Current Surveillance After Treatment is Not Sufficient for Patients With Rectal Cancer With Negative Baseline CEA

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ABSTRACT

Background: Serum CEA has been widely used to screen for potential recurrent disease after resection in rectal cancer. However, the influence of baseline CEA on the performance of CEA in recurrence surveillance needs to be investigated. Patients and Methods: This longitudinal cohort study included 484 patients with nonmetastatic rectal cancer from 18,013 patients in a prospectively enrolled institutional database program of colorectal disease. Baseline CEA levels were determined before treatment, and CEA-based follow-up tests and examinations were applied in the surveillance after treatment. Results: A total of 62.6% (62/99) overall, 53.5% (23/43) local, and 64.9% (50/77) distant recurrences were seen in patients who had similar CEA levels with their baseline statuses. The sensitivity of elevated CEA levels during surveillance for overall recurrence was significantly lower in patients with negative baseline CEA than in those with elevated baseline CEA levels (41.3% vs 69.4%; P = .007). Moreover, similar results were observed in the surveillance for local (50% vs 61.5%; P = .048) and distant (39.6% vs 72.4%; P = .005) recurrences between these 2 patient groups. However, CEA had comparable and excellent specificity during surveillance for recurrent disease in these groups. The addition of CA19-9 to the CEA assay significantly improved the sensitivity in recurrence surveillance for patients with negative baseline CEA (49.2% vs 41.3%; P = .037). Finally, we identified a subgroup of CEA-turn recurrences characterized by negative CEA at baseline, elevated CEA at recurrence, and worse survival outcomes after recurrence (hazard ratio, 1.88; 95% CI, 1.07–3.30; P = .026). Conclusions: In patients with rectal cancer with negative baseline CEA, serum CEA had insufficient sensitivity in recurrence surveillance after treatment, and additional surveillance may improve oncologic outcomes. Baseline CEA should be considered before CEA-based surveillance can be applied in the follow-up trials.

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Background

Colorectal cancer (CRC) is one of the most common cancers and is a leading cause of cancer-related mortality worldwide.1,2 Approximately 25% to 40% of patients will develop recurrent disease after a curative resection with systemic therapies, which largely contributes to death from CRC.3 Previous studies reported that an intensive surveillance protocol could shorten the time to detect recurrent disease and increase the rate of curative treatment in recurrent disease.4,5 Moreover, one study showed that patients under strict surveillance after treatment had 5-year recurrence-free survival rates that increased from 69% to 94%.6 These studies indicate that early detection of recurrent disease is of significance in improving the overall survival (OS) of patients with rectal cancer.

According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer (Version 2.2021),7 serum CEA is a crucial test in surveillance for rectal cancer after treatment, and serial CEA elevation is regarded as a strong marker of potential recurrence that requires more examination or intensive surveillance to confirm it. Briefly, when CEA level is elevated during surveillance, recurrent disease should be suspected, and colonoscopy or radiographic examination, including CT and PET, is recommended to confirm the recurrent disease. However, rectal cancer is heterogeneous at the molecular and cellular levels, and there exists a considerable heterogeneity in the expression of several molecules, including CEA.8 Approximately 70% of colorectal tumors consist largely of CEA-negative cell lines, and they are documented to have scarce or no CEA secretion,9 which is consistent with previous findings that CEA-negative tumors constitute 49% to 75% of CRCs.10–13 Therefore, we speculated that the recurrent disease that develops from primary tumors with negative CEA tends to sustain a low serum CEA level in surveillance tests and that the role of

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CEA in surveillance for patients with negative baseline CEA needs to be evaluated with a cohort study.

Considering that the patients with recurrent disease are likely to have CEAs consistent with their baseline status, we hypothesized that the performance of elevated CEA in surveillance for recurrent disease may vary in patients with different baseline CEA, and the early detection of recurrence is more difficult in patients with negative baseline CEA owing to the limited sensitivity of CEA in screening potential recurrent tumors before relevant symptoms or radiologic findings can be observed with current surveillance protocols. Therefore, we conducted a longitudinal analysis based on the prospectively collected and maintained cohort of patients with rectal cancer to determine the diagnostic performance of CEA in surveillance for patients with different baseline CEA.

