



# Combination of Changes in CEA and CA199 Concentration After Neoadjuvant Chemoradiotherapy Could Predict the Prognosis of Stage II/III Rectal Cancer Patients Receiving Neoadjuvant Chemoradiotherapy Followed by Total Mesorectal Excision

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**Background:** Previous studies have shown that the levels of serum tumor markers CEA and CA19-9 were related to chemoradiotherapy. Therefore, it has been assumed that dynamic monitoring of these markers could predict the prognosis of stage II/III rectal cancer (RC). Therefore, this study proposed to evaluate the prognostic value of changes in serum tumor biomarkers for stage II/III RC patients undergoing neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision (TME).

**Methods:** A total of 217 patients with stage II/III RC receiving NCRT followed by TME were retrospectively analyzed. Serum CEA and CA199 levels were measured within one week before NCRT and one week before TME. The optimal cut-off points of  $\Delta$ CEA% and  $\Delta$ CA199% for prognosis prediction were calculated by receiver operating characteristics (ROC) analysis. Independent prognostic predictors were identified by univariate and multivariate Cox regression analyses. To avoid the efficiency of  $\Delta$ CEA% and  $\Delta$ CA199% on serum tumor biomarker change (STBC) score, two models including and excluding  $\Delta$ CEA% and  $\Delta$ CA199% were established separately in multivariate analysis.

**Results:** The optimal cut-off point for  $\Delta$ CEA% and  $\Delta$ CA199% were  $-30.29\%$  and  $20.30\%$ , respectively. Univariate analysis showed that  $\Delta$ CEA%,  $\Delta$ CA199%, STBC score, ypT staging and yN staging could predict OS. ypT staging and STBC score could predict DFS. In multivariate analysis, only  $\Delta$ CA199% (HR = 0.468, 95% CI: 0.220–0.994,  $p = 0.048$ ), ypT staging (HR = 0.420, 95% CI: 0.182–0.970,  $p = 0.042$ ), and STBC score (HR = 0.204, 95% CI: 0.078–0.532,  $p = 0.001$ ) were independently related to OS; and STBC score (HR = 0.412, 95% CI: 0.216–0.785,  $p = 0.007$ ) and ypT staging (HR = 0.421, 95% CI: 0.224–0.792,  $p = 0.007$ ) were independently related to DFS.

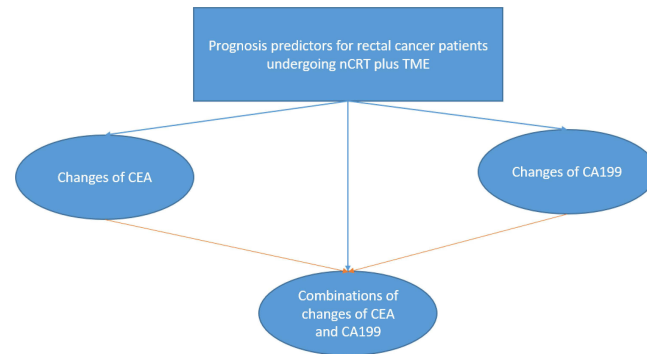
**Conclusion:** We established a combined STBC score to predict the prognosis of stage II/III RC patients receiving NCRT followed by TME. The predictive value of the combined score was stronger than a single marker alone and even stronger than several pathological indicators.

**Keywords:** neoadjuvant chemoradiotherapy, stage II/III rectal cancer, total mesorectal excision, prognosis, STBC score

## Introduction

The treatment of stage II/III rectal cancer (RC) is the most controversial part in the treatment of RC. Although NCCN guidelines recommend NCRT as the treatment of stage II/III RC followed by total mesorectal excision (TME),<sup>1</sup> since it could reduce the local recurrence rate from 21% to 10%, it could not prevent distant metastasis, and additional systemic chemotherapy after NCRT before the operation should be administered in patients with high poor prognosis. However,

## Graphical Abstract



additional systemic chemotherapy could cause an increased risk of toxicity.<sup>2,3</sup> Therefore, it is essential to distinguish stage II/III RC patients with good prognosis from those with poor.

