invasion, nerve infiltration, and positive surgical margin (5), would have a worse prognosis. Currently, postoperative monitoring is based on specific computed tomography (CT) or magnetic resonance imaging (MRI) exams. However, long-term survival was not always associated with radiologic data as this data lacked a predictive effect.

Carcinoembryonic antigen (CEA) is a sensitive cancer biomarker for gastrointestinal tumors and is widely expressed in CRC tissue and serum. Serum CEA has been commonly used in clinical practice since 1965 (6). As a classical marker for this disease, vast of studies have extensively assessed the prognostic role of serum CEA levels in CRC. In practice, serum CEA levels are widely used for posttreatment surveillance because it is easily detected without radiation injury. Vast reports have shown that the preoperative CEA level is an independent predictive factor of unfavorable prognosis for CRC (7,8). Some studies showed that CEA levels independently predict poor chemotherapy response. Most reports investigated the relation between serum CEA level and chemotherapy based on the preoperative level, and the clinical significance of the CEA value was barely studied among the patients whose CEA level was normal before surgery.

However, increasingly, investigators recognized that the CEA measurement lacked sensitivity and specificity in CRC surveillance (9). Therefore, some previous studies have redefined the CEA classification or combined CEA with other biomarkers for more accurate monitoring (10,11). Saito *et al.* found that the diagnostic accuracy of postoperative CEA levels for recurrence in patients with normal preoperative CEA levels was significantly higher than that among the population with positive preoperative serum CEA levels (12). Limited data assessed the diagnostic value and cutoff level of CEA among the population with normal preoperative CEA levels but elevated CEA levels after resection. Hence, in the present study, we sought to determine the clinical significance of the postoperative CEA levels in CRC patients who had normal CEA levels before surgery.

Methods

In this study, the clinical and pathological materials were

based on the databases of Sir Run Run Shaw Hospital of Zhejiang University. A total of 1,492 patients diagnosed with CRC and who underwent R0 surgery between 2012 and 2016 were included in this search, among which 110 patients had a normal preoperative CEA level of 5 ng/mL or less and then subsequently developed an elevated CEA level at least one time. Among these patients, 16 patients were excluded because they had distant metastasis at the time of resection, histology that was not adenocarcinoma or unknown follow-up information. A total of 94 patients with p-stage I to p-stage III CRC were enrolled in the present study according to the American Joint Committee on Cancer (AJCC) eighth edition. All the therapies of these patients were based on the corresponding National Comprehensive Cancer Network (NCCN) guidelines. The clinicopathologic baseline features and follow-up data of each patient were collected. This study obtained approval from the Institutional Review Board, and the data were analyzed anonymously.

The serum levels of all 94 patients were measured every 3–6 months after surgery. All blood samples were sent to the Clinical Laboratory at Sir Run Run Shaw Hospital and analyzed using Unicel DxI800 (Beckman Coulter, Fullerton, CA, USA) for the detection of CEA. According to the postoperative serum CEA peak levels and variation trends, the patients were divided into different groups as follows: Group A1: the peak CEA level was no more than 10 ng/mL; Group A2: the peak CEA level was higher than 10 ng/mL; Group B1: the CEA level reached a normal level at least once during follow-up; and Group B2: the patients had persistently elevated CEA levels. This classification was defined as the CEA-stage. Additionally, we combined the TNM stage with the CEA-stage as follows: stage I-A1, stage I-A2, stage I-B1, stage I-B2 and so on. The primary end points of this study were disease-free survival (DFS) and OS. For each patient, recurrences and metastases were diagnosed by CT imaging examinations. DFS was measured from the surgical date to the time of recurrence (or death) or until the date of the last follow-up in patients who maintained a disease-free status. OS was calculated from the date of surgical resection to the time of death or deadline in survivors. The median follow-up time was 38 months.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics 23 (IBM Corp., NY, USA). Differences in clinicopathological factors according to CEA levels were

