

# Prognostic value of carbohydrate antigen125 and carcino embryonic antigen expression in patients with colorectal carcinoma and its guiding significance for chemotherapy

Jie Mao<sup>a</sup>, Peng Du<sup>a,\*</sup>, Han-teng Yang<sup>a</sup>, Huan Hu<sup>b</sup>, Shi-Yao Wang<sup>b</sup>, Xia Wu<sup>a</sup>, Zhi-Bin Cheng<sup>a,\*</sup>

## Abstract

The aim of this study is to evaluate the predictive value of carbohydrate antigen125 (CA125) and carcino embryonic antigen (CEA) expression and its guiding role of choosing chemotherapy regimen in post-operation patients with colorectal carcinoma.

The clinical data of all patients, including laboratory data and pathological data, were collected from the electronic medical records. Kaplan-Meier Log rank test, COX regression model and subgroup analyses were employed to assess the correlation between the expression of CA125 and CEA in patients with colorectal carcinoma and the survival, and the effect on chemotherapy efficacy.

Kaplan-Meier showed that CA125 expression is negatively related to the progression-free survival (PFS) of the post-operative patients, Median PFS was 1140 days in the patients with high expression, and Median PFS was 1387 days in the patients with low expression ( $\chi^2 = 4.715$ ,  $P = .030$ ); CEA expression is also negatively associated with the PFS of the post-operative patients, Median PFS was 1197 days in the patients with high expression, and Median PFS was 1424 days in the patients with low expression ( $\chi^2 = 4.992$ ,  $P = .025$ ). Subgroup analysis also showed that the patients with normal CA125 and CEA had better prognosis, median PFS was 1505 days, and the patients with CA125 and (or) CEA high expression had poor prognosis and median PFS was 1162 days ( $\chi^2 = 13.346$ ,  $P = .001$ ), and found that there was no statistical difference in patients with oxaliplatin plus capecitabine (XELOX) and oxaliplatin, 5-fluorouracil and Calcium folinate (FOLFOX) chemotherapy in patients with CA125 and CEA low expression. However, in these patients with CA125 or (and) CEA high expression, the median PFS of patients treated with XELOX was 1082 days, and the median PFS of patients treated with FOLFOX chemotherapy was 1335 ( $\chi^2 = 4.547$ ,  $P = .033$ ).

Expression of CA125 and CEA associated with the survival of patients, and have some guiding significance for chemotherapy in patients with colorectal cancer after operation; Compared with XELOX, FOLFOX chemotherapy is more effective for CA125 or (and) CEA high expression patients with colorectal carcinoma.

**Abbreviations:** CA125 = carbohydrate antigen125, CA199 = carbohydrate antigen 199, CEA = carcino embryonic antigen, FOLFOX = oxaliplatin, 5-fluorouracil and Calcium folinate, HGB = hemoglobin, OS = overall survival, PFS = progression-free survival, TNM stage = tumor node metastasis stage, XELOX = oxaliplatin plus capecitabine.

**Keywords:** carbohydrate antigen125, carcino embryonic antigen, colorectal carcinoma, progression-free survival

## 1. Introduction

Tumor markers refer to a class of substances produced by tumor cells and tissues in the process of tumorigenesis and progression or produced by normal tissue after stimulation of tumor. It plays an important role in tumor early diagnosis,

tumor progression and monitoring therapeutic effect.<sup>[1]</sup> Carbohydrate antigen125 (CA125) and carcino embryonic antigen (CEA) are common clinical monitoring indexes about tumor, especially gastrointestinal tumors.<sup>[2-4]</sup> However, there is still a lack of more precise markers that can provide guidance for clinical chemotherapy.

Editor: Lindsay Calderon.

JM and PD contributed equally to this work.

This work was supported by grants from Lanzhou Science and Technology Bureau Project (No. 2017-RC-64); Cuiying Scientific, Technological Innovation Program of Lanzhou University Second Hospital (CY2017-BJ09); Project of Gansu Provincial Administration of Traditional Chinese Medicine(GZK-2019-47); The scientific research project of Gansu health industry (No. GSWST2013-03).

