World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i17.2121

World J Gastroenterol 2012 May 7; 18(17): 2121-2126
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

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

Bin-Bin Su, Hui Shi, Jun Wan

Bin-Bin Su, Hui Shi, Jun Wan, Department of Gastroenterology, South Building, Chinese People's Liberation Army General Hospital, Beijing 100853, China
Author contributions: Su BB and Wan J designed the research; Su BB and Shi H performed the research and analyzed the data; Su BB and Wan J wrote the paper.
Correspondence to: Jun Wan, Professor, Department of Gastroenterology, South Building, Chinese People's Liberation Army General Hospital, Beijing 100853, China. wanjun301@126.com
Telephone: +86-10-66876246 Fax: +86-10-68295664
Received: February 25, 2011 Revised: December 19, 2011
Accepted: March 9, 2012
Published online: May 7, 2012

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 (e.g., ≤ 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.

Key words: Colorectal cancer; Carcinoembryonic antigen; Recurrence

Peer reviewers: Francesco Crea, MD, PhD, Division of Pharmacology, University of Pisa, Via Roma 55, 56100 Pisa, Italy; Dr. Kevin J Spring, PhD, Conjoint Gastroenterology Laboratory, The Queensland Institute of Medical Research, the Bancroft Centre, rm H07, PO Royal Brisbane Hospital, Herston, QLD 4029, Australia

Su BB, Shi H, Wan J. Role of serum carcinoembryonic antigen in the detection of colorectal cancer before and after surgical resection. *World J Gastroenterol* 2012; 18(17): 2121-2126 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i17/2121.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i17.2121

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[1]. Furthermore, despite progress that has been made in the treatment of advanced cases of CRC, the clinical outcome of this disease still remains poor[2]. 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[4] 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 χ^2 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.

Table 1 Parameters of colorectal cancer patients enrolled in this study (*n* = 413)

Variable	*n* (%)
Gender	
Male	270 (65.4)
Female	143 (34.6)
Age (yr)	
< 40	56 (13.6)
40-60	147 (35.6)
> 60	210 (50.8)
Preoperative S-CEA	
≤ 5 ng/mL	260 (63.0)
> 5 ng/mL	153 (37.0)
Location	
Colon	174 (42.1)
Rectum	239 (57.9)
Differentiation	
Well	281 (32.0)
Poor	132 (68.0)
Size (cm)	
≤ 5	275 (66.6)
> 5	134 (32.4)
PT	
T1	8 (1.9)
T2	88 (21.3)
T3	229 (55.4)
T4	88 (21.3)
PN	
N0	245 (59.3)
N1	108 (26.2)
N2	60 (14.5)
Lymphovascular invasion	
Present	23 (5.6)
Absent	390 (94.4)

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

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), ⅡA (*n* = 140), ⅡB (*n* = 35), ⅢA (*n* = 23), ⅢB (*n* = 85), and ⅢC (*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.

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.

