An Integrated Model of Pathological Complete Response and Postoperative CEA Predicts Survival and Benefit of Adjuvant Chemotherapy for Locally Advanced Rectal Cancer

Shu-Biao Ye
Sun Yat-sen University Sixth Affiliated Hospital
Dong-Wen Chen
Sun Yat-sen University Sixth Affiliated Hospital
Pei-Si Li
Sun Yat-sen University Sixth Affiliated Hospital
Zhen-Sen Lin
Sun Yat-sen University Sixth Affiliated Hospital
Jia-Hui Long
Sun Yat-sen University Sixth Affiliated Hospital
Yi-Kan Cheng (chengyk3@mail.sysu.edu.cn)
Sun Yat-sen University Sixth Affiliated Hospital https://orcid.org/0000-0001-6801-794X
Ping Lan
Sun Yat-sen University Sixth Affiliated Hospital

Primary research

Keywords: locally advanced rectal cancer, pathological complete response, postoperative CEA, prognostic model, adjuvant chemotherapy, distant metastasis-free survival

Posted Date: June 2nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-546136/v1

Abstract

Background:

Pathological complete response (pCR) and postoperative carcinoembryonic antigen (CEA) respectively represent pathological and biological response to treatment and prognostic indictors for locally advanced rectal cancer. However, the prognostic significance of integrated pCR and postoperative CEA model is rarely investigated.

Methods:

This big-data intelligence platform-based cohort biomarker study extracted clinicopathological characteristics and postoperative CEA of 919 locally advanced (clinical stage II-III) rectal cancer patients receiving neoadjuvant treatment from 6125 cases between April 2011 through September 2018 at Sun Yat-sen University, the Sixth Affiliated Hospital. An integrated model was constructed using pCR combined with the cut-off value of postoperative CEA generated from the receiver operating characteristic (ROC) curve. The model stratified locally advanced rectal cancer patients into four groups.

Results:

Both pathological response-pCR and biological response-postoperative CEA were independent prognostic indicators. In all patients, the 3-year distant metastasis-free survival (DMFS) (70.0%) and disease-free survival (DFS) (64.8%) rates were significantly lower in patients without pCR and postoperative CEA > 2.78 ng/ml (all p values < 0.05). Among patients treated with < 3 months of postoperative adjuvant chemotherapy (ACT), all others had higher 3-year DMFS and DFS rates. Among patients receiving ≥ 3 months of ACT, those without pCR had similar 3-year DMFS rates regardless of postoperative CEA level.

Conclusions:

The response integrated model with pCR and postoperative CEA not just effectively predict DMFS and DFS in locally advanced rectal cancer patients, but also was a predictive tool to potentially modify the optimal duration of ACT for locally advanced rectal cancer patients.

Introduction

With the introduction of preoperative chemoradiotherapy (CRT) and standardized total mesorectal excision (TME), a milestone surgical technique, locoregional control has greatly improved with local recurrence rate of 7%-10% for locally advanced rectal cancer patients, while the distant control is not promising[1–4]. Therefore, distant metastasis has currently become the major challenge for disease failure. The American Joint Committee on Cancer/the International Union Against Cancer (AJCC/UICC) tumor–

node–metastasis (TNM) staging system is the key determinant in aiding diagnosis, monitoring treatment decisions and predicting prognosis including distant metastasis[5]. However, among rectal cancer patients within the same staging categories, survival patterns, especially metastasis, vary widely[6, 7]. Thus, great efforts have been undertaken to determine the prognostic significance of potential biomarkers.

The degree of response to neoadjuvant treatment appears to be a prognosticator of survival in locally advanced rectal cancer[8]. Strong evidence exists that complete eradication of the tumor, which was defined as pathologic complete response (pCR), has been associated with better overall and disease-free survival[9, 10]. Almost 20% of patients responded well to neoadjuvant treatment and achieved pCR, who had a lower risk of developing distant metastases[11, 12]. Carcinoembryonic antigen (CEA) levels has been considered to be level I prognostic marker. Thus, some investigators have suggested that it be a supplement for the TNM staging system[13–15]. Not only patients with elevated pretreatment CEA[15, 16] but also postoperative CEA are associated with higher rates of distant metastases[17, 18]. Moreover, postoperative CEA level could be a biological indicator for treatment response.

Although pCR and postoperative CEA represent promising pathologic and biological biomarkers to predict treatment response and distant metastasis, there is a paucity of data to cooperate pCR and postoperative CEA into an integrated model. Postoperative adjuvant chemotherapy (ACT) has been the routine use based on an extrapolation of colon cancer patients[19–21]; however, the role of ACT in locally advanced rectal cancer is questioned due to the improvement of imaging, neoadjuvant treatment, and routine use of TME[22, 23]. Therefore, there is great demand to identify whether integration of pCR and postoperative CEA model after curative resection could effectively predict metastasis and survival outcomes among patients in different ACT duration groups. The aim of the present study was to develop and assess an integrated pCR and postoperative CEA prognostic model.

