CEA Dynamics for Prediction of Response after Anti-EGFR Monoclonal Antibodies Treatment in Metastatic Colorectal Cancer

Sora Kang
Chungnam National University Hospital
Sun Young Kim
Asan Medical Center
Yong Sang Hong
Asan Medical Center
Tae Won Kim
Asan Medical Center
Ki Eun Choi
Asan Medical Center
Min Jung Kim
Asan Medical Center
Jeong Eun Kim (jeongeunkim@amc.seoul.kr)
Asan Medical Center

Research Article

Keywords: Colorectal cancer, CEA, disease response, depth of response, anti-EGFR antibody

Posted Date: April 4th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1508420/v1

Abstract

Purpose: Carcinoembryonic antigen (CEA) is the most widely used tumor marker in metastatic colorectal cancer (mCRC), but its potential as a predictive marker of progression in mCRC during systemic chemotherapy, particularly in patients receiving monoclonal antibodies as a combination therapy, has remained a question of interest. We here investigated whether CEA changes could predict disease progression and clinical outcomes in mCRC patients who had been co-administered systemic chemotherapy and biologic agents.

Methods: A total of 1261 mCRC patients undergoing a first-line systemic treatment were included in this retrospective study. We analyzed the optimal cut-off for CEA changes to predict progression at the first re-evaluation by the treatment arm (chemotherapy alone, chemotherapy plus anti-VEGF monoclonal antibodies [mAb], and chemotherapy plus anti-EGFR mAb). These cut-off values were then used to predict overall survival (OS) and progression-free survival (PFS).

Results: When stratified by their treatment arm, 891 (70.6%), 266 (21.0%), and 104 (8.2%) of the study patients were included in the chemotherapy alone-, anti-VEGF mAb-, and anti-EGFR mAb groups, respectively. The optimal CEA cut-off values were 16.5% and 38.9% increase in the whole cohort and anti-EGFR mAb group, respectively, and showed high sensitivity and specificity for predicting disease progression. The patients in the entire population and anti-EGFR mAb group with CEA changes below these cut-off values had significantly better OS and PFS outcomes. Among the mCRC cases treated with the anti-VEGF mAb, no associations were found between the OS and PFS outcomes, and CEA changes.

Conclusion: CEA is potentially a good surrogate marker for predicting disease progression and survival outcomes in mCRC patients receiving first-line systemic chemotherapy, especially when combined with anti-EGFR mAb.

Introduction

Although novel biomarkers such as circulating tumor DNA (ctDNA) are currently under investigation (Dasari et al. 2020), serum carcinoembryonic antigen (CEA) is still the most widely used tumor marker for colorectal cancer (CRC) worldwide (Duffy et al. 2007; Duffy et al. 2014). CEA has a unique advantage compared to ctDNA in terms of inexpensive cost and less time required to wait for results, and it is a marker of choice for postoperative surveillance and monitoring disease response during systemic chemotherapy in CRC (Duffy et al. 2007; Duffy et al. 2014; Konishi et al. 2017; Ramphal et al. 2019).

In real-world clinical practice, it is important for medical oncologists to define whether the cancer is progressive or not during systemic chemotherapy for optimizing the treatment. Since changes in the CEA level may reflect tumor burden (Hammarström 1999; Quayle 1982), several previous studies of CRC have reported a correlation between changes in CEA level and the disease response, suggesting that changes in CEA level may be a good surrogate marker for predicting the disease response during systemic chemotherapy (Grem et al. 1998; Gulhati et al. 2020; Haas et al. 2010; Iwanicki-Caron et al. 2008; Moretto et al. 2021; Wang et al. 2001; Yu et al. 2018). However, most of those studies had a limited sample size, and most of the included patients were treated with chemotherapy alone.

Currently, anti-VEGF monoclonal antibody (mAb) and anti-EGFR mAb are recommended by both the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines as part of the first-line systemic treatments in combination with cytotoxic chemotherapy for eligible CRC patients (National Comprehensive Cancer Network 2021; Van Cutsem et al. 2016). As the chemotherapy and mAb combination was

established as standard-of-care for eligible patients, it has remained a question of interest that the clinical value of CEA changes in predicting the response in mCRC patients who were treated with targeted therapy.

In this study, we aimed to evaluate the association between the level of CEA changes and disease response at the time of their first re-evaluation in mCRC patients who were treated with first-line chemotherapy, especially those treated with mAb combination. We divided mCRC patients in our cohort into three groups and analyzed the changes in CEA and assessed the serum CEA threshold that could be used to predict the disease response by their treatment regimen i.e., chemotherapy alone, chemotherapy with anti-VEGF mAb, and chemotherapy with anti-EGFR mAb. In addition, we evaluated the prognostic value of these cut-offs for predicting long-term clinical outcomes in our mCRC patients.

Method

Patients

We identified patients treated for metastatic colorectal cancer (mCRC) between 2008 and 2015 (n = 2962) at Asan Medical Center, a tertiary hospital in Seoul, South Korea. Among this initial population, we excluded patients for whom CEA data at baseline or from their first response evaluation were not available (n = 766), or whose disease response information was not evaluable due to follow-up loss, death, and/or an unavailable restaging image (n = 935). For inclusion in the analyses, the available baseline CT was required to be within 4 weeks of the chemotherapy initiation, and the CT scan from the response evaluation had to be within 12 weeks of the commencement of the chemotherapy. Moreover, the CEA level was required to be within 2 weeks of the response evaluation scan. A final total of 1261 patients were included in the analysis. We retrospectively reviewed their medical records and collected data on age, sex, tumor characteristics including the grade and mutation, mismatch repair (MMR) and microsatellite instability (MSI) status, the BRAF mutation status, the CEA levels at baseline and at the time of the first re-evaluation, treatment regimen, and response assessment. The systemic disease response was evaluated by using response evaluation criteria in solid tumors (RECIST) version 1.1. Enzyme immunoassays (ELISA-2-CEA kit; CIS Biointernational, Marcoule, France) were used to measure the serum CEA.

Outcomes

A central goal of these analyses was to determine whether CEA changes from the period before chemotherapy initiation to the first re-evaluation could predict CRC progression on the first re-evaluation imaging scan, which was conducted 6–8 weeks after initiation of chemotherapy, or when the disease progression was clinically suspected. We aimed to define an optimal cut-off value for the serum CEA level at the time of the first re-evaluation imaging scan for predicting the treatment response (progressive disease [PD] vs non-PD) in mCRC patients undergoing first-line chemotherapy. In addition, we aimed to evaluate the association between any CEA changes at the first re-evaluation and clinical outcomes, such as progression-free survival (PFS) and overall survival (OS) in the mCRC patients.

Statistical analysis

We conducted our present analysis according to the treatment arm i.e. chemotherapy alone, chemotherapy plus anti-VEGF mAb, and chemotherapy plus anti-EGFR mAb. The optimal cut-off values for the serum CEA changes were estimated using receiver operating characteristic (ROC) analysis. Using these cut-off values, the sensitivity, specificity, and positive and negative predictive values were estimated to predict their performance. A multivariate logistic regression model including age (age $\geq$ 60 vs < 60), tumor site (right vs left), the CEA change percentage (above vs below the cut-off), and BRAF mutation status (wild type vs mutant) was used to estimate the adjusted odds ratio (OR)

and the corresponding 95% confidence interval (CI). Patients for whom information on the tumor site and BRAF mutation status were not available were excluded in this model; thus, a total of 1109 patients were included.

