CEA Monitoring in Colorectal Cancer

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Carcinoembryonic antigen (CEA) monitoring in patients with stage I-IV colorectal cancer has been, and remains, a controversial issue in oncology practice. Recommendations vary from bimonthly monitoring to no monitoring in the surveillance setting (for stage I-III disease). In the metastatic setting, there are no clear guidelines for CEA follow-up, although continued monitoring in such patients is common in the oncology community. This manuscript reviews the accuracy of CEA testing, its value as a prognostic indicator, and its role in surveillance and response assessment. The limitations of the test in the adjuvant and metastatic settings are illustrated through several case reports from the Colorectal Oncology Clinic at Roswell Park Cancer Institute. Guidelines for CEA monitoring are provided, based on a detailed literature review and institutional experience.

In 1965, Gold and Freedman described an oncofetal antigen expressed in human fetal colonic tissues and in colonic carcinomas but not in adult colon; they named it carcinoembryonic antigen (CEA).[1,2] CEA was subsequently characterized as a glycosylated cell surface glycoprotein with a molecular weight of 180,000 daltons.[3] Variance in CEA glycosylation between normal and tumor tissue explains the difference in reported molecular weights.[4] CEA is detectable in the serum through a radiimmunoassay technique first developed by Thomson et al in 1969.[5] It is present at very low serum concentrations in healthy adults and at high concentrations in a variety of cancers, particularly epithelial tumors.

Sensitivity and Specificity in Colorectal Cancer

A lower limit of normal varies according to the performing laboratory but usually ranges from 2.5 to 5 ng/mL. Serum CEA was < 2.5 ng/mL in more than 87% and < 5 ng/mL in more than 95% of 1,020 subjects attending primary prevention clinics.[6] Elevated CEA levels are more common in smokers and in patients with inflammatory conditions but rarely exceed 10 ng/mL.[7-9] The test can also be elevated in a variety of other carcinomas, including lung, breast, gastrointestinal, and gynecologic cancers.[10]

Detecting Primary Colorectal Cancer

The sensitivity and specificity of CEA depends on the immunoassay in place, the tested patient population, and the performing facility.[11-13] The sensitivity of CEA for early colon cancer patients is low and increases with an increasing stage of the disease. In a study of 358 patients who presented to surgery with a diagnosis of colon cancer, only 4% of patients with stage I disease had an elevated CEA (> 5 ng/mL), whereas 25%, 44%, and 65% of patients with stage II, III, and IV disease, respectively, had abnormal levels.[14] In another study of 319 surgical patients, CEA was elevated in only 26% of resectable patients and in 72% of patients with unresectable or metastatic disease.[15]

Fletcher reviewed the sensitivity and specificity of this test at various stages of disease.[16] The sensitivity was 36% with a specificity of 87% for a CEA > 2.5 ng/mL in patients with stage I and II disease.[16] The sensitivity for stage III and IV disease at similar CEA levels was 74% and 83%, respectively.[16] The sensitivity decreased while the specificity increased for higher CEA cutpoints (5 ng and 10 ng).[16] The poor reliability of this test in early colorectal cancer and the imperfect specificity in the normal population makes this test unsuitable for primary colorectal cancer screening.

Detecting Disease Recurrence

CEA has been studied extensively as a marker for disease recurrence in patients undergoing curative intent resection of a colorectal cancer primary. Patients with resected colorectal cancer should normalize their CEA levels within weeks from surgery, and failure to do so by 4 months is highly suspicious for systemic disease.[17,18] This time frame of a few weeks to several months is...
consistent with an estimated CEA half-life of 3 to 13 days; longer half-lives are associated with higher preoperative CEA levels.[19]

Specificity and sensitivity in detecting disease recurrence depends largely on the definition of abnormal CEA levels (cutoff CEA). The higher the cutoff for abnormal CEA levels, the higher the specificity and the lower the sensitivity.[20,21] Using a CEA cutoff of 5 ng/mL, Moertel and colleagues reported a sensitivity of 34%, specificity of 84%, and median lead time of 4.5 months from detection of clinical recurrence.[22] Interestingly, the sensitivity of CEA depends on the site of recurrence, with sensitivities exceeding 70% for liver and retroperitoneal metastases and lower than 50% for lung, peritoneal, and locoregional recurrences.[22] Solitary lung recurrence was detectable by CEA in only 15% of instances.[22]