Method

Data extraction and patient cohort

Consecutive patients who received neoadjuvant treatment and curative resection for clinical stage II-III rectal cancer were extracted from the prospectively maintained databases from April 2011 through September 2018 at Sun Yat-sen University, the Sixth Affiliated Hospital. Then we reviewed their clinical data from a big-data intelligence platform which had aggregated data from numerous hospital information systems (eg, admission, discharge, and transfer), electronic medical records, resource information systems (pathology, laboratory information), and endoscopy, ultrasound, and electrocardiography systems. The exclusion criteria for patients was lack of postoperative CEA. This study was approved by the Institutional Review Board of Sun Yat-sen University, the Sixth Affiliated Hospital and followed the reporting recommendation of tumor marker studies (REMARK) guidelines. All patients signed informed consent before the treatment.

CEA assessment and definition of pCR

Postoperative CEA was defined as the latest CEA value checked within 3 months after operation and before the initiation of ACT. Serum CEA was assayed at our institution using a Tosoh automated analyzer (TOSOH Inc., Tokyo, Japan). The reference range for pretreatment CEA was 0.0 to 5.0 ng/mL. Two gastrointestinal pathologists reviewed the surgical specimen independently according to the routine procedure of our institution. pCR was defined as no residual tumor cell in primary tumor and regional lymph nodes.

Treatment

All patients received neoadjuvant treatment and curative resection. Fluorouracil -based chemotherapy was delivered concurrently with radiation. Radiation was delivered at 1.8 to 2.0 Gy per day with a total of 23 to 25fractions (total dose, 46.0 to 50.4 Gy). The clinical target volume (CTV) included the mesorectal facia region, lymphatic drainage areas, i.e., mesorectal, internal iliac, and presacral lymph nodes. The regimens of neoadjuvant chemotherapy alone were mFOLFOX6 (fluorouracil and oxaliplatin) and FOLFOXIRI (fluorouracil, oxaliplatin and irinotecan) as FOWARC[24] and FORTUNE[25] clinical trial described.

Follow-up and statistical analysis

Follow-up duration was measured from the first day of treatment to either the day of death or the day of last follow-up. Surveillance of patients included physical examination, interval history, serum CEA testing, imaging and colonoscopy. Patients were followed every 3–6 months during the first 2 to 3 years, and every 1 year thereafter. Distant metastasis-free survival (DMFS) or local recurrence-free survival (LRFS)was defined as the duration of the first day of treatment to the day of distant or local recurrence. Disease-free survival (DFS) was defined as time to the date of confirmed relapse of disease or death.

SPSS 22.0 (SPSS, Inc, Chicago, IL) was used to perform all statistical analyses. The cut-off point for postoperative CEA level was determined using the receiver operating characteristics (ROC) curve analysis. Mann-Whitney U test and $\chi 2$ test (or Fisher's exact test, if appropriate) was used to compare continuous clinical variables and categorical data, respectively. Univariable survival was compared using the log-rank test and Kaplan-Meier curves was used to generate time-to-event data. The Cox multivariate proportional-hazards regression analysis was used to calculate P values, hazard ratios (HRs), and 95% confidence intervals (CIs). Clinical characteristics (age, gender, BMI, T and N categories, postoperative CEA, pCR and ACT) were included as covariates. Two-side p-value less than 0.05 was considered significant.

Results

Clinical characteristics and patient outcomes

Clinical characteristics of patients were shown in Table 1. A total of 1065 patients who received neoadjuvant treatment and curative resection for clinical stage II-III rectal cancer patients were identified from the big-data intelligence platform. One hundred forty-six patients were excluded due to the lack of postoperative CEA, which mainly caused by loss of follow-up examination. Among the remaining 919 patients, 650 (70.7%) patients were male and the median (IQR) age was 55 (19–88) years old. The

median (IQR) preoperative and postoperative CEA value was 3.83 ug/ml (0.5– 705.3 ug/ml) and 1.54 ug/ml (0.5– 54.1 ug/ml), respectively. The median (IQR) body mass index (BMI) was 22.5 kg/m^2 (12.8–34.9 kg/m^2). A total of 170 (18.5%) patients achieved pCR after neoadjuvant treatment. Median (IQR) duration of follow-up was 33.3 months (4.4-106.4 months). A total of 184 (19.7%) patients developed distant metastases, and 72 (7.8%) patients died and 5 of them died of non-cancer causes. Sixty-four patients (7.0%) developed local or regional recurrence. The 3-year DMFS, DFS, and LRFS rates for all patients were 77.5%, 72.9%, and 92.4%, respectively.