The wilcoxon rank-sum test was used to compare the percentage change in the serum CEA level between patients confirmed to have progressive or non-progressive disease at the first re-evaluation. To analyze categorical variables, the Chi-square test or Fisher's exact test was used as appropriate. The OS was calculated from the date of the first-line chemotherapy initiation to the date of death from any cause. The PFS was calculated from the date of first-line chemotherapy initiation to the date of disease progression or death, whichever occurred first. The Kaplan-Meier method was used to estimate the OS and PFS, and the log-rank test was used to compare the clinical outcomes of the subgroups. Multivariate Cox proportional-hazards models were used to estimate the hazard ratio [HR] and 95% CIs for evaluating the prognostic value of each variable for the OS and PFS. P values < 0.05 were considered to indicate statistical significance, and all analyses were conducted using statistical software R (version 4.0.5, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of the included patients are summarized in Table 1. The median age was 57 years (range 20-82) and 61% (n=775) of these cases were male. Most of the tumors in this population were located on the left side (n = 959, 76%) and 79% of the patients (n = 998) had a moderately differentiated tumor grade. When stratified using the treatment arm, 891 (70.6%), 266 (21.0%), and 104 (8.2%) patients were treated with chemotherapy alone, chemotherapy plus anti-VEGF mAb, and chemotherapy plus anti-EGFR mAb, respectively. The median baseline CEA was 8 ng/L (interquartile range [IQR], 2-57) and the median CEA at the first evaluation was 5 ng/mL (IQR, 2 - 34). The median duration from the initiation of the first-line chemotherapy to the first re-evaluation was 7.57 weeks (range 1.57 - 12). The most commonly used chemotherapy regimens among our current study patients were FOLFIRI (folinic acid, fluorouracil, and irinotecan) in the chemotherapy only group (n=354, 40% of 891), bevacizumab plus FOLFIRI (n=181, 68% of 266) in the chemotherapy plus anti-VEGF antibody group, and cetuximab plus FOLFIRI (n = 86, 83% of 104) in the chemotherapy plus anti-EGFR antibody group (Supplementary Table 1). The number of patients who showed progressive disease at first re-evaluation was 142 (16%), 18 (6.8%), and 8 (7.7%) in chemotherapy alone, chemotherapy plus anti-VEGF mAb, and chemotherapy plus anti-EGFR mAb group, respectively.

Table 1

Variables	All patients (n = 1,261)	CTx alone (n = 891)	CTx + Anti-VEGF antibody (n = 266)	CTx + anti-EGFR antibody (n = 104)
Age, median (range)	57 (20-82)	57 (20-82)	56 (27-79)	54 (25-77)
Sex				
Male	775 (61%)	555 (62%)	153 (58%)	67 (64%)
Female	486 (39%)	336 (38%)	113 (42%)	37 (36%)
Primary tumor site				
Right	296 (23%)	202 (23%)	78 (29%)	16 (15%)
Left	959 (76%)	685 (77%)	186 (70%)	88 (85%)
Multifocal	2 (0.2%)	2 (0.2%)	0 (0%)	0 (0%)
Unknown	4 (0.3%)	2 (0.2%)	2 (0.8%)	0 (0%)
Tumor grade				
Well differentiated	91 (7.2%)	69 (7.7%)	13 (4.9%)	9 (8.7%)
Moderate differentiated	998 (79%)	701 (79%)	213 (80%)	84 (81%)
Poorly differentiated	117 (9.3%)	79 (8.9%)	29 (11%)	9 (8.7%)
Unknown	55 (4.4%)	42 (4.7%)	11 (4.1%)	2 (1.9%)
Baseline CEA, ng/mL median (IQR)	8 (2, 57)	7(2, 44)	11(2, 74)	17(5, 170)
CEA at first re-staging, ng/mL, median (IQR)	5 (2, 34)	5 (2,28)	6 (2,44)	7 (3,40)
Progression at first re-evaluation	168 (13%)	142 (16%)	18 (6.8%)	8 (7.7%)
KRAS mutation				
Wild	716 (57%)	500 (56%)	118 (44%)	98 (94%)
Mutant	436 (35%)	297 (33%)	139 (52%)	0 (0%)
Unknown	109 (8.6%)	94 (11%)	9 (3.4%)	6 (5.8%)
NRAS mutation				
Wild	326	97 (11%)	174 (65%)	55 (53%)

	(26%)			
Mutant	15 (1.2%)	8 (0.9%)	7 (2.6%)	0 (0%)
Unknown	920 (73%)	786 (88%)	85 (32%)	49 (47%)
BRAF mutation				
Wild	1,062 (84%)	733 (82%)	236 (89%)	93 (89%)
Mutant	52 (4.1%)	34 (3.8%)	16 (6.0%)	2 (1.9%)
Unknown	147 (12%)	124 (14%)	14 (5.3%)	9 (8.7%)
MMR status				
proficient MMR	857 (68%)	593 (67%)	192 (72%)	72 (69%)
deficient MMR	37 (2.9%)	31 (3.5%)	4 (1.5%)	2 (1.9%)
Unknown	367 (29%)	267 (30%)	70 (26%)	30 (29%)
MSI				
MSS & MSI-low	806 (63.9%)	574 (64.4%)	174 (65.4%)	58 (55.7%)
MSI-High	18 (1.4%)	14 (1.6%)	3 (1.1%)	1 (1.0%)
Unknown	437 (35%)	303 (34%)	89 (33%)	45 (43%)

Abbreviations: CTx, chemotherapy; MMR, mismatch repair; dMMR, deficient MMR; pMMR, proficient MMR; MSI, microsatellite instability; MSS, microsatellite stable

The dynamics of the CEA change at the first re-evaluation according to the treatment arm.

In the whole cohort, the median CEA percentage change from the baseline to the first re-evaluation was -25% in the non-PD cases and 70.9% in patients with PD (Figure 1a, $P < 0.001$). These values in the anti-EGFR mAb combination subgroup were -63.29% and 187.31% (Figure 1b, $P <0.001$), and in the chemotherapy alone and anti-VEGF combination therapy groups were -20% and 70.8%, and -29.06% and 31.19% (Figure 1c, 1d, $P < 0.001$ for both), respectively. Among the non-PD patients, the median CEA decrease was largest in the anti-EGFR mAb treatment group (-63.2%) compared to the chemotherapy alone (-20%) or anti-VEGF mAb groups (-29.0%; Figure 2).