Patients and Methods

Patient Cohorts

This study was conducted based on the longitudinal analysis of patients that originated from the institutional database program of colorectal disease (IDPCD) at the Sixth Affiliated Hospital of Sun Yat-sen University. The IDPCD has prospectively enrolled and followed 18,013 patients with CRC since 2007. The IDPCD cohort integrated the patients from the National Basic Research Program of Evolution from Precancerous Disease to Cancer and the National Key Research and Development Project of CRC Screen, Surveillance, and Intervention.

The patients’ disposition flow and timeline for the longitudinal analysis in this study are described in Figure 1. Briefly, patients with histologically confirmed stage I–III rectal cancer who underwent a curative-intent resection from June 2007 through June 2012 were included. The selection of this time interval permitted an adequate follow-up. Patients who received prior anticancer treatment, underwent a noncurative resection, had concurrent cancer other than CRC, had hereditary cancer disease, lacked information about clinical and follow-up tests, and had a history of nonmalignant chronic conditions, including inflammatory bowel disease, hepatic insufficiency, peptic ulcers, end-stage lung disease, and hypothyroidism, were excluded. Patients were staged according to the seventh edition of the AJCC Cancer Staging Manual based on pelvic MRI and CT imaging.

Measurement of Tumor Markers

CEA and CA 19-9 levels were determined according to the standard protocol in the clinical laboratory setting. The reference range was 0 to 5 ng/mL for CEA and 0 to 37 ng/mL for CA19-9 in the test for CRC, as previously described. Baseline CEA was obtained at the time of diagnosis and surveillance CEAs were obtained during follow-up until the confirmed recurrence or last follow-up. According to the reference range, patients with rectal cancer were divided into negative and elevated CEA groups at baseline or during surveillance. Patients with “CEA-turn” recurrent disease were defined as those with negative CEA at baseline and elevated CEA when recurrent disease was confirmed.

Treatment and Surveillance Protocol

According to the institutional standard protocols for CRC management based on the NCCN Guidelines, patients in the IDPCD cohort were treated and followed up with the details described in previous publications. Briefly, patients were followed up every 3 to 6 months for the first 2 years after surgery and every 6 months for the next 3 years. Routine visits consisted of pertinent medical history, physical examination, and measurement of serum CEA and CA19-9 levels. Radiologic examinations consisting of chest and abdominopelvic CT were scheduled every 6 to 12 months after surgery for a total of 5 years, and colonoscopy was scheduled 1 year after surgery and repeated in 1 to 3 years. If an elevated CEA level was found, then the serum CEA assays would be repeated within 1 week. Patients with sustained elevated CEA were followed intensively to ensure no delay in the diagnosis of recurrence, and those with elevated CEA that returned to a normal level in the following serial tests were treated as having no evidence of recurrence. Radiologic images were carefully reviewed, and a definitive diagnosis of local or distant recurrence was established based on the appearance of new lesions on CT, MRI, or PET images and/or histologic confirmation with biopsy. Overall recurrence in this study referred to local recurrence and/or distant recurrence after curative resection. The primary endpoints were disease-free survival (DFS), postrecurrence survival (PRS), and OS. DFS was calculated from the date of curative resection to the date of recurrence, death, or last follow-up. PRS was defined as the time from confirmed recurrence to death or last follow-up. OS was defined as the time from curative resection to death.

Statistical Analysis

Continuous variables were described as median (interquartile range) and were compared using the Mann-Whitney U test because of their abnormal distribution. Categorical variables were reported as numbers with percentages, and they were assessed using the chi-square test or the Fisher exact test where appropriate. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated and used to examine the performance of CEA or CA19-9 in the
surveillance for recurrent disease. The performance of surveillance was compared between patients with negative and elevated baseline CEA using the Pearson chi-square test. For follow-up data, the date of death or last follow-up was recorded. DFS, PRS, and OS rates were calculated using the Kaplan-Meier method, and group comparisons were performed using a log-rank test. Univariate survival analysis for OS was evaluated using a Cox proportional hazards model. Data analyses were performed using SPSS statistics, version 22 (IBM Corp), GraphPad Prism 8 (GraphPad Software), and R version 3.5.1 (R Project, Institute for Statistics and Mathematics). A 2-sided \( P \) value <.05 was considered statistically significant.

