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ORIGINAL ARTICLE – COLORECTAL CANCER

Serum Carcinoembryonic Antigen Monitoring After Curative Resection for Colorectal Cancer: Clinical Significance of the Preoperative Level

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ABSTRACT

Aim. We evaluated preoperative serum carcinoembryonic antigen (CEA) as a prognostic factor for colorectal cancer and determined when surveillance of this marker was useful.

Methods. Serum CEA was measured preoperatively in 1,263 patients who underwent curative resection for colorectal cancer at 3-month intervals for the first 2 postoperative years and at 6-month intervals thereafter. Mean follow-up was 48 months (range 1–156 months).

Results. The 5-year disease-free survival was less in patients with a high preoperative serum CEA level ($P < 0.0001$). Among patients with a tumor recurrence, 38.5% had high follow-up serum CEA levels. The number of patients with high postoperative serum CEA levels exceeded the number of patients with high preoperative levels. High preoperative and follow-up serum CEA levels were independent prognostic factors for tumor recurrence ($P = 0.003$ and $P < 0.001$, respectively). In patients with high preoperative serum CEA levels, CEA surveillance had a 92.3% positive predictive value (PPV) and a 96.1% negative predictive value (NPV). The mean interval between postoperative serum CEA elevation and the diagnosis of a tumor recurrence [diagnostic interval (DI)] was 2.5 months (range 5–17 months). The DI was 0 in 18.8% of patients with a tumor recurrence.

Conclusion. High serum CEA levels preoperatively and at follow-up are prognostic factors for colorectal cancer. Postoperative serum CEA surveillance is used most effectively when patients have high preoperative serum CEA levels. Considering the DI of 0 in 18.8% of the patients, the current CEA surveillance schedule might be changed.

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An elevated concentration of the serum tumor marker, carcinoembryonic antigen (CEA), has been reported to be associated with a poor postoperative prognosis in patients with colorectal cancer.[1–5] Although preoperative CEA concentration has been shown to be a prognostic factor for colorectal cancer, the usefulness of postoperative CEA monitoring for improving the early detection of colorectal cancer recurrence is unclear.[6–8] Although several studies have reported that postoperative serum CEA level is a marker of colorectal cancer recurrence, the value of this measurement has been questioned, especially in patients with normal preoperative CEA levels.[9–13] Others have reported that postoperative serum CEA monitoring is of little use in the detection of recurrences.[14] There is also no clear consensus on the frequency or duration of optimal CEA monitoring, although the current American Society of Clinical Oncology (ASCO) guidelines recommend monitoring every 2–3 months for at least 2 years after diagnosis. An important objective of patient follow-up is to detect locoregional recurrences, distant metastases (e.g., in the lungs or liver) or metachronous cancers as early as possible, thus offering the possibility for adjuvant therapy or salvage surgery when appropriate. Serum markers, such as CEA, have been investigated as prognostic markers in patients with colorectal cancer, but the sensitivity of serum markers has limited the use to postoperative surveillance.[15]

In the present study, we evaluated preoperative serum CEA concentrations as prognostic factors in patients with colorectal cancer, with a focus on the value and kinetics of CEA as a surveillance tool.

PATIENTS AND METHODS

This study was based on prospective follow-up programs for colorectal cancer patients conducted in the Department of Surgery of Kyungpook National University Hospital (Daegu, Korea). Patients with synchronous metastatic disease or patients undergoing palliative resection, and those with carcinoma in situ, inflammatory bowel disease, familial adenomatous polyposis or pathology other than adenocarcinoma were excluded, as were patients with T1 cancer treated by endoscopic mucosal resection or transanal excision. In addition, patients with chronic obstructive lung disease, chronic liver disease, peptic ulcer, and diabetes were excluded.