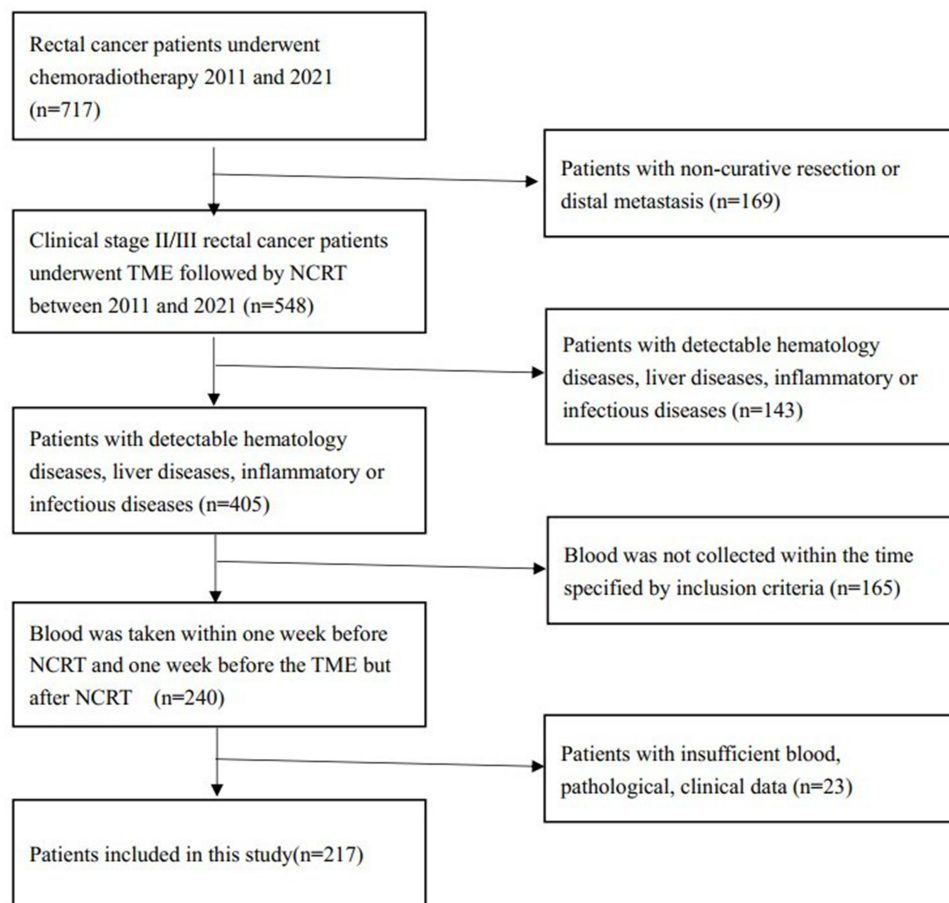
Previous studies have proposed many methods to predict the prognosis of stage II/III RC patients receiving NCRT followed by TME.<sup>4–8</sup> However, these methods had the following disadvantages: Firstly, some risk factors, such as pathological predictors, could only be obtained after surgery, which could not assist in deciding whether patients need extra systematic chemotherapy after NCRT but before surgery.<sup>4–8</sup> Secondly, the cost of some molecular or protein predictors could be substantial and would increase the burden on patients of the healthcare system.<sup>4–8</sup> Therefore, it is of great clinical significance to find a cheap and convenient predictor to predict the prognosis of stage II/III RC patients receiving NCRT followed by TME.

CEA and CA19-9 are cancer-specific markers widely applied in clinical practice. Blood tests for them are cheap, convenient and minimally invasive. And they are usually elevated in patients with cancers.<sup>9</sup> During chemotherapy, CEA and CA19-9 usually change dynamically.<sup>10</sup> Previous studies have shown CEA and CA19-9 have good diagnostic and prognostic value in gastric, breast and colorectal cancers.<sup>9–11</sup> However, these studies were either limited to CEA and CA19-9 changes after chemotherapy instead of after NCRT or focused on stage IV RC instead of stage II/III.<sup>12,13</sup> Moreover, previous research only evaluated the prognostic value of single tumor biomarker changes, instead of combining them.<sup>14,15</sup> It was predicted that a combination of changes of tumor markers might predict tumor shrinkage or growth and prognosis better.<sup>15</sup> To verify this hypothesis, we retrospectively analyzed the CEA and CA19-9 levels of stage II/III RC patients who received NCRT followed by TME in our center. Subsequently, we evaluated the potential of the combination of changes in these markers as prognostic predictors.