The study protocol was reviewed and approved by the Institutional Review Board of The Sixth Affiliated Hospital of Sun Yat-sen University (number 2017ZSLYEC-006). Written informed consent was obtained from all patients or their representatives for study participation. The study was performed in accordance with the Declaration of Helsinki.

**Results**

**Patient Characteristics**

A total of 484 patients with rectal cancer were included in this study; 279 were male and 205 were female, with a median age of 58 years. TNM staging among patients was distributed as 26.7%, 32.6%, and 40.7% for stages I, II, and III, respectively. A total of 52.3% of patients received adjuvant chemotherapy after R0 resections. With a median follow-up period of 52.0 months, overall,
local, and distant recurrences were detected in 99 (20.5%), 43 (8.9%), and 77 (15.9%) patients, respectively. Demographic and clinicopathologic features of the entire cohort are shown in Table 1. Among the 484 patients, 350 (72.3%) had negative baseline CEA and 134 (27.7%) had elevated baseline CEA. Overall, the patients with elevated baseline CEA were characterized as having more aggressive clinicopathologic characteristics; they were also older (P = .017) and presented with a more advanced TNM stage, deeper tumor infiltration, and more regional lymph node metastasis (all P < .05). The proportions of patients with low tumor differentiation (22.4% vs 14.0%; P = .043), mucinous and signet-ring rectal carcinoma (20.1% vs 12.0%; P = .022), perineural invasion (13.4% vs 6.3%; P = .011), and elevated baseline CA19-9 levels (22.4% vs 8.6%; P < .001), and who needed perioperative blood transfusion (20.9% vs 13.1%; P = .034) were significantly higher in the group with elevated baseline CEA levels than

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Population</th>
<th>Baseline CEA</th>
<th>P Value*</th>
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<tr>
<td>Total, n</td>
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<td>350</td>
<td>134</td>
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<tr>
<td>Age, median (IQR), y</td>
<td>58 (50–68)</td>
<td>58 (48–67)</td>
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<td>Sex</td>
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<td>Male</td>
<td>279 (57.6)</td>
<td>198 (56.6)</td>
<td>81 (60.4)</td>
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<td>205 (42.4)</td>
<td>152 (43.4)</td>
<td>53 (39.6)</td>
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<td>&lt;5</td>
<td>175 (36.2)</td>
<td>129 (36.9)</td>
<td>46 (34.3)</td>
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<td>5–12</td>
<td>296 (63.8)</td>
<td>209 (63.1)</td>
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<td>TNM stage</td>
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<tr>
<td>I</td>
<td>129 (26.7)</td>
<td>115 (32.9)</td>
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<td>108 (30.9)</td>
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<td>III</td>
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<td>2</td>
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<td>49 (14.0)</td>
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<td>High</td>
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<td>325 (92.9)</td>
<td>123 (91.8)</td>
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<td>Perineural invasion</td>
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<tr>
<td>Negative</td>
<td>444 (91.7)</td>
<td>328 (93.7)</td>
<td>116 (86.6)</td>
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<tr>
<td>Positive</td>
<td>40 (8.3)</td>
<td>22 (6.3)</td>
<td>18 (13.4)</td>
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(continued on next page)
the group with negative CEA. Furthermore, patients with elevated baseline CEA had significantly higher incidences of overall recurrence (26.9% vs 18.0%; \( P = .031 \)) and distant recurrence (21.6% vs 13.7%; \( P = .033 \)).

CEA Monitoring in Recurrence Surveillance After Treatment

Overall, 62.6% (62/99) of patients with recurrent disease presented with a CEA level similar to that of their primary disease at baseline. In the longitudinal analysis of the 36 patients with recurrent disease and elevated CEA at baseline, 25 (69.4%) had elevated levels during surveillance before the recurrent disease was confirmed. Similarly, in the 63 patients with recurrent disease and negative CEA at baseline, 37 (58.7%) presented with sustained negative CEA during surveillance, whereas the other 26 (41.3%) in the CEA-turn group had elevated CEA during surveillance before the recurrent disease was confirmed. Interestingly, when we stratified the overall recurrence outcomes by local and distant sites, 53.5% of patients (23/43) with local recurrence and 64.9% (50/77) with distant recurrence had a CEA level consistent with their primary disease at baseline.