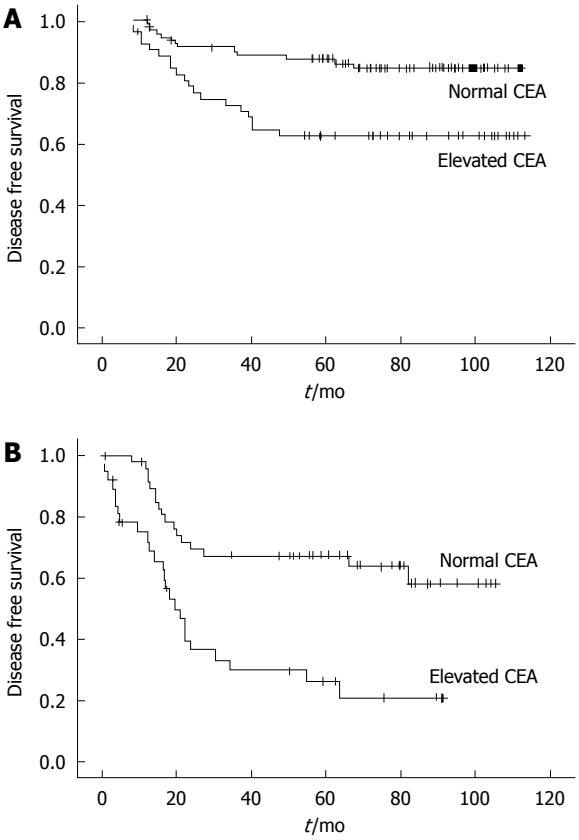

Figure 1 Disease-free survival curves for patients with stage ⅡA colorectal cancer (A) and stage ⅢB colorectal cancer (B) based on preoperative serum levels of carcinoembryonic antigen.

cording to the 6th International Union Against Cancer (UICC) Tumor Node Metastasis (TNM) staging system[5]. 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 in 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 (range, 3-118 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 ⅡA, ⅡB, ⅢA, ⅢB, and ⅢC stages, the 5-year DFS rate for normal and elevated levels of serum CEA patient groups were 84% and 62% for stage ⅡA CRC patients, and 64% and 21% for the stage ⅢB 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 ⅡB, ⅢA, and ⅢC CRC was observed.

Recurrence 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 4 Patterns of colorectal cancer recurrence according to serum carcinoembryonic antigen levels *n* (%)

Patterns of CRC recurrence	CEA levels		*P* value
	≤ 5 ng/mL	> 5 ng/mL	
Local relapse	26 (63.4)	15 (36.6)	
Metastasis (single)	11 (33.3)	22 (66.7)	0.007
Metastases (multiple)	4 (25.0)	12 (75.0)	

CEA: Carcinoembryonic antigen; CRC: Colorectal cancer.

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
	≤ 5 ng/mL	> 5 ng/mL	
Gender			
Male	27 (40.3)	40 (59.7)	0.097
Female	14 (60.9)	9 (39.1)	
Age (yr)			
≤ 40	7 (53.8)	6 (46.2)	0.805
40-60	13 (43.3)	17 (56.7)	
≥ 60	21 (44.7)	26 (55.3)	
Preoperative S-CEA			
≤ 5 ng/mL	31 (67.4)	15 (32.6)	0.001
> 5 ng/mL	10 (22.7)	34 (77.3)	
Location			
Colon	17 (44.7)	21 (55.3)	0.894
Rectum	24 (46.2)	28 (53.8)	
Differentiation			
Well	22 (37.9)	36 (62.1)	0.051
Poor	19 (59.4)	13 (40.6)	
PT			
T1	0 (0.0)	0 (0.0)	0.438
T2	5 (41.7)	7 (58.3)	
T3	19 (40.4)	28 (59.6)	
T4	17 (54.8)	14 (45.2)	
PN			
N0	14 (46.7)	16 (53.3)	0.364
N1	14 (37.8)	23 (62.2)	
N2	13 (56.5)	10 (43.5)	

CRC: Colorectal cancer; PT: Pathologic T stage; PN: Pathologic N stage; S-CEA: Serum levels of carcinoembryonic antigen.

49/90 (54.4%), and 16/90 (17.8%) patients, respectively. The types of metastasis detected included 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).

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*[6] first described and characterized CEA in 1965, it has become the one of the most widely known tumor markers for gastrointestinal tract diseases, especially for CRC. However, although 90% of CRCs produce CEA[7], elevated serum levels of CEA are not often detected at the time of diagnosis. In this study, normal serum levels of CEA (e.g., < 5 ng/mL) were detected in 67% of the 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. Despite this, a semi-quantitative relationship between CEA levels and tumor volume has previously been described[11], suggesting that elevated serum levels of CEA detected preoperatively may indicate a larger tumor burden. In the present study, preoperative levels of serum CEA were found to be significantly associated with tumor size and T category, but not with N category or tumor differentiation. Moreover, preoperative CEA levels also correlated 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 ⅡA and ⅢB 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 levels of serum CEA were compared with stage Ⅲ CRC patients with normal levels of serum 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-

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[19]. For example, Ogata *et al*[20] 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[21]. 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[22,23]. Therefore, the need for monitoring CEA levels in patients who initially exhibit normal levels of CEA remains to be determined[24]. 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[25,26] 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[27]. 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[28-30], 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[31]. 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, preoperative 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.