## Methods

### Participants

This study was approved by the Ethics Committee of West China Hospital and complied with the Declaration of Helsinki. The informed consent was waived because it is a retrospective study and the data are anonymous. Patients with stage II/III RC receiving NCRT followed by TME between 2011 and 2021 at our center were reviewed. Patients fulfilling the inclusion criteria were enrolled: 1) Adenocarcinoma proven by colonoscopy. 2) Clinical Stage II/III. 3) The patient received NCRT (radiotherapy (45–54Gy) with concomitant oral capecitabine or intravenous infusion of 5-Fu) followed by TME. 4) Blood was taken within one week before NCRT (and one week before the TME but after NCRT). 5) Patients with annal canal preserved. The following patients were excluded: 1) Patients with other cancers of distal metastasis. 2) patients treated with non-radical surgery. 3) Patients with liver dysfunction or liver disease. 4) Patients with insufficient blood, pathological, and clinical data. 5) Patients only received neoadjuvant chemotherapy. The patient screening flowchart is shown in [Figure 1](#).



**Figure 1** Patients screening flow chart.

Diagnosis and treatment of patients were all following NCCN guidelines.<sup>1</sup> Before treatment, the RC stage and metastasis status were evaluated by chest and abdomen enhanced CT, pelvic MRI, and rectal ultrasound. TME was performed 6–10 weeks after the end of NCRT.<sup>1</sup>

This study was approved by the committee of West China Hospital, and informed consent was waived since this was a retrospective study.

## Follow Up

Cancer recurrence was based on imaging or colonoscopy diagnosis. Physical examination and tumor marker detection (CEA, CA19-9) were performed every three months for three years, thereafter every six months until the fifth year. In the first three years, CT or MRI was reexamined every three months, and then every six months. The colonoscopy was performed every year.<sup>1,16,17</sup>

Primary outcomes were disease-free survival (DFS) and overall survival (OS).<sup>18,19</sup> The time interval from operation to local recurrence or distant metastasis was defined as DFS.<sup>20</sup> OS was defined as survival time from operation until death by any reason or last follow-up.<sup>19</sup> Patients were censored if no local recurrence and distant metastasis were detected at the last follow-up or on the date of death.<sup>18</sup>

## Definitions and Data Collection

Clinicopathological data were gained from patients' electronic medical records. The collected clinicopathological data were all closely related to the prognosis of RC patients reported by previous studies, including ypT staging, ypN staging,

pathological CRM status, pathological perineural invasion, pathological lymphatic invasion, pathological vascular invasion, CEA level, and CA199 level.

$\Delta$ CEA% was defined as follows: (post-chemoradiotherapy CEA – pre-chemoradiotherapy CEA)/pre-chemoradiotherapy CEA\*100%.  $\Delta$ CA199% as follows: (post-chemoradiotherapy CA199 – pre-chemoradiotherapy CA199)/pre-chemoradiotherapy CA199\*100%. The optimal cut-off points of  $\Delta$ CEA% and  $\Delta$ CA199% for prognosis prediction were calculated by receiver operating characteristic analysis. Serum tumor biomarker change (STBC) score was defined as follows: Score 0:  $\Delta$ CEA% <-30.29% and  $\Delta$ CA199% <20.30%. Score 2:  $\Delta$ CEA% >-30.29% and  $\Delta$ CA199% >20.30%. Score 1: other situations.

## Statistical Analysis

Receiver operator characteristic (ROC) curves were employed to determine cut-off points.<sup>21</sup> The Kaplan–Meier method was adopted for survival analysis, and the Log rank test was used to test the significance of differences between groups.<sup>22,23</sup> The factors affecting the prognosis of RC were measured by univariate and multivariate Cox regression models.<sup>24</sup> Multivariate analysis was conducted with all factors of  $P < 0.05$  in the univariate.<sup>25</sup> All statistical analyses were carried out by SPSS ver. 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered if  $p < 0.05$ .<sup>26</sup>

To prevent the effect of  $\Delta$ CEA% and  $\Delta$ CA199% on STBC score in multivariate analysis, two models including and excluding STBC score were established separately.

## Results

### Patients' Characteristics

Finally, a total of 217 patients were included in this study (Figure 1), with 137 males and 80 females. The median age of all included patients was 56.0, with an interquartile range (IQR) of 50.6 to 66.0. Pathological data presented that thirteen patients had vascular invasion, thirty-eight patients had perineural invasion, six patients had positive CRM status, and thirteen patients had lymphatic invasion. One hundred and eight patients were in ypT0-2 staging, while 109 in ypT3-4 staging. Fifty-four patients had lymph node metastasis, while 163 patients did not have.

