Role of serum carcinoembryonic antigen in the detection of colorectal cancer before and after surgical resection

Bin-Bin Su, Hui Shi, Jun Wan

Abstract

AIM: To determine whether serum levels of carcinoembryonic antigen (CEA) correlate with the presence of primary colorectal cancer (CRC), and/or recurrent CRC following radical resection.

METHODS: A total of 413 patients with CRC underwent radical surgery between January 1998 and December 2002 in our department and were enrolled in this study. The median follow-up period was 69 mo (range, 3-118 mo), and CRC recurrence was experienced by 90/413 (21.8%) patients. Serum levels of CEA were assayed preoperatively, and using a cutoff value of 5 ng/mL, patients were divided into two groups, those with normal serum CEA levels (≤ 5 ng/mL) and those with elevated CEA levels (> 5 ng/mL).

RESULTS: The overall sensitivity of CEA for the detection of primary CRC was 37.0%. The sensitivity of CEA according to stage, was 21.4%, 38.9%, and 41.7% for stages I-III, respectively. Moreover, for stage II and stage III cases, the 5-year disease-free survival rates were reduced for patients with elevated preoperative serum CEA levels (P < 0.05). The overall sensitivity of CEA for detecting recurrent CRC was 54.4%, and sensitivity rates of 36.6%, 66.7%, and 75.0% were associated with cases of local recurrence, single metastasis, and multiple metastases, respectively. In patients with normal serum levels of CEA preoperatively, the sensitivity of CEA for detecting recurrence was reduced compared with patients having a history of elevated CEA prior to radical resection (32.6% vs 77.3%, respectively, P < 0.05).

CONCLUSION: CRC patients with normal serum CEA levels prior to resection maintained these levels during CRC recurrence, especially in cases of local recurrence vs cases of metastasis.

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Key words: Colorectal cancer; Carcinoembryonic antigen; Recurrence

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INTRODUCTION

Globally, colorectal cancer (CRC) is the third most common cancer diagnosed, and is associated with high rates of incidence and mortality for both men and women. Furthermore, despite progress that has been made in the treatment of advanced cases of CRC, the clinical outcome of this disease still remains poor. Carcinoembryonic antigen (CEA) is a classic tumor marker for CRC,
and has been used to monitor CRC recurrence and as a prognostic factor for CRC patients. Currently, the serum CEA test is recommended by the American Society of Clinical Oncology[3] and the European Group on Tumor Markers[6] as a prognostic biomarker for recurrent CRC following curative resection. However, the effectiveness of CEA as a preoperative and postoperative marker for CRC remains to be evaluated. In particular, it remains unclear how accurate a negative CEA value is for excluding primary and recurrent CRC, and under what conditions CEA values are inaccurate. Therefore, this study was designed to evaluate the role of serum CEA levels in the diagnosis of primary and recurrent CRC following radical resection.

MATERIALS AND METHODS

Patients
A total of 464 patients with stage I, II, or III CRC were admitted to our hospital between January 1998 and December 2002. Of these patients, 51/464 did not have preoperative serum CEA data available. Therefore, a total of 413 CRC patients were included in this retrospective study.

Surgical procedures
Enrolled patients underwent curative resection for the treatment of CRC. Curative resection was defined as the absence of any gross residual CRC in the surgical bed, in addition to a surgical resection margin that was pathologically negative for tumor invasion. Recurrence in this study included metastasis and local recurrence that was secondary to primary CRC at least 3 mo after radical resection. Recurrent CRC was confirmed by at least one of the following examinations: pathology, computed tomography (CT), magnetic resonance imaging, or X-ray. Of these examinations, a pathologic diagnosis based on biopsy and body-fluid cytological examinations represents the most reliable detection method for CRC. For an imaging-based diagnosis of CRC, successive imaging examinations are required to verify cancer progression. Patient characteristics are summarized in Table 1. The median follow-up time was 69 mo (range, 3-118 mo), during which CRC recurred in 90 patients. For these patients, serum CEA assays were performed within 1 wk of CRC recurrence being confirmed.

Measurement of serum CEA levels
Serum CEA levels in CRC patients were measured using CEA Elecsys analyzers (Roche Diagnostics GmbH, United States) with a reference range of 5.0 ng/mL. CRC patients were then divided into two groups, those with normal serum CEA levels (e.g., ≤ 5 ng/mL) and those with elevated serum CEA levels (> 5 ng/mL).