Table 1 Clinicopathological features according to CEA in CRC patients

Variable	No. patients	Serum CEA level			Trend of CEA		
		Group A1	Group A2	P value	Group B1	Group B2	P value
Sex							
Male	66	39	27	0.883	24	42	0.121
Female	28	17	11		15	13	
Age (years)	61.989	61.357	62.921	0.529	61.641	62.236	0.3
Peak CEA level	61.133	6.57	141.543	0.093	14.672	94.079	0.153
Tumor size (mm)	38.0	35.929	41.053	0.176	36	39.418	0.60
T category							
T ₁ , T ₂	11	9	2	0.113	6	5	0.403
T ₃ , T ₄	80	44	36		33	47	
Lymphatic invasion							
Absence	40	28	12	0.076	15	25	0.499
Presence	54	28	26		24	30	
Location							
Colon	41	22	19	0.304	22	19	0.035*
Rectum	53	17	36		17	36	
Recurrence and metastasis							
Absence	35	31	4	0.000*	23	12	0.000*
Presence	59	25	34		16	43	

*, statistically significant. CRC, colorectal cancer; CEA, carcinoembryonic antigen.

analyzed for all patients. Chi-squared or Fisher's exact test was performed to compare the categorical characteristics of the groups. Student's *t*-test was selected to examine the differences in continuous data. The DFS and OS of each group were assessed using the Kaplan-Meier curve. In addition, Cox's proportional hazards regression model was used to identify the effect of the independent prognostic predictor on OS. Survival outcomes between groups were compared with the log-rank test. A P value of less than 0.05 derived from two-sided tests was considered statistically significant.

Results

Patient characteristics

In the present study, CRC patients with a normal preoperative CEA level that subsequently developed an elevated CEA level were observed in 6.30% colorectal

patients. The majority of the included patients were stage II (30.9%) and stage III (58.5%) cases. The median age of these 94 patients was 63 years old (range, 31–94 years old). Most of the included patients were male (70.2%). Up to the date of the last follow-up, 48 (51.1%) patients had died, and 59 (62.8%) patients were diagnosed with CRC recurrence or distant metastasis.

Recurrence and metastasis according to clinicopathology

Patients in Group A2 and Group B2 had greater opportunities for recurrence and metastasis than Group A1 and Group B1, respectively ($P < 0.05$). The baseline characteristics of all the 94 patients are summarized in *Table 1*. The data showed that the median peak level of CEA among all patients was 8.26 ng/mL (range, 5.03–2,879.00 ng/mL), and the average levels of peak CEA in Group A1 and Group A2 were 6.570 ng/mL and

Table 2 Recurrence and metastasis in CRC patients

Recurrence and metastasis	No. patients	Peak CEA			Trend of CEA			Deep of invasion			Node metastasis		
		Group A1	Group A2	P value	Group B1	Group B2	P value	T1,2	T3,4	P value	Positive	Negative	P value
Yes	35	31	4	0.000*	23	12	0.000*	11	24	0.000*	20	15	0.028*
No	59	25	34		16	43		2	57		20	39	

*, statistically significant. CRC, colorectal cancer; CEA, carcinoembryonic antigen.

Table 3 Univariate analysis of OS and DFS for 94 patients

Variables	OS		DFS	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Female	1.031 (0.521–2.039)	0.931	1.171 (0.655–2.094)	0.595
Male	Ref ^a			
Peak CEA level		0.001*	1.949 (1.106–3.433)	0.021*
Group A2	2.993 (1.600–5.598)			
Group A1	Ref ^a			
Trend of CEA		0.002*	2.534 (1.322–4.859)	0.005*
Group B2	2.914 (1.475–5.756)			
Group B1	Ref ^a			
T stage		0.766	4.338 (1.009–18.651)	0.049*
T _{3,4}	1.212 (0.342–4.293)			
T _{1,2}	Ref ^a			
Lymph nodes		0.433	1.487 (0.855–2.585)	0.160
Positive	1.295 (0.679–2.473)			
Negative	Ref ^a			
Location		0.070	0.826 (0.473–1.443)	0.502
Rectum	0.558 (0.297–1.048)			
Colon	Ref ^a			

^a, reference; *, statistically significant. CEA, carcinoembryonic antigen; OS, overall survival; DFS, disease-free survival.

