Differences in carcinoembryonic antigen levels between colon and rectal cancer

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Abstract. The aim of the present study was to investigate the levels of the serum tumor biomarker carcinoembryonic antigen (CEA) in patients with carcinoma of the colon and rectum in different clinical stages. Colorectal cancer (CRC) is one of the most commonly diagnosed types of cancer worldwide and previous studies have reported rapidly updated therapeutic regimes. While the majority of studies focus on CRC as a single entity, certain studies distinguish colon cancer (CC) from rectal cancer (RC), as there is a hypothesis stating that CC and RC are two naturally different entities. CEA is reported to be an important tumor-associated antigen overexpressed in CRC, which is routinely detected as a significant indicator of CRC. Our study aimed to identify potential differences in the expression of CEA between CC and RC, which may, to some degree, reflect the natural differences between the two. We investigated 240 CRC cases between July, 2010 and December, 2012 from The First and Second Affiliated Hospitals of Dalian Medical University, including 117 CC and 123 RC patients with tumors classified by Duke's staging as A-D. The serum CEA level was measured preoperatively by radioimmunoassays as a routinely used auxiliary indicator. The expression of CEA differed between CC and RC, with the former exhibiting variation among the four stages, whereas no variation was observed in RC. In addition, there were differences between CC and RC regarding the CEA level in stage C and D. Furthermore, the CEA level in stage C of CC was significantly lower compared to that in any other stage. In conclusion, the intrinsic distribution of the CEA level between CC and RC suggests that CC and RC may be two naturally different entities; the significantly low CEA level in stage C of CC indicates that stage C may be crucial in the evolution of CC.

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Introduction

Colorectal cancer (CRC) is the second most commonly diagnosed type of cancer in females and the third in males worldwide, with an estimated >1.2 million new cancer cases and 608,700 deaths in 2008 (1). While colon cancer (CC) and rectal cancer (RC) are often referred to as CRC due to their adjacent anatomic location, several studies investigating risk factors to underlying molecular mechanisms, have reported differences between CC and RC.

Dietary risk factors appeared to be considerably different between CC and RC (2) and the Cancer Genome Atlas Network reported differences between tumors located in the right colon and all other sites (3). Whether CC and RC are of a markedly different nature has not been clearly determined and the number of clinical studies that have emphasized the differences between CC and RC is currently limited.

Several tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19.9 and CA 12.5, have been detected in a number of malignancies, including CRC. The levels of CEA and CA19.9 are often elevated in advanced CRC (4) and have been considered as an early sign of CRC recurrence (5).

CEA, originally identified in human fetal intestine and adult CC tissue in 1965 by Gold and Freedman (6), was subsequently characterized as a glycosylated cell-surface glycoprotein with a molecular weight of 180,000 Da (7); further research identified it as a significant tumor-associated antigen that is highly overexpressed in breast, lung and pancreatic cancer and, particularly, in CRC (8,9). CEA is routinely detected as a tumor biomarker and an auxiliary indicator for the preoperative diagnosis of CRC (10), as well as an early predictor of recurrence (5), which to some extent accounts for CEA reflecting the nature of CRC.

As there are currently few available studies reporting the variations in the expression of CEA between CC and RC, the present study aimed to investigate the possible differences in

the serum CEA level between CC and RC, which may highlight the distinct natures of these two types of cancer.

Materials and methods

Serum CEA concentrations. A total of 240 cases were investigated between July, 2010 and July, 2012 from The First and Second Affiliated Hospitals of Dalian Medical University, including 117 CC and 123 RC patients. The patients underwent potentially curative resection of colorectal carcinomas, which were classified as Duke's stage A-C and patients diagnosed as stage D were classified by biopsy or radiographic findings (endorectal ultrasound, computed tomography and magnetic resonance imaging). The disease stage was determined according to the Dukes' staging system, which is equivalent to the TNM staging system of the American Joint Committee on Cancer (11). All the clinical findings were prospectively recorded in detail and stored in computerized files, which included name, gender, age, family history, CEA level and the location and stage of the tumors.