Statistical analysis
All data were analyzed using SPSS, version 11.5 (SPSS Inc., Chicago, IL). A P-value less than 0.05 was considered statistically significant. In addition, a two-sided Pearson χ² test and Fisher’s exact test were used to analyze the potential correlation between serum levels of CEA and clinicopathologic features of the study subjects. Variables associated with a P value less than 0.10 by univariate analysis were applied to a Cox model for multivariate analysis. Disease-free survival (DFS) rates were analyzed using the Kaplan-Meier method and compared using the log-rank test.

RESULTS
For a total of 413 patients that were diagnosed with CRC between January 1998 and December 2002 in our department and were enrolled in this retrospective study, serum levels of CEA were assayed prior to surgical resection. Based on a cutoff value of 5 ng/mL, two patient groups were established. One group was associated with elevated levels of serum CEA (e.g., > 5 ng/mL) (n = 153; 37.0%), while the second group was associated with normal levels of serum CEA (e.g., < 5 ng/mL) (n = 260; 63%). The stages of CRC associated with these cases included stage I (n = 70), II A (n = 140), II B (n = 35), III A (n = 23), III B (n = 85), and III C (n = 60), ac-
Table 2 Correlation between preoperative serum levels of carcinoembryonic antigen levels and clinicopathologic characteristics n (%)  

| Characteristics | Preoperative S-CEA | P value |
|-----------------|------------------|---------|
|                  | ≤ 5 ng/mL | > 5 ng/mL |         |
| Gender           |           |          |         |
| Male             | 167 (61.9)| 103 (38.1)| 0.524   |
| Female           | 93 (65.0)| 50 (35.0)|         |
| Age (yr)         |           |          |         |
| < 40             | 35 (62.5)| 21 (37.5)| 0.178   |
| 40-60            | 101 (68.7)| 46 (31.3)|         |
| > 60             | 124 (59.0)| 86 (41.0)|         |
| Location         |           |          |         |
| Colon            | 106 (60.9)| 68 (39.1)| 0.223   |
| Rectum           | 154 (64.4)| 85 (35.6)|         |
| Size (cm)        |           |          |         |
| ≤ 5              | 188 (68.4)| 87 (31.6)| 0.002   |
| > 5              | 70 (52.2)| 64 (47.8)|         |
| Differentiation  |           |          |         |
| Well             | 176 (62.9)| 104 (37.1)| 0.997   |
| Poor             | 83 (62.9)| 49 (37.1)|         |
| PT               |           |          |         |
| T1               | 8 (100.0)| 0 (0.0)| 0.005   |
| T2               | 64 (72.7)| 24 (27.3)|         |
| T3               | 141 (61.8)| 87 (38.2)|         |
| T4               | 46 (52.3)| 42 (47.7)|         |
| PN               |           |          |         |
| N0               | 162 (66.1)| 83 (33.9)| 0.260   |
| N1               | 64 (59.3)| 44 (40.7)|         |
| N2               | 34 (56.7)| 26 (43.3)|         |
| Lymphovascular invasion | | | |
| Present | 11 (47.8)| 12 (52.2)| 0.122   |
| Absent | 249 (63.8)| 141 (36.2)|         |
| TNM stage | | | |
| I                | 55 (78.6)| 15 (21.4)| 0.011   |
| II               | 107 (61.1)| 68 (38.9)|         |
| III              | 98 (58.3)| 70 (41.7)|         |

PT: Pathologic T stage; PN: Pathologic N stage; TNM: Tumor Node Metastasis; S-CEA: Serum levels of carcinoembryonic antigen.

According to the 6th International Union Against Cancer (UICC) Tumor Node Metastasis (TNM) staging system. Moreover, elevated serum levels of CEA were detected preoperatively in 21.4% of stage I CRC patients, 38.9% of stage II CRC patients, and 41.7% of stage III CRC patients, respectively. As a result, preoperative CEA levels were found to correlate with CRC diagnoses according to the UICC TNM staging system (P = 0.01). A comparison of preoperative CEA levels with clinicopathological characteristics of the enrolled patients further detected a significant association between serum CEA levels and tumor size and T category (Table 2). However, serum CEA levels did not correlate with patient age, patient gender, tumor location, tumor differentiation, N category, or lymphovascular invasion.