Predicting the Response to the First-Line Treatment at the First Restaging using the CEA levels

Using ROC analysis, the optimal cut-off value for the CEA percentage changes to predict PD was defined for each treatment arm of our mCRC cohort. In the total population, this was estimated to be an increase of over 16.5% (AUC 77%, 95% CI 74.1-81.4; Figure 3a). The sensitivity and specificity of this cut-off value were 72.0% and 70.0%, respectively (Table 2). Patients with a CEA increase above 16.5% showed a higher probability of PD development

(adjusted OR; 4.06 [95% CI 2.80-5.90], P < 0.001; Table 3). Among the patients treated with the anti-EGFR mAb combination, the optimal cut-off value was defined as an increase of over 38.9% (AUC 95.8%; Figure 3b). The sensitivity and specificity of this cut-off value for predicting PD and non-PD were 87.5% and 94.8%, respectively (Table 2). The CEA cut-off value and their sensitivities and specificities in the chemotherapy alone and the anti-VEGF mAb group were summarized in Table 2.

Table 2. Progression prediction via the percentage change in the serum CEA level at the time of the first restaging scan in patients treated with chemotherapy alone or chemotherapy + anti VEGF antibody

Progression prediction by CEA	Change in CEA*, %	AUC#, (95% CI) %	Sensitivity, %	Specificity, %	Negative predictive value, %
All Patients	16.5	77 (74.1-81.4)	72.0	70.0	94.2
Chemotherapy only	16.4	76 (71.7-80.3)	72.53	66.62	92.7
Chemotherapy + anti-VEGF mAb	-32.6	74.5 (64.4-84.6)	94.4	48.0	99.2
Chemotherapy + anti-EGFR mAb	38.9	95.8 (89.1-100)	87.5	94.8	98.9

#AUC, Area Under the Curve; mAb, monoclonal antibody

*Change in CEA = (CEA at 1st evaluation- baseline CEA)/baseline CEA

Table 3. Univariate and multivariate regression analysis of prediction progression in the whole cohort (n=1109)

	Univariate logistic regression			**Multivariate logistic regression**		
	Unadjusted ORR	**95% CI**	**P value**	**Adjusted ORR**	**95% CI**	**P value**
Elevated CEA changes above the cut-off value (*vs* those below the cut-off value*)	4.01	2.76-5.81	<0.001	4.06	2.80-5.90	<0.001
Age >=60 (*vs* < 60)	0.76	0.52-1.1	0.15	0.71	0.48-1.04	0.08
Primary tumor location, left (*vs* right)	0.85	0.57-01.28	0.44	0.90	0.58-1.38	0.62
BRAF mutant (*vs* wild type)	0.91	0.38-2.16	0.82	0.75	0.30-1.85	0.52

*cut off value: CEA increase equal to or more than 16.5%

Correlation between the Percentage Change in the CEA levels measured at the First Restaging and Clinical Outcomes

With the median follow-up duration of 43.0 months (95% CI 38.9 – 45.8) of surviving patients, the median PFS and OS in the whole cohort (n=1261) were 8.71 months (95% CI 8.38 – 9.21) and 29.8 months (95% CI 28.2 – 32.2), respectively. To evaluate the association between the percentage changes in the serum CEA levels and the clinical outcomes in our present mCRC series, we conducted a survival analysis and estimated these variables by stratifying

the patients in each treatment arm in accordance with the cut-off value for that group. Among the total study population, 449 and 812 patients were classified as being above (CEA increase equal or more than 16.5%) and below (decreased or increased by less than 16.5%) the cut-off value, respectively. The median PFS of the patients in the whole population who were above the cut-off was 7.07 months [95% CI 6.25-7.69], and that for the cases below the cut-off value was 9.50 months [95% CI 8.94 - 9.93] (P < 0.001; Figure 4a). The median OS was 26.9 months (95% CI 23.4-30.7) and 31.7 months (95% CI 29.1-34.0) for the patients above and below this cut-off value, respectively (P < 0.001; Figure 4b).

Among the patients who had been treated with chemotherapy plus anti-EGFR mAb (n=104), 12 patients were included in the group with a CEA increase above the cut-off value (an equal to or more than 38.9% increase) and 92 cases were assigned to the opposite group (a decreased CEA or an increase of less than 38.9%). Patients in the above-the-cut-off group that had undergone an anti-EGFR mAb combination therapy showed significantly worse PFS and OS outcomes (median PFS, 2.5 months (95% CI 1.84 - NA) vs 12.0 months [95% CI 10.68-14], P < 0.0001; Figure 5a; median OS, 15.2 months [95% CI 7.29-NA] vs 70.4 months [95% CI 42.12-NA], P < 0.0001; Figure 5b).

In patients who received a chemotherapy plus anti-VEGF mAb group, no significant differences were identified between above-the-cut-off group (n = 146) and below-the-cut-off group (n = 120) in terms of the PFS (median PFS, 10.6 months [95% CI 9.44 - 11.8] vs 11.7 months [95% CI 10.42 - 13.9], P=0.11) or OS (median OS, 63 months [95% CI 37.7 – NR] vs not-reached, P = 0.11) (Supplementary figure 1). Among the patients treated with chemotherapy alone (n = 891), patients who showed a CEA change above the cut-off value (n=353) had a significantly worse PFS compared to those with below the cut-off value (n=538) (median PFS, 6.21 months [95% CI 5.49-7.07] vs 8.40 months [95% CI 8.09-8.88], P = 0.0039), but no significant differences were observed in terms of OS between these two groups (median OS, 25.4 months [95% CI 21.2-28.7] vs 27.0 months [95% CI 25.4-29.2], P = 0.35) (Supplementary figure 2).

Prognostic factor analysis

In multivariate analysis of the total study cohort, patients whose CEA level was increased over the cut-off (increased by at least 16.5%) had both a significantly worse PFS (HR 1.25, 95% CI 1.10-1.41, P <0.001) and OS (HR 1.26, 95% CI 1.07-1.47, P = 0.004) (Table 4). An age ≥ 60 years and right tumor location were not associated with a better PFS or OS. Patients harboring a BRAF mutation showed a significantly lower OS (HR 1.96, 95% CI 1.40-2.76, P < 0.001) but no significant association was found between the PFS outcomes and these mutations.

Table 4. Prognostic factor analysis for both progression free and overall survival

	Progression free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Elevated CEA change above the cut-off value (*vs* those below the cut-off value)	1.25	1.10-1.41	<0.001	1.23	1.08-1.39	<0.001	1.29	1.10-1.51	<0.001	1.26	1.07-1.47	0.004
Age >=60 (*vs* < 60)	1.07	0.94-1.20	0.26	1.05	0.93-1.18	0.41	1.07	0.91-1.25	0.39	1.04	0.89-1.22	0.55
Primary tumor location, left (*vs* right)	0.86	0.75-0.99	0.04	0.90	0.78-1.04	0.16	0.77	0.64-0.93	0.006	0.82	0.68-0.99	0.04
BRAF mutant (*vs* wild type)	1.34	1.01-1.78	0.03	1.31	0.99-1.73	0.056	2.05	1.46-2.88	<0.001	1.96	1.40-2.76	<0.001

Abbreviations: HR, Hazard ratio; CI, Confidential Interval

Discussion

The measurement of the serum CEA level as a tumor marker is inexpensive, non-invasive, and convenient and this underlies why is it a widely used test in mCRC patients worldwide. In our present study, we have observed that CEA changes at the first re-evaluation of these cases after palliative chemotherapy can predict disease progression with high sensitivity and specificity in a large mCRC cohort. Of note, in particular, the sensitivity and specificity of the CEA cut-off value were nearly 90% and 95%, respectively, in the patients treated with anti-EGFR mAb plus chemotherapy. Additionally, the percentage change in the CEA level was found to be significantly associated with clinical survival outcomes and to be an independent prognostic factor for mCRC.