Table 1
Clinicopathological characteristics of patients with locally advanced rectal cancer (n = 919)

Characteristics	No of patients (%)
Gender	
Male	650 (73.5)
Female	269 (26.5)
Age (y)	
<60	577 (72.6)
≥60	342 (27.4)
Comorbidity	
Yes	190 (58.8)
No	729 (41.2)
Clinical T stage*	
T1	1 (0.1)
T2	33 (3.6)
T3	691 (75.2)
T4	193 (21.0)
NA	1 (0.1)
Clinical N stage*	
N0	192 (20.9)
N1	432 (47.0)
N2	293 (31.9)
NA	2 (0.2)
Clinical stage*	
II	192 (20.9)
III	725 (78.9)
NA	2 (0.2)
Distance from anal verge	

*According to the 8th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/ UICC) of the staging system.

Characteristics	No of patients (%)
≤ 5 cm	430 (46.8)
> 5 and ≤ 10 cm	421 (45.8)
> 10 cm	65 (7.1)
NA	3 (0.3)
Differentiation	
Well	524 (57.0)
Moderately	230 (25.0)
Poorly	109 (11.9)
NS	56 (6.1)
Adjuvant chemotherapy (ACT)	
No	104 (11.3)
< 6 cycles	366 (39.8)
≥ 6 cycles	449 (48.9)
*According to the 8th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/ UICC) of the staging system.	

Identification of the postoperative CEA cut-off value

Since postoperative CEA could normalize after neoadjuvant treatment and curative resection for the vast majority of patients, we attempted to identify the optimal cut-off point to investigate the prognostic value of postoperative CEA. The cut-off value of postoperative CEA was identified using the ROC curve. The points were 1.18 ng/ml for DMFS [AUC (area under the ROC) = 0.544, $p < 0.05$] and 2.78 ng/ml for DFS (AUC = 0.547, $p < 0.05$), respectively. According to a multi-institution analysis, the cut-off value for postoperative CEA for DMFS was 2.5ng/ml[26]. Therefore, a uniform cutoff value of 2.78 ng/ml (> 2.78 ng/ml versus ⩽2.78 ng/ml) was selected from DFS to stratify patients into high and low postoperative CEA groups. Both postoperative CEA cut-off value and pCR were significant prognostic indicators for DMFS and DFS (Table S1).

Prognostic value of pCR and postoperative CEA cut-off points

The 3-year DMFS (Fig. 1a), DFS, and LRFS rates for patients with pCR and without pCR were 95.8% versus 73.3%, 92.9% versus 68.4%, and 96.5 versus 91.4%, respectively (all p-values < 0.01). The 3-year DMFS (Fig. 1c), DFS, and LRFS rates for patients with a postoperative CEA ⩽2.78 and > 2.78 ng/ml were

79.0% versus 70.1%, 75.8% versus 58.9%, and 94.0% versus 84.6%, respectively (all p-values < 0.05). Altogether, patients with pCR or postoperative CEA ⩽2.78 ng/ml had better DMFS, DFS, and LRFS.

Integrated model of the pCR and postoperative CEA

To determine whether pCR plus postoperative CEA would be a more efficient tool to predict prognosis than either one alone, patients with locally advanced rectal cancer were assigned into four groups as follows: Group 1 (pCR and postoperative CEA ⩽2.78 ng/ml), Group 2 (pCR and postoperative CEA > 2.78 ng/ml), Group 3 (without pCR and postoperative CEA ⩽2.78 ng/ml), and Group 4 (without pCR and postoperative CEA > 2.78 ng/ml). The prognostic validity was compared using ROC curves. The AUCs of DMFS for pCR and postoperative CEA were 0.588 and 0.528, respectively, and rose to 0.621 when these two variables were integrated (all p values < 0.05, Fig. 2).

The prognostic value of the integrated model

The 3-year DMFS rates for the patients among Groups 1–4 were 98.0%, 94.6%, 79.5%, and 70.0%, respectively. And the 3-year DFS rates of 98.0%, 90.0%, 84.6%, and 64.8%, respectively. Group 4 patients had the worst 3-year DMFS (Fig. 3a) and DFS (Figure S1a) rates among the four groups (all *p*-values < 0.01), while patients in Group 3 had the second lowest rates (all *p*-values < 0.05). There was no significant difference between Group 1 and Group 2 in terms of the 3-year DMFS or DFS rates ($p = 0.413$ and $p = 0.195$).