The median follow-up time for this study was 69 mo, and the 5-year DFS rate was 67% after patients underwent radical resection. Moreover, univariate and multivariate analysis revealed that preoperative serum levels of CEA were a significant independent prognostic factor for 5-year DFS rates (Table 3). The 5-year DFS rate was also found to significantly differ for stage II and stage III CRC patients independent of serum CEA levels (P < 0.05), yet did not differ for stage I CRC patients following radical resection. When stage II and stage III CRC cases were further subdivided into II A, II B, III A, III B, and III C stages, the 5-year DFS rate for normal and elevated levels of serum CEA patient groups were 84% and 62% for stage II A CRC patients, and 64% and 21% for the stage III B CRC patients, respectively in each case (P < 0.05, Figure 1A and B). However, no significant difference in the 5-year DFS rates associated with stage II B, III A, and III C CRC was observed.

Recurrent of CRC was experienced by 90/413 patients, with local recurrence, single CRC metastasis, and multiple CRC metastases occurring in 41/90 (45.6%),

Table 3 Multivariate analysis of factors for 5-year disease-free survival rates

| Factor | Hazards ratio (CI) | P value |
|--------|-------------------|---------|
| PT     | 1.448 (1.081-1.940) | 0.013   |
| PN     | 1.624 (1.264-2.088) | 0.000   |
| Preoperative S-CEA | 1.663 (1.127-2.455) | 0.010   |
| Differentiation | 1.347 (0.873-2.079) | 0.178   |
| Lymphovascular invasion | 1.738 (0.890-3.394) | 0.105   |
| Lymph nodes evaluated | 1.013 (0.780-1.316) | 0.925   |

PT: Pathologic T stage; PN: Pathologic N stage; CI: Confidence interval; S-CEA: Serum levels of carcinoembryonic antigen.

Figure 1 Disease-free survival curves for patients with stage II A colorectal cancer (A) and stage III B colorectal cancer (B) based on preoperative serum levels of carcinoembryonic antigen.
CEA: Carcinoembryonic antigen; CRC: Colorectal cancer.

### Table 4 Patterns of colorectal cancer recurrence according to serum carcinoembryonic antigen levels \(n(\%)\)

| Patterns of CRC recurrence | CEA levels | \(P\) value |
|---------------------------|------------|------------|
| Local relapse              | <= 5 ng/mL | > 5 ng/mL  |
| Metastasis (single)        | 26 (63.4)  | 15 (36.6)  |
| Metastases (multiple)      | 11 (33.3)  | 22 (66.7)  |

### Table 5 Correlation between serum carcinoembryonic antigen levels in patients with recurrent colorectal cancer and clinicopathologic characteristics \(n(\%)\)

| Clinicopathologic characteristics | S-CEA levels in patients with recurrent CRC | \(P\) value |
|----------------------------------|------------------------------------------|------------|
| Gender                           | <= 5 ng/mL                               | > 5 ng/mL  |
| Male                             | 27 (40.3)                                | 40 (59.7)  |
| Female                           | 14 (60.9)                                | 9 (39.1)   |
| Age (yr)                         | <= 40                                    | > 40       |
|                                 | 7 (53.8)                                 | 6 (46.2)   |
|                                 | 13 (43.3)                                | 17 (56.7)  |
|                                 | > 60                                     | 21 (44.7)  | 26 (55.3) |
| Preoperative S-CEA               | <= 5 ng/mL                               | > 5 ng/mL  |
|                                 | 31 (67.4)                                | 15 (32.6)  |
|                                 | 10 (22.7)                                | 34 (77.3)  |
| Location                         | Colon                                    | Recrum     |
|                                 | 17 (44.7)                                | 24 (46.2)  |
|                                 | 21 (55.3)                                | 28 (53.8)  |
| Differentiation                  | Well                                     | Poor       |
|                                 | 22 (37.9)                                | 19 (59.4)  |
|                                 | 36 (62.1)                                | 13 (40.6)  |
| PT                              | T1                                       | T2         |
|                                 | 0 (0.0)                                  | 5 (41.7)   |
|                                 | 0 (0.0)                                  | 7 (58.3)   |
| T3                              | 19 (40.4)                                | 28 (59.6)  |
| T4                              | 17 (54.8)                                | 14 (45.2)  |
| PN                              | N0                                       | N1         |
|                                 | 14 (46.7)                                | 14 (37.8)  |
|                                 | 16 (53.3)                                | 23 (62.2)  |
|                                 | N2                                       | 13 (56.5)  | 10 (43.5) |