To investigate the diagnostic performance of elevated surveillance CEA for recurrent rectal cancer, we analyzed the difference in sensitivity, specificity, PPV, and NPV between the negative and elevated baseline CEA groups. As shown in Figure 2, elevated surveillance CEA had an equivalent excellent performance in specificity, PPV, and NPV for predicting recurrence between the 2 groups, whereas the sensitivity for the detection of recurrent disease varied in patients with negative versus elevated CEA. The sensitivity of elevated CEA during surveillance for overall recurrence in patients with negative baseline CEA was significantly lower than that in patients with elevated baseline CEA (41.3% vs 69.4%; \( P = .007 \)). Moreover, similar results could be observed in the surveillance for local (50.0% vs 61.5%; \( P = .048 \)) and distant (39.6% vs 72.4%; \( P = .005 \)) recurrence.

Additional Surveillance With CA19-9 Assay

Next, we sought to investigate whether addition of the CA19-9 assay to the CEA assay would improve surveillance for recurrence in patients with negative baseline CEA levels. In the CEA/CA19-9 surveillance assay, patients were assigned to the CEA/CA19-9–elevated group if they had any elevated CEA and CA19-9 levels. As shown in Figure 3, the CEA/CA19-9 surveillance assay could increase the sensitivity in diagnosing overall recurrence (49.2% vs 41.3%;
and distant recurrence (50.0% vs 39.6%; \(P = .030\)) compared with the CEA assay alone, respectively. The CEA/CA19-9 assay tended to be more sensitive than the CEA assay alone in surveillance for local recurrence, although no statistical significance was found. Unexpectedly, addition of the CA19-9 assay could not improve the surveillance performance of CEA in patients with elevated baseline CEA levels (supplemental eFigure1, available with this article at JNCCN.org).

Survival Outcomes of Patients With Different Baseline and Surveillance CEA Levels

Not surprisingly, patients with elevated CEA levels at baseline had significantly worse OS (hazard ratio [HR], 2.33; 95% CI, 1.51–3.61; \(P < .001\)) and DFS (HR, 1.83; 95% CI, 1.27–2.62; \(P < .001\)) compared with those with negative baseline CEA (supplemental eFigure 2A, B). Moreover, patients with elevated CEA during surveillance showed strikingly worse OS (HR, 10.70; 95% CI, 3.88–16.65; \(P < .001\)) and DFS (HR, 11.86; 95% CI, 8.14–17.27; \(P < .001\)) compared with those with negative CEA during surveillance (supplemental eFigure 2C, D). Next, we performed subset analyses to determine whether the association of surveillance CEA with survival would be affected by baseline CEA. We observed that the association remained in the negative and elevated baseline CEA cohorts (supplemental eFigure 2E–H). Notably, this association was stronger in the patients with negative baseline CEA. Therefore, we defined this subgroup of patients as the CEA-turn group and further analyzed their survival outcomes after recurrence confirmation. As a result, we found that patients in the CEA-turn group had worse PRS compared with other patients (HR, 1.88; 95% CI, 1.07–3.30; \(P = .026\); Figure 4). This result indicated that patients in the CEA-turn group had aggressive recurrent disease with an unfavorable prognosis.

Discussion

This study specifically focused on the performance of serum CEA in recurrence surveillance for patients with nonmetastatic rectal cancer stratified by baseline CEA. The main findings were that elevated CEA levels during surveillance presented with insufficient sensitivity but comparably excellent specificity, PPV, and NPV for the detection of recurrence in patients with negative baseline CEA compared with those with elevated baseline CEA. In our longitudinal analysis, most patients with recurrent disease presented with a CEA level similar to that of their baseline status before treatment, whereas a subgroup of
patients with recurrent disease had CEA-turn disease that had significantly worse survival outcomes after recurrence. Our findings support the current CEA-based surveillance protocols for patients with elevated baseline CEA. However, we recommend that the role of CEA in recurrence surveillance for patients with negative baseline CEA should be reconsidered, and additional surveillance assays and examinations, including CA19-9 assay, medical visit, and radiologic imaging, should be applied to avoid a delayed diagnosis of recurrent disease. These results may provide a valuable reference for developing and interpreting the next-generation surveillance protocols for rectal cancer in clinical guidelines.