The prognostic value of the integrated model for patients with different duration of ACT (< 3 months, and ≥ 3 months of ACT cohort)

One hundred and four patients refused to receive adjuvant chemotherapy. The adherence to ACT after neoadjuvant treatment and surgery is poor and the median duration of ACT is 3 months. As the benefit of the use and intensity of ACT in the setting of neoadjuvant treatment followed by surgery remains unclear, the prognostic significance of the integrated model were further investigated among patients stratified by different duration of ACT (no ACT, < 3 months, and ≥ 3 months). Since only 104 patients did not receive ACT, the trend was not obvious when patients were divided into 4 groups. For patients receiving < 3 months of ACT, the 3-year DMFS (Fig. 3b), and DFS (Supplementary Figure S1b) rates for patients in Groups 1 to 3 were 100.0% *versus* 95.1% *versus* 79.9%, 100.0% *versus* 90.1% *versus* 72.2%, and 95.5% *versus* 91.7% *versus* 77.5% respectively (all *p*-values > 0.05). The 3-year DMFS (Fig. 3b), and DFS (Supplementary Figure S1b) rates (68.3%, and 63.6%, respectively, all *p*-values < 0.05) were the lowest for Group 4.

For patients receiving ≥ 3 months of ACT, patients in Group 4 had the lower 3-year DMFS rates than those of Group 1 and Group 2, (70.0% *versus* 91.7%, 70.0% *versus* 95.5%, all *p*-values < 0.05). However, patients in Group 3 and Group 4 had similar 3-year DMFS rates (70.0% *versus* 77.5%, $p > 0.05$) (Fig. 3c). Moreover, Group 4 patients had the lowest 3-year DFS (Supplementary Figure S1c) rate (64.4%) in all four groups (all *p*-values < 0.05). Group 3 patients had lower 3-year DFS rates than patients among Group 1 and 2

(74.6% *versus* 95.5%, 74.6% *versus* 91.7%; all *p*-values < 0.05), whose 3-year DFS rates were similar (*p*-values > 0.05).

Both pCR and postoperative CEA were independent and significant prognostic indicators in multivariate analysis for DMFS and DFS in patients receiving ≥ 3 months of ACT and for DFS in patients with < 3 months of ACT, while only pCR was independent predictor for DMFS in patients treated with < 3 months of ACT. (Table 2).

Table 2
Multivariate analysis of the prognostic factors for distant recurrence-free survival and disease-free survival of patients with < 3 months and ≥ 3 months of adjuvant chemotherapy

Endpoints	variable	HR (95%CI)	*p* value
Patients with < 6 cycles of ACT			
Distant recurrence-free survival			
	pCR	9.116 (2.229–37.284)	0.002
Disease-free survival			
	pCR	4.306 (1.738–10.669)	0.002
	Postop CEA	1.864 (1.132–3.069)	0.014
Patients with ≥ 6 cycles of ACT			
Distant recurrence-free survival			
	pCR	3.444 (1.506–7.880)	0.003
	Postop CEA	1.766 (1.074–2.903)	0.025
Disease-free survival			
	pCR	4.146 (1.821–9.441)	0.001
	Postop CEA	1.984 (1.273–3.091)	0.002
pCR, pathologic complete response; postop CEA, postoperative carcinoembryonic antigen;			
The following variables were included in the Cox proportional hazards model by backward elimination: age (≥ 60 versus < 60 years), gender (male versus female), clinical T category (T4 versus T1–3), clinical N category (N2 versus N1 versus N0), postop CEA (> 2.78 versus ⩽2.78 ng/ml) and pCR (with versus without).			

Discussion

Applying neoadjuvant treatment and improved surgical technique- TME in locally advanced rectal cancer, local disease control has greatly improved during recent decades, while distant metastasis is now the leading cause of disease failure[1, 27]. Limited evidence for postoperative response biomarkers to predict distant metastasis was established. Therefore, it is necessary and urgent to identify postoperative prognostic factor for distant metastasis to aid physicians to optimize systemic ACT and follow-up surveillance.

pCR represents well pathologic response to neoadjuvant treatment and postoperative CEA represents biological response to neoadjuvant therapy and curative resection. Both of them have been identified as important prognostic factors in rectal cancer patients[11, 26]. The present study showed that patients with a postoperative CEA value more than 2.78 ng/ml had poor prognosis and pCR confirmed its prognostic value in identifying patients with various survival outcomes. To further stratify patients at high risk for distant metastasis, pCR and postoperative CEA were cooperated and the integrated model was showed an enhanced prognostic value. The present study is the largest study, to our knowledge, that assesses the association between integrated model and survival outcomes in patients with locally advanced rectal cancer.

The integrated model of pCR and postoperative CEA in our study effectively stratified locally advanced rectal cancer patients into three response subgroups. Patients with Group 4 (without pCR and higher post-operative CEA), Group 3 (without pCR and lower post-operative CEA), and Group 1 and 2 (with pCR) had the worst, intermediate, and best 3-year DMFS and DFS, respectively. These finding seems reasonable because pCR indicates tumor eradication and well response to treatment. Thus, patients with pCR had similar survival outcomes regardless of the level of postoperative CEA. Although CEA has been considered to promote metastasis[28] and cause treatment resistance through inhibition of programmed cell death[29], induction of cytokines[30] that promote cancer cell survival, inhibition of inflammatory responses[31], and increased cell adhesion[32], higher level of postoperative CEA in patients with pCR may be caused by other non-cancer related conditions. The current study supports the notion that a pCR is associated with excellent clinical outcome and represents a strong positive prognostic factor, and extensive efforts has been undertaken to improve the rate of pCR. The concept of total neoadjuvant therapy (TNT) is to administer chemoradiation and chemotherapy prior to resection, which aim to reduce the risk of micrometastases. Moreover, clinical evidence and phase II clinical trials demonstrated that TNT improved the compliance rates and the incidence of pCR[33, 34]. Furthermore, a phase III, randomized clinical trial NCT03177382 has been ongoing to compare TNT plus surgery with standard treatment. Other attempts to intensify neoadjuvant therapy have been investigated. The addition of oxaliplatin to concurrent chemoradiation is well known to achieve promising rate of pCR[24], and the introduction of immunotherapy to neoadjuvant treatment (NCT03854799, NCT04109755) might further improve the pCR rates and prognosis. However, patients without pCR and higher post-operative CEA had poorest treatment outcomes since neither pathologic nor biological response was promising. Overall, this is the first study to support the integration of response biomarkers- pCR and postoperative CEA as a prognostic tool using an intelligence platform.

Although ACT has been recommended in patients with locally advanced rectal cancer, the role of ACT remains to be defined due to many challenges[35] especially suboptimal compliance to complete chemotherapy on ACT. Thus, we further verified the prognostic utility of our integrated model among patients treated with different durations of ACT. The current integrated model classified patients underwent < 3 months of ACT into two response subgroups based on the risk of distant metastasis: low-risk (Group 1, 2, and 3), and high-risk (Group 4). Patients in Group 1 and 2 were sensitive to neoadjuvant therapy, achieved pCR and had the lowest risk of distant metastases. For Group 3 patients, the risk of distant metastasis was reduced by short duration of ACT; thus, there is no significant difference in risk of distant disease failure between low risk group (Group 1, 2) and intermediate risk group (Group 3). Additionally, among patients receiving ≥ 3 months of ACT, the integrated model failed to classify patients in Group 3 and Group 4, which seemed reasonable. Reinforced ACT may eradicate the micrometastatic loci to reduce the risk of distant metastasis for poor-response subgroup (Group 4) patients, which led to similar DMFS among patients between Group 3 and Group 4.

The present integrated model of response biomarkers is effective to predict survival and provided a way to explore appropriate therapeutic strategies for locally advanced rectal cancer patients. Consistent with numerous previous studies, the present research demonstrated that pathologic response biomarker- pCR is a beneficial prognostic factor. Therefore, intensification of neoadjuvant therapy to increase the incidence of pCR is suggested. TNT, more intensive chemoradiation or immunotherapy combined with chemoradiation might be alternative and should be encouraged to be investigated in clinical trials. The National Comprehensive Cancer Network (NCCN) guidelines recommend ACT for all patients receiving neoadjuvant therapy[36]. Nevertheless, more concern about risk-adopted ACT strategy has been raised and investigated[22, 37]. For patients who did not achieve pCR, biological response biomarker- postoperative CEA classify patients into two groups. Similar to IDEA trials[38] and a recent Veterans Health Administration analysis for locally advanced rectal cancer[22], our study indicated that short duration of ACT (< 3 months) might be sufficient for patients at intermediate risk after neoadjuvant treatment and curative resection. In contrast, more aggressive ACT therapy (≥ 3 months) was suggested for high risk patient to reduce the rate of distant metastasis.

The current study is the largest study to show the prognostic value and clinical applicability of the integrated model of pathologic response biomarker-pCR and biological response biomarker-postoperative CEA in locally advanced rectal cancer. However, several limitations of our study exist. First, this retrospective study has inevitable bias. Multi-institutional prospective studies are warranted to validate our findings in the future. Second, some portion of patients received neoadjuvant chemotherapy alone. However, our integrated model only cooperated postoperative response biomarkers after neoadjuvant treatment, which would be crucial to determine the administration of ACT and the following surveillance. Third, no evidence about the role of ACT on patients with pCR was provided due to limited sample of patients not undergoing ACT. Finally, other prognostic factors, such as circumferential resection margin, extramural vascular invasion (EMVI), perineural invasion (PNI), tumor deposit and molecular subtypes are warranted to achieve better predictions in prognosis. Above factors should be

included to establish effective nomograms to validate our findings in the future prospective multicenter studies.

Conclusion

The integrated pathologic response biomarker- pCR and biological response biomarker-postoperative CEA model predicts treatment outcomes more precisely, stratifies patients with different duration of ACT into different risk groups, and might aid clinicians to individualize ACT strategies to improve survival outcomes for locally advanced rectal cancer patients.

Abbreviations

Pathological complete response	pCR
carcinoembryonic antigen	CEA
receiver operating characteristic	ROC
distant metastasis-free survival	DMFS
disease-free survival	DFS
adjuvant chemotherapy	ACT
chemoradiotherapy	CRT
total mesorectal excision	TME
tumor–node–metastasis	TNM
clinical target volume	CTV
hazard ratios	HRs
confidence intervals	CIs
body mass index	BMI
extramural vascular invasion	EMVI
perineural invasion	PNI

Declarations

Funding

This work was supported by National Natural Science Foundation of China (Grant No. 81802441, 81703060), Natural Science Foundation of Guangdong Province (Grant No. 2017A030310644), China Postdoctoral Science Foundation funded project (Grant No. 2018T110911), the National Key Research and Development Program of China (N0.2017YFC1308800), Science and Technology Planning Project of

Guangdong Province (No. 201803040019, 20160916, 2014SC111), Key-Area Research and Development Program of Guangdong Province (2019B020229002), the Guangzhou Science and Technology Plan Project (201902020009), and National Key Clinical Discipline.

Ethics approval and consent to participate

Our study was approved by the Ethics Committee of Sun Yat-sen University, the Sixth Affiliated Hospital.

Consent for publication

Not applicable

Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

We declare no potential conflicts of interest.

Acknowledgement

We thank the staff members and appreciate their efforts at Medio Labs, a company that concentrates on the processing of medical data processing and the utilization of medical technology, for the establishment of the Medio Labs Intelligence Platform.

AUTHOR CONTRIBUTIONS

Conception and design: Ping Lan, Yi-Kan Cheng, Shu-Biao Ye

Financial support: Ping Lan, Yi-Kan Cheng, Shu-Biao Ye

Provision of study materials or patients: Ping Lan,

Collection and assembly of data: Yi-Kan Cheng, Shu-Biao Ye, Dong-Wen Cheng, Pei-Si Li, Zhen-Sen Lin, Jia-Hui Long

Data analysis and interpretation: Yi-Kan Cheng, Shu-Biao Ye, Ping Lan

Manuscript writing: All authors

Final approval of manuscript: All authors

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Figures

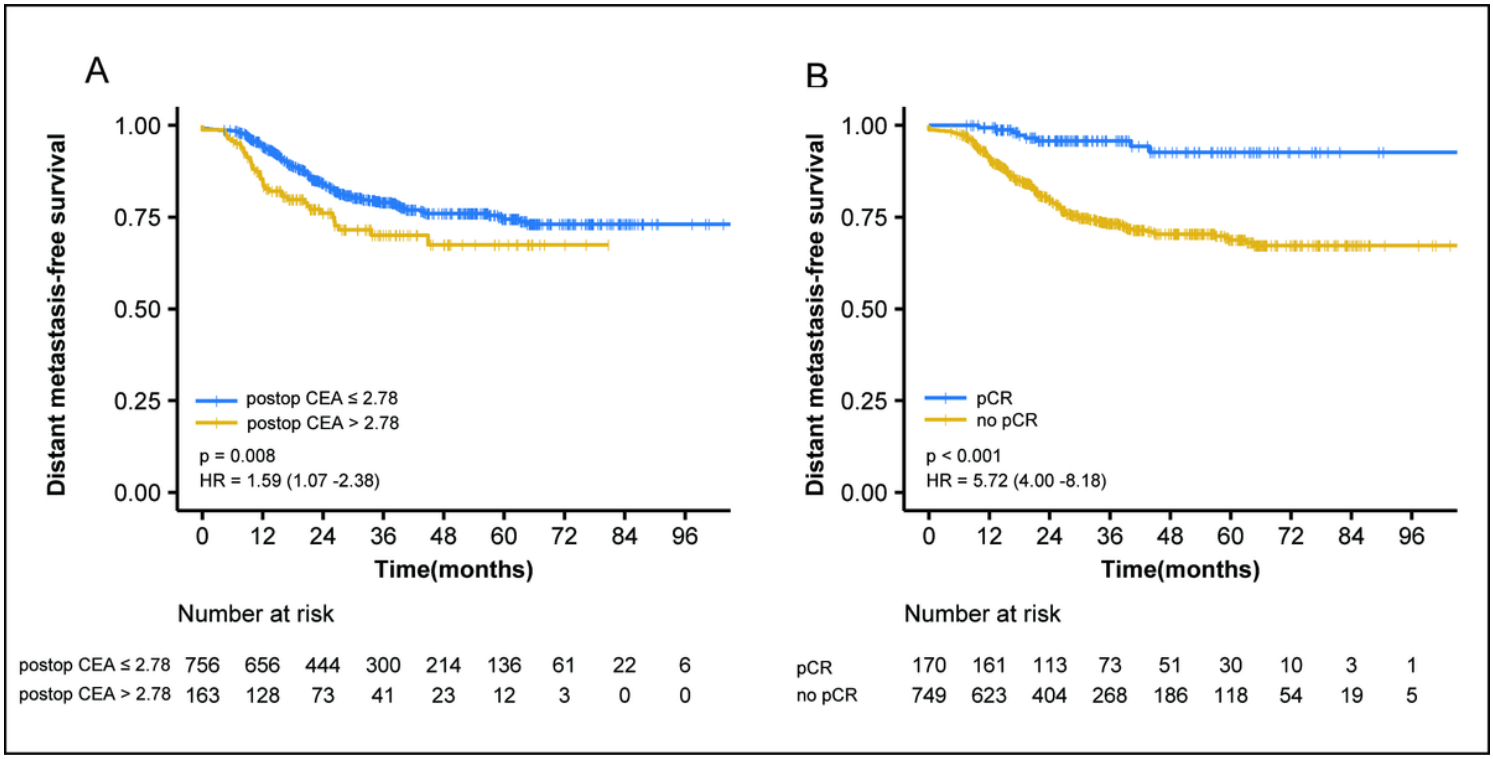

Figure 1

Distant metastasis-free survival analysis for pCR (a) and postoperative CEA (b) for the prognostic prediction. pCR, pathological complete response; postop CEA, postoperative carcinoembryonic antigen.

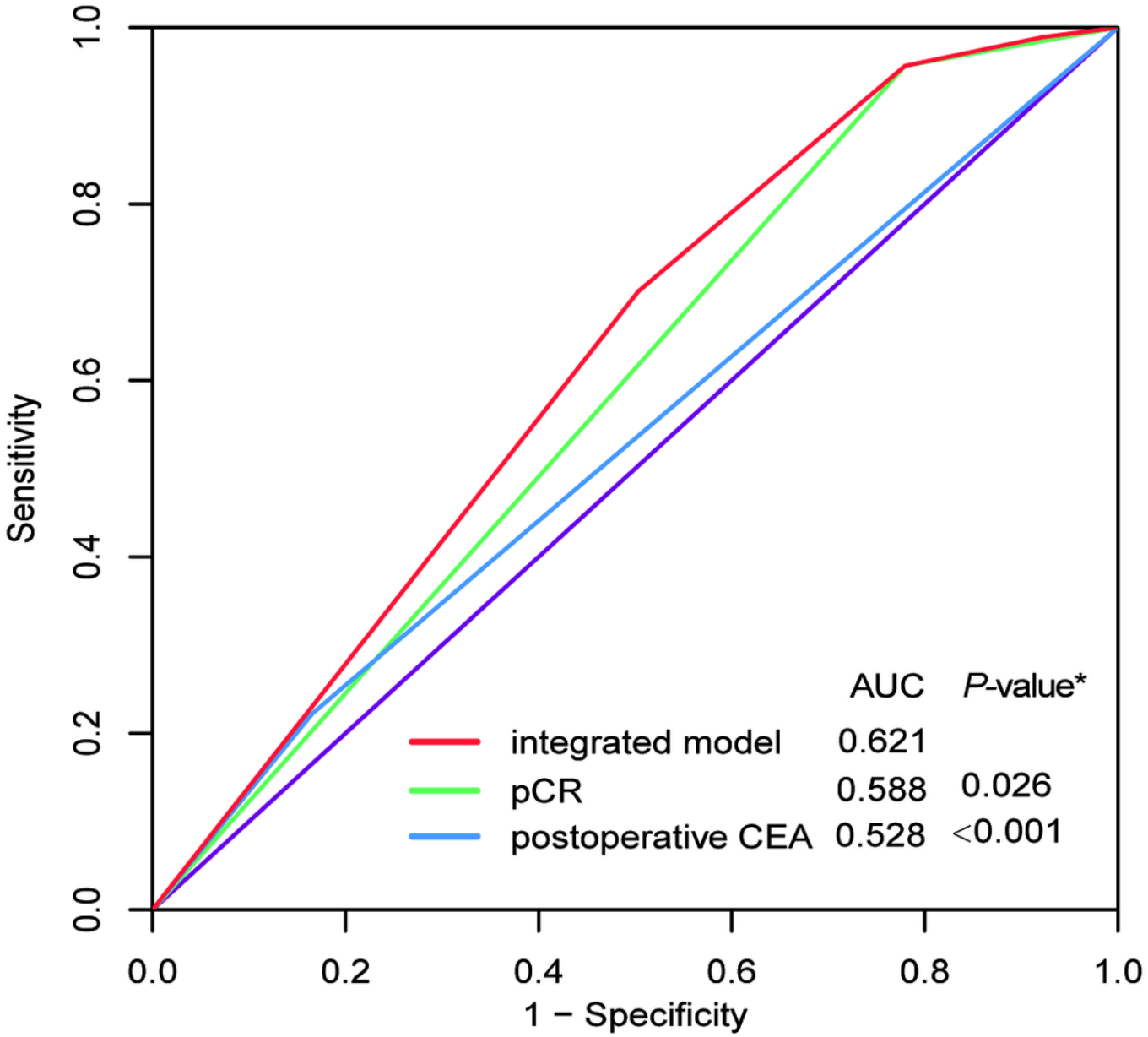

Figure 2

ROC curves for the cut-off points for pCR, postoperative CEA, and the integrated model. *Compared with the integrated model. pCR, pathological complete response; postop CEA, postoperative carcinoembryonic antigen; ROC, receiver operator characteristic.

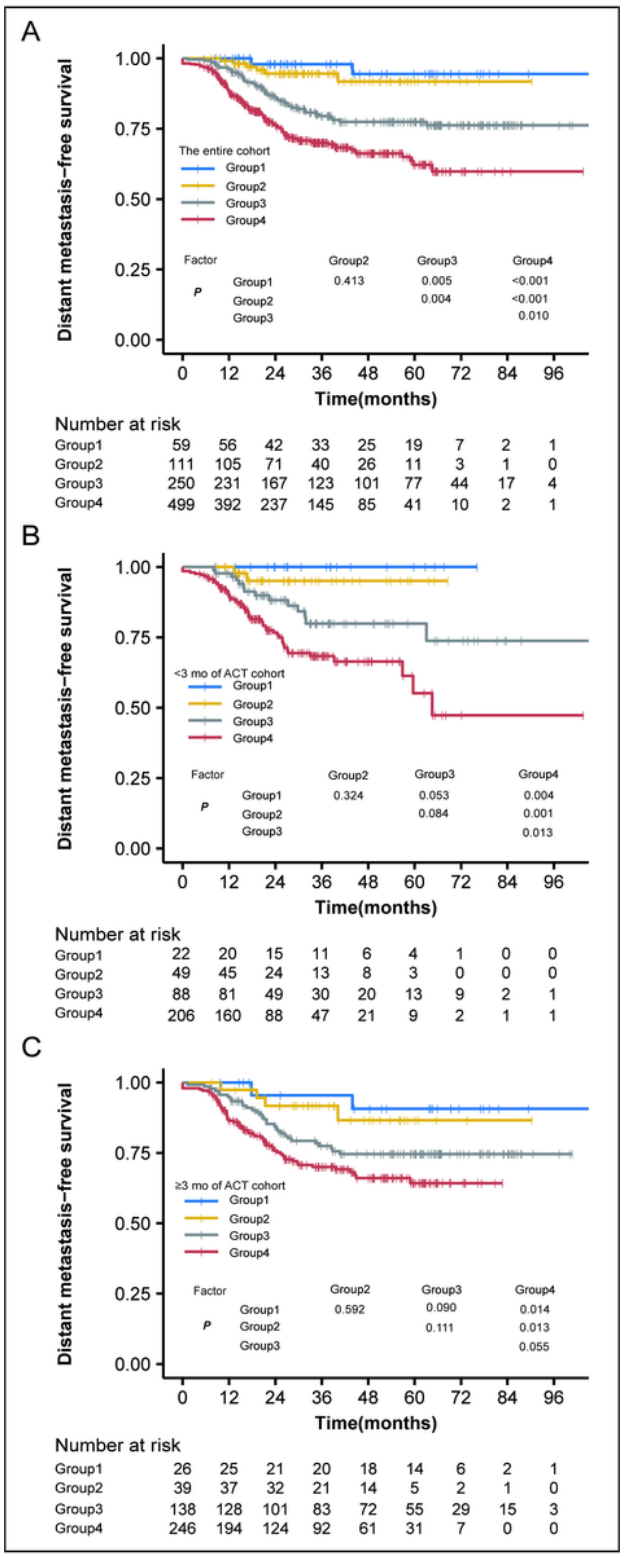

Figure 3

Survival analysis using the integrated model of pCR and postoperative CEA for the prognostic prediction of DMFS in all patients (a), and patients receiving <3 months of ACT (b) or patients receiving ≥3 months (c) of ACT. Group 1 (patients with pCR and postoperative CEA ⩽2.78 ng/ml), Group 2 (patients with pCR and postoperative CEA >2.78 ng/ml), Group 3 (patients with no pCR and postoperative CEA ⩽2.78 ng/ml), and Group 4 (patients with no pCR and postoperative CEA >2.78 ng/ml). DMFS, distant metastasis-free

survival; pCR, pathological complete response; postop CEA, postoperative carcinoembryonic antigen; ACT, adjuvant chemotherapy. mo, months.

Supplementary Files

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