The serum CEA concentrations were measured preoperatively in the 240 patients by radioimmunoassays performed in the clinical laboratories of the two affiliated hospitals. CEA kits from Roche Diagnostics (Basel, Switzerland) were used for detection following the manufacturer's instructions. High CEA concentrations were redefined as those >5 ng/ml.

Statistical analysis. In the present study, all the data were included in the analysis and are expressed as means ± SD. Statistical significance was calculated using the non-parametric t-test and differences were considered to be statistically significant when $P<0.05$.

Results

Clinicopathological characteristics of CRC patients. A total of 240 patients with primary CRC (mean age, 62.0±12.3 years; range, 33-89 years), including 117 CC patients (mean age, 62.5±12.5 years; range, 33-89 years) and 123 RC patients (mean age, 61.4±12.1 years; range, 34-86 years), were recruited for this study. The Duke's stage and other relevant information are summarized in Table I.

Table I. Clinicopathological characteristics in colon and rectal cancer patients.

	Total (n=261)*	Colon (n=129)*	Rectum (n=132)*
Characteristics	No. (%)	No. (%)	No. (%)
Gender			
Male	139 (57.9)	68 (58.1)	71 (57.7)
Female	101 (42.1)	49 (41.9)	52 (42.3)
Age, years			
≤50	45 (18.8)	19 (16.2)	26 (21.1)
>50	195 (81.2)	98 (83.8)	97 (78.9)
Duke's stage			
A	57 (23.8)	29 (24.8)	28 (22.8)
B	58 (24.2)	31 (26.5)	27 (21.9)
C	60 (25.0)	29 (24.8)	31 (25.2)
D	65 (26.1)	28 (23.9)	37 (30.1)

*The sum of all the patients. The data of patients that were outliers is not mentioned in this Table.

Table II. Differences in the serum carcinoembryonic antigen level among patients with colorectal cancer.

Variables	Mean, ng/ml	P-value
Duke's stage		
A/B	34.14/33.66	0.3508
A/D	34.14/60.05	0.3967
B/C	33.66/23.35	0.2577
B/D	33.66/60.05	0.0711
Gender		
Male/female	29.47/49.70	0.9735
Age, years		
≤50/>50	10.90/43.95	0.0509

Lower CEA level in stage C of CRC differs from that in other stages. The mean value of CEA in patients with CRC in stage A, B, C and D were 34.14, 33.66, 23.35 and 60.05 ng/ml, respectively. Of note, the CEA level in patients with CRC at stage C was lower compared to that in any of the other stages, with significant differences from stages A and D (Fig. 1), indicating the significance of stage C, which contrasts the previous hypotheses that CEA levels increased with advancing stage (12,13). Additionally, the CEA level of the non-distant metastasis (NDM) group was different from that in the distant metastasis (DM) group, whereas no differences were observed between the non-metastasis (NM) and metastasis (M) groups. An analysis of other factors, such as patient gender and age, revealed no statistically significant differences (Table II).

CC and RC are generally considered to be of the same nature due to their neighbouring anatomical position. Therefore, the indices of CC and RC are analyzed considering these two types of cancer as a singe entity. In order to investigate the hypothesis that CC and RC may be of different natures, possibly reflected by the differences in the serum CEA level among different stages of CRC (Fig. 1), we divided the cases into two groups and analyzed them accordingly.

Significant differences in serum CEA level are observed among the four stages of CC, but not RC. The mean values of CEA in patients with CC of stage A, B, C and D were 21.25, 12.37, 4.96 and 113.40 ng/ml, respectively (Table III), whereas those in RC patients were 47.04, 56.28, 42.29 and 15.34 ng/ml, respectively (Table IV). The statistical analysis revealed that CC exhibited a more significant variation among the four stages (Fig. 2) compared to that in the RC group (Fig. 3). No differences were observed between male and female patients and between patients aged <50 and >50 years regarding the distribution of serum CEA levels.

