False-Positive Elevations of Carcinoembryonic Antigen in Patients With a History of Resected Colorectal Cancer

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Abstract

Routine monitoring of carcinoembryonic antigen (CEA) levels is standard in patients with resected colorectal cancer (CRC). The incidence of false-positives and the upper limits of false-positive elevations have not been previously well characterized. A search of medical records at Memorial Sloan-Kettering Cancer Center identified 728 patients who underwent an R0 resection of locoregional CRC between January 2003 and December 2012 and who had an increase in CEA level above the normal range after a normal perioperative CEA level. Of these, 358 had a false-positive elevation of CEA level, 335 had a true-positive elevation indicative of recurrent CRC, and 35 had a true-positive elevation indicative of the development of a new, non-CRC malignancy. Of those with false elevations, 111 had a single isolated CEA level elevation (median highest CEA level of 5.5 ng/mL) with no further abnormal measurements, whereas 247 had elevations on 2 or more readings, with a median highest level of 6.7 ng/mL. Of these 247 patients with confirmed false-positive CEA level elevations, only 5 (2%) had measurements greater than 15 ng/mL, and no confirmed elevation greater than 35 ng/mL was a false-positive. False-positive CEA test results in the range of 5 to 15 ng/mL are common. Confirmation of CEA elevation in this range before initiating imaging studies may be appropriate. False-positive results greater than 15 ng/mL are rare, and all confirmed CEA levels greater than 35 ng/mL were associated with cancer recurrence. (*J Natl Compr Canc Netw* 2014;12:907–913)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Recognize the high incidence of false-positive elevations of CEA in patients with a history of resected CRC
- Identify a level of CEA elevation that would indicate the need for imaging and diagnostic evaluations for possible recurrent disease
- Discuss some of the possible effects of false-positive CEA elevation in patients with resected CRC

In 1965, Gold and Freedman[1,2] discovered an oncofetal antigen expressed in human fetal colonic tissues and in colonic carcinomas, which they named carcinoembryonic antigen (CEA). In 1969, Thomson et al[3] developed a radioimmunoassay technique that could detect CEA in the serum. Later, CEA was found to be a glycosylphosphatidylinositol cell surface–anchored glycoprotein that serves as a functional colon carcinoma ligand of the cell adhesion molecules (CAMs) L-selectin and E-selectin.[4,5]

Since shortly after its discovery, CEA level has been widely used as a surveillance tool in patients after curative-intent resection of a colorectal cancer (CRC) primary. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer recommend routine monitoring of CEA levels every 3 to 6 months (to view the most recent version of these guidelines, visit NCCN.org).[6] Abnormal elevations in CEA levels (>5 ng/mL in most assays) are regarded by physicians as concerning for possible recurrent disease, and are used as a basis for initiating more-intensive imaging and other diagnostic evaluations.

It is well-known that false-positive CEA elevations occur, defined as elevations in CEA not associated with active cancer. The frequency and range of these false-positives have not been well characterized, however, and have not been examined extensively in the era of modern high-quality imaging. The objective of this study was to evaluate the incidence and range of false-positive elevations of CEA in patients with a history of resected stage I, II, or III CRC and to identify a maximum level of false-positive CEA elevation.

Patients and Methods

Electronic medical records at Memorial Sloan-Kettering Cancer Center (MSKCC) were searched using a proprietary search engine. Patients were identified who underwent resection of locoregional colon or rectal cancer from January 2003 through December 2012 who had a normal perioperative CEA level of 5 ng/mL or less and then subsequently developed a CEA elevation higher than normal range. Charts were then manually reviewed to confirm that patients had either stage I, II, or III CRC, an R0 resection, and no other active, clinically relevant malignancies at the time of resection. Data were collected to identify the CEA level at the time of diagnosis, surgery date, resection margin status, perioperative CEA nadir, time of first elevated postoperative CEA level, highest postoperative CEA measurement, and disease status at last follow-up. The maximum level of CEA attained and the identification, or lack thereof, of a recurrence of malignancy, or development of a new malignancy, was determined. Radiographic imaging reports were reviewed and a definitive diagnosis of recurrence was established based on the appearance of new lesions on CT scan and/or PET scan imaging thought to be indicative of recurrence, and/or histologic confirmation of recurrence through biopsy. For the purposes of this analysis, a false-positive was described as a CEA level higher than the upper range of normal (ie, ≥5.1 ng/mL) with no evidence of cancer on either imaging studies or other diagnostic procedures, with either follow-up of (1) at least 1 year since the first abnormal CEA or (2) abnormal CEA elevations followed by spontaneous normalization, with at least 2 consecutive subsequent normal CEA measurements in the absence of a therapeutic intervention.