REFERENCES

1 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249

2 **van der Pool AE**, Damhuis RA, Ijzermans JN, de Wilt JH, Eggermont AM, Kranse R, Verhoef C. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. *Colorectal Dis* 2012; **14**: 56-61

3 **Locker GY**, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, Somerfield MR, Hayes DF, Bast RC. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; **24**: 5313-5327

4 **Duffy MJ**, van Dalen A, Haglund C, Hansson L, Holinski-Feder E, Klapdor R, Lamerz R, Peltomaki P, Sturgeon C, Topolcan O. Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. *Eur J Cancer* 2007; **43**: 1348-1360

5 **Greene FL**, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M. AJCC Cancer Staging Manual, 6th ed. New York, NY: Springer-Verlag, 2002

6 **Gold P**, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *J Exp Med* 1965; **121**: 439-462
7 **Gold P**, Shuster J, Freedman SO. Carcinoembryonic antigen (CEA) in clinical medicine: historical perspectives, pitfalls and projections. *Cancer* 1978; **42**: 1399-1405
8 **Eleftheriadis N**, Papaloukas C, Pistevou-Gompaki K. Diagnostic value of serum tumor markers in asymptomatic individuals. *J BUON* 2009; **14**: 707-710
9 **Gambert SR**, Garthwaite TL, Tate PW. Clinical implications of the endogenous opiates: Part I. Physiological. *Psychiatr Med* 1983; **1**: 93-105
10 **Macdonald JS**. Carcinoembryonic antigen screening: pros and cons. *Semin Oncol* 1999; **26**: 556-560
11 **Bronstein BR**, Steele GD, Ensminger W, Kaplan WD, Lowenstein MS, Wilson RE, Forman J, Zamcheck N. The use and limitations of serial plasma carcinoembryonic antigen (CEA) levels as a monitor of changing metastatic liver tumor volume in patients receiving chemotherapy. *Cancer* 1980; **46**: 266-272
12 **Wang WS**, Lin JK, Chiou TJ, Liu JH, Fan FS, Yen CC, Lin TC, Jiang JK, Yang SH, Wang HS, Chen PM. Preoperative carcinoembryonic antigen level as an independent prognostic factor in colorectal cancer: Taiwan experience. *Jpn J Clin Oncol* 2000; **30**: 12-16
13 **Huh JW**, Oh BR, Kim HR, Kim YJ. Preoperative carcinoembryonic antigen level as an independent prognostic factor in potentially curative colon cancer. *J Surg Oncol* 2010; **101**: 396-400
14 **Takagawa R**, Fujii S, Ohta M, Nagano Y, Kunisaki C, Yamagishi S, Osada S, Ichikawa Y, Shimada H. Preoperative serum carcinoembryonic antigen level as a predictive factor of recurrence after curative resection of colorectal cancer. *Ann Surg Oncol* 2008; **15**: 3433-3439
15 **Pignatelli M**, Durbin H, Bodmer WF. Carcinoembryonic antigen functions as an accessory adhesion molecule mediating colon epithelial cell-collagen interactions. *Proc Natl Acad Sci USA* 1990; **87**: 1541-1545
16 **Hammarström S**, Baranov V. Is there a role for CEA in innate immunity in the colon? *Trends Microbiol* 2001; **9**: 119-125
17 **Li Y**, Cao H, Jiao Z, Pakala SB, Sirigiri DN, Li W, Kumar R, Mishra L. Carcinoembryonic antigen interacts with TGF-{beta} receptor and inhibits TGF-{beta} signaling in colorectal cancers. *Cancer Res* 2010; **70**: 8159-8168