Table III. Differences in the serum carcinoembryonic antigen level among patients with colon cancer.

Variables	Mean, ng/ml	P-value
Duke's stage		
A/B	21.25/12.37	0.0634
A/D	21.25/113.40	0.0506
B/C	12.37/4.96	0.1792
Gender		
Male/female	34.16/40.26	0.6475
Age, years		
≤50/>50	9.731/42.02	0.3259

Table IV. Differences in the serum carcinoembryonic antigen level among patients with rectal cancer.

Variables	Mean, ng/ml	P-value
Duke's stage		
A/B	47.04/56.28	0.6420
A/C	47.04/42.29	0.7360
A/D	47.04/15.34	0.6140
B/C	56.28/42.29	0.5951
B/D	56.28/15.34	0.3007
C/D	42.29/15.34	0.8738
AB/CD	51.80/28.05	0.3801
ABC/D	48.50/15.34	0.4766
Gender		
Male/female	24.97/59.13	0.6279
Age, years		
≤50/>50	11.85/45.92	0.0771

Serum CEA level is the lowest in stage C of CC. Similar to the tendency reported for CRC, the CEA value in stage C of CC (4.96 ng/ml) was lower compared to that in stages A (21.25 ng/ml) and D (113.40 ng/ml). Of note, the CEA level was the lowest in stage C with a significant difference from stages A (P=0.0031) and D (P<0.0001), as shown in Fig. 2A. A significant difference was also observed between stages B and D (P=0.0004; Fig. 2B), whereas no significant difference was observed between stages B and C (P=0.3216). Additionally, due to the high CEA level in stage D coexisting with the lower CEA level in stages A, B and C, a significant difference was also observed between the NDM and DM groups (P<0.0001; Fig. 2D). However, no difference was observed between the NM and M groups (P=0.5781; Fig. 2C). There were no differences among other factors, such as patient gender and age (Table III).

Significant differences in the serum CEA level are observed in stages C and D between CC and RC. As described above, the different variation tendencies of the serum CEA level between CC and RC prompted the comparison of the CEA level in the four stages between CC and RC. The results revealed no differences in the CEA levels in stage A (P=0.9764), or in stage B (P=0.1221) between CC and RC (Table V). However, the CEA level in stage C of CC was lower compared to that in stage C of RC, with a significant difference (P=0.0096); the difference between stage D of CC and RC was also significant (P=0.0063) (Fig. 4). There were also differences in the CEA level in the NDM group between CC and RC (P=0.0155), whereas there were no differences in the other factors shown in Table V.

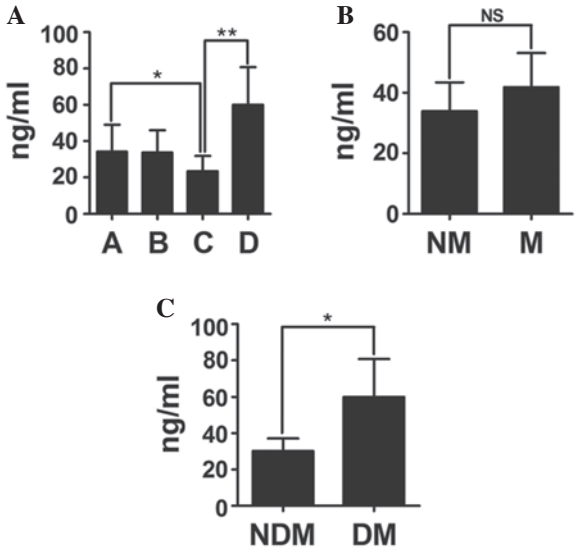

Figure 1. Differences in the serum carcinoembryonic antigen (CEA) level among different stages of colorectal cancer. (A) The CEA level of stage C was found to be lower compared to that in any other stage and exhibited significant variation compared to stages A and D. (B) No differences were observed between the non-metastasis (NM) and metastasis (M) groups. (C) Differences in the CEA level between the non-distant metastasis (NDM) and distant metastasis (DM) groups. *P<0.05 and **P<0.01. NS, not statistically significant.