Because this was a retrospective review, practice patterns and the frequency of CEA sampling varied. The general practice for surveillance of patients with CRC who had definitive colorectal resection at MSKCC during the study period was to monitor serum CEA levels at 3- to 6-month intervals for approximately 5 years after resection. Diagnostic imaging, most frequently with CT scans, was typically performed at a minimum of every 12 months for a total of 5 years, or more frequently if symptoms developed or CEA levels were found to be elevated. Colonoscopy was typically performed at 1 year from the date of surgery (or 6 months from surgery if complete colonoscopy had not been performed preoperatively), and then repeated every 3 to 5 years unless advanced adenomas were detected. PET/CT scans

were not routinely used unless a questionable lesion on CT scan warranted further evaluation.

All CEA levels were determined using a commercially available assay through the MSKCC laboratories. The CEA assay used was a Tosoh AIA-2000 automated analyzer (Tosoh Bioscience, Inc., South San Francisco, CA). The assay is a 2-site immunoenzymometric assay that uses a CEA-directed monoclonal antibody immobilized on a magnetic solid phase and a second enzyme-labeled CEA-directed monoclonal antibody. After the magnetic beads are washed to remove unbound enzyme-labeled antibody, a fluorogenic substrate is added and the resulting fluorescence is proportional to the amount of CEA in the sample. The reference range for this assay is 0 to 5.0 ng/mL.

Results

Patient Characteristics

A total of 805 patients were identified who underwent R0 resection for stage I–III CRC with a normal perioperative CEA level who subsequently had at least one abnormal CEA measurement. Of these patients, 77 were excluded: 11 had noncolorectal malignancies at the time of resection, which could potentially elevate the CEA level; 38 were lost to follow-up or died within 1 year of first elevated CEA level without identification of a source (peak CEA range, 5.1–25.5 ng/mL); and 27 were excluded because less than 1 year had elapsed since the first elevated CEA level until time of data cutoff, with persistence of CEA elevation without identification of a source (peak CEA range, 5.1–9.4 ng/mL). The remaining patient was excluded as indeterminate, because recurrent disease was strongly suspected but not verified; this patient had known cirrhosis and resected T3,N2 colon cancer with normal perioperative CEA level. He then had an increase in his CEA level up to 24 ng/mL at 8 months after resection and died in hospice 6 months later with tense ascites.

Of the 728 evaluable patients, 358 patients (49%) were determined to have had a false-positive CEA elevation without evidence of recurrent cancer, 335 patients (46%) had a true-positive CEA elevation indicative of recurrent CRC, and 35 patients (5%) had a true-positive CEA elevation indicative of the development of a new noncolorectal malignancy. Of the 335 patients who developed documented CRC relapse and CEA elevation (true-positives), the median lowest normal perioperative CEA level recorded was 2.9 ng/mL (range, 0.6–5.0 ng/mL).

The 35 patients who developed a CEA elevation while under surveillance were found to have developed a noncolorectal CEA-producing malignancy, accounting for their elevated postoperative CEA level. Of these, 12 patients developed lung cancer, 6 developed prostate cancer, 5 developed breast cancer, 5 developed a noncolorectal gastrointestinal malignancy, 3 developed bladder cancer, 2 developed thyroid cancer, 1 developed thymic cancer, and 1 developed endometrial cancer. In these 35 patients, the median peak CEA level after colorectal resection was 9.5 ng/mL, the median interval from time of colorectal resection to time of first elevated CEA level was 1.6 years, and the median time to diagnosis of second malignancy was 2.5 years.