The median follow-up period was 33 months (interquartile range 23–49 months), with ten patients (4.6%) lost to follow up. During this period, 30 patients died, and 45 patients developed tumour recurrence. Among these 45 patients, only two patients presented local recurrence, the rest were distal metastasis. All characteristics of the included patients are summarized in Table 1.

### Survival Outcome by Kaplan–Meier Curves

ROC curves yielding that the best cut-off point of  $\Delta$ CEA% and  $\Delta$ CA199% for survival status were –30.29% and 20.30%, separately.

Kaplan–Meier curves presented that, in terms of OS,  $\Delta$ CEA% < –30.29%,  $\Delta$ CA199% < 20.30% and lower STBC score were all related to better outcomes (Figures 2–34). Regarding DFS,  $\Delta$ CEA% > –30.29%,  $\Delta$ CA199% > 20.30% trends toward a worse outcome. However, the difference was not significant (Figures 5–67). Only a higher STBC score had a significantly poorer outcome.

### Univariate and Multivariate Analysis for OS

In terms of univariate analysis,  $\Delta$ CEA%,  $\Delta$ CA199%, STBC score, ypT staging and ypN staging were able to predict prognosis (Table 2). Multivariate analysis model 1 revealed that  $\Delta$ CA199% (HR = 0.468, 95% CI: 0.220–0.994,  $p = 0.048$ ) could independently predict patients prognosis, while  $\Delta$ CEA% (HR = 0.558, 95% CI: 0.259–1.201,  $p = 0.136$ ) failed (Table 3). Multivariate analysis model 2 suggested that STBC score (HR = 0.204, 95% CI: 0.078–0.532,  $p = 0.001$ ) and ypT staging (HR = 0.426, 95% CI: 0.184–0.986,  $p = 0.046$ ) were independent prognosis predictors, and STBC score had the highest prediction potency among all clinic-pathological indicators (Table 3).

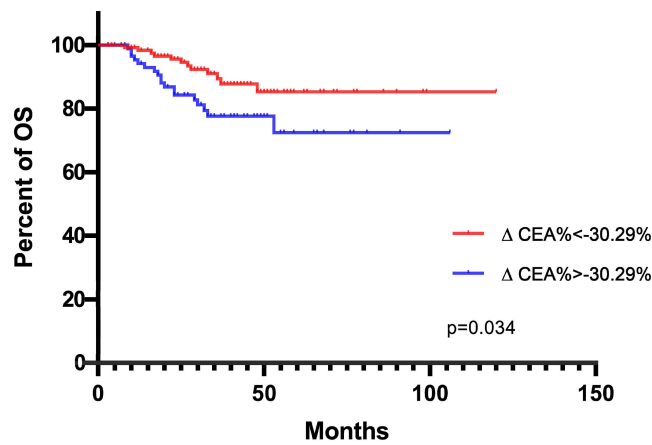


Figure 2 K-M curves depicting OS according to  $\Delta \text{CEA}\%$  status.

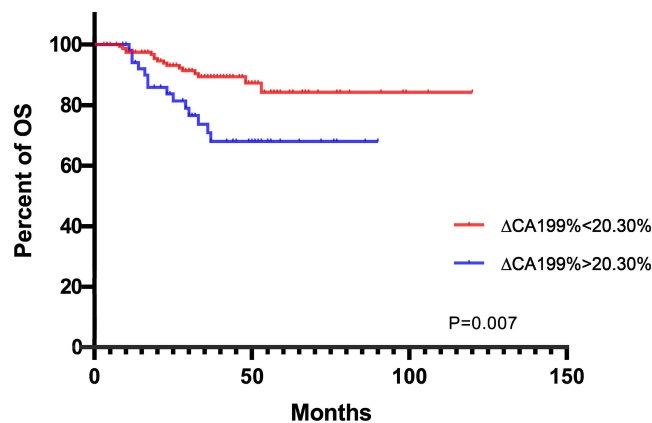


Figure 3 K-M curves depicting OS according to  $\Delta \text{CA199}\%$  status.