Several recent reports have indicated that CEA changes can precisely predict non-progression after systemic chemotherapy in the mCRC cohort, which is in line with our current study (Gulhati et al. 2020; Moretto et al. 2021). Gulahati et. al described a percentage of CEA change cut-off value at the time of the first re-evaluation in different treatment groups (chemotherapy alone: -7.5%, and chemotherapy plus anti-VEGF mAb: -62.0%), and reported that a CEA change well correlated with long-term clinical outcomes. Morreto et.al proposed that at least a 120% increase of CEA cut-off value from the nadir was predictive of disease progression after the end of induction chemotherapy in patients treated with the anti-VEGF mAb combination (n = 434). Both studies have suggested that a CT scan could be

avoided in approximately 70% of patients, and the measurement of CEA changes was an effective surrogate marker for predicting disease progression. Although the CEA change cut-off values and the timing of the first patient evaluations have slightly differed between prior reports, these previous studies and our current data collectively indicate that the use of CEA changes to predict the disease response in mCRC patients after systemic therapy has real-world clinical utility, particularly when assessments by imaging studies are inconclusive or unavailable.

Considering the aforementioned studies focused on patients treated with anti-VEGF mAb or chemotherapy alone, less is known about the role of CEA as a marker of CRC progression in patients who have undergone an anti-EGFR mAb combination regimen in real-world practice. In our present study, we observed that the percentage of CEA change was significantly lower in patients who had received an anti-EGFR mAb combination (-63.29%) compared to patients who had been treated with an anti-VEGF mAb combination (-29.06%), among the non-PD cases at the first re-evaluation ($P < 0.001$). This result is consistent with those of the pooled analysis in the previous FIRE-3 study, which reported a greater CEA response in patients treated with anti-EGFR antibody compared to those treated with anti-VEGF antibody (Michl et al. 2016).

Notably in this regard also, the original FIRE-3 study demonstrated that more patients treated with cetuximab experienced an early tumor shrinkage (68%) than those treated with bevacizumab (49%) (Heinemann et al. 2021). Considering that CEA reflects the tumor burden in mCRC (Quayle 1982), we speculate that an increased CEA response may be a reflection of tumor shrinkage and a greater depth of response (DpR) in patients receiving an anti-EGFR mAb regimen rather than an anti-VEGF mAb treatment. The DpR is a recently proposed efficacy outcome that is defined as the percentage of tumor shrinkage observed at the nadir compared to the baseline (Mansmann et al. 2013), and an increased DpR is regarded as a good prognostic marker for survival outcomes (Cremolini et al. 2015; Piessevaux et al. 2013; Schwartzberg et al. 2014). Hence, a greater CEA response may also be a predictive marker of clinical outcomes in patients who are treated with anti-EGFR mAb, as also indicated by our present findings (Figure 4).

It was of interest that the predictive performance of the CEA response in our current study was lower in the patients who had been treated with anti-VEGF mAb compared to the other two treatment groups. Similar results were also presented in a previous report, which indicated that the predictive performance of the CEA changes in a chemotherapy alone group was better than that in an anti-VEGF mAb group (Gulhati et al. 2020). Furthermore, we observed no significant differences in the PFS and OS outcomes among the mCRC patients treated with the anti-VEGF antibody according to the CEA-cut-off value for this treatment, contrary to our findings in the anti-EGFR mAb group (Figure S1). These findings suggest that the sensitivity and specificity of using CEA changes to predict mCRC progression and clinical outcomes are less effective in patients treated with anti-VEGF mAb compared to those receiving anti-EGFR mAb therapy. One of the potential explanations for this is that CEA may induce angiogenesis independently of VEGF (Bramswig et al. 2013; Prager et al. 2014). Hence, anti-VEGF mAb is less effective than anti-EGFR mAb in terms of tumor shrinkage, which was also indicated by the FIRE-3 study (Heinemann et al. 2021). Further investigations will be needed to elucidate the mechanisms behind this.

The strength of our current study was the relatively large sample size. In addition, we evaluated the role of CEA dynamics by comparing different treatment arms, including the combined use of biologic agents. Considering that monoclonal antibody combination regimens are now standard first-line therapies for mCRC, our present findings are highly relevant to current treatment trends for this disease and to real-world clinical practices.

There were several limitations of our current study of note. First, it was a single-center retrospective study, which was susceptible to selection bias. However, our cohort contained a large number of patients treated in a relatively homogenous way with regard to their chemotherapy regimen. Another limitation was that we only evaluated the

disease response as PD or non-PD and did not further stratify our non-PD patients as stable disease, partial response, or complete remission cases. However, considering that the main purpose of disease evaluation during systemic chemotherapy for mCRC is the detection of PD, our present results may be clinically meaningful in terms of predicting the treatment response. Thirdly, we only evaluated the CEA date taken at the first re-evaluation, and the availability of serial follow-up CEA values was limited. Further investigations involving long-term follow-ups will be needed to evaluate the association between CEA dynamics and disease response in mCRC.

Conclusion

The measurement of the CEA tumor marker is convenient and non-invasive, and it could be a good surrogate predictive marker of disease progression and survival outcomes in mCRC patients treated with first-line systemic chemotherapy, particularly in cases treated with anti-EGFR mAb. In addition, a greater CEA response may reflect DpR in the anti-EGFR mAb group, which suggests that it could be a potential prognostic marker for those patients. Further investigations including prospective cohort studies are required to definitively evaluate the association between CEA changes and treatment responses in mCRC patients treated with biologic agents.

Declarations

Funding:

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Jeong Eun Kim contributed study design and conceptualization. All authors contributed to material preparation and data collection. The data analysis and interpretation were performed by Sora Kang and Jeong Eun Kim. The first draft of the manuscript was written by Sora Kang, and all authors commented on previous version of the manuscript. All authors read and approved the final manuscript.

Data Availability

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

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No.: 2017-1098). The requirement for patient informed consent was waived by the IRB due to the retrospective nature of the study.