### Table 6 Multivariate analysis of parameters for recurrent colorectal cancer patients using the Cox proportional hazards model

| Parameter evaluated | Hazards ratio (CI) | \(P\) value |
|---------------------|--------------------|------------|
| Gender              | 0.49 (0.151-1.607) | 0.241      |
| Differentiation     | 0.42 (0.142-1.245) | 0.118      |
| Preoperative S-CEA  | 0.27 (0.094-0.767) | 0.014      |
| Recurrence pattern  | 0.34 (0.119-0.950) | 0.040      |

CI: Confidence interval; S-CEA: Serum levels of carcinoembryonic antigen.

**DISCUSSION**

Since Gold et al.\(^1\) first described and characterized CEA in 1965, it has become one of the most widely known tumor markers for gastrointestinal tract diseases, especially for CRC. However, although 90% of CRCs produce CEA, elevated serum levels of CEA are not often detected at the time of diagnosis. In this study, normal serum levels of CEA detected preoperatively were detected in 67% of CRC patients assayed, and in 79% of stage I CRC patients. While a correlation between stage of CRC and preoperative CEA levels has previously been observed, a low sensitivity is associated with serum CEA assays in the detection of early stage CRC.\(^8\)-\(^10\). Accordingly, the usefulness of serum CEA assays for screening of CRC is limited. Thus, other markers such as carbohydrate antigens, tumor-associated molecules, and genes associated with CEA and other tumor markers for gastrointestinal tract diseases, especially CRC. While a correlation between stage of CRC and preoperative CEA levels has previously been described, suggesting that elevated serum levels of CEA detected preoperatively may indicate a larger tumor burden. In the present study, serum levels of CEA were found to be significantly associated with tumor size and T category, but not with N category or tumor differentiation. Moreover, preoperative serum levels of CEA were associated with stage of disease, while providing a prognostic determinant of survival. These results are consistent with other studies,\(^12\)-\(^14\), and also confirmed that elevated levels of serum CEA represent an independent prognostic factor for 5-year DFS, especially for cases of stage II A and III B CRC.

In colon cancer, CEA modulates intercellular adhesion, functions as a promoter of cellular aggregation, regulates the innate immune system, and mediates signal transduction.\(^15\)-\(^17\). Accordingly, it is hypothesized that CEA plays an important role in tumor invasion and metastasis. In this study, the 5-year DFS rate of stage II CRC patients with elevated serum CEA levels was compared with stage III CRC patients with normal serum levels of CEA, and no significant difference was found (data not shown). This finding is consistent with another study,\(^18\), and suggests that a diagnosis of CRC accompanied by elevated levels of serum CEA may be an indica-

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49/90 (54.4%), and 16/90 (17.8%) patients, respectively. The types of metastasis detected were hepatic (\(n = 17\)), pulmonary (\(n = 10\)), osseous (\(n = 7\)), renal (\(n = 2\)), adrenal (\(n = 3\)), distal lymphatic (\(n = 2\)), brain (\(n = 1\)), and spinal (\(n = 1\)). Serum CEA levels were found to be higher in patients with CRC metastases compared to patients with local recurrent CRC (\(P < 0.05\)). Moreover, the percentage of patients with elevated CEA levels and local recurrence was less than that of CRC patients with elevated CEA levels and single or multiple metastases (36.6% vs 66.7% and 75.0%, respectively) (\(P < 0.05\), Table 4). Patients with a history of elevated CEA levels prior to surgery were also associated with elevated CEA levels directly prior to surgery in 77.3% of cases, whereas patients with no prior history of elevated CEA levels exhibited elevated levels of CEA levels directly prior to surgery in 32.6% of cases (Table 5). Univariate and multivariate analysis also revealed that preoperative serum levels of CEA and recurrence patterns were significantly associated with serum levels of CEA detected during recurrence (Table 6).
tor for tumor restaging even after surgery. Furthermore, it has been shown that genetic vaccines targeting CEA may be a feasible strategy for the treatment of CRC. For example, Ogata et al. observed that stage II CRC patients with elevated levels of CEA may be candidates for adjuvant chemotherapy following curative resection.