The authors have no conflicts of interest to disclose.

<sup>a</sup> The Department of General Surgery, Lanzhou University Second Hospital, <sup>b</sup> Second Clinical Medical College, Lanzhou University, Lanzhou, Gansu, China.

\* Correspondence: Peng Du, Zhi-Bin Cheng, The Department of General Surgery, Lanzhou University Second Hospital, No. 82, Cuiying gate, Chengguan District, Lanzhou, 730030, Gansu Province, China (e-mail: yxydp@126.com, Zhibin\_cheng@hotmail.com).

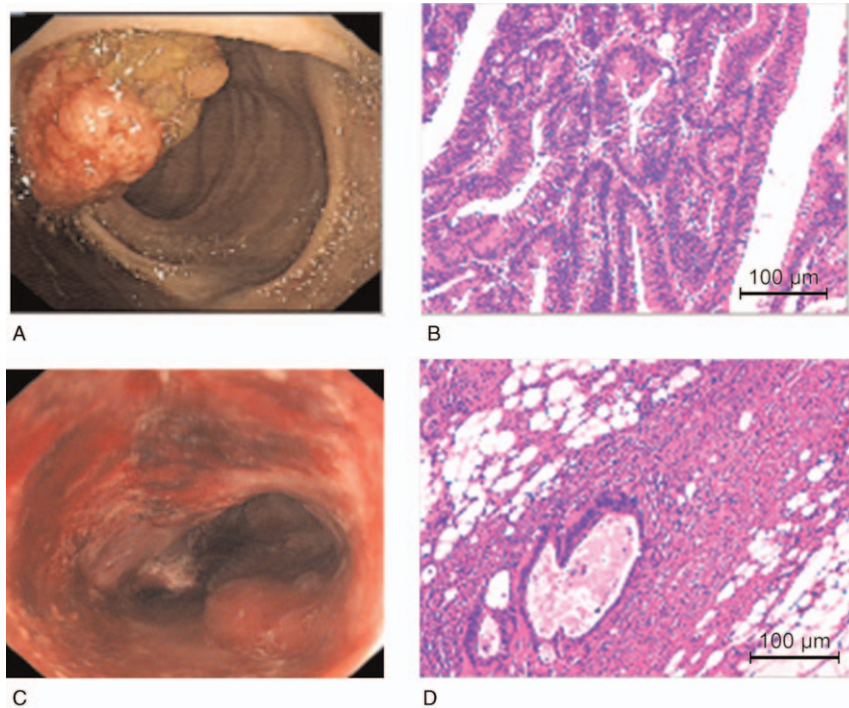
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How to cite this article: Mao J, Du P, Yang Ht, Hu H, Wang SY, Wu X, Cheng ZB. Prognostic value of carbohydrate antigen125 and carcino embryonic antigen expression in patients with colorectal carcinoma and its guiding significance for chemotherapy. *Medicine* 2020;99:14(e19420).

Received: 25 September 2019 / Received in final form: 17 January 2020 / Accepted: 3 February 2020

<http://dx.doi.org/10.1097/MD.00000000000019420>



**Figure 1.** Figures of electronic colonoscopy (Fig. 1A 1Aand C) and pathology (Fig. 1B and D) from typical cases.

Colorectal carcinoma is a health problem worldwide, and the morality and mortality are increased gradually in recent years,<sup>[5–8]</sup> which was also becoming the leading cause of death in the population.<sup>[9]</sup> For decades, translational medicine plays an important role in the treatment of malignant tumor and clinical research.<sup>[10]</sup> Therefore, some tumor related substances as biomarkers are used to diagnose early stage of cancers, assess tumor progression and efficacy of anti-carcinoma therapies.<sup>[9]</sup> Some drugs specifically targeting tumor markers have been used to treat the patients with colon carcinoma.<sup>[7,11,12]</sup> Some serum biomarkers, such as carbohydrate antigen 199 (CA199), CA125, and CEA, are associated with the prognosis of patients with carcinoma, and it is easy to detect in the clinical work. CA199 is a kind of tumor marker of digestive system cancer. The increase of CA199 is mainly seen in pancreatic cancer. Second, in cholangiocarcinoma and colorectal cancer, the level of CA199 will also increase.<sup>[13–15]</sup> CEA is mainly produced by gastrointestinal tumors. Its chemical component is glycoprotein. As an adhesion molecule, CEA promotes the aggregation and invasion of tumor cell. Elevated CEA levels often indicate tumor progression and recurrence. At present, it is mainly used as a marker of gastrointestinal tumors.<sup>[15]</sup> CA125 interacts with some receptors to inhibit the apoptosis of cancer cells and promote the implantation and metastasis of tumor cells.<sup>[16]</sup>

Research on biomarkers of tumors has a great progress in the last 2 decades. The value of potential diagnostic and therapeutic of biomarkers is also becoming more and more evident. In this study, the clinical data of 206 patients, including laboratory data and pathological data, were collected from the electronic medical records of the Second Hospital of Lanzhou University, and investigated the correlation between the survival and clinico-pathological parameters in patients with colorectal carcinoma, and to explore serum tumor markers that can be used to guide clinical treatment.

**Table 1**

**The correlation between clinical data and PFS of patients with colorectal carcinoma were analyzed by Log-rank test.**

Clinical parameters	Cases	Median PFS (d)	Log-Rank $\chi^2$	P
gender				
male	107	1281	1.204	.273
female	99	1388		
Age				
<59	102	1434	3.580	.058
≥60	104	1227		
HGB				
<99	47	1324	0.013	.894
≥100	159	1338		
WBC				
<4	24	1308	0.956	.328
≥4.1	182	1490		
Percentage of neutrophils				
<70%	111	1397	2.611	.106
≥71%	95	1258		
Percentage of lymphocyte				
<40%	187	1333	0.215	.643
≥41%	19	1402		
CA125				
<35	165	1387	4.715	.030
≥36	41	1140		
CA199				
<27	158	1379	1.425	.233
≥28	48	1215		
CEA				
<3.4	126	1424	4.992	.025
≥3.5	80	1197		
TNM stage				
I-II	73	1439	4.114	.043
III-IV	133	1275		
Pathology grade				
I-II	122	1416	5.511	.019
III-IV	84	1198		
Lymphatic metastasis				
Positive	96	1432	6.385	.012
Negative	110	1212		
Chemotherapy regimen				
XELOX	128	1287	3.250	.071
FOLFOX4	78	1404		

Whether it is high or not that is based on the normal reference value range of the clinical test result report. A higher than normal reference value is specified as a high expression, and a lower than reference value is specified as a low expression, such as CA125, CA199, CEA and so on.

CA125 = carbohydrate antigen125, CA199 = carbohydrate antigen 199, CEA = carcino embryonic antigen, FOLFOX = oxaliplatin, 5-fluorouracil and Calcium folinate, HGB = haemoglobin, PFS = progression-free survival, TNM stage = tumor node metastasis stage, WBC = white blood cell, XELOX = oxaliplatin plus capecitabine.

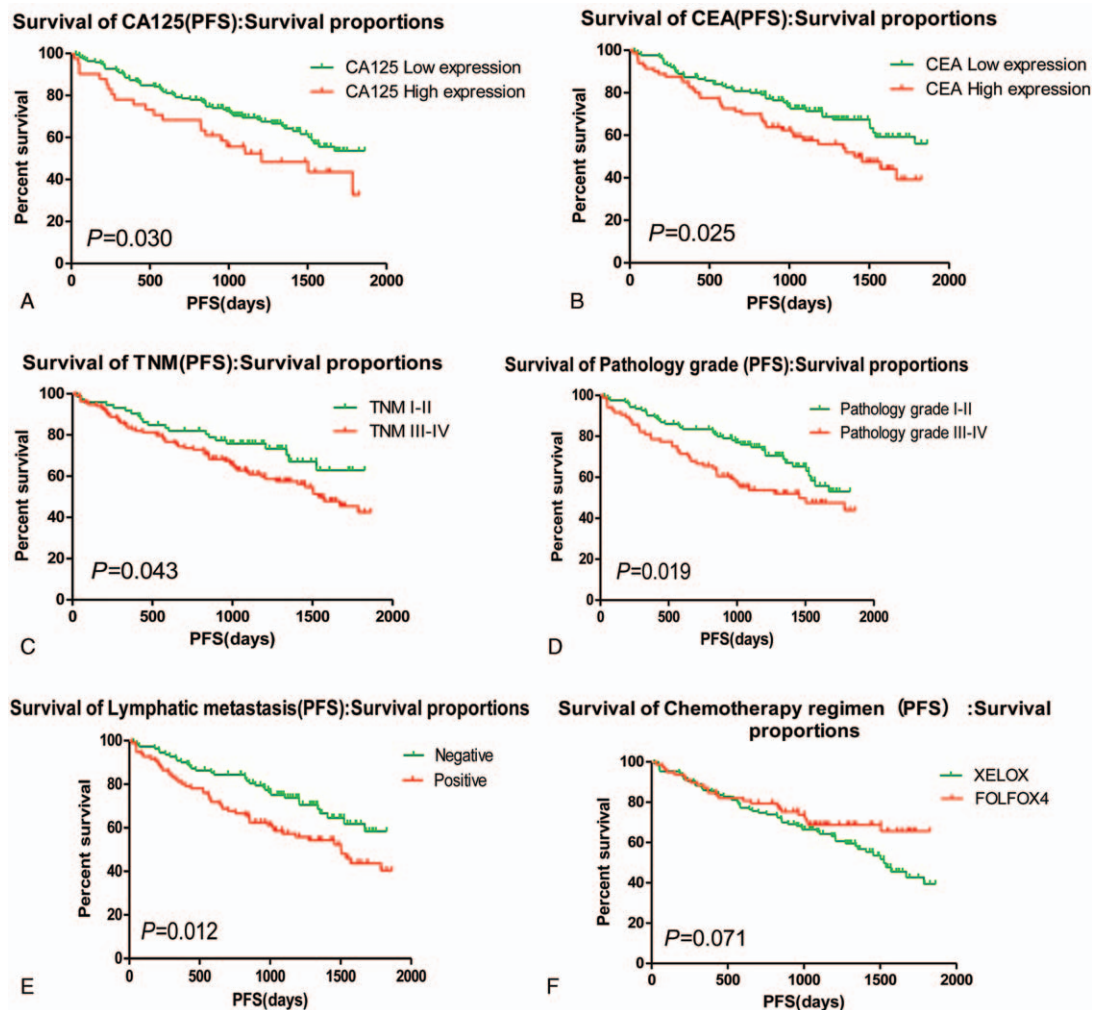


Figure 2. Clinical factors affecting the PFS of patients. PFS = progression-free survival.

## 2. Materials and methods

### 2.1. Patients

We enrolled 206 patients with colorectal carcinoma who underwent tumor resection at Lanzhou University Second Hospital (Gansu Province, China) between 2010 and 2015. The study was approved by the Ethics Committee of at the Lanzhou University Second Hospital, and the data were anonymously obtained and analyzed. Informed consents from participants were also waived due to the complete anonymity of the patients. The data of all patients, including laboratory data and pathological data, were collected from the electronic medical records of the Lanzhou University Second Hospital. This study was performed in accordance with the relevant guidelines and regulations, and conformed to the Declaration of Helsinki.<sup>[17]</sup> The inclusion criteria of patients included complete pathological and follow-