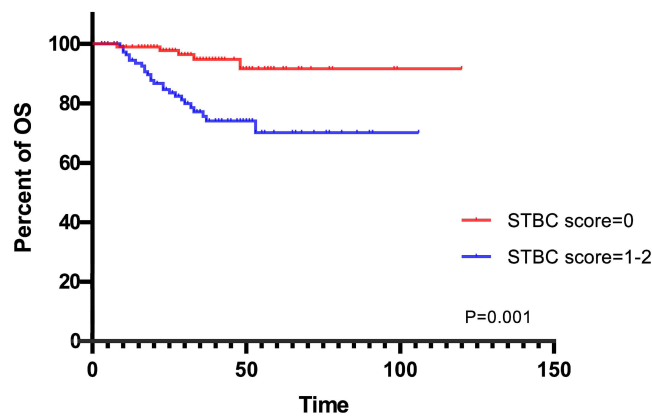


Figure 4 K-M curves depicting OS according to STBC score.

## Univariate and Multivariate Analysis for DFS

According to the Cox regression analysis,  $\Delta \text{CEA}\%$  and  $\Delta \text{CA199}\%$  failed to predict DFS. Only STBC score (HR = 0.412, 95% CI: 0.216–0.785,  $p = 0.007$ ) and ypT staging (HR = 0.421, 95% CI: 0.224–0.792,  $p = 0.007$ ) could independently predict DFS whether in terms of univariate or multivariate analysis (Tables 4 and 5).

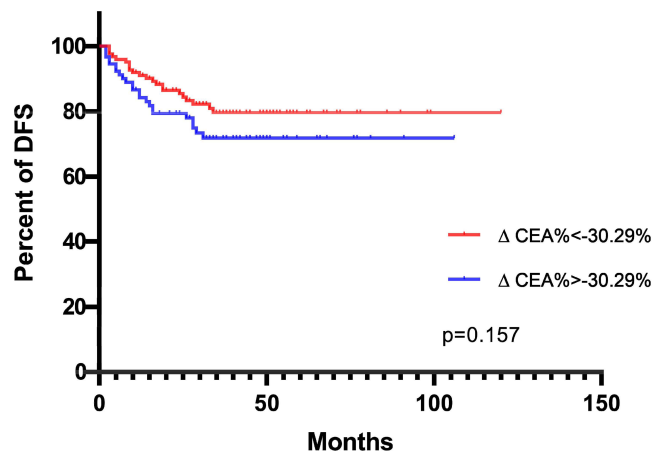


Figure 5 K-M curves depicting DFS according to  $\Delta$ CEA% status.

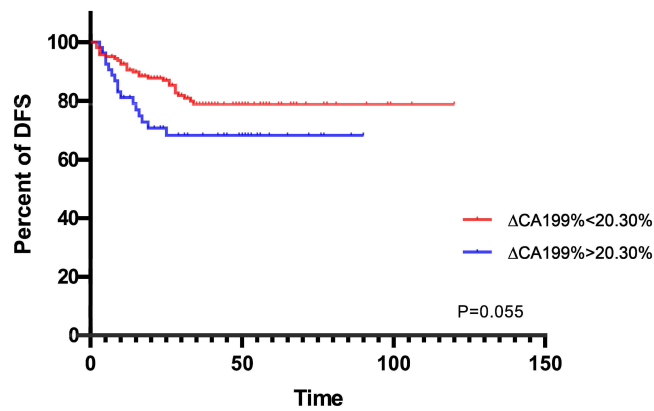


Figure 6 K-M curves depicting DFS according to  $\Delta$ CA199% status.

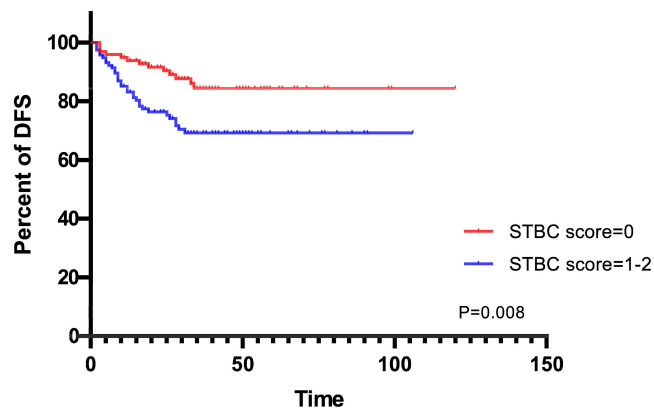


Figure 7 K-M curves depicting DFS according to STBC score.