CRC recurrence has been reported for 30%-40% of patients who undergo curative resection. During the follow-up period of surgical resection, CEA monitoring is typically performed. However, the accuracy and efficacy of CEA monitoring is not always consistent. For example, in the present study, only 54.5% of patients experiencing recurrence had elevated serum levels of CEA. Moreover, these results are consistent with previously reported findings. Typically, elevated levels of CEA detected postoperatively have a high probability of indicating tumor recurrence, while normal levels of CEA detected postoperatively are not useful for excluding the probability of recurrence. Therefore, the need for monitoring CEA levels in patients who initially exhibit normal levels of CEA remains to be determined.

In the present study, according to the preoperative CEA levels assayed, 77% of recurrent CRC patients had elevated CEA levels, while 32% had normal CEA levels. These results indicate that normal CEA levels may be associated with the relatively early stages of tumor progression, and also with the presence of a non-CEA producing tumor. For example, production of CEA may be reduced in poorly differentiated adenocarcinomas. Furthermore, some studies have reported an inverse relationship between tumor grade and CEA levels among patients with nodal metastases and unresectable disease.

Another consideration is the rate of rise for CEA levels that can vary depending on the site of recurrence. It has previously been proposed that monitoring of serum CEA levels is useful for the detection of liver metastases, yet is not useful for the detection of local recurrence or other types of metastasis. In the present study, patients with CRC metastasis, especially multiple metastases, were associated with higher CEA levels, whereas those with local recurrent CRC had a lower CEA level during recurrence (75.0% vs 36.6%, respectively, P < 0.05). In combination, these results suggest that CEA alone should not determine whether “second-look” surgeries are performed, or whether CT scan or other imaging tools should be required to identify precise sites of recurrence.

As a retrospective study, the limitations associated with this work include the absence of a standard adjuvant therapy protocol and monitoring strategy. For example, CRC monitoring was not at regular time intervals, resulting in a sensitivity bias. In comparison, the cut-off values used to determine elevated CEA levels in other studies have ranged from 3-15 ng/mL, thereby affecting the sensitivity of serum CEA assays for tumor detection. Furthermore, since CEA levels were found to be associated with T stage and tumor size in the present study, additional large-scale studies are needed to establish the specific cut-off value needed, according to different tumor burden volumes, in order to facilitate the detection of primary and recurrent CRC.

Currently, an ideal tumor marker for CRC is not available. For example, although CEA is a well-known tumor marker for CRC, the detection of serum CEA levels has not proven to be sufficiently sensitive for detecting primary CRC, especially early stage CRC. However, pre-operative serum levels have been found to be an independent prognostic factor for patients with CRC following curative resection. Moreover, CRC patients with normal serum levels of CEA have a higher probability of maintaining these levels during CRC recurrence, especially during local recurrence compared with metastasis. Therefore, monitoring of serum CEA levels can facilitate the detection of primary and recurrent CRC; however, this assay must be complemented by other clinical and laboratory assessments.

**COMMENTS**

**Background**

Although detection of serum carcinoembryonic antigen (CEA) is widely used to monitor recurrence following curative resection for colorectal cancer (CRC), the sensitivity associated with this readout is not ideal. Therefore, it is important that factors associated with a negative CEA test, when recurrence has been confirmed, be further studied.

**Research frontiers**

The presence of elevated serum levels of CEA prior to surgical resection for CRC has previously been identified as a prognostic factor for CRC, and therefore, has been well studied. For these patients, postoperative serum CEA surveillance is effective for detecting recurrence. However, for patients who initially present with normal levels of CEA, the need to further monitor CEA levels remains controversial.

**Innovations and breakthroughs**

In this study, CRC patients with normal CEA levels prior to operation were more likely to maintain these levels when recurrence occurred, especially in cases of local recurrence compared with metastasis.

**Applications**

The findings of this study provide further insight into CRC monitoring strategies, especially for patients with normal CEA levels prior to surgical resection.

**Peer review**

This is a well designed study, which formally needs few revisions.

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