Other studies that have imposed strict CEA monitoring guidelines reported higher sensitivity rates. In a follow-up of 311 patients with potentially curative resections of colorectal cancer, CEA was measured every 3 months for 2 years, then every 6 months for 3 years.[20] The sensitivity of CEA in detecting recurrence was 58%, with a median lead time of 6 months. The specificity was the highest for the hepatic metastases group (80%). The specificity, positive predictive value, and negative predictive value were 93%, 79%, and 83%, respectively.[20]

Other investigations have confirmed sensitivities and specificities exceeding 60%.[23-25] The highest sensitivities reported (89% and 91%) were associated with studies implementing frequent CEA monitoring (4 to 8 weeks) with a low abnormal cutoff of 2.5 to 3 ng/mL.[21,26] It is important to note that most studies that evaluated the sensitivity and specificity of CEA in detecting recurrence did not stratify patients according to their preoperative CEA levels (before resection of the original primary). However, there is no evidence at this time that CEA would be a less effective test in detecting recurrences in patients with normal CEA at the time of original diagnosis. In fact, one study evaluated the frequency of elevated CEA upon recurrence in patients with a history of CEA-negative stage III disease (CEA < 5 ng/mL at time of diagnosis).[27] In this report, 44% of patients had an elevated CEA at the time of recurrence, supporting the usefulness of the test in the surveillance of patients with a resected normal- and high-CEA primary.[27]

CEA monitoring is more sensitive in detecting any disease recurrence than liver function tests, ultrasound of the liver, chest x-ray, or colonoscopy.[28-30] Sensitivity was shown to be comparable to computed tomography (CT) scan, but the combination was more effective in detecting recurrences than either modality alone.[21,31] In a surveillance study of 530 patients with resected stage II/III colon cancer, patients underwent a CT scan of the chest, abdomen, and pelvis at baseline, 12 months, and 24 months after initiation of adjuvant chemotherapy. The same patients underwent CEA testing every 3 months during the first year, every 6 months in the second year, and then annually.[31] Overall, 32% of recurrences were detected by CT scan and 29% by CEA. Only 28% of recurrences detected by CT scan showed an abnormal CEA, suggesting that CT scan may offer an added advantage in improving detection of recurrences when added to CEA monitoring.[31]

**CEA as a Prognostic Marker**

Given the positive association between an elevated CEA and the stage of colorectal cancer at time of initial presentation, it is natural to expect a higher risk of relapse in patients with an elevated preoperative CEA level. However, an association between CEA levels and disease outcome has been reported even when controlling for disease stage. A linear inverse correlation between preoperative levels and estimated mean time to recurrence in patients with stage II and III disease has been demonstrated.

Patients with stage III disease had a median time to recurrence of 13 months if preoperative levels were > 5 ng/mL, and 28 months if < 5 mg/mL.[14] Patients with stage II disease were evaluated for outcome based on preoperative CEA level. Patients with CEA < 5 mg/mL had the best outcome, followed by patients with CEA of 5 to 10 ng/mL, and patients with CEA > 10 ng/mL had the worst outcome.[32] A multivariate analysis accounting for nodal metastases and depth of invasion found preoperative CEA elevation (> 5 ng/mL) to be an independent prognostic factor for survival after curative-intent surgery.[33] Another study suggested a similar prognostic value for patients with stage IV disease.[34] Others failed to show a prognostic value for CEA when stage was controlled for.[34,35]

CEA has also been investigated as a prognostic factor in patients undergoing resection of hepatic metastases of colorectal origin. Several large series have shown that an elevated CEA prior to hepatic metastases resection is associated with a higher risk of disease recurrence and decreased overall survival, independent from other prognostic factors such as nodal stage, synchronous disease, and size and number of metastases.[36-41] Others have failed to confirm an association;
however, those series included a small number of patients and were likely underpowered to adequately investigate CEA as a prognostic variable.[42-44]

**CEA Cost-Effectiveness**

Limited data are available regarding the cost-effectiveness of CEA in detecting potentially curable recurrences. In the follow-up of patients receiving adjuvant therapy on a large randomized study of 1,356 patients, 2.2% of resectable recurrences were attributed to CEA screening.[28] The cost of CEA monitoring per detected resectable recurrence was $5,696, comparing favorably to colonoscopies and chest x-rays.[28] A recent study suggests a cost of $25,289 for each surviving patient after surgery for CEA detected recurrence.[45] Others have estimated that CEA costs are $500,000 per patient cured secondary to CEA screening, while some have suggested a range of $22,963 to $4,888,208 per quality-adjusted life-year saved.[46,47] Most estimates would be considered cost-effective when taking into consideration the current costs of treating metastatic colorectal cancer.