Among the 358 patients with false-positive CEA elevations, the median follow-up time from definitive colorectal resection to last contact was 4.2 years (range, 0.8–10.1 years), and the median follow-up time from first elevated postoperative CEA level to last contact was 2.9 years (range, 0.4–9.5 years). The median lowest perioperative serum CEA level was 3.8 ng/mL (range, 0.7–5.0 ng/mL) and the median peak CEA level during surveillance was 6.3 ng/mL (range, 5.1–5.2 ng/mL).

Also among the 358 patients with false-positive CEA elevations, 111 had only a single elevated CEA measurement, followed by spontaneous normalization with at least 2 consecutive subsequent CEA mearurements. The median peak CEA level in this group was 5.5 ng/mL (range, 5.1–45.2 ng/mL). Of these 111 patients, the peak CEA level was between 5.1 and 10.0 ng/mL in 104 patients (93%), between 10.1 and 15.0 ng/mL in 3 patients (3%), between 5.1 and 20.1 ng/mL in 1 patient (1%), between 25.1 and 30.0 ng/mL in 1 patient (1%), and between 40.1 and 50.0 ng/mL in 2 patients (2%).

A total of 247 patients had CEA elevations documented on 2 or more readings (Table 1). The median peak CEA level during surveillance for these patients with confirmed elevations was 6.7 ng/mL (range, 5.2–34.9 ng/mL). Among these 247 patients, the peak CEA level was between 5.1 and 10.0 ng/mL in 224 patients (91%), between 10.1 and 15.0 ng/mL in 18 patients (7%), between 15.1 and 20.0 ng/mL in 2 patients (1%), between 20.1 and 30.0 ng/mL in 1 patient (0.4%), and between 30.1 and 35.0 ng/mL

Table 1 Range of Highest CEA Levels Recorded During Postoperative Surveillance

Peak CEA (ng/mL)	Patients Without Recurrence and ≥2 Elevated Postoperative CEA Levels (N=247)	Patients Without Recurrence and One-Time Elevation in CEA Level (N=111)	Patients With Recurrence (N=335)	Patients With CEA-Producing Noncolorectal Malignancy (N=35)	Patients With Malignancy (%)
5.1–10.0	224 (90.7%)	104 (93.7%)	79 (24%)	19 (54%)	23
10.1–15.0	18 (7.3%)	3 (2.7%)	35 (11%)	1 (3%)	63
15.1–20.0	2 (0.8%)	1 (0.9%)	21 (6%)	2 (6%)	88
20.1–25.0	1 (0.4%)	0 (0%)	23 (7%)	5 (14%)	97
25.1–30.0	1 (0.4%)	1 (0.9%)	24 (7%)	1 (3%)	93
≥30.1	1 (0.4%)	0 (0%)	153 (46%)	7 (21%)	99
≥35.1	0 (0%)	2 (1.8%)	145 (43%)	7 (21%)	99

Abbreviation: CEA, carcinoembryonic antigen.

in 1 patient (0.4%). No confirmed CEA elevation greater than 35.0 ng/mL was a false-positive.

Table 2 shows the false-positive rates of at least 2 elevated postoperative CEA levels based on CEA cutoffs.

Test Performance Analysis

Because negative results (CEA level ≤5 ng/mL) were not obtained for this study, these were modeled using the sensitivity and specificity of the assay. A cutoff of 10 ng/mL was used because the data necessary for this calculation were available from both the assay package insert (Tosoh) and the current study (MSKCC). The calculation was as follows:

- Sensitivity (Tosoh) at 10 ng/mL: 0.40
- Specificity (Tosoh) at 10 ng/mL: 0.98
- True-positives (MSKCC) at 10 ng/mL: 272
- False-positives (MSKCC) at 10 ng/mL: 23
- False-negatives=true-positives*[1-sensitivity]/sensitivity=272[1.00–0.40]/0.40 = 408
- True-negatives=specificity*false-positives/[1-specificity] = 0.98*23/[1.00–0.98] = 1127

Based on these results, the values at other cutoff points could be determined and a resulting receiver operating characteristic (ROC) curve could be generated (Figure 1). Compared with the package insert, the assay did not perform as well in patients from MSKCC, because the area under the curve is 0.76 for the Tosoh data and 0.67 for the MSKCC data. However, the optimum cutoff would be at a similar point: 7.9 ng/mL for MSKCC (sensitivity, 0.44 and specificity, 0.95) and 8.0 ng/mL for Tosoh (sensitivity, 0.54 and specificity, 0.90). At the cutoff of 5.0 ng/mL used at MSKCC, the sensitivity is 0.54 and the specificity is 0.79.

To better illustrate the difficulty in choosing an appropriate cutoff and why many false-positive results occur at a decision point of 5.0 ng/mL, the number of results at each CEA level was graphed for the patients with and without cancer (Figure 2). The data presented at levels greater than 5.0 ng/mL are the actual results, whereas the data appearing for levels less than 5.0 ng/mL are modeled. This analysis shows that actually more false-positives than true-positives occur at CEA levels up to approximately 10 ng/mL.

Discussion

The role of CEA in monitoring in the care of patients with resected CRC continues to evolve. Earlier efforts in the 1970s and 1980s were focused on attempts to use CEA to identify recurrent disease before it was evident on diagnostic imaging studies. During this period, serious consideration of CEA-directed "second-look" operations was advocated, with the hope that these surgeries might lead to R0 resections of recurrent disease in an early, oligometastatic pattern, and therefore might increase the salvage cure rate. Because the accuracy of diagnostic imaging studies improved and the utility of CEA-directed surgery failed to show benefit and is therefore no longer advocated, the role of CEA monitoring has become more of a means to reduce the frequency and number of CT scans performed, thereby saving

Table 2 False-Positive Rates of Sustained Elevated Postoperative CEAs Based on CEA Cutoffs

Peak CEA Level	Nonrecurrence With ≥2 Elevated Postoperative CEA Levels	Recurrence	Noncolorectal Malignancy	False-Positive Rates
≥5.1 ng/mL	247	335	35	40%
≥10.1 ng/mL	23	256	16	8%
≥15.1 ng/mL	5	221	15	2%
≥20.1 ng/mL	3	200	13	1%
≥25.1 ng/mL	2	177	8	1%
≥30.1 ng/mL	1	153	7	0.6%
≥35.1 ng/mL	0	145	7	0%

Abbreviation: CEA, carcinoembryonic antigen.

the patient from radiation exposure, anxiety, and expense. Therefore, current NCCN Guidelines for Colon Cancer[6] advocate CEA monitoring 2 to 4 times per year, while recommending CT scanning once annually. However, according to these guidelines, an elevation in CEA level leads to a recommendation for additional CT scanning to be performed, and repeated more frequently, until the cause of the CEA elevation is identified (to view the most recent version of these guidelines, visit NCCN.org). Thus, a false-positive CEA level, aside from its obvious anxiogenic potential, results in unnecessary increases in radiation exposure, diagnostic workup, and expense, with no benefit to the patient.

Although false-positive CEA elevations are well-known to occur, their frequency and range have not been previously well characterized. One report by Moertel et al[7] showed a 16% false-positive rate of CEA elevation when a cutoff of 5 ng/mL was used, and a false-positive rate of 4% when 10 ng/mL was used. That study, reported in 1993 and based on data accrued in the 1980s, used scanning that was far less sensitive and accurate than what is currently available.

The present study provides the first large, modern data set for determining the frequency and range of false-positive CEA measurements during the surveillance period. The study focused on patients with stages I–III CRC who underwent R0 resection. The patients in this trial all experienced a complete clinical and serologic response (CEA level ≤5 ng/mL) and then developed an increase in their serum CEA level greater than 5 ng/mL during the postoperative surveillance period. Therefore, the incidence of CEA elevation during the surveillance period was not defined, but rather the patients with new CEA elevations were used as the denominator and the true-positive and false-positive rates assessed within this group. Furthermore, the authors required that patients be followed for at least 1 year after the first sustained elevated CEA level or have a spontaneous normalization with at least 2 consecutive subsequent CEA measurements. Although older literature suggests that CEA elevations may precede clinical evidence of recurrence by as much as 6 to 10 months, these reports are from an era with far less sensitive and accurate scanning techniques, and likely greatly overstate the lead time that CEA monitoring might offer. For this reason, the authors believe that the likelihood a false-positive with 1 year of negative follow-up could still represent a true-positive with insufficient follow-up would be extremely low.

The current findings identified 2 distinct groups of patients with false-positive CEA elevations: those with a single, isolated elevated reading, and those with confirmed CEA elevations. Isolated, one-time elevations in CEA level with spontaneous normalization were considered either transient false-positives from some acute process, or the result of simple laboratory or specimen labeling errors. The frequency of these one-time false-positives—111 of the 358 patients (31%) with false-positive CEA elevations and 111 of the 728 patients (15%) with any CEA elevations—and the finding that 93% of these one-time elevations were low-level elevations of between 5.1 and 10.0 ng/mL support a recommendation to repeat and confirm any abnormal CEA test results with

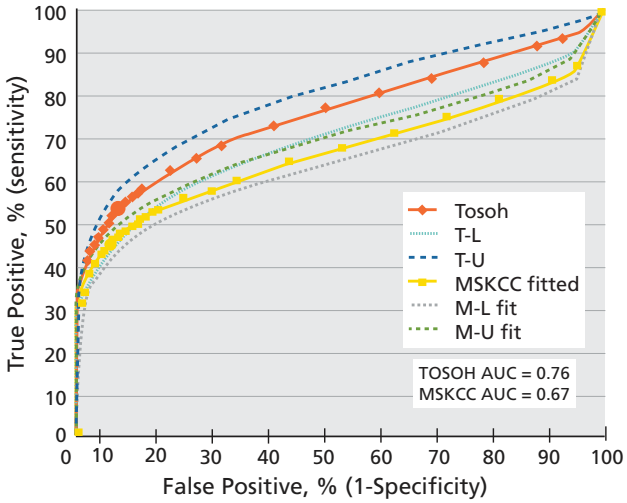

Figure 1 Receiver operating curves (ROC) comparing manufacturer's expected performance with performance at Memorial Sloan-Kettering Cancer Center (MSKCC).
Abbreviations: AUC, area under the curve; CEA, carcinoembryonic antigen; M-L, MSKCC lower (limit of the confidence interval); M-U, MSKCC upper; T-L, Tosoh lower; T-U, Tosoh upper.

measurements less than 10 ng/mL before embarking on further workup.

In patients with a repeated and confirmed CEA elevation, results showed that the confirmed false-positive rate of an elevated sustained CEA level was 40% when the standard CEA cutoff of 5 ng/mL was used, which is far greater than would have been expected based on the limited earlier literature. Hypothetically, if a cutoff of 10 ng/mL were used, the false-positive rate would be reduced to 8%. However, the authors found that 27% of patients with true-positive CEA elevations had a CEA level between 5 and 10 ng/mL when recurrent disease was first seen on a scan, and therefore such a change in the upper limit of normal would likely result in an unacceptable loss in sensitivity.

The authors also found that the most false-positive CEA elevations were in the trace-elevated range of 5 to 10 ng/mL. False-positive CEA levels greater than 15 ng/mL were rare. Furthermore, only 1 of the 247 patients with a confirmed false-positive CEA elevation had a CEA level greater than 30 ng/mL. All sustained CEA elevations greater than 35 ng/mL were associated with actual cancer recurrence. Hence, CEA levels greater than 35 ng/mL seem to be virtually diagnostic of the presence of cancer. This information is potentially useful for patients and doctors in terms of putting the meaning of the CEA elevation into context; the authors do not advocate initiation of chemotherapy or other therapeutic maneuvers based on an abnormal CEA level alone. Recurrent disease should be identified based on diagnostic imaging studies and/or biopsy results before consideration is given to a therapeutic intervention.

This study is not designed to comment on the usefulness of CEA monitoring in terms of the overall management of CRC, and no conclusions on that topic should be drawn. The authors also have no basis for directly evaluating false-negatives, because they did not collect data on how often cancer was found to have recurred in the absence of a CEA elevation. This study does not address the cause or causes of false-positive elevations in CEA, nor was it designed to do so. False-positive CEA elevations have been reported to occur in smokers and in pa-

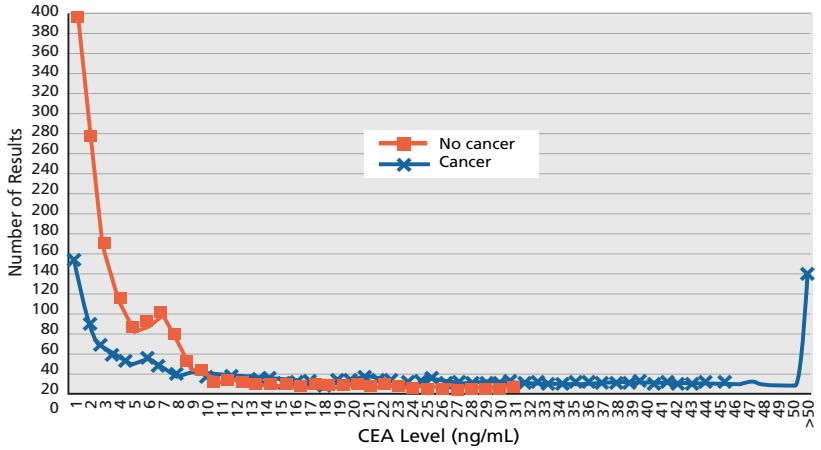

Figure 2 Comparison of results at each carcinoembryonic antigen (CEA) level for patients with and without actual cancer. Levels > 5 ng/mL represent actual data; values < 5 ng/mL are calculated.

tients with nonmalignant conditions, including gastrointestinal disease (eg, inflammatory bowel disease, pancreatitis, liver disease, diverticulitis, hepatitis, peptic ulcers, biliary obstruction, cirrhosis), lung disease (eg, chronic obstructive pulmonary disease, lung infection, pleural effusions), and hypothyroidism. This review of published cases suggests that most of these elevations are modest, with most less than 10 ng/mL. Furthermore, because all patients had a normal perioperative CEA level, chronic conditions such as smoking are unlikely to account for the increase detected in these patients. These data confirm that the likelihood of one of these benign conditions causing CEA elevations greater than 10 ng/mL is exceedingly small,[8,9] and the likelihood of one causing a CEA elevation greater than 35 ng/mL seems too rare to be reportable.

This study suggests that a low-level elevation of CEA between 5 and 10 ng/mL has a substantial likelihood of representing a false-positive elevation. Although some clinicians perform initial repeat CEA testing, this study suggests that confirmation of an ongoing increase in CEA level should be universal practice before an extensive workup is initiated. However, a repeated and confirmed serum CEA level greater than 15 ng/mL is strongly predictive of disease recurrence, and a confirmed serum CEA level greater than 35 ng/mL seems to be virtually diagnostic of the presence of cancer. These data can be used for prognostic purposes, to help set realistic expectations, and to guide individualization of the diagnostic workup for patients with CRC with a new abnormal CEA measurement.

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PostTest Questions

1. NCCN Guidelines for Colon Cancer recommend routine monitoring of CEA levels how often after curative intent resection of CRC in stage II and III patients for the first 2 years?
   a. Not at all
   b. Every 3–6 months
   c. Every 6–12 months
   d. Every 12 months
2. Repeated and confirmed CEA levels >15 ng/mL is strongly predictive of cancer recurrence. Recurrent disease should be confirmed based on diagnostic imaging studies and/or biopsy results before consideration is given to a therapeutic intervention.
   a. True
   b. False
3. Possible effects for patients with false-positive CEA elevation after CRC resection include which of the following:
   a. Anxiety
   b. Unnecessary radiation exposure
   c. Increased expenses
   d. All of the above