References

1. Bramswig KH, Poettler M, Unseld M, Wrba F, Uhrin P, Zimmermann W, Zielinski CC, Prager GW (2013) Soluble Carcinoembryonic Antigen Activates Endothelial Cells and Tumor Angiogenesis. Cancer Research 73:6584–6596.

https://doi.org/10.1158/0008-5472.can-13-0123

2. Cremolini C, Loupakis F, Antoniotti C, Lonardi S, Masi G, Salvatore L, Cortesi E, Tomasello G, Spadi R, Zaniboni A, Tonini G, Barone C, Vitello S, Longarini R, Bonetti A, D'Amico M, Di Donato S, Granetto C, Boni L, Falcone A (2015) Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. Ann Oncol 26:1188–1194. https://doi.org/10.1093/annonc/mdv112
3. Dasari A, Morris VK, Allegra CJ, Atreya C, Benson AB, Boland P, Chung K, Copur MS, Corcoran RB, Deming DA, Dwyer A, Diehn M, Eng C, George TJ, Gollub MJ, Goodwin RA, Hamilton SR, Hechtman JF, Hochster H, Hong TS, Innocenti F, Iqbal A, Jacobs SA, Kennecke HF, Lee JJ, Lieu CH, Lenz H-J, Lindwasser OW, Montagut C, Odisio B, Ou F-S, Porter L, Raghav K, Schrag D, Scott AJ, Shi Q, Strickler JH, Venook A, Yaeger R, Yothers G, You YN, Zell JA, Kopetz S (2020) ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal–Anal Task Forces whitepaper. Nature Reviews Clinical Oncology 17:757–770. https://doi.org/10.1038/s41571-020-0392-0
4. Duffy MJ, Dalen Av, Haglund C, Hansson L, Holinski-Feder E, Klapdor R, Lamerz R, Peltomaki P, Sturgeon C, Topolcan O (2007) Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. European Journal of Cancer 43:1348–1360. https://doi.org/10.1016/j.ejca.2007.03.021
5. Duffy MJ, Lamerz R, Haglund C, Nicolini A, Kalousová M, Holubec L, Sturgeon C (2014) Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. International Journal of Cancer Journal International du Cancer 134:2513–2522. https://doi.org/10.1002/ijc.28384 PMID – 23852704
6. Grem JL, Steinberg SM, Chen AP, McAtee N, Cullen E, Hamilton JM, Allegra CJ (1998) The utility of monitoring carcinoembyronic antigen during systemic therapy for advanced colorectal cancer. Oncol Rep 5:559–567. https://doi.org/10.3892/or.5.3.559
7. Gulhati P, Yin J, Pederson L, Schmoll H-J, Hoff P, Douillard J-Y, Hecht JR, Tournigand C, Tebbut N, Chibaudel B, Gramont AD, Shi Q, Overman MJ (2020) Threshold Change in CEA as a Predictor of Non-Progression to First-Line Systemic Therapy in Metastatic Colorectal Cancer Patients With Elevated CEA. JNCI: Journal of the National Cancer Institute 112:1127–1136. https://doi.org/10.1093/jnci/djaa020
8. Haas RJd, Wicherts DA, Flores E, Ducreux M, Lévi F, Paule B, Azoulay D, Castaing D, Lemoine A, Adam R (2010) Tumor Marker Evolution: Comparison with Imaging for Assessment of Response to Chemotherapy in Patients with Colorectal Liver Metastases. Annals of Surgical Oncology 17:1010–1023. https://doi.org/10.1245/s10434-009-0887-5
9. Hammarström S (1999) The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. Seminars in Cancer Biology 9:67–81. https://doi.org/10.1006/scbi.1998.0119
10. Heinemann V, Weikersthal LFv, Decker T, Kiani A, Kaiser F, Al-Batran S-E, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Moehler M, Scheithauer W, Held S, Miller-Phillips L, Modest DP, Jung A, Kirchner T, Stintzing S (2021) FOLFIRI plus cetuximab or bevacizumab for advanced colorectal cancer: final survival and per-protocol analysis of FIRE-3, a randomised clinical trial. British Journal of Cancer 124:587–594. https://doi.org/10.1038/s41416-020-01140-9
11. Iwanicki-Caron I, Fiore FD, Roque I, Astruc E, Stetiu M, Duclos A, Tougeron D, Saillard S, Thureau S, Benichou J, Paillot B, Basuyau JP, Michel P (2008) Usefulness of the Serum Carcinoembryonic Antigen Kinetic for Chemotherapy Monitoring in Patients With Unresectable Metastasis of Colorectal Cancer. Journal of Clinical Oncology 26:3681–3686. https://doi.org/10.1200/jco.2007.15.0904

12. Konishi T, Shimada Y, Hsu M, Tufts L, Jimenez-Rodriguez R, Cercek A, Yaeger R, Saltz L, Smith JJ, Nash GM, Guillem JG, Paty PB, Garcia-Aguilar J, Gonen M, Weiser MR (2017) Association of Preoperative and Postoperative Serum Carcinoembryonic Antigen and Colon Cancer Outcome. JAMA Oncology 4:309. https://doi.org/10.1001/jamaoncol.2017.4420
13. Mansmann UR, Sartorius U, Laubender RP, Giessen CA, Esser R, Heinemann V (2013) Deepness of response: A quantitative analysis of its impact on post-progression survival time after first-line treatment in patients with mCRC. Journal of Clinical Oncology 31:427–427. https://doi.org/10.1200/jco.2013.31.4_suppl.427
14. Michl M, Stintzing S, Fischer von Weikersthal L, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmueller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Mueller S, Lerch MM, Modest DP, Kirchner T, Jung A, Heinemann V (2016) CEA response is associated with tumor response and survival in patients with KRAS exon 2 wild-type and extended RAS wild-type metastatic colorectal cancer receiving first-line FOLFIRI plus cetuximab or bevacizumab (FIRE-3 trial) < sup>†.Annals of Oncology 27:1565–1572. https://doi.org/10.1093/annonc/mdw222
15. Moretto R, Rossini D, Conca V, Lonardi S, Rasola C, Antoniotti C, Santini D, Marmorino F, Tomasello G, Borelli B, Caponnetto S, Zucchelli G, Zaniboni A, Ambrosini M, Buonadonna A, Fanchini L, Cupini S, Masi G, Falcone A, Cremolini C (2021) CEA increase as a marker of disease progression after first-line induction therapy in metastatic colorectal cancer patients. A pooled analysis of TRIBE and TRIBE2 studies. British Journal of Cancer 125:839–845. https://doi.org/10.1038/s41416-021-01483-x
16. National Comprehensive Cancer Network (2021) Colon Cancer. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 24, 2021
17. Piessevaux H, Buyse M, Schlichting M, Van Cutsem E, Bokemeyer C, Heeger S, Tejpar S (2013) Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol 31:3764–3775. https://doi.org/10.1200/jco.2012.42.8532
18. Prager GW, Braemswig KH, Martel A, Unseld M, Heinze G, Brodowicz T, Scheithauer W, Kornek G, Zielinski CC (2014) Baseline carcinoembryonic antigen (CEA) serum levels predict bevacizumab-based treatment response in metastatic colorectal cancer. Cancer Science 105:996–1001. https://doi.org/10.1111/cas.12451
19. Quayle JB (1982) Ability of CEA blood levels to reflect tumour burden: a study in a human xenograft model. British Journal of Cancer 46:220–227. https://doi.org/10.1038/bjc.1982.187
20. Ramphal W, Boeding JRE, Iwaarden Mv, Schreinemakers JMJ, Rutten HJT, Crolla RMPH, Gobardhan PD (2019) Serum carcinoembryonic antigen to predict recurrence in the follow-up of patients with colorectal cancer. The International Journal of Biological Markers 34:60–68. https://doi.org/10.1177/1724600818820679
21. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS, Go WY (2014) PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 32:2240–2247. https://doi.org/10.1200/jco.2013.53.2473
22. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJG, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of Oncology 27:1386–1422. https://doi.org/https://doi.org/10.1093/annonc/mdw235