**CEA Surveillance Post-Curative-Intent Surgery**

Complete resection of limited colorectal disease recurrence has been associated with a favorable clinical outcome in patients with recurrent disease arising in the liver, lungs, and other sites. Patients undergoing resection of metastatic disease, whether involving liver or lung, have experienced improved 5-year survival rates exceeding 30% in most series.[36-44,48-56] These numbers compare favorably to a 5-year survival of < 10% with combination chemotherapy. This favorable outcome associated with resection has resulted in the embracement of curative-intent resection as a standard approach despite the lack of definitive randomized studies.

It would seem reasonable to assume that earlier diagnosis of recurrent disease, at a time when it is still amenable to resection, would result in a higher rate of resectability, and thus a better chance of long-term survival. Given its sensitivity and specificity in detecting disease recurrence, CEA monitoring has been advocated as a routine surveillance method following primary tumor resection.

**Supportive Evidence**

- Randomized Studies—Although six randomized studies have addressed the issue of intensive vs nonintensive surveillance, none was designed to define the value of CEA monitoring in patients with a resected colorectal primary.[57-62] These randomized studies involved various intervals of follow-up in the intensive and control arms. Furthermore, many of the intensive follow-up arms included CT scans along with CEA as part of the surveillance regimen. Only two studies included CEA in the intense surveillance arm only.[60,62] Both studies showed an increase in curative resections in their intensive screening arms, but only one translated into an improvement in survival.[60,62]

TABLE 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Surveillance Type</th>
<th>Recurrence Rate</th>
<th>Survival Improvement</th>
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<tr>
<td>Secco et al</td>
<td>Scheduled screening (CEA, no CT scans) vs minimal follow-up</td>
<td>2.2%</td>
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Secco et al showed a similar rate of recurrences among patients undergoing scheduled screening (CEA, no CT scans) vs minimal follow-up.[62] However, patients undergoing scheduled screening were more likely to undergo curative resection for local or distant recurrences than patients with minimal follow-up. All but one study showed any increased number of curative resections in patients undergoing intensive screening vs a control arm. Only two studies, however, showed an
improvement in overall survival in favor of intensive screening. A summary of the surveillance regimens, recurrence rates, curative-intent resections, and survival rates are outlined in Table 1. Unfortunately, these data cannot be regarded as conclusive with respect to the value of CEA surveillance due to the presence of multiple other confounding screening variables and the inability to demonstrate a definite survival advantage across all randomized studies.

• Meta-analyses—Given the difficulty in assessing a beneficial role for surveillance in colorectal cancer through individual trials (inadequate power), three meta-analyses have addressed this issue by combining data from randomized and single-arm studies. Bruinvels and colleagues analyzed data from two randomized studies and seven nonrandomized studies, including a total of 3,283 patients. [63] Recurrences were 20% more likely to be resected with curative intent in the intensive screening arm compared to no or minimal follow-up. [63] No difference in overall survival was noted in the more intensive screening arms. However, when only intensive screening arms including CEA monitoring were included, a statistically significant 9.1% improvement in 5-year overall survival was noted. [63]

Rosen et al reviewed two randomized and three comparative cohort studies that included history, physical examination, and at least three CEA tests per year. [64] A total of 2,005 patients were included in the analysis. Survival was improved in the intensive surveillance group (1.16 times more likely to be alive at 5 years, \( P = .003 \)). [64] Patients diagnosed with recurrent disease in the intensely screened arm were more than threefold likely to be alive at 5 years, compared to the less intensely screened arm (\( P = .0004 \)). [64]

Renehan and coworkers included a meta-analysis of five randomized studies comparing intense follow-up with less intense or minimal follow-up. [65] Recurrences were diagnosed in the intense follow-up arms at an average of 8.5 months earlier than the control arms. [65] Furthermore, there was evidence of an increased detection rate of isolated metastases in the intensely monitored arms, thus increasing the likelihood of curative-intent surgeries. [65] This meta-analysis, again, showed a statistically significant survival benefit in patients screened intensely, compared with a less intense regimen. [65]

These meta-analyses confirm that intensive screening including CEA monitoring is associated with an improved outcome and a better chance of resectability of recurrent disease. It is impossible from these studies to quantitate the benefit obtained from CEA monitoring alone, compared to the other modalities used in follow-up. However, given the high sensitivity and specificity of CEA compared to other modalities of screening, it is likely that the benefit noted is in large part attributable to CEA monitoring.

• Other Supporting Evidence—Other retrospective analyses support a role for CEA surveillance in improving resectability and outcome of patients with recurrent disease. In a retrospective study of 285 resected colorectal cancers, 62 patients were identified as having a recurrence based on CEA monitoring. [66] Of all patients with recurrences identified by CEA monitoring, 11 (18%) were able to undergo curative-intent resections, 3 of whom were disease-free more than 5 years after resection. [66] This is in line with a recent study confirming a resectability rate of 17.8% in patients with recurrent disease detected by CEA monitoring. [31] In contrast, a resectability rate of only 3% was found in patients diagnosed with recurrent disease based on symptoms. [31] A retrospective analysis of 211 patients with liver metastases presenting for evaluation for resection showed a resectability rate of 51.3% in patients diagnosed upon a rise in CEA vs 28.1% in those diagnosed based on symptoms. [67]

• Summary of Existing Data—Although no single large randomized study has convincingly shown a role for CEA in improving overall survival, the overall evidence points to an increased resectability rate in patients undergoing CEA monitoring. It has been clearly shown, through the outcome analysis of a large intergroup study, that patients with recurrent disease who undergo salvage surgery experience an improved overall survival in comparison to unresectable patients. [68] Patients with recurrent disease undergoing resection had a 5-year-survival rate of 27% vs only 6% in the nonresected cohort. [68] The improved outcomes found in that study are in line with other retrospective series of resected hepatic and pulmonary metastases detailed above.
Based on the improved recurrence detection and improved resectability associated with CEA monitoring, it is recommended that patients undergo CEA surveillance after their primary tumor resection. No studies have adequately addressed the frequency of CEA monitoring, although the majority have implemented an every-3-to-4-month schedule for the first 2 years with less frequent monitoring in subsequent years. The increased frequency of CEA testing in the first 2 years is supported by a higher risk of recurrence during that period.[69] It is unlikely that CEA surveillance for more than 5 years would result in added benefits, as the risk of recurrence beyond that time point is considered minimal. Table 2 summarizes the current CEA screening guidelines recommended by the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the National Comprehensive Cancer Center Network (NCCN).

### Pitfalls in CEA Surveillance After Curative-Intent Resection

#### FIGURE 1

**CEA Surge During Chemotherapy**

Transient elevations in CEA have been noted in patients with resected colorectal cancer during adjuvant therapy. Figure 1 illustrates a surge in CEA during adjuvant bolus fluorouracil (5-FU) therapy in a patient with a resected rectal cancer. The surge in this case lasted for several weeks and resolved spontaneously; the patient remains free of disease more than 1 year later. In the follow-up of 1,017 patients with resected colon cancer, Moertel et al described a 16% false-positive rate of CEA elevation when a cutoff of 5 ng/mL was used and a 4% false-positive rate when 10 ng/mL was used.[22] This was attributed to 5-FU and levamisole in the majority of cases.[22] These findings are consistent with preclinical data demonstrating an increased expression of CEA in response to chemotherapy exposure when agents such as 5-FU and platinum drugs are used.[70,71]

#### FIGURE 2

**Transient Increase in CEA With Vaccine Therapy**

Similar CEA surges can be seen with immunologic therapy. Figure 2 depicts a transient increase in CEA during adjuvant CEA anti-idiotype vaccine treatment several months after resection of hepatic metastases. The patient had subsequent spontaneous normalization of CEA and remains free of disease recurrence.

Given the possibility of false-positivity of CEA levels during the surveillance of patients with resected colorectal primary or resected metastatic disease, it is prudent to confirm an ongoing rise in CEA prior to the initiation of an extensive disease recurrence work-up. The degree in CEA rise is important in estimating the likelihood of false-positivity: Elevations of more than 15 ng/mL are unlikely to reflect anything but disease recurrence.[22]

### CEA in Monitoring Treatment of Advanced Colorectal Cancer

More than 70% of patients with advanced colorectal cancer have elevated CEA levels.[15] In patients with baseline CEA elevation prior to the initiation of chemotherapy, the antigen may serve as a
valuable marker with which to assess response to treatment. CEA changes have been shown to predict response in several studies. For example, in a study of 33 patients undergoing 5-FU-based chemotherapy, the positive-predictive value of CEA was 54% for a partial response, 77% for minor and partial responses combined, and 100% for progressive disease.[72]

In a larger study of 136 patients receiving fluoropyrimidine therapy, the sensitivity of CEA in predicting a radiographic response was 72%, and in predicting progressive disease, 81%.[73] The positive-predictive value of CEA response for a true radiographic response was 53%, and for progressive disease, 85%.[73] Patients with a CEA response had a significantly better outcome that those without.[73] In general, CEA is not a perfect predictive test of response or progressive disease and should not be used as the sole basis for decision-making when other means of assessing radiographic tumor response are available.[74,75] The ASCO guidelines state that there is insufficient evidence to recommend the routine use of CEA alone for monitoring response to chemotherapy.[76] In the absence of radiologic assessments, ASCO has defined a rise in CEA on two subsequent occasions (2 months apart) as an indication of progressive disease.[76]

Limitations of CEA Monitoring

To illustrate the limitations of CEA in monitoring colon cancer response to chemotherapy, we show CT scans of a patient with progressive colorectal metastatic disease in association with a drop in CEA (Figure 3). Such a decrease in CEA may be attributed to tumor dedifferentiation or to the selection of non-CEA-producing resistant clones with chemotherapy treatment. If treatment decisions in this patient were made solely on the basis of CEA monitoring, no change in chemotherapy would have been instituted. Similarly, significant elevations in CEA are not always indicative of progressive disease. We have previously documented a rise of more than 20% followed by a drop of more than 20% compared to baseline in 10 out of 89 patients with metastatic colorectal cancer followed with CEA and CT scans.[77] All 10 patients with a CEA surge derived a clinical benefit without a change in chemotherapy.[77]

CEA Surge on FOLFOX Therapy

Figure 4 illustrates a case of CEA surge on FOLFOX therapy (5-FU, leucovorin, oxaliplatin [Eloxatin]) associated with a marked radiographic and clinical benefit and a time to progression exceeding 6 months, without a change in chemotherapy dosing or schedule. Of note, none of our documented CEA surges lasted more than 4 months, and thus, none would have been consistent with the definition of CEA progression as defined by ASCO. However, one case of CEA surge lasting beyond 4 months and associated with a radiographic response has been previously reported.[78]

CEA monitoring in the metastatic setting has significant limitations and should not be the sole guide in decision-making. Radiographic assessment is the most dependable way of monitoring tumor response and should overrule CEA in guiding physicians in their treatment decisions. In the presence of measurable disease and adequate radiographic follow-up, we do not see a clear role for CEA monitoring. At best, a rise in CEA in the presence of measurable disease should guide the physician to repeat radiographic staging rather than discontinue treatment. CEA may be more helpful in the monitoring of patients with minimal peritoneal disease when CT scans have shown limited sensitivity.

Conclusions
CEA monitoring is helpful in detecting early recurrences in patients with resected colorectal cancer. Early detection of disease recurrence will enhance the chances of curative intent resection, resulting in a positive impact in a select patient population. The percentage of patients rendered curable secondary to CEA monitoring is likely less than 5% based on the reviewed literature. Thus, a definite impact on overall survival is unlikely to be detected unless a large randomized study addressing this issue is conducted.

**REFERENCE GUIDE**

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<tr>
<td>Fluorouracil (5-FU)</td>
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<td>Levamisole</td>
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<td>Oxaliplatin (Eloxatin)</td>
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The current evidence from randomized studies and meta-analyses evaluating intensive surveillance (including CEA) suggests a benefit from screening all patients with resected colorectal cancer who have no medical contraindication for potential future metastectomies. Given the higher rate of recurrence during the first 2 years following resection, we advise CEA testing every 3 months in the first 2 years and every 6 months for another 3 years, as recommended by the NCCN. We caution, however, that the possibility of false-positivity must be considered during adjuvant therapy and vaccine studies. In those particular settings, we recommend repeat testing at least 2 weeks after the initial elevation to confirm an ongoing rise before the initiation of expensive and extensive work-up. In the metastatic setting, we do not see a definite role for CEA monitoring in the presence of adequately measurable lesions. If obtained in the metastatic setting, CEA testing should be regarded as complementary to radiographic monitoring and should not be the sole basis for decision-making. A surge in CEA in the first 2 to 4 months after chemotherapy initiation is not uncommon in patients treated with combination chemotherapy and, unless associated with an increase in radiographic tumor measurement, should not result in a change in chemotherapy. Furthermore, a drop in CEA can occasionally be associated with disease progression, which reinforces routine radiographic restaging even in the face of a CEA response. In the presence of nonmeasurable advanced disease requiring therapy (such as nonmeasurable carcinomatosis), a CEA rise on at least two occasions and at least 2 months apart almost always indicates progressive disease.

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**References:**


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