The postoperative surveillance program in our institute is as follows. Patients are followed routinely at 2- or 3-month intervals for the first 2 years and at 6-month intervals thereafter. At each visit, CEA levels are assayed, a full history is obtained, and a physical examination is performed. A serum CEA assay is performed with at least a 2-week interval after the administration of chemotherapy. Colonoscopy is performed within 6 months to 1 year following surgery, and every 3 years thereafter. Chest radiographs and abdominopelvic computed tomography (CT) are performed 6 months postoperatively and then at yearly intervals. Unscheduled CT or positron emission tomography (PET) scans were performed on patients with increased serum CEA concentrations or patients who were symptomatic. We included both local tumor recurrence and systemic metastasis. Metachronous lesions during the follow-up period were not classified as tumor recurrences. The diagnosis of a tumor recurrence was confirmed by biopsy or examination of the resected specimen. Otherwise, tumor recurrence was documented from the first clinical or radiologic sign of disease that showed an unrelenting course leading to tumor progression and/or death. The criteria for establishment of recurrent disease included histologic confirmation, palpable disease, or radiographic evidence of disease with subsequent clinical progression and supportive biochemical data, particularly an increased CEA level. Time to recurrence was determined by the date of the follow-up visit at which tumor recurrence was discovered, or by reviewing hospital records for patients who were admitted.

Among 1,707 patients who underwent curative resection for colorectal cancer, 1,263 patients (74.1%) were followed in the regular surveillance program. The study population consisted of 1,263 patients with a median follow-up period of 48 months (range 1–156 months). Serum CEA concentrations were measured, with CEA concentrations >7.0 ng/ml regarded as elevated in our institute.

We recorded an elevated follow-up serum CEA level in patients with a tumor recurrence as the first increase in the serum CEA level before the detection of the tumor recurrence. If there was no elevation in the surveillance serum CEA level throughout the follow-up period, we considered the patient to have normal follow-up serum CEA levels. In contrast, if there was an elevated serum CEA level during the follow-up period, we considered the patient to have a high follow-up serum CEA level, even if the elevation was an isolated occurrence. The diagnostic interval was defined as the interval between the elevation of the follow-up CEA and the diagnosis of the tumor recurrence.

We compared the clinical and pathologic characteristics of the patients with and without elevated preoperative serum CEA levels. The patients with and without tumor recurrences were also compared regarding clinicopathologic characteristics. The clinicopathologic variables between the groups were compared using an unpaired *t*-test or one-way analysis of variance (ANOVA) with the least significant difference (LSD) multiple comparison. The two groups were compared using a cross-table analysis and Fisher's exact test. The Cox proportional hazards model was applied for multivariate analysis to determine the important predictors of recurrence. Variables were included in the multivariate analysis only if the P value was <0.05 in the univariate analysis. Recurrence-free survival was compared using the Kaplan–Meier method with a log-rank test. The confidence intervals (CIs) were set at 95% and the significance level at a P-value of 0.05.

RESULTS

Clinicopathologic Characteristics of the Patients

Of the 1,263 patients, 696 (55.1%) were males. The average patient age was 61 years (range 21–90 years). Of the 1,263 patients, 631 (50%) had primary tumors in the colon and 632 (50%) had primary tumors in the rectum. The tumor differentiation was as follows: moderately differentiated, 990 (78.4%); well-differentiated, 171 (13.5%); poorly differentiated, 45 (3.6%); and mucinous, 47 (3.7%). Of the tumors, 212 (16.8%) were stage I, 514 (40.7%) were stage II, and 537 (42.5%) were stage III. Lymphatic invasion was detected in 690 patients (54.6%), vascular invasion in 86 (6.8%), and perineural invasion in 492 (39%). Tumor recurrence occurred in 291 patients (23%); among these, liver metastasis was most common.

Characteristics of Patients Relative to Preoperative Serum CEA Levels and the Prognostic Significance of Preoperative Serum CEA Levels

Patients with high preoperative serum CEA levels (>7.0 ng/ml) were significantly more likely to have

perineural invasion, more aggressive tumor stage, and tumor recurrence than were patients with normal preoperative serum CEA. Gender, tumor location, histologic differentiation, and lymphatic and vascular invasion did not differ significantly in patients with normal and high preoperative serum CEA levels (Table 1). The 5-year disease-free survival (DFS) rate was significantly lower in patients with high preoperative serum CEA levels ($P < 0.0001$). Subgroup analysis of these patients by tumor–node–metastasis (TNM) stage revealed a lower DFS in patients with stage II and III disease. While the DFS was lower in patients with stage I disease with high preoperative CEA levels, this did not reach statistical significance ($P = 0.24$; Fig. 1).

To determine the independent prognostic covariates for the 5-year DFS, a multivariate analysis was performed using the Cox proportional hazard regression model. The preoperative serum CEA level was an important prognostic factor for tumor recurrence, combined with the pT and pN categories. When we divided the preoperative serum CEA into normal and high levels, preoperative serum CEA was an important prognostic factor, but CEA level as a continuous variable was not a significant prognostic factor for recurrence (Table 2).

TABLE 1 Clinicopathologic characteristics of patients with normal and high preoperative serum CEA concentrations

	Normal preoperative serum CEA ($n = 1{,}002$)	High preoperative serum CEA ($n = 261$)	P
Gender			0.80
Male	554 (55.3)	42 (54.4)	
Female	448 (44.7)	119 (45.6)	
Location			0.93
Colon	500 (49.9)	131 (50.2)	
Rectum	502 (50.1)	130 (49.8)	
Histology			0.79
Well	140 (14.0)	31 (11.9)	
Moderately	780 (77.8)	210 (80.5)	
Poorly	36 (3.6)	9 (3.4)	
Mucinous	36 (3.6)	11 (4.2)	
Signet ring cell	5 (1.0)	0 (0)	
Lymphatic invasion	536 (53.4)	155 (59.4)	0.08
Vascular invasion	68 (6.8)	18 (6.9)	0.95
Perineural invasion	374 (37.6)	118 (45.6)	0.02
Stage			<0.001
I	198 (19.8)	14 (5.4)	
II	404 (40.3)	110 (42.1)	
III	400 (39.9)	137 (52.5)	
Recurrence	185 (18.5)	106 (40.6)	<0.001

The sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) of the preoperative serum CEA level for tumor recurrence were calculated. Preoperative serum CEA level >7 ng/ml was considered to be a positive test. The sensitivity and specificity were 36.4% and 84.1%, respectively. The PPV and NPV of the preoperative serum CEA level for recurrence were 40.6% and 81.5%, respectively.

Relationship of Pre- and Postoperative Serum CEA Levels with Recurrence

Among the patients with tumor recurrences diagnosed by imaging modalities, such as CT, PET, or biopsy, 38.5% had high postoperative serum CEA levels measured before the diagnosis of the recurrence. The proportion of patients with a high postoperative serum CEA level was significantly higher in patients with a high preoperative serum CEA level. The mean interval between the detection of an elevated postoperative serum CEA and the diagnosis of a tumor recurrence [diagnostic interval (DI)] using imaging or biopsy was 2.5 months (range 1–17 months), excluding patients with a DI of 0. The mean disease-free interval (DFI) was similar between patients with normal and high preoperative serum CEA levels. Patients with liver metastases were significantly more likely to have elevated serum CEA levels than patients with metastases to other sites with both normal and high preoperative serum CEA levels (Table 3).

The sensitivity, specificity, PPV, and NPV of the follow-up serum CEA levels for tumor recurrence were calculated. When classified by preoperative serum CEA levels, the follow-up serum CEA levels had a high PPV, NPV, and specificity in patients with high preoperative serum CEA levels (Table 4).

When the DFI and DI were analyzed together, the DI was 0 in 18.8% of the patients who had tumor recurrences and high follow-up serum CEA levels. Thus, in 18.8% of the patients with a tumor recurrence, timing of the elevated CEA level was coincident with the diagnosis of the recurrence via another modality, such as imaging. The elevated CEA level was similar between patients with a DFI $\leq$ 2 years and a DFI $>$ 2 years. Sixty-five of 107 patients (60.7%) with a DFI $\leq$ 2 years, and 9 of 15 patients (60%) with a DFI $>$ 2 years had a DI $\leq$ 3 months (Fig. 2).

DISCUSSION

Our results show that high preoperative serum CEA concentrations are markers of poor prognosis in patients

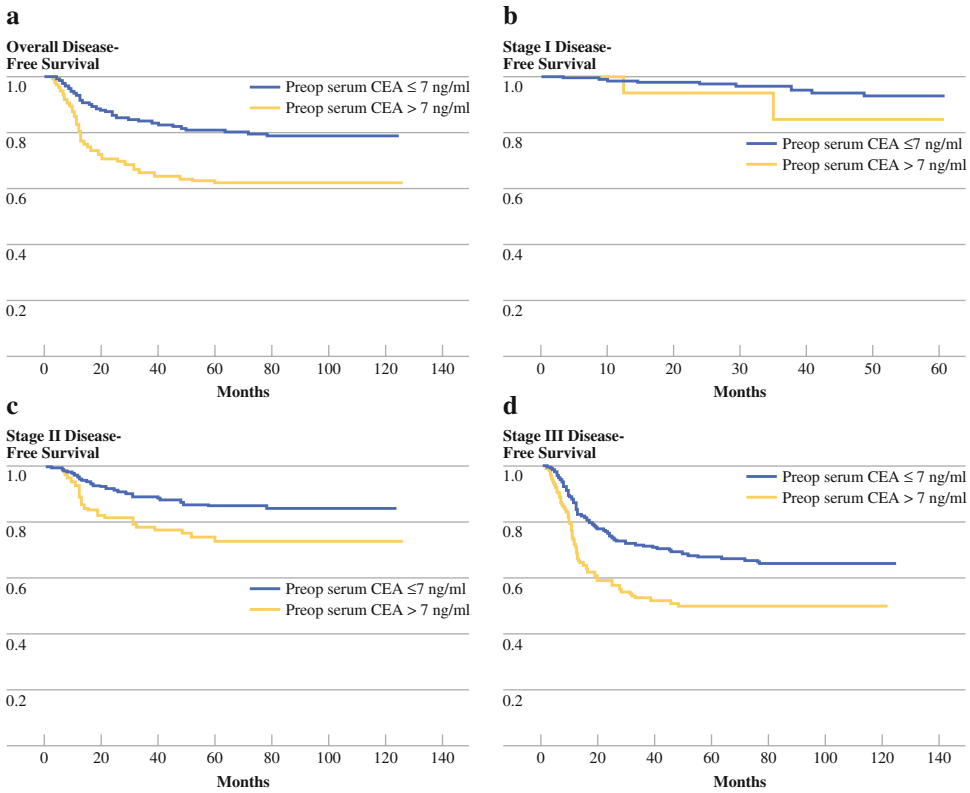

FIG. 1 Disease-free survival curves stratified by preoperative serum CEA concentrations. Patients with American Joint Committee on Cancer (AJCC) stage I tumors showed no difference relative to preoperative serum CEA ($P = 0.194$). Patients with AJCC stage II ($P = 0.0002$) and III ($P < 0.001$) tumors, and preoperative serum CEA >7 ng/ml, had a poorer prognosis than did those patients with normal preoperative serum CEA concentrations

TABLE 2 Risk factors for recurrence based on multivariate analysis

Variables	Odds ratio	Confidence interval	*P*
pT category			0.005
T1 + T2			
T3 + T4	2.15	1.08–8.00	
pN category			<0.001
N negative			
N positive	2.10	1.62–2.74	
Lymphatic invasion	1.39	1.04–1.86	0.03
Vascular invasion			0.84
Perineural invasion			0.67
Histologic differentiation			0.32
Preoperative serum CEA			0.003
Normal			
High	1.59	1.17–2.15	
Preoperative serum CEA level (continuous variable)			0.57

with colorectal cancer. This finding is in agreement with previous results, showing that an elevated preoperative CEA is a marker of poor prognosis and correlates with reduced overall survival after surgical resection of colorectal cancer.[6,7,16]

Serum CEA concentrations have been used as factors indicative of malignant potential and/or poorer prognosis in patients with colorectal carcinoma.[17,18] CEA concentration has been reported to correlate with colorectal cancer stage, but CEA level is considered unreliable as a tumor marker in patients with early-stage colorectal cancer. In patients with stage II colorectal cancer, those with elevated levels of CEA have been reported to have significantly poorer prognoses than those with normal CEA concentrations.[6] Others have demonstrated that CEA levels have a prognostic impact in all patient groups, but without significant between-stage differences.[19–21] We showed that DFS was not statistically different with respect to preoperative serum CEA levels in patients with stage I disease, which may have been because of the small number of patients in our study with both stage I colorectal cancer and high preoperative serum CEA concentrations. Further, CEA levels may be related to the advancement in tumor stage, and may therefore be relatively less effective in predicting outcomes in patients with early-stage disease.

Whereas elevated preoperative serum CEA concentrations have been associated with poor prognosis, postoperative monitoring of CEA levels may identify patients with metastatic disease in whom surgical resection or other localized therapy might be of benefit. Guidelines recommend postoperative serum CEA testing every 3 months for the first 2 years after surgery. Elevated CEA, if confirmed by retesting, warrants further evaluation for metastatic disease, but does not justify commencement of

TABLE 3 Relationship between postoperative serum CEA concentration and preoperative serum CEA level, and site of tumor recurrence among patients with recurrence

	Normal preoperative CEA ($n = 185$)	High preoperative CEA ($n = 106$)	P
Disease-free interval	14.7	13.1	0.37
High postoperative serum CEA	50 (27%)	72 (67.9%)	<0.001
Mean CEA level, ng/ml	43.7	70.8	0.57
Diagnostic interval, months	3.1	1.8	0.59
Site of recurrence			<0.001
Liver			
Normal postoperative CEA	32 (52.5%)	8 (20%)	
High postoperative CEA	29 (47.5%)	32 (80%)	
Other sites			
Normal postoperative CEA	103 (83.1%)	26 (39.4%)	
High postoperative CEA	21 (16.9%)	40 (60.6%)	

TABLE 4 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of high postoperative serum CEA for recurrence

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall	76.3	84.7	76.3	84.7
Regarding preoperative serum CEA				
Normal	27	96.1	61	85.3
High	67.9	96.1	92.3	96.1

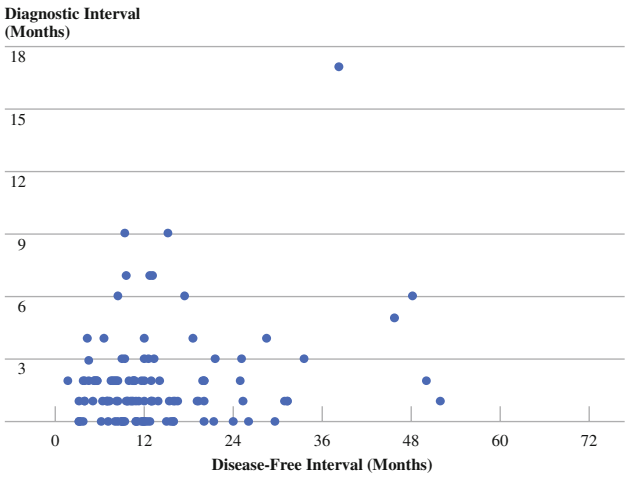

FIG. 2 Relationship between diagnostic interval and disease-free interval; approximately 60% of the patients had a diagnostic interval <3 months

adjuvant or systemic therapy for presumed metastatic disease.[22] CEA elevations within 1–2 weeks following chemotherapy should be interpreted with caution.[23] Despite the widespread use of CEA during follow-up, there are still some unresolved issues concerning the effectiveness of CEA levels as a postoperative marker. In the present study, postoperative CEA had more than 70% sensitivity, specificity, NPV, and PPV for detection of tumor recurrence. When preoperative CEA was high, the NPV and PPV of postoperative CEA for predicting recurrence were 96.1%, and 92.3%, respectively. Regarding results in the present study, postoperative CEA could be used as a valuable surveillance tool, especially in case of elevated preoperative CEA level. One issue is how accurately an elevated CEA level detects the recurrence of colorectal cancer and another is whether a postoperative CEA level becomes elevated upon tumor recurrence in patients with a negative preoperative CEA level. Therefore, it is still unclear whether clinicians can rely solely on CEA measurements for follow-up of patients with colorectal cancer.

Periodic CEA monitoring has been contraindicated by high cost, as well as by the frequency of negative second-look procedures.[7,14,24] In a retrospective review of an intergroup surgical adjuvant trial in 1,217 patients who underwent resections for colon cancer, 1,017 patients were monitored postoperatively with CEA levels.[7] Of these 1,017 patients, 417 (41.0%) developed a recurrence of colorectal cancer and 246 (59%) of the 417 patients had elevated CEA concentrations (>5 ng/ml) prior to the recurrence.[7] These results are similar to the results reported herein, although we did not perform second-look operations. However, the percentage of patients with elevated serum CEA levels prior to tumor recurrence was less than one-half, suggesting a need to identify patients who could benefit from regular postoperative serum CEA monitoring. In addition, second-look operations on patients based solely on postoperative CEA elevations should not be performed.