23. Wang WS, Lin JK, Lin TC, Chiou TJ, Liu JH, Fan FS, Yen CC, Chen WS, Jiang JK, Yang SH, Wang HS, Chen PM (2001) Carcinoembryonic antigen in monitoring of response to systemic chemotherapy in patients with metastatic colorectal cancer. Int J Colorectal Dis 16:96–101. https://doi.org/10.1007/s003840000266
24. Yu P, Zhou M, Qu J, Fu L, Li X, Cai R, Jin B, Teng Y, Liu J, Shi J, Zhang J (2018) The dynamic monitoring of CEA in response to chemotherapy and prognosis of mCRC patients. BMC Cancer 18:1076. https://doi.org/10.1186/s12885-018-4987-0

Figures

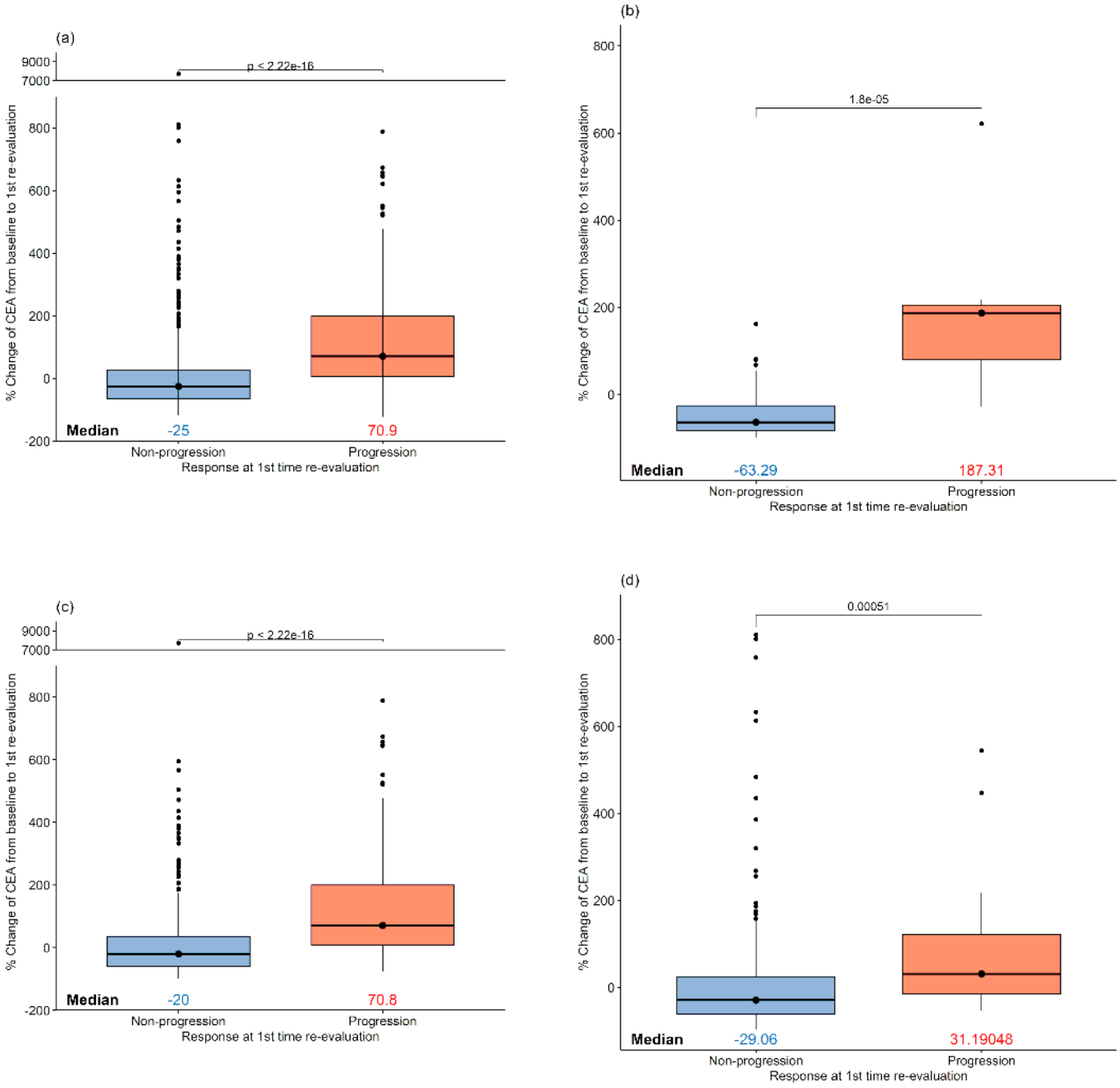

Figure 1

Boxplots of CEA changes from baseline to the first re-evaluation. (a) whole cohort (b) Chemotherapy plus anti-EGFR monoclonal antibodies group (c) chemotherapy alone group (d) chemotherapy plus anti-VEGF monoclonal antibodies group

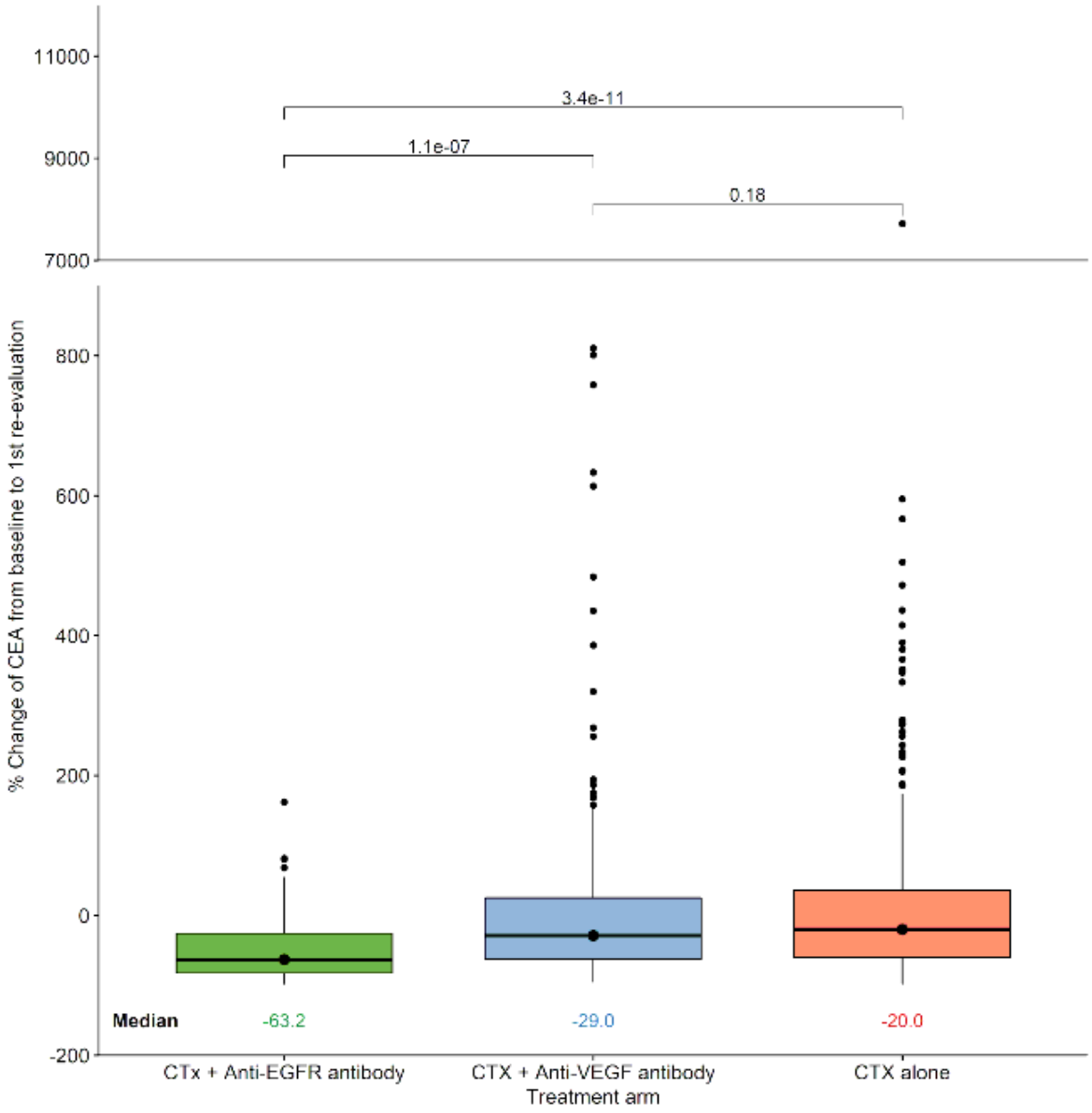

Figure 2

Box plots of CEA changes from baseline to the first re-evaluation in non-progression patients according to treatment arm

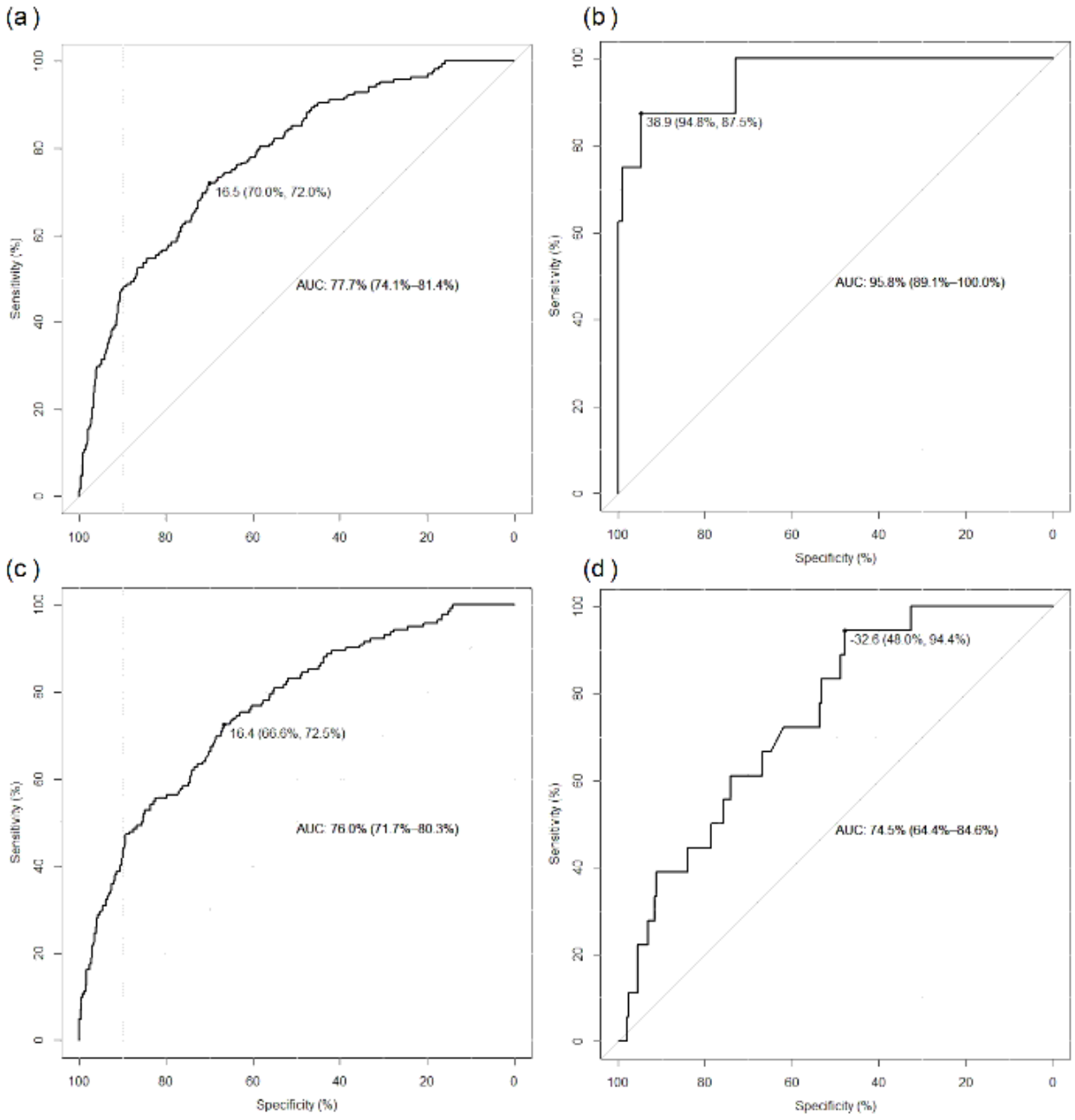

Figure 3

Receiver operating characteristic (ROC) curve analysis with the AUC method in (a) the whole cohort; (b) patients treated with chemotherapy plus anti-EGFR monoclonal antibodies; (c) patients treated with chemotherapy alone; and (d) patients treated with chemotherapy plus anti-VEGF monoclonal antibodies

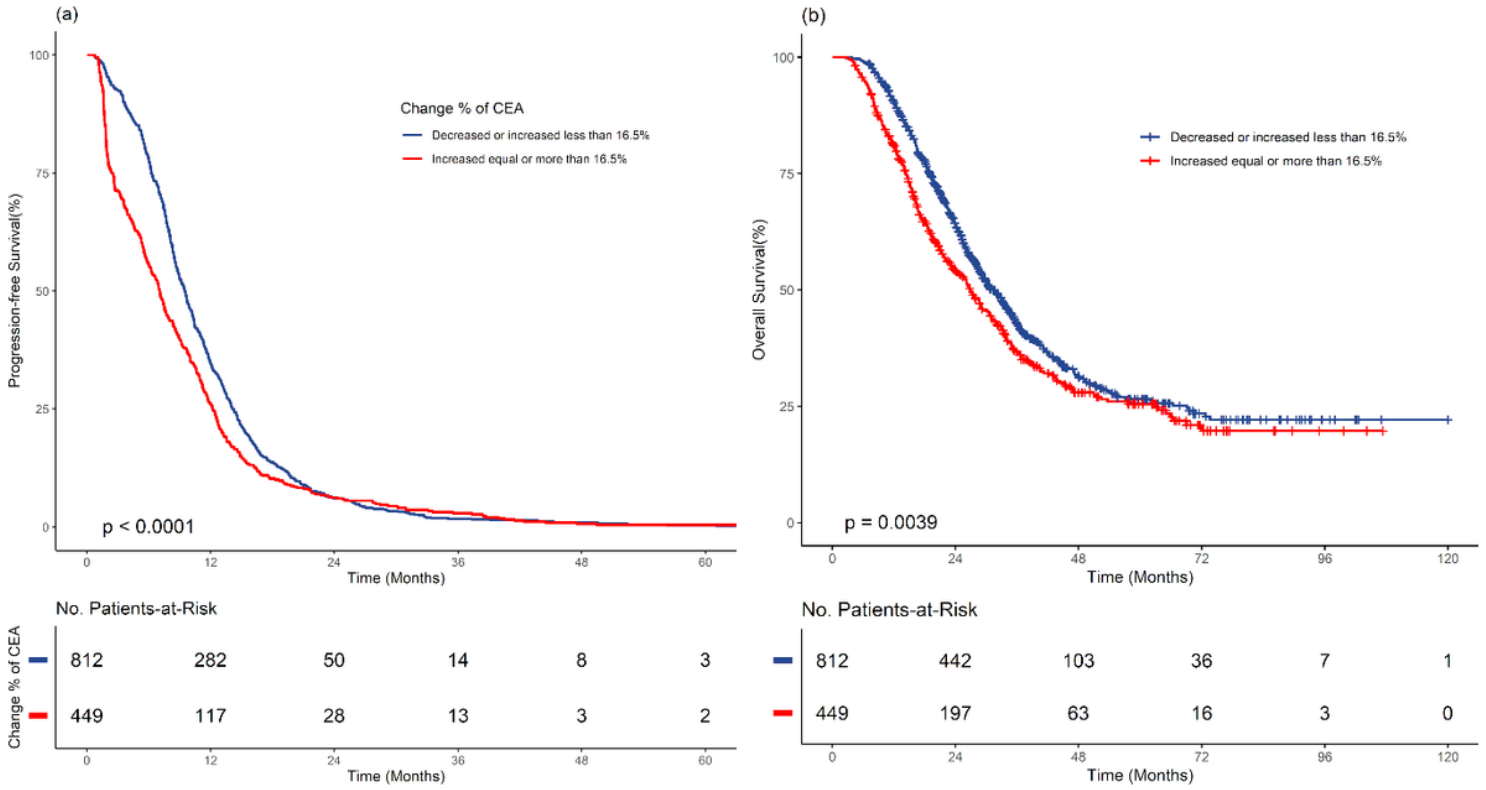

Figure 4

(a) Progression-free survival and (b) overall survival analysis according to the CEA cut-off value for the whole cohort

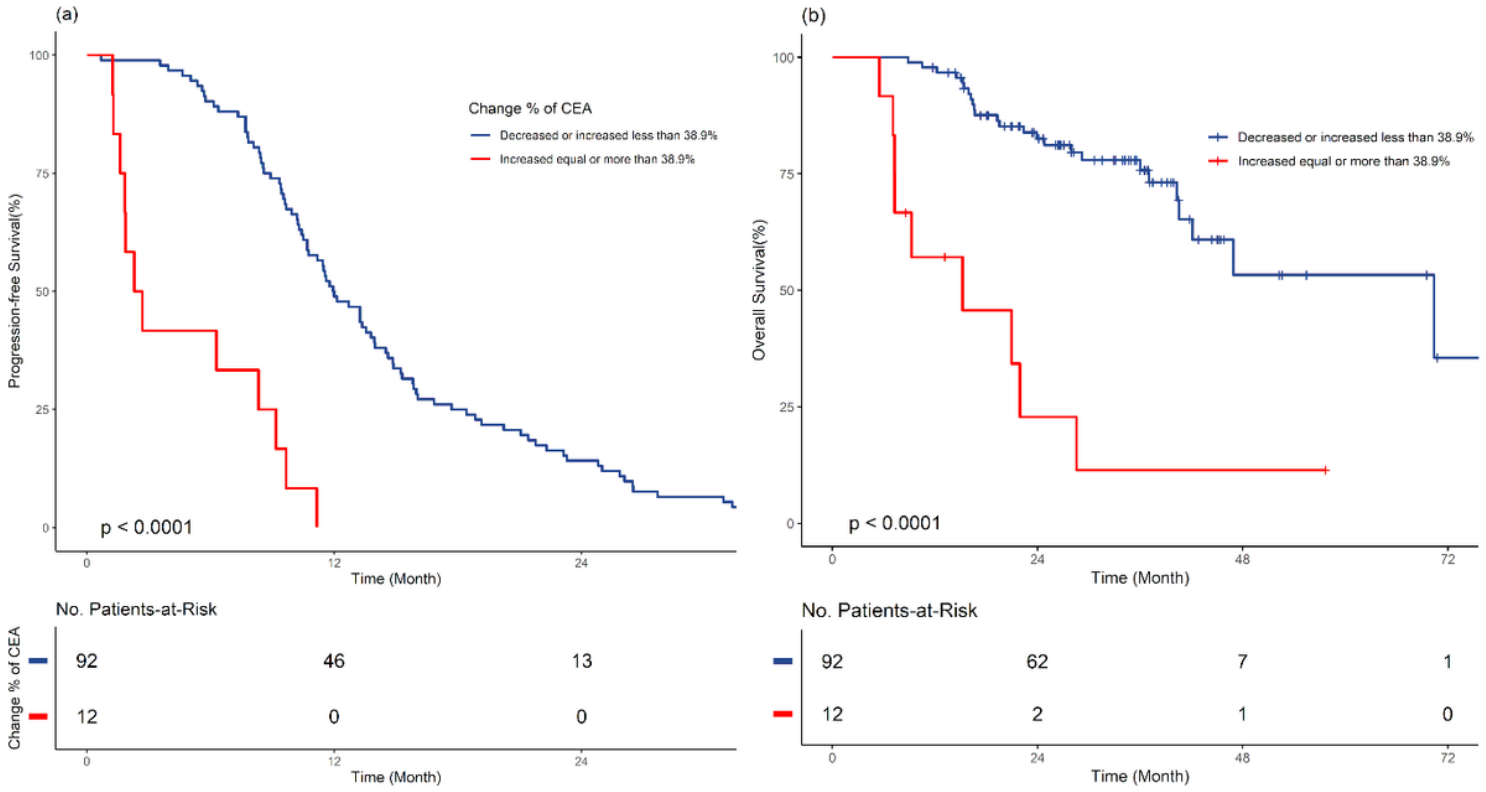

Figure 5

(a) Progression-free survival and (b) overall survival analysis according to the CEA cut-off value for patients who received chemotherapy plus anti-EGFR antibody

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- figureS1.tiff
- figureS2.tiff
- supplementarytable.docx