## Discussion

The present study results showed that the combination of changes in tumor markers after NCRT was more effective in predicting prognosis than using one indicator alone. In terms of OS, although univariate analysis proved that lower  $\Delta$ CEA% and  $\Delta$ CA199% were potential factors for better outcomes, in multivariate analysis, only STBC score,

**Table 1** Characteristics of Patients with Rectal Cancer Who Underwent Preoperative CRT

Variables	Number (%) / Median (IQR)
Age	56.0 (50.0–66.0)
$\Delta$ CEA%	-35.8% (-69.5% to - 5.50%)
$\Delta$ CA199%	-3.39% (-35.21% to 19.12%)
STBC score	
Score 0	99 (45.6%)
Score 1–2	118 (54.4%)
Gender	
Male	137 (63.1%)
Female	80 (36.9%)
Pathologic status	
Vascular invasion	13 (6.0%)
Lymphatic invasion	13 (6.0%)
Perineural invasion	38 (17.5%)
CRM invasion	6 (2.8%)
ypT staging	
ypT0-2	108 (49.8%)
ypT3-4	109 (50.2%)
ypN staging	
ypN negative	163 (75.1%)
ypN positive	54 (24.9%)
Follow-up period (months)	33 (23–49)
Numbers of patients lost to follow up	10 (4.6%)
Numbers of patients died during follow-up	30 (13.8%)
Numbers of patients developed recurrence during follow-up	45 (20.7%)

**Abbreviations:** yp, pathologic status after neoadjuvant chemoradiotherapy;  $\Delta$ CEA %, (post-chemoradiotherapy CEA – pre-chemoradiotherapy CEA)/pre-chemoradiotherapy CEA\*100%;  $\Delta$ CA199 %, (post-chemoradiotherapy CA199 – pre-chemoradiotherapy CA199)/ pre-chemoradiotherapy CA199\*100%.

**Table 2** Univariate Cox Regression Analysis for OS

Characteristics		HR (95% CI)	P- value
Gender	Male vs female	1.939 (0.832–4.520)	0.125
$\Delta$ CEA%	< -30.29% vs > -30.29%	0.454 (0.219–0.943)	0.034
$\Delta$ CA199%	< 20.30% vs > 20.30%	0.374 (0.183–0.767)	0.007
STBC score	0 vs 1–2	0.208 (0.080–0.544)	0.001
Pathological vascular invasion	Absent vs present	0.498 (0.1501.648)	0.253
Pathological lymphatic invasion	Absent vs present	0.357 (0.124–1.030)	0.057
Pathological perineural invasion	Absent vs present	0.600 (0.256–1.407)	0.240
Pathological CRM	Negative vs positive	0.552 (0.131–2.330)	0.419
ypT staging	(0–2) vs (3–4)	0.376 (0.168–0.845)	0.018
ypN staging	Negative vs positive	0.468 (0.225–0.972)	0.042

**Abbreviations:** yp, pathologic status after neoadjuvant chemoradiotherapy;  $\Delta$ CEA %, (post-chemoradiotherapy CEA – pre-chemoradiotherapy CEA)/pre-chemoradiotherapy CEA\*100%;  $\Delta$ CA199 %, (post-chemoradiotherapy CA199 – pre-chemoradiotherapy CA199)/ pre-chemoradiotherapy CA199\*100%; STBC score, serum tumor biomarkers change score.

$\Delta$ CA199%, and pT staging were associated with prognosis independently. Moreover, the STBC score was more significant. In terms of DFS,  $\Delta$ CEA% and  $\Delta$ CA199% failed to significantly predict prognosis. Only STBC score and yp T staging were. Generally speaking, pathological indicators had the strongest predictive value in predicting prognosis.

**Table 3** Multivariate Cox Regression Analysis for OS

Characteristics		Multivariate Analysis			
		Model 1		Model 2	
		HR (95% CI)	p- value	HR (95% CI)	p- value
ΔCEA%	< -30.29% vs > -30.29%	0.558 (0.259–1.201)	0.136		
ΔCA199%	< 20.30% vs > 20.30%	0.468 (0.220–0.994)	0.048		
STBC score	0 vs 1–2			0.204 (0.078–0.532)	0.001
ypT staging	(0–2) vs (3–4)	0.420 (0.182–0.970)	0.042	0.426 (0.184–0.986)	0.046
ypN staging	Negative vs positive	0.680 (0.315–1.465)	0.324	0.574 (0.269–1.226)	0.152

**Notes:** Model 1, ΔCEA% and ΔCA199% were included in multivariate analysis, STBC score was not. Model 2: STBC score was in multivariate analysis, ΔCEA% and ΔCA199% were not.

**Abbreviations:** yp, pathologic status after neoadjuvant chemoradiotherapy; ΔCEA %, (post-chemoradiotherapy CEA – pre-chemoradiotherapy CEA)/pre-chemoradiotherapy CEA\*100%; ΔCA199 %, (post-chemoradiotherapy CA199 – pre-chemoradiotherapy CA199)/ pre-chemoradiotherapy CA199\*100%; STBC score, serum tumor biomarkers change score.

**Table 4** Univariate Cox Regression Analysis for DFS

Characteristics		HR (95% CI)	P- value
Gender	Male vs female	0.600 (0.310–1.163)	0.130
ΔCEA%	< -30.29% vs > -30.29%	0.656 (0.366–1.177)	0.157
ΔCA199%	< 20.30% vs > 20.30%	0.550 (0.298–1.013)	0.055
STBC score	0–1 vs 2	0.419 (0.220–0.800)	0.008
Pathological vascular invasion	Absent vs present	0.456 (0.180–1.156)	0.098
Pathological lymphatic invasion	Absent vs present	0.463 (0.182–1.174)	0.105
Pathological perineural invasion	Absent vs present	0.554 (0.286–1.074)	0.080
Pathological CRM	Negative vs positive	1.392 (0.192–10.107)	0.744
ypT staging	(0–2) vs (3–4)	0.429 (0.228–0.807)	0.009
ypN staging	Negative vs positive	0.606 (0.326–1.126)	0.113

**Abbreviations:** yp, pathologic status after neoadjuvant chemoradiotherapy; ΔCEA %, (post-chemoradiotherapy CEA – pre-chemoradiotherapy CEA)/pre-chemoradiotherapy CEA\*100%; ΔCA199 %, (post-chemoradiotherapy CA199 – pre-chemoradiotherapy CA199)/ pre-chemoradiotherapy CA199\*100%; STBC score, serum tumor biomarkers change score.

**Table 5** Multivariate Cox Regression Analysis for DFS

Characteristics		HR (95% CI)	P- value
STBC score	0 vs 1–2	0.412 (0.216–0.785)	0.007
ypT staging	(0–2) vs (3–4)	0.421 (0.224–0.792)	0.007

**Abbreviations:** yp, pathologic status after neoadjuvant chemoradiotherapy; STBC score, serum tumor biomarkers change score.

However, in multivariate analysis, STBC score had stronger prognostic power than pathological vascular invasion, perineural invasion, lymphatic invasion, CRM status, and lymph node metastasis, in terms of both DFS and OS.

In recent years, it has been a hot spot in clinical research to distinguish patients with poor prognoses after NCRT and admit more aggressive treatment.<sup>2,27,28</sup> Radiological examinations (CT and MRI) are routine examinations after NCRT, which could evaluate tumor regression.<sup>29–31</sup> Unfortunately, due to the high cost and/or fear of radiation damage, numerous patients have poor compliance with imaging examination.<sup>29–31</sup> In addition, numerous studies proved that although NCRT could promote tumor regression and reduce local recurrence, it could not improve the long-term prognosis of patients.<sup>2,27,28,32</sup>

Some molecular or protein could also be prognostic predictors. Voboril et al revealed that high NF-k $\alpha$ /P65 positivity in RC samples was associated with worse OS and DFS.<sup>33</sup> Qin et al disclosed that OS was improved in XRCC2-negative

RC patients compared with XRCC2-positive RC patients.<sup>34</sup> Zaanan displayed that RC with high Beclin 1 expression was significantly less likely to regression after chemoradiation treatment.<sup>35</sup> Nevertheless, these molecules or protein markers had the following disadvantages in clinical practice: First of all, the detection of these markers could increase the economic burden for patients since it was expensive. Secondly, these new molecules or proteins could only be detected in large medical centers, which was difficult to use widely in clinical practice. Lastly, these new indicators lack uniform standards, and the test results of different medical centers may vary greatly. CEA and CA199 have been widely detected in clinic, which are cheap and convenient, and the detection standards among different hospitals are relatively uniform.

Pathological indicators are usually considered as the most accurate prognostic indicators.<sup>36,37</sup> Previous studies revealed that pathological lymphatic invasion, perineural invasion, vascular invasion, CRM invasion, and LN metastasis were associated with a worse outcome.<sup>36–38</sup> Nevertheless, pathological features were incomprehensible to collect, frequently impacted by the quality of operation and specimen processing, had high subjectivity and were difficult to quantitate.<sup>36,37</sup> Additionally, the pathological indicator could only be retrieved after surgery, and extra chemotherapy before and after NCRT could not be determined.<sup>37</sup> Meanwhile, the STBC score could be obtained before surgery.

Tumor markers were cheap and widely used in clinical practice. RECIST standard stipulates that tumor markers could be used as additional indexes to evaluate the curative effect.<sup>39,40</sup> For example, after a retrospective analysis of 531 cases of ovarian cancer, Duffy pointed out that continuous monitoring of CA125 levels could reflect the efficacy of chemotherapy for ovarian cancer.<sup>41</sup> Furthermore, the decrease of CA125 levels was related to the prognosis of ovarian cancer.<sup>41</sup> Numerous studies have also revealed that CEA and CA19-9 levels were closely associated with the chemotherapy efficacy of advanced and metastatic RC.<sup>42–44</sup>

Serum carcinoembryonic antigen (CEA) is a glycoprotein anchored on the surface of glycosylphosphatidylinositol (GPI) cells,<sup>45,46</sup> which plays an essential part in the metastasis and dissemination of RC cells.<sup>45,46</sup> The impact of serum CEA level on prognosis has been thoroughly discussed: Patients with elevated CEA levels have a poor tumor response and increased risk of recurrence.<sup>47,48</sup> Yang et al also pointed out that for RC patients with pre-CRT CEA greater than 6 ng/mL, the decrease rate of serum CEA level after CRT could be the prognostic factor of DFS.<sup>48</sup> Our study result was consistent with many previous studies.

CA19-9 is an antigen expressed by the glycosylated extracellular MUC1 protein that promotes angiogenesis and cell adhesion.<sup>49,50</sup> The prognostic value of CA199 in RC patients has been established by research. Zheng et al reported that the elevated CA199 was an independent risk factor for worse prognosis in LARC patients.<sup>51</sup> Nonetheless, CA19-9 is affected by various gastrointestinal tumors. Esophageal cancer, colorectal cancer, and hepatocellular carcinoma can all secrete CA199.<sup>49,50</sup> Despite cancer, pancreatitis, liver cirrhosis, and bile duct diseases could all increase CA199.<sup>52</sup> Consequently, it has not been widely used to predict the prognosis of RC patients in clinic, especially in RC patients who underwent NCRT.

Instead of the single serum tumor biomarker at a single time point, STBC was a score that combined  $\Delta$ CEA% and  $\Delta$ CA199%. We supposed that the STBC score could better predict prognosis in RC patients mainly based on three reasons. First, the STBC score combined two serum tumor biomarkers that were closely related to prognosis. Second, the STBC score considered changes in tumor biomarkers at multi-time points. Finally, the application of the ROC curve, not just whether the tumor index exceeds the standard value, contributed to finding the best cut-off value of prognosis prediction.

Our study's most important clinical significance was as follows: Firstly, we focused on the changes of serum tumor markers at multi-time points. Moreover, we focused specifically on Stage II/III patients undergoing NCRT, a research hot spot. Thirdly, we adopted the ROC curve to determine the optimal cut-off point. Finally, we combined changes of serum tumor markers. STBC score may not only assess the risk of Stage II/III patients but also contributed to making treatment decisions. In detail, patients with high STBC scores should be treated aggressively, and postoperative adjuvant therapy may be more helpful and adaptable to these patients.

However, potential bias may exist due to the small sample size, the relatively strict criteria, and the analyzed data only from a single center. Consequently, further research is needed, especially multi-center prospective research. Additionally, it is possible that the cut-off values were not adequate for patients from other hospital centers, which need further investigation. However, the ideas and methods in this research can be widely used.

## Conclusion

In this research, we established a combined serum tumor biomarker change score to predict the prognosis of stage II/III RC patients receiving NCRT followed by TME. The combined score could effectively predict the prognosis. Its predictive value was stronger than a single marker alone and even stronger than several pathological indicators closely related to prognosis.

## Abbreviations

NCRT, neoadjuvant chemoradiotherapy; STBC, serum tumor biomarkers change score; OS, overall survival; DFS, disease-free survival; ROC, receiver operating characteristic.

## Data Sharing Statement

Inquiries can be directed to the corresponding author yuxixi1052006@126.com.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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