Consistent with our hypothesis, most patients with recurrent disease presented with a CEA level similar to that of their baseline status, which would impair the performance of CEA in surveillance for recurrence after treatment in patients with negative baseline CEA. Interestingly, some patients had distinct CEA levels when recurrent disease developed. Among them, those in the CEA-turn group were recognized as having a subgroup of aggressive diseases with worse survival outcomes after recurrence. The CEA-turn recurrence was characterized by negative CEA at baseline and elevated CEA at recurrence, indicating a distinction between recurrent and primary tumors. We speculate that the unfavorable clinical outcome of CEA-turn recurrence may derive from cancer evolution with cell reprogramming and clonal expansion of dominant cells. Sequencing-based studies would be helpful to uncover the change in the molecular signature in tumor recurrence and understand CEA-turn disease.

Since shortly after the first report on CEA in 1965, CEA has been the most widely accepted surveillance tool in patients with CRC after curative resection because of its noninvasive, standardized, and cost-effective measurement. The most updated NCCN Guidelines for rectal

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**Figure 3.** (A) Sensitivity, (B) specificity, (C) PPV, and (D) NPV of CEA/CA19-9 surveillance assay for diagnosing overall and distant recurrence in patients with negative baseline CEA. A CEA/CA19-9 assay was recognized as a positive when a patient had any elevated CEA and CA19-9 levels. Abbreviations: DR, distant recurrence; LR, local recurrence; NPV, negative predictive value; OR, overall recurrence; PPV, positive predictive value. *The differences in sensitivity between these groups were considered statistically significant (P<.05).
These previous studies did not assess sensitivity in patients with negative baseline CEA. By collecting the data at baseline and surveillance timepoints and using longitudinal cohort analysis, we found that elevated CEA during surveillance presented insufficient sensitivity for detecting overall, local, and distant recurrence in patients with negative baseline CEA. Our findings were supported by a Japanese study of 106 patients with recurrent CRC, in which a CEA assay with a cutoff value of 5 ng/mL had sensitivities of 44.1% and 75.0% in diagnosing recurrence in patients with negative and elevated baseline CEA, respectively.12 Therefore, we propose a surrogate surveillance protocol characterized by an increased frequency of medical visits for relevant signs or symptoms, colonoscopy, and radiologic examinations in patients with negative baseline CEA levels (Figure 5).

Elevated CEA levels during surveillance may originate from recurrent tumors in local or distant organs. Therefore, we stratified the overall recurrence outcomes by local and distant sites. We found that the distant recurrences had more patients with CEA levels consistent with their primary tumors than did the local recurrences. In addition, the sensitivity for distant recurrence declined more than it did for local recurrence when patients with negative baseline CEA were isolated to analyze. These results suggest that CEA monitoring performed with less sensitivity in surveillance for distant recurrence among patients with negative baseline CEA.

There is substantial evidence showing that intensive surveillance of patients with resected CRC results in early detection of recurrence, although survival outcomes are not significantly improved.4,5,36,37 Considering that patients with negative CEA represent a large proportion of those with CRC,10–13 we speculate that when CEA assay is reconsidered, and additional assays and examinations are applied for patients with negative CEA in future follow-up trials, the early detection of recurrence with improved survival

Figure 4. PRS outcomes of patients in the CEA-turn group and other patients. Kaplan-Meier curves of PRS for patients with negative CEA at baseline and elevated CEA when recurrent disease was confirmed (CEA-turn group) and other subgroups (non–CEA-turn group) with recurrent disease.

Abbreviations: HR, hazard ratio; PRS, postrecurrence survival.

Surveillance

- History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/Abdominal/Pelvic CT/MRI every 6–12 mo for a total of 5 y
- Colonoscopy in 1 y after surgery, repeat in 3 y, then every 5 y

Elevated baseline CEA

Figure 5. Suggested surveillance protocols based on baseline serum CEA level. The current surveillance protocols for patients with rectal cancer should be further stratified based on the baseline CEA level. An additional CA19-9 assay, other verified assays, and intensive medical visits and radiologic examinations are recommended for surveillance in patients with negative baseline CEA.
surveillance performance of CEA in patients with rectal cancer. Therefore, we propose a new and more efficient surveillance protocol for patients with rectal cancer in the clinical setting. We recommend that the baseline CEA level should be considered and stratified before CEA can be applied in the surveillance protocol of the NCCN Guidelines. Considering the insufficient sensitivity of CEA for recurrence surveillance in patients with negative baseline CEA, this subgroup of patients may obtain a survival benefit from the additional surveillance, including a CA19-9 assay, medical visit, and radiologic imaging.