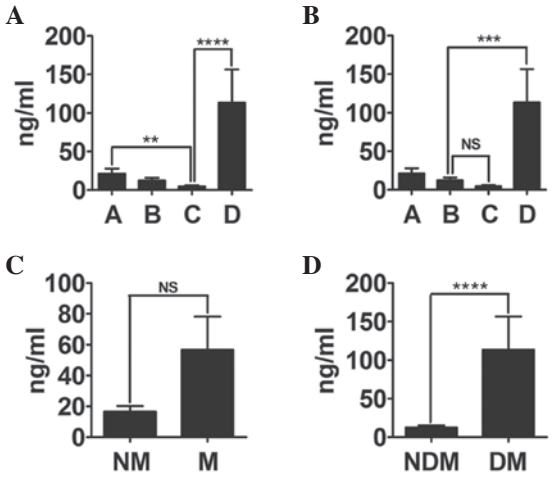

Figure 2. Differences in the serum carcinoembryonic antigen (CEA) level among different stages of colon cancer. (A) The CEA level in stage C was the lowest among all stages, with a significant difference from stages A and D. (B) The CEA level in stage B was the second lowest among all stages, with differences from stage D. (C) No differences were observed between the non-metastasis (NM) and the metastasis (M) groups. (D) A significant difference was observed between the non-distant metastasis (NDM) and distant metastasis (DM) groups. **P<0.05, ***P<0.001 and ****P<0.0001. NS, not statistically significant.

Table V. Differences in the serum carcinoembryonic antigen level between patients with colon and rectal cancer.

	Mean (ng/ml)		
Variables	Colon	Rectum	P-value
Duke's stage			
A	21.25	47.04	0.9764
B	12.37	56.28	0.1221
AB	16.53	51.80	0.2465
CD	56.68	28.05	0.8897
ABC	12.52	48.50	**0.0155**
ABCD	36.76	39.21	0.3516
Gender			
Male	34.16	24.97	0.7250
Female	40.26	59.13	0.3373
Age, years			
≤50	9.73	11.85	1.0000
>50	42.02	45.92	0.2963

Bold print denotes statistical significance.

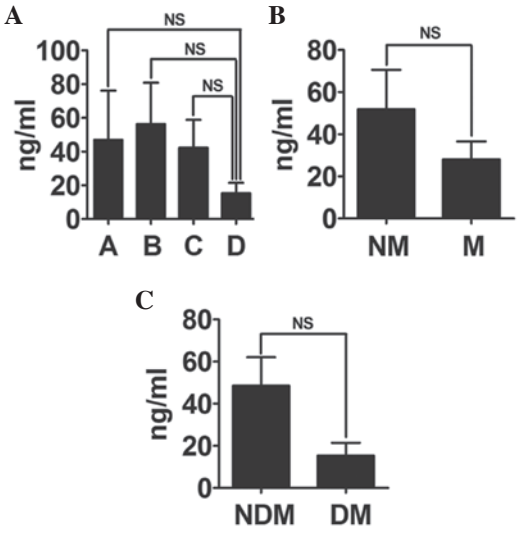

Figure 3. Differences in the serum carcinoembryonic antigen level among different stages in patients with rectal cancer. (A) No significant differences were observed among the four stages of colon cancer. (B) No significant differences were observed between non-metastasis (NM) and metastasis (M) groups. (C) There was no difference between the non-distant metastasis (NDM) and distant metastasis (DM) groups. NS, not statistically significant.

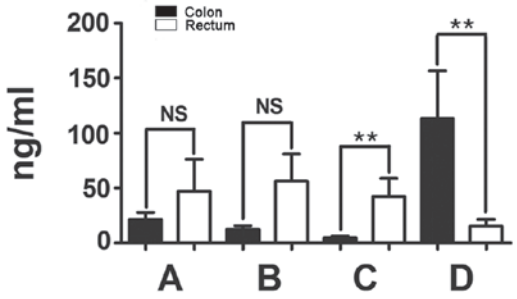

Figure 4. Differences in the serum carcinoembryonic antigen (CEA) level in each stage between colon and rectal cancer. There were significant differences in the CEA level in stages C and D between colon and rectal cancer. However, no significant differences were observed in stages A and B. **P<0.01. NS, not statistically significant.

Discussion

Previous studies by Midiri *et al* (13) and Chen *et al* (12) reported a different tendency of the serum CEA levels in CRC patients with advancing stage. Our results of the present study revealed that the lowest CEA level was observed in stage C, with significant differences from stages A and D. The impacts of patient number, age and gender was not taken into consideration as they could not be controlled in this analysis and there were no differences between them. The physical condition of the patients, including the coexistence of other benign diseases (14), may affect the CEA level to a certain extent. Additionally, the CC/RC ratio, which was reported to be 56/44% by Chen *et al* (12) and 58.4/41.6% by Lin *et al* (15), was different from the 49/51% that was observed in the present study, which may lead to a different tendency if there is internal variation between CC and RC.

As regards CC, there was significant variation among stages, with the lowest CEA level in stage C, whereas there was no such variation in RC. In addition, CC and RC are distinguished by the CEA level in stages B (P=0.0327), C (P=0.0092) and D (P=0.0073). We cannot exclude the possibility of a deviation arising due to insufficient patient number (<30 in several stages), patient physical condition and statistical error. To reduce the error arising from the insufficient number of patients, several patients were added to the follow-up study; however, the inner differences between CC and RC were not affected.

Several studies focused on the hypothesis that CC and RC are likely two naturally different diseases; however, the majority of the currently available studies consider CC and RC as a single entity. Wakai *et al* (2) reported that the dietary risk factors appeared to differ between CC and RC. Li *et al* (16) reported that the survival of CC patients was significantly superior to that of RC patients. Nielsen *et al* (17) also reported that a combination of plasma tissue inhibitor of metalloproteinase 1 and CEA may be useful for the early detection of CRC, particularly CC. Additionally, the Cancer Genome Atlas Network has reported certain differences between tumors from the right colon and all other sites (3). This prompted us to investigate whether the differences in the CEA levels between CC and RC, despite the overall close association between CRC and CEA, reflect the fact that CC and RC are of a different nature, which requires further investigation.

The lowest CEA level was observed in stage C of CC, with significant differences from stages A and D. Despite the fact that we added more patients in our subsequent study, we cannot exclude the possibility that the patient number was insufficient for analysis, resulting in the unusually low-level of CEA in stage C, which is inconsistent with the findings of Lee *et al* (18), who investigated 233 stage C patients and reported that stage C patients are more significantly associated with increased preoperative CEA levels, as well as the findings of other studies. We also cannot exclude the possibility that there may be a distinction

between stage C and other stages in several studies stressing the individual effects of treatment on stage C. Li *et al* (16) reported that the survival of stage C patients was significantly superior to that of other CRC patients. Stage C refers to those patients suffering from cancer cell metastasis to the lymph nodes. The 5-year overall survival improved as the number of nodes sampled increased for patients with CC (19) and the lymph node ratio is known to be an independent prognostic factor in CC patients with stage C disease (20). Therefore, the improved survival rate mentioned above for CC patients with stage C disease may be correlated with the number of lymph nodes and should be investigated in the follow-up study. Due to the limited number of studies on stage C of CC, the unique character of stage C possibly plays a significant role in the evolution of CC; however, the underlying mechanisms require further investigation in the follow-up study.

In the present study, we demonstrated that there is variation in CEA levels among different stages in patients with CC, while no such variation was observed among RC patients. Of note, the CEA level in stage C was the lowest among all stages in CC patients. Apart from the factors affecting the results, including age, gender, patient number and physical condition, any unknown internal distinctions between CC and RC and between stage C and other CC stages remain to be further investigated. Elucidating whether there actually is a difference in the nature of CC and RC may have important implications regarding treatment and prognosis of these two types of cancer.

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