141.543 ng/mL, respectively, but there were no statistically significant differences between these two groups ($P>0.05$). Interestingly, it was harder for rectal cancer patients to regain normal postoperative CEA levels than colon cancer patients ($P<0.05$). A Chi-squared analysis showed that peak CEA level higher than 10 ng/mL ($P<0.05$), trend of CEA level ($P<0.05$), invasion depth ($P<0.05$), and node metastasis ($P<0.05$) after resection were significant independent predictors of relapse (Table 2). No significant differences were found among age, sex, or tumor location after curative

resection.

Evaluation of prognosis using the TNM-CEA-stage system

Using the Cox regression model, we found that high CEA levels (HR =2.993, 95% CI, 1.600–5.598) and consistently elevated CEA levels (HR =2.914, 95% CI, 1.475–5.756) were significantly associated with worse OS. The same results were seen in DFS (HR =1.949, 95% CI, 1.106–3.433 and HR =2.534, 95% CI, 1.322–4.859, respectively) (Table 3).

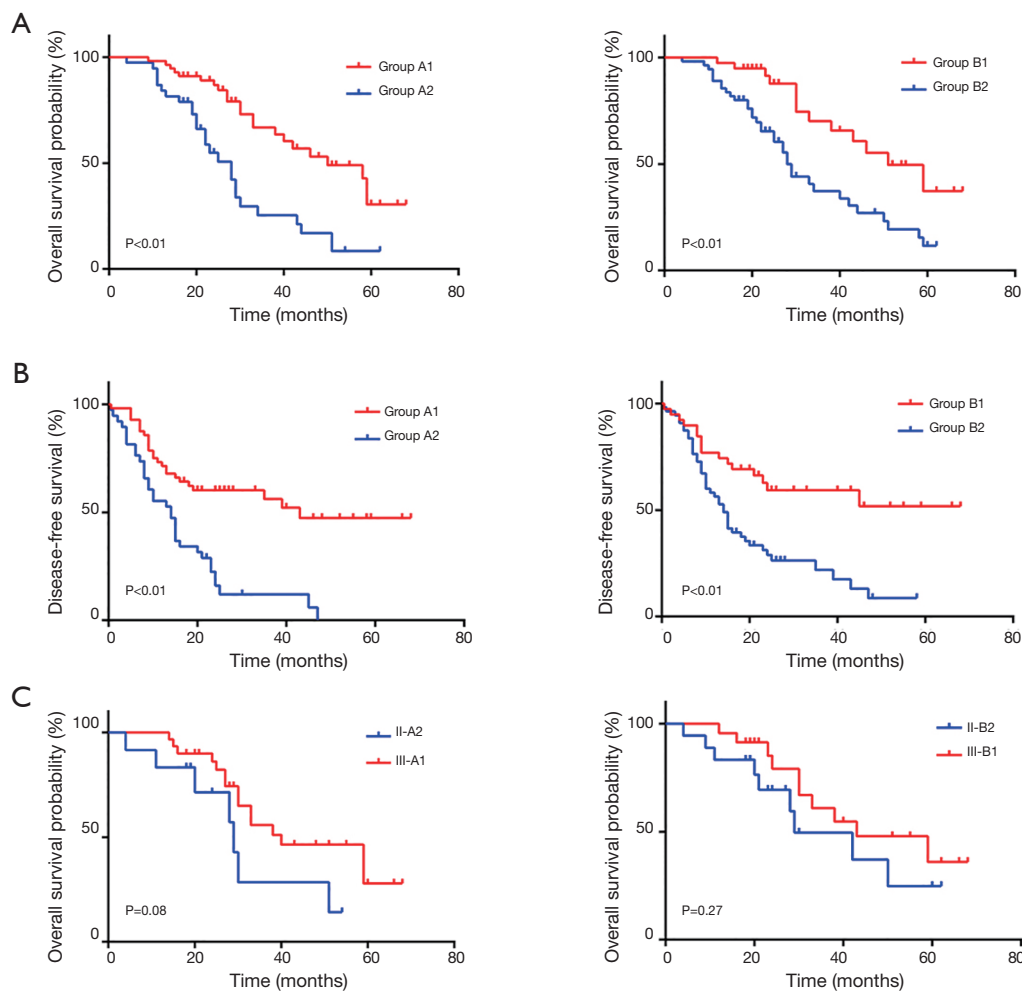


Figure 1 Kaplan-Meier survival curves of patients with CRC according to CEA levels and variation. (A) The median overall survival and (B) disease-free survival in patients from Group A1, A2, B1 and B2. (C) The median overall survival in patients with stage II-A2, stage III-A1, stage II-B2 and stage III-B1. CRC, colorectal cancer; CEA, carcinoembryonic antigen.

As shown in *Figure 1A*, the Kaplan-Meier curve indicated that patients in Group B2 had a worse prognosis than patients in Group B1 (median survival 28 *vs.* 51 months, $P<0.01$). The same result was seen between Groups A2 and A1 (median survival 28 *vs.* 50 months, $P<0.01$) (*Figure 1B*). Poor DFS was also detected in Groups B2 and A2 compared to Groups B1 and A1, respectively ($P<0.01$). To further assess the prognostic roles of CEA levels, we established the prognostic values of the TNM-CEA-stage system. Though there were no significant differences, patients with stage II CRC in Group A2 demonstrated worse OS compared with the stage III-A1 patients (median survival 29 *vs.* 40 months, $P=0.08$). This result was consistent with the comparison between stages II-B2 and III-B1, which indicated that the

prognosis of stage II patients with persistently elevated CEA levels was worse than that of stage III patients (median survival 29 *vs.* 43 months, $P=0.27$) (*Figure 1C*).

Discussion

After curative resection of primary CRC, a large number of patients' CEA levels declined to normal values within 4–6 weeks. Residual disease should be suspected if the CEA level does not return to normal. Furthermore, the patients with persistent elevation of CEA levels following surgery could suggest worse survival (13), which might mean that an increased amount of CEA secreted was associated with greater tumor load. However, 49% of patients had a false

increase of CEA at least once in follow-up, and more than 90% of these had values ranging from 5 to 10 ng/mL (14). In this retrospective study, we defined the cutoff as 10 ng/mL. One report by Moertel *et al.* (15) showed a false-positive rate of 4% when a cutoff of 10 ng/mL was used. Our results showed that only 4 patients remained disease-free until death once the CEA level was higher than 10 ng/mL.

Although other study (16) suggested that CRC patients with an increase in postoperative CEA levels were also associated with aggressive characteristics, including poor T stage and differentiation, there were no significant differences in basic clinicopathological features between CRC patients in Groups A1 and A2. When the comparison was made between the patients in Groups B1 and B2, the same conclusion was drawn. These results showed that the relationship between basic features and the preoperative CEA level was tighter than postoperative CEA levels, which was in accordance with previous studies.

In practice, CRC is mainly classified according to the TNM stage system, including the local invasion depth (T stage), the lymph node invasion (N stage), and the presence of distant metastases (M stage) (17). The TNM stage system has provided valuable prognostic messages and guided therapy. Regarding the pathological features at the time of diagnosis, the CRC was classified into early stage I disease (T1-T2, N0, and M0), stage II disease (T3-T4, N0, and M0), stage III disease (any T, N1-2, and M0), and advanced stage IV disease (any T, any N, and M1). The current recommended treatment for stages I, II, and III is surgical resection, and stage III patients are advised to receive adjuvant chemotherapy (18). For stage II patients, adjuvant chemotherapy is only recommended for patients with high-risk factors (19-21), but a definite consensus for this treatment has not yet been reached. In fact, the responses of systemic adjuvant chemotherapy for stage II and III patients were not predicted. Therefore, there is special attention and controversy regarding stages II and III disease.

Even with the advancement of chemotherapy regimens and targeted therapies, among patients with stages II and III disease, the survival rates were 62.1 and 36.5%, respectively, in the present study. The survival above was worse than the same stage CRC patients in a large population, which was consistent with epidemiological investigations that corroborated that high postoperative serum CEA levels were a significantly increased risk for CRC patients (22). Our study showed that both the patients in Groups A2 and B2 had a shorter OS than those in Groups A1 and B1, and the results were significantly different ($P < 0.05$).

Additionally, the prognosis of both Groups A2 and B2 was worse than that of Groups A1 and B1 with the same TNM stage. Thus, our data suggested that postoperative CEA level is an important prognostic marker in stage II/III CRC patients. The COX regression analysis showed that the CEA level or the trend was also a dependent risk factor for recurrence and metastasis. Either Group A2 or B2 accounted for a relatively higher proportion of relapse and metastasis in stage II/III CRC patients than Group A1 or B1. In our study, 89.5% of patients in Group A2 had developed relapse or metastasis. Therefore, irrespective of the stage of cancer, both the high level and the increasing trend of the postoperative CEA level determined poor OS in CRC.

Thus, for patients with elevated postoperative CEA levels, the current TNM staging system may not be enough to evaluate the prognosis and clinical outcomes. In this study, we examined the prognostic role of the level of the postoperative CEA serum biomarker combined with the TNM staging system in those patients. In addition, adding the CEA information to the TNM staging system indeed improved the survival predictive value compared with the TNM stage system alone. Interestingly, the OS of stage II-B2 patients was worse than that of stage III-B1 patients. In the future, the trend of postoperative CEA levels has the potential to serve as a marker in disease prognosis and may be a predictor of chemotherapy response. Similar results were drawn in the survival competition of stage II-A2 and stage III-A1 patients. As a result, among stage II patients with high CEA levels after surgery could be eligible patients for adjuvant chemotherapy and other therapies.

In clinical practice, patients came to hospital for a check-up every 3 months in the first 2 years and then every 6 months for a total of 5 years. Routine monitoring of the CEA level was suggested for all the patients with resected CRC. For this subgroup of CRC patients in our investigation, we recommended that the serum CEA level be surveilled more intensively once the level was greater than 10 ng/mL during follow-up. In particular, the use of serum protein biomarkers was noninvasive and inexpensive for the detection of CRC compared to a CT scan. Each follow-up, blood tumor markers and rectal examination should be conducted to assist oncologists in the early discovery of possible local recurrence and metastasis. Our study found that it was unlikely for the postoperative CEA levels for rectal cancer patients to be normal again. This information was potentially useful for doctors in terms of putting more comprehensive examination to detect disease

progression.

A large number of reports demonstrated that the change in imaging tests was secondary to serum markers. The CEA level detected recurrent disease 2 to 5 months prior to discovery by any other means (23,24). Any rise in CEA level higher than 10 ng/mL should prompt thorough assessment for disease recurrence; however, false-positive elevated CEA levels have been reported to occur in patients who are smokers and patients with inflammatory states, including chronic obstructive lung diseases (25) and rheumatoid arthritis (26). In addition, the CEA level is not specific to CRC and could be elevated in many other cancers. Therefore, the multiphase influences resulting in CEA variation were one of the weaknesses of CEA to be used to guide the treatment and prognosis of CRC.

There were other limitations in the present study. This was a retrospective study with a relatively small sample size, which might be responsible for some negative results in terms of clinical characteristics or OS in different groups. The lack of pathology confirmed that recurrence or metastasis was also a potential limitation.

Conclusions

In conclusion, the present study revealed a new predictive method of serum CEA levels as a possible prognostic marker in colorectal tumors, especially for stage II patients during the following-up period. Among patients with an initially normal CEA level, CEA monitoring was found to be effective for assessing tumor progression. Hence, a personal posttreatment surveillance plan is needed for CRC patients to receive effective treatment.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.11.27>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study obtained ethics approval of Sir Run Run Shaw Hospital (No. 20190814-4). Informed consent was waived.

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