Our results showed that only 38.5% of patients diagnosed with a tumor recurrence had high serum CEA concentrations before the diagnosis of a recurrence. Only 27% of patients with normal preoperative serum CEA levels had high serum CEA levels before a tumor recurrence, compared with 67.9% of patients with high preoperative serum CEA levels. These results indicate that, although a postoperative CEA elevation indicates a high probability of recurrence, a normal postoperative CEA

level, which is especially common in patients with a normal preoperative serum CEA level, cannot exclude the possibility of a recurrence.

The correlation between an elevated CEA level and a recurrence has been reported to be greater for liver metastases than for recurrent disease at other anatomic sites.[7,25] In the present study, a postoperative CEA elevation predicted liver metastasis with high reliability in patients with normal and high preoperative serum CEA levels. We found that 60.4% of our patients with liver metastases had high postoperative serum CEA concentrations, compared with 32.1% of the patients with metastases at other sites. In patients with liver metastases, those with high preoperative serum CEA levels had a much higher rate of high postoperative serum CEA levels (80%) than did those with normal preoperative serum CEA levels (47.5%). These findings indicate that CEA elevation is more effective in predicting liver metastasis than other types of metastasis.

The mean interval between the postoperative serum CEA elevation and the diagnosis of recurrence (i.e., DI) was 2.5 months (range 1–17 months) among patients with a DI other than 0. The serum levels of CEA may increase prior to the development of cancer-related symptoms, with a median lead time of 4.5–8 months.[25–27] In our study, the lead time was shorter than reported in other studies, which might be due to the overall follow-up program schedule. In our institution, imaging studies, such as CT and PET, are performed earlier than in other programs.[28–30]

In 18.8% of the patients, the DI was 0, so the patients had surveillance serum CEA levels and imaging performed on the same schedule. Approximately 60% of the patients had a DI <3 months. According to our postoperative surveillance strategy, the postoperative serum CEA was examined in our institute every 2–3 months during the first 2 postoperative years. Chest radiographs and abdominopelvic CT scans were performed at 6-month, and then yearly intervals. Therefore, at 6 and 18 months postoperatively, a CT scan and a serum CEA level were checked at the same time. Our results showed that elevation of the CEA level occurred <3 months before the diagnosis of the tumor recurrence using an imaging modality in >80% of the patients, suggesting that the schedule for assessment of serum CEA levels had improved compared with the program currently in use; thus, it was better to separate the laboratory and imaging schedule. Currently, the laboratory and imaging studies are performed at the same time. If we perform CEA and other imaging methods at different visits, the information would be more useful, especially 2 years postoperatively when the interval between visits is lengthened. The only drawback to such a follow-up scheme would be the additional hospital visits required by the patients. Sugarbaker et al. reported that monthly CEA monitoring was more sensitive than physical examination, abdominal CT scan, liver/spleen scintiscan, and chest tomography every 4 months, as well as annual intravenous pyelogram, barium enema, and bone scan, in detecting the presence of recurrent disease.[31]

In a randomized controlled trial of postoperative CEA monitoring, although more resections were performed in the CEA-monitored group, no survival benefit was demonstrated.[32] In our study, we did not analyze the survival benefit or impact on treatment for recurrent disease with postoperative CEA monitoring. Nevertheless, it will be studied when we set the program change according to the results of the current study.

This study had several limitations. It was retrospective in design, although the data were collected prospectively. Thus, analysis of postoperative serum CEA levels, especially in the interval between the postoperative elevation of CEA and the diagnosis of recurrence, may have a subjective bias. In addition, we did not evaluate the value of postoperative serum CEA measurements for detecting recurrent disease. We found that patients with high preoperative serum CEA levels were more likely to have higher postoperative serum CEA concentrations, and those patients with liver metastasis had higher CEA concentrations than did those patients with other types of metastases.

In conclusion, we have shown that preoperative serum CEA levels are important prognostic factors for recurrent colorectal cancer. Postoperative serum CEA levels were more elevated when preoperative serum CEA levels were high. The mean interval between elevation of serum CEA and diagnosis of a tumor recurrence was 2.5 months, suggesting the need for a change in monitoring of serum CEA concentrations after curative resection, especially in patients with high preoperative serum CEA concentrations.

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