Conclusions

Serum CEA level has insufficient sensitivity for recurrence surveillance after treatment in patients with negative baseline CEA. Based on our findings, we propose a new and more efficient surveillance protocol for patients with rectal cancer in the clinical setting. We recommend that the baseline CEA level should be considered and stratified before CEA can be applied in the surveillance protocol of the NCCN Guidelines. Considering the insufficient sensitivity of CEA for recurrence surveillance in patients with negative baseline CEA, this subgroup of patients may obtain a survival benefit from the additional surveillance, including a CA19-9 assay, medical visit, and radiologic imaging.

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Outcomes will be observed. In addition, crowdsourcing-based and patient-reported symptoms that we are currently collecting could be included as a part of the medical visit in the future follow-up trial for early detection of recurrent disease and reducing cancer-specific mortality.

It is well-known that elevated circulating CEA levels can also be found in some benign statuses and inflammation-derived diseases, such as COVID-19, and the specificity of CEA for diagnosing primary gastrointestinal tumors is limited. Interestingly, elevated CEA levels showed excellent specificity and NPV in surveillance for both local and distant recurrence in our entire cohort and each subgroup (all >85%). Our findings support the role of elevated CEA during surveillance as a strong and specific marker for potential recurrent diseases that require a further physical examination, colonoscopy, or radiographic scan in the current surveillance protocols for both patients with negative CEA and those with elevated CEA levels.

CA19-9 is currently one of the most widely used biomarkers for gastrointestinal tumors, including biliary and pancreatic cancers. Previous studies have reported that postoperative CA19-9 is a valuable marker for monitoring lung and liver metastasis, and can also be used as an additional marker to monitor recurrent disease in patients with CRC. In our cohort, patients were followed up with surveillance protocols including both CEA and CA19-9 assays. We found that the addition of CA19-9 could improve the surveillance performance of CEA in patients with rectal cancer with negative baseline CEA. Notably, the sensitivity increased from 41.3% to 49.2% after the CA19-9 assay was added, although it was not significant when compared with the CEA assay alone in patients with elevated baseline CEA. Although few markers for recurrence surveillance in CRC have been investigated in randomized trials or meta-analyses, we anticipated that the addition of other verified markers or the application of surrogate marker assays could further improve the surveillance performance. Furthermore, we did not observe an improving effect of the CA19-9 assay in patients with elevated baseline CEA. Therefore, we propose an updated surveillance protocol in which the CEA alone and the combined CEA/CA19-9 assays are recommended for surveillance in patients with elevated and negative baseline CEA levels, respectively (Figure 5).

Although a longitudinal cohort study with sufficient patients could provide robust evidence to support our findings, the analysis of a follow-up trial with arms that prospectively test enrolled patients according to pre-determined protocols may decrease the impact from the heterogeneity of time to recurrence detection. Our study suggests that baseline CEA should be considered in the design of future trials with CEA-based follow-up tests to achieve reliable results.

References


Supplemental online content for:

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**eFigure 1:** Surveillance Performance of CEA/CA19-9 Assay in Patients With Elevated Baseline CEA Levels

**eFigure 2:** Survival Outcomes of Patient Groups by Baseline and Surveillance CEA Levels
eFigure 1. Surveillance performance of CEA/CA19-9 assay in patients with elevated baseline CEA levels. No significantly improved sensitivity was found in recurrence surveillance for patients with elevated baseline CEA after CA19-9 was added to the CEA assay. Abbreviations: DR, distant recurrence; LR, local recurrence; OR, overall recurrence.
eFigure 2. Survival outcomes of patient groups by baseline and surveillance CEA levels. Kaplan-Meier curves of OS and DFS for different (A, B) baseline CEA levels and (C, D) surveillance CEA levels in all patients. Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

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Survival outcomes of patient groups by baseline and surveillance CEA levels. Kaplan-Meier curves of OS and DFS for different surveillance CEA in patients with (E, F) negative baseline CEA level and (G, H) elevated baseline CEA level. Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival.