

The validity of carcinoembryonic antigen as a surveillance marker according to the pattern of recurrence in colorectal cancer

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Abstract

Background Even though the validity of the carcinoembryonic antigen (CEA) test has been shown for monitoring colorectal cancer recurrence after surgery, it has been applied without specification to the site of recurrence. In the present study, we aimed to verify the validity of CEA as a site-specific surveillance tool in colorectal cancer after curative resection by analyzing the sensitivity of CEA according to the pattern of recurrence. **Methods** A total of 722 patients diagnosed with recurrent colorectal cancer after curative resections were enrolled, and their medical records were reviewed. Using a cutoff CEA value of 5 ng/ml at the time of detection, the sensitivity of the CEA test according to the pattern of recurrence (locoregional or systemic recurrence) and detailed information about the location of the recurrence sites were investigated. **Results** In patients with recurrence in the peritoneum, combined sites, and the liver, the sensitivities of CEA test were 59.4%, 51.3%, and 44.8%, respectively. These values were higher than those in the para-aortic lymph nodes, lungs, and the brain, with sensitivities of 30.4%, 23.6%, and 16.7%, respectively. In the subset analysis, the CEA test sensitivities for patients with recurrence in the peritoneum, liver, and para-aortic lymph nodes were 61.9%, 53.2%, and 22.2% in colon cancer and 54.5%, 36.0%, and 35.7% in rectal cancer, respectively. **Conclusions** Postoperative surveillance CEA levels may have different values according to the site of recurrence. Therefore, a follow-up strategy considering site-specific CEA sensitivity after surgery could improve early detection of recurrent colorectal cancer.

Background

Carcinoembryonic antigen (CEA) is the most widely accepted and readily available tumor marker used for the management of colorectal cancer (CRC). Since it was first described and characterized by Gold and Freedman in 1965, CEA has been used for postoperative surveillance, monitoring advanced disease, determining CRC prognoses, and is generally believed to be the best available noninvasive test for detecting recurrence in patients after CRC surgical resections.[1–5] Consequently, current international guidelines recommend postoperative CEA testing for a minimum of 5 years after surgery.[6]

Even though the validity of CEA testing has been shown for monitoring CRC recurrence after surgery, it has been applied without specification to the site of recurrence. The expression of CEA is affected by the location of the recurrence through differences in circulation, metabolism, and the adjacent biological environment.[7–9] Some reports have shown that CEA has a lower sensitivity for local recurrences and a relatively higher sensitivity for hepatic metastases.[10–14] However, the association between the pattern of recurrence and the expression of CEA has not been clearly demonstrated.

Recent technical advances in radiological imaging and intensified follow-up surveillance have increased the probability of detecting and surgically treating asymptomatic recurrences, which has improved survival outcomes.[15] In this context, determining the sensitivity of CEA according to the pattern of recurrence and establishing a radiological surveillance strategy could aid in the detection of curable recurrences. In the present study, we aimed to verify the validity of CEA as a recurrence site-specific

surveillance tool in CRC after curative resection by analyzing the sensitivity of CEA tests according to the pattern of recurrence.

Patients And Methods

A total of 4,327 patients underwent potentially curative resections for clinically diagnosed and histologically confirmed colorectal cancer without distant metastases between January 2001 and December 2010. CRC was defined as a histologically confirmed adenocarcinoma arising from the mucosa of the colon and rectum and was staged according to the 8th edition of the American Joint Committee on Cancer staging system.[16] For this retrospective study, we included 857 patients with recurrent disease detected during the follow-up period and excluded 106 patients who lacked CEA laboratory data when recurrence was detected. Additionally, on postoperative day 7 and 30, a dual check of CEA levels demonstrated that 29 patients had sustained CEA elevation above 5 ng/ml, and they were excluded from the study to clarify the association between CEA elevation and detection of recurrence. Thus, 722 patients who underwent curative resections for stage I, II, and III adenocarcinomas of the colon and rectum were included in this analysis to determine the sensitivity of CEA tests for detecting CRC recurrence. The study was reviewed and approved by the institutional review board. Informed consent was waived, given the retrospective nature of the study.

Patients were followed up every 3 months for the first 3 years after surgery, every 6 months for the following 2 years, and yearly thereafter. Each visit included a medical history, a physical examination, and a serum CEA test. Routine imaging studies consisted of a chest radiography and a computed tomography (CT) of the chest, abdomen, and pelvis. The chest radiography and abdominopelvic CT were performed 6 months after surgery for 5 years and annually thereafter. Chest CTs were performed annually after surgery, or when an abnormal finding was suspected on chest radiography. A colonoscopy was performed 6 months after surgery and annually thereafter. Ultrasonography, whole-body bone scintigraphy, and positron emission tomography were performed when recurrence was suspected on routine imaging studies. Recurrence was determined by clinical and radiological examinations or by histological confirmation. Recurrences were classified into locoregional recurrences (tumor tissue at the primary site of resection, either intra- or extraluminal) or systemic recurrences (distant spread of CRC). A combination of locoregional and systemic recurrence was considered a systemic recurrence.

CEA levels were measured by chemiluminescence immunoassay using a Dxl 800 Access Immunoassay System (Beckman Coulter Inc., Brea, CA, USA) with a reference range of ≤ 5 ng/ml. Patients were categorized into two groups, the normal CEA group and the abnormal CEA group, according to their serum CEA concentrations at the time recurrence was detected. The normal CEA group had a CEA concentration ≤ 5 ng/ml and, the abnormal CEA group had a concentration > 5 ng/ml. We compared general descriptive profiles such as age, sex, tumor location, CEA level before surgery, and the stage and histology of the primary tumor between the two groups. We analyzed the pattern of recurrence (locoregional or systemic recurrence) between the two groups and investigated the sensitivity of the CEA test using 5 ng/ml as the cutoff value according to the location of recurrence in patients with systemic recurrences.

All statistical analyses were performed using SPSS statistics version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive results were presented as means with standard deviations or medians with interquartile ranges (Q1-Q3) for continuous outcomes and as frequencies and percentages for categorical outcomes. The χ^2 and linear-by-linear tests were used for categorical outcomes and the Student's *t*-test was used to compare continuous outcomes. A P-value less than 0.05 was considered statistically significant.

Results

A total of 722 patients with recurrent CRC were included in the analysis, with a median follow-up period of 51.0 months (range, 30.0–76.0 months). The median CEA level for these patients was 3.3 ng/ml (range, 1.6–9.2 ng/ml). For colon and rectal cancers, the median CEA levels were 3.9 ng/ml (range, 2.0–10.2 ng/ml) and 2.9 ng/ml (range, 1.5–8.6 ng/ml), respectively.

Comparison of clinicopathological features

The clinicopathological features of the CEA groups categorized by serum CEA level when recurrence was detected are summarized in Table 1. There were 444 patients (61.5%) in the normal CEA group and 278 patients (38.5%) in the abnormal CEA group. There were no significant differences between the two groups with regard to age, sex, and pathologic findings of the primary tumor (pathologic stage, histologic grade, and lymphovascular invasion), except tumor location and preoperative CEA level. The proportion of patients in the abnormal CEA group who had colon cancer (43.4%) was higher than that with rectal cancer (34.9%), with statistical significance ($p = 0.021$). In abnormal CEA group, more patients had preoperative CEA levels above 5.0 ng/ml than levels at or below 5.0 ng/ml (53.7% versus 30.8%, $p < 0.001$).

Table 1
Patients' characteristics (n = 722)

	Normal ^a CEA (n = 444)	Abnormal CEA (n = 278)	P-value
Age, mean (± SD, year)	59.7 (± 12.1)	61.3 (± 10.5)	0.067
Gender			0.182
Male	301 (67.8%)	175 (62.9%)	
Female	143 (32.2%)	103 (37.1%)	
Tumor location			0.021
Colon	172 (38.7%)	132 (47.5%)	
Rectum	272 (61.3%)	146 (52.5%)	
Preoperative CEA			< 0.001
≤ 5 ng/ml	331 (74.5%)	147 (52.9%)	
> 5 ng/ml	113 (25.5%)	131 (47.1%)	
Primary tumor stage			0.328
Not assessable	6 (1.4%)	3 (1.1%)	
I	46 (10.4%)	20 (7.2%)	
II	130 (29.3%)	74 (26.6%)	
III	262 (59.0%)	181 (65.1%)	
Histologic grade			0.230
I	39 (8.8%)	30 (10.8%)	
II	359 (80.9%)	210 (75.5%)	
III	46 (10.4%)	38 (13.7%)	
Lymphovascular invasion			0.739
Present	129 (29.1%)	84 (30.2%)	
Absent	315 (70.9%)	194 (69.8%)	
^a CEA: carcinoembryonic antigen			

Recurrence patterns according to CEA group

Of the 722 patients with recurrent CRC, 90 (12.5%) and 632 (87.5%) presented with local and systemic recurrence, respectively. There was no significant relationship between the recurrence pattern and the CEA group (Table 2). Median CEA levels for local and systemic recurrence were 3.5 ng/ml (range, 1.6–

9.9 ng/ml) and 3.3 ng/ml (range, 1.7–9.1 ng/ml), respectively. Additionally, in the subset analysis of colon and rectal cancer, no significant relationship between the recurrence pattern and the CEA group were identified.

Table 2
Systemic and local recurrence according to aCEA level (n = 722)

	Local recurrence	Systemic recurrence	Total	P value
Colorectal cancer				
Normal CEA	53 (58.9%)	391 (61.9%)	444 (61.5%)	P = 0.587
Abnormal CEA	37 (41.1%)	241 (38.1%)	278 (38.5%)	
Colon cancer				
Normal CEA	27 (58.7%)	145 (56.27%)	172 (56.6%)	P = 0.753
Abnormal CEA	19 (41.3%)	113 (43.8%)	132 (43.4%)	
Rectal cancer				
Normal CEA	26 (59.1%)	246 (65.8%)	272 (65.1%)	P = 0.379
Abnormal CEA	18 (40.9%)	128 (34.2%)	146 (34.9%)	
^a CEA: carcinoembryonic antigen				

Sites of systemic recurrence and sensitivity of the CEA test

Of the 632 patients with systemic recurrence, the lungs (36.2%) and the liver (24.4%) were the most common sites for recurrence, not including combined recurrence sites. For colon cancer, the liver (30.6%) was the most common site and the lungs (27.1%) were the second most common. For rectal cancer, the lungs (42.5%) were the most common and the liver (20.1%) was the second most common. The median CEA level for recurrence in the peritoneum, combined sites, and liver were 8.0 ng/ml (range, 2.6–16.6 ng/ml), 5.3 ng/ml (range, 1.9–16.0 ng/ml), and 4.2 ng/ml (range, 1.7–10.9 ng/ml), respectively. Additionally, the median CEA levels for a recurrence in the para-aortic lymph nodes and lungs were 3.7 ng/ml (range, 2.3–5.9 ng/ml) and 2.4 ng/ml (range, 1.4–4.5 ng/ml), respectively.

The sites of systemic recurrence and the proportion of patients with abnormal CEA levels, representing CEA sensitivity, are summarized in Fig. 1. For patients with recurrences in the peritoneum, combined sites, and the liver, the sensitivities of the CEA test were 59.4%, 51.3%, and 44.8%, respectively. These sensitivities were relatively higher than those in the para-aortic lymph nodes, lungs, and brain, with sensitivities of 30.4%, 23.6%, and 16.7% (p = 0.008), respectively. In the subset analysis for colon cancer, the sensitivities of the CEA test were 61.9%, 58.9%, and 53.2% for patients with recurrence in the peritoneum, combined sites, and liver, respectively. The sensitivities for recurrence in the bone, lung, and para-aortic lymph nodes were relatively low, at 28.6%, 22.9%, and 22.2%, respectively. For rectal cancer,

the sensitivities were 54.5%, 50.0%, and 46.9% in patients with recurrence in the peritoneum, bone, and combined sites, respectively. The sensitivities for recurrence in the liver, para-aortic lymph node, and lungs were 36.0%, 35.7%, and 23.9%, respectively.

Discussion

The current standard CEA threshold is 5 ng/ml, where any value below this level is generally recognized as a normal value.[17] After surgical resection, CEA usually progressively falls and returns to normal levels within 4–6 weeks.[18, 19] Subsequent elevation of CEA level in a patient after surgical resection of CRC is indicative of tumor recurrence through metastatic disease and is frequently the first observed indication. In the present study, we categorized patients into two CEA groups using the standard threshold of 5 ng/ml. The proportion of patients in the abnormal CEA group was used to determine the sensitivity of the CEA test to detect recurrences. We excluded patients with persistent elevation of CEA levels postoperatively, since it could indicate incomplete surgical resection or the presence of occult metastatic disease.[20, 21]

The CEA test's overall sensitivity for detecting recurrence after curative resection in this study was 38.5%. In a recent Cochrane review investigating blood CEA levels and recurrent CRC detection, the sensitivity for detecting recurrence after curative resection using a CEA threshold of 5 ng/ml ranged from 43% – 93% in 23 studies, and the pooled sensitivity of these studies was 71%.[17] In another meta-analysis of 20 studies reporting the sensitivity of the CEA test, the pooled estimate using a threshold of 5 ng/ml was 63%.[22] The CEA test's relatively low sensitivity to tumor recurrence detection in the present study might be associated with intensive follow-up imaging studies and good patient compliance. Since a semi-quantitative relationship between CEA levels and tumor volume has previously been described, good compliance with intensive follow-up examinations allows the tumor to be detected at a low burden.[23] Due to the low sensitivity of the CEA test to detect recurrences, most national guidelines recommend that CEA tests be used in conjunction with another mode of diagnosis (such as CT imaging of the thorax, abdomen, and pelvis).[17] A recent randomized clinical trial determined that measuring blood CEA levels every 3 to 6 months for 5 years, augmented by a single CT scan at 12 to 18 months, leads to earlier diagnosis of recurrence and increases the proportion of patients that can be treated with curative intent about threefold.[24]

The sensitivity of postoperative CEA monitoring for tumor recurrence detection varies according to the site of recurrence.[14, 25–27] During follow-up, CEA appears to be more sensitive for hepatic and retroperitoneal metastases and is least sensitive for local recurrences and peritoneal or pulmonary disease.[28, 29] In the present study, after comparing the sensitivity of CEA tests according to the pattern of recurrence, whether local or systemic, there was no significant difference found between them. One possible reason could be the difficulty in discriminating early local recurrence from postoperative changes at the peri-procedural site radiologically. Due to the distortion of normal architecture and newly developed fibrotic tissues, early local recurrences could be masked or misdiagnosed and may require serial follow-up, which makes a time to increase the CEA level above normal value. Another possible

reason could be the relatively high proportion of pulmonary metastases in patients with systemic recurrence. In previous studies, CEA tests performed to detect pulmonary metastases showed low sensitivity, and our data showed that metastases confined to the lungs accounted for 36.2% of total systemic recurrences.[28, 29]

Of the sites of systemic recurrence, the sensitivities for detecting peritoneal carcinomatosis and recurrent hepatic metastasis were relatively high. However, the sensitivities for recurrence in the para-aortic lymph node and lungs were relatively low. These results were consistent with previous studies. In particular, the CEA test's sensitivity for detecting recurrence in the lungs was only 23.6% and the median CEA level was the lowest of the systemic recurrence sites, at 2.4 ng/ml. In previous studies, the CEA test was not sensitive to pulmonary recurrence, with reports as low as 15% for solitary pulmonary recurrence.[14, 28, 29] Following radical surgery, most international guidelines recommend intensive follow-up regimens including CEA tests and CTs. However, these guidelines do not consider differences in CEA sensitivity according to the sites of recurrence. For pulmonary recurrence in particular, which is a frequent extra-abdominal metastatic site, annual chest CTs have been recommended after surgery to compensate for the low sensitivity of CEA testing and should be considered.[6]

In the present study, which considered the primary location of the tumor (colon or rectal cancer), there were differences in the CEA test's sensitivity depending on the recurrence site. In colon cancer, the sensitivity of the CEA test for recurrences in the liver was 53.2%, whereas in rectal cancer, it was 36.0%. The sensitivity for recurrence in the para-aortic lymph node was 22.2% in colon cancer and 35.7% in rectal cancer. This result was not found in the current literature, suggesting the need to precisely determine the surveillance strategy according to the primary tumor location.

We acknowledge the limitations of the present study. First, this was a retrospective study from a single institution. Therefore, uncontrollable and unknown biases, including recall bias, information bias, and selection bias may have been present. Second, since we did not include information on smoking status, alcohol consumption, and other benign conditions that may cause increases in CEA, our findings must be interpreted with caution. Third, since the surgeries were performed over a 10-year span between January 2001 and December 2010, progress in surgical techniques and neoadjuvant/adjuvant chemotherapy treatment for colorectal cancer were made, which likely influenced patient outcomes. Despite these limitations, however, this study provides a detailed description of recurrence site-specific CEA test sensitivities, revealing the validity of CEA as a surveillance marker according to the pattern of recurrence in colorectal cancer. Certainly, further studies are needed to increase our knowledge of the diagnostic value of CEA to better help in managing these patients.

Conclusions

In conclusion, postoperative surveillance using CEA levels may result in different values according to the site of recurrence. Therefore, a follow-up strategy considering the site-specific sensitivity of CEA after surgery could improve early detection of recurrent CRC.

Abbreviations

CEA: Carcinoembryonic antigen; CRC: Colorectal cancer; CT: Computed tomography

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Severance Hospital Institutional Review Board. Given the retrospective nature of the study, the IRB waived the requirement for written informed consent. (No. 4-2018-0505)

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests. There was no funding for this study.

Authors' contributions

GT Noh developed study concept and design and participated in the drafting and revising of manuscript and interpretation of data. SY Yang participated in the acquisition and analysis of the data. MS Cho, H Hur, BS Min, and NK Kim participated in the acquisition of data and revising manuscript. KY Lee developed study concept and design and participated in acquisition, analysis and interpretation of data and revising manuscript. All authors read and approved the final manuscript

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Figures

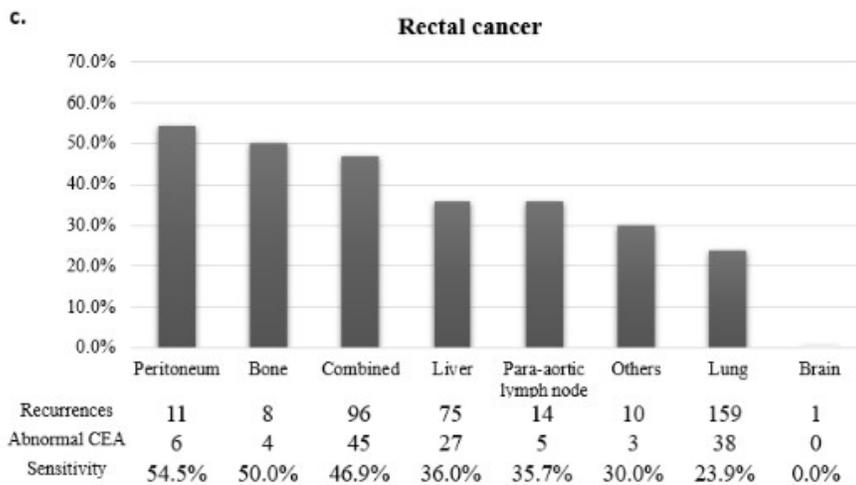
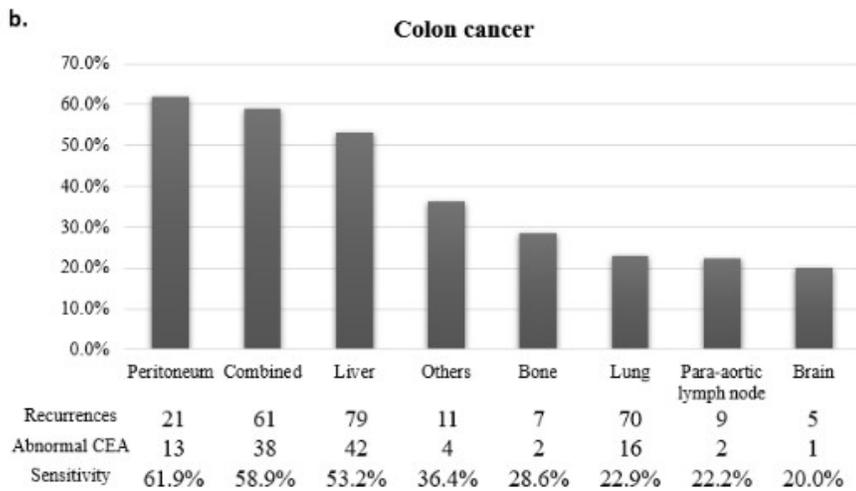
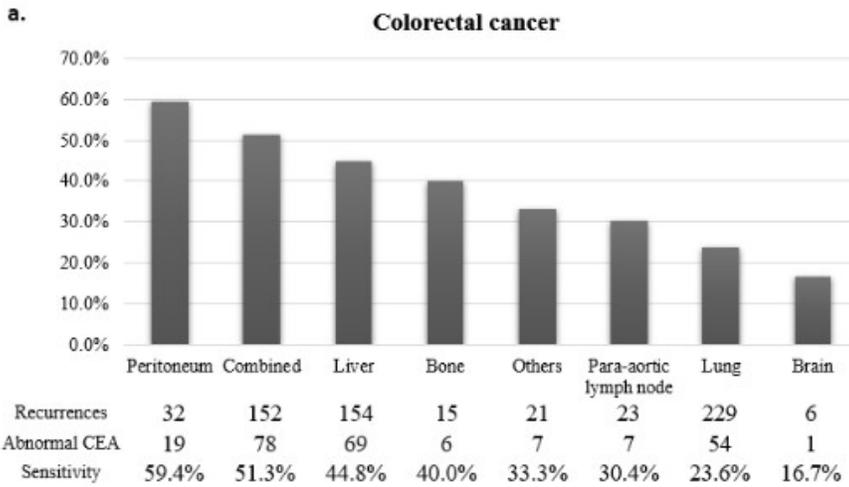


Figure 1

The proportion of patients with abnormal carcinoembryonic antigen (CEA) presenting with systemic recurrence after colorectal cancer surgical resections, and the sensitivity of the CEA tests according to the recurrence site. a: Patients with recurrence and an abnormal CEA test for colorectal cancer; b: Patients

with recurrence and an abnormal CEA test for colon cancer; c: Patients with recurrence and an abnormal CEA test for rectal cancer. Combined: synchronous metastatic lesions at more than one site; Others: lymph node metastasis other than the para-aortic node (i.e., supraclavicular, mediastinal, inguinal node, etc.), or the spleen, kidney, etc.