18 **Thirunavukarasu P**, Sukumar S, Sathaiah M, Mahan M, Pragatheeshwar KD, Pingpank JF, Zeh H, Bartels CJ, Lee KK, Bartlett DL. C-stage in colon cancer: implications of carcinoembryonic antigen biomarker in staging, prognosis, and management. *J Natl Cancer Inst* 2011; **103**: 689-697
19 **Mori F**, Giannetti P, Peruzzi D, Lazzaro D, Giampaoli S, Kaufman HL, Ciliberto G, La Monica N, Aurisicchio L. A therapeutic cancer vaccine targeting carcinoembryonic antigen in intestinal carcinomas. *Hum Gene Ther* 2009; **20**: 125-136
20 **Ogata Y**, Murakami H, Sasatomi T, Ishibashi N, Mori S, Ushijima M, Akagi Y, Shirouzu K. Elevated preoperative serum carcinoembrionic antigen level may be an effective indicator for needing adjuvant chemotherapy after potentially curative resection of stage II colon cancer. *J Surg Oncol* 2009; **99**: 65-70
21 **Tan E**, Gouvas N, Nicholls RJ, Ziprin P, Xynos E, Tekkis PP. Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. *Surg Oncol* 2009; **18**: 15-24
22 **Yakabe T**, Nakafusa Y, Sumi K, Miyoshi A, Kitajima Y, Sato S, Noshiro H, Miyazaki K. Clinical significance of CEA and CA19-9 in postoperative follow-up of colorectal cancer. *Ann Surg Oncol* 2010; **17**: 2349-2356
23 **Park IJ**, Choi GS, Lim KH, Kang BM, Jun SH. Serum carcinoembryonic antigen monitoring after curative resection for colorectal cancer: clinical significance of the preoperative level. *Ann Surg Oncol* 2009; **16**: 3087-3093
24 **Hara M**, Kanemitsu Y, Hirai T, Komori K, Kato T. Negative serum carcinoembryonic antigen has insufficient accuracy for excluding recurrence from patients with Dukes C colorectal cancer: analysis with likelihood ratio and posttest probability in a follow-up study. *Dis Colon Rectum* 2008; **51**: 1675-1680
25 **Goslin R**, O'Brien MJ, Steele G, Mayer R, Wilson R, Corson JM, Zamcheck N. Correlation of Plasma CEA and CEA tissue staining in poorly differentiated colorectal cancer. *Am J Med* 1981; **71**: 246-253
26 **Moertel CG**, O'Fallon JR, Go VL, O'Connell MJ, Thynne GS. The preoperative carcinoembryonic antigen test in the diagnosis, staging, and prognosis of colorectal cancer. *Cancer* 1986; **58**: 603-610
27 **McCall JL**, Black RB, Rich CA, Harvey JR, Baker RA, Watts JM, Toouli J. The value of serum carcinoembryonic antigen in predicting recurrent disease following curative resection of colorectal cancer. *Dis Colon Rectum* 1994; **37**: 875-881
28 **Moertel CG**, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen C. An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. *JAMA* 1993; **270**: 943-947
29 **Körner H**, Söreide K, Stokkeland PJ, Söreide JA. Diagnostic accuracy of serum-carcinoembryonic antigen in recurrent colorectal cancer: a receiver operating characteristic curve analysis. *Ann Surg Oncol* 2007; **14**: 417-423
30 **Chuang SC**, Su YC, Lu CY, Hsu HT, Sun LC, Shih YL, Ker CG, Hsieh JS, Lee KT, Wang JY. Risk factors for the development of metachronous liver metastasis in colorectal cancer patients after curative resection. *World J Surg* 2011; **35**: 424-429
31 **Sharma S**. Tumor markers in clinical practice: General principles and guidelines. *Indian J Med Paediatr Oncol* 2009; **30**: 1-8

S- Editor Shi ZF **L- Editor** A **E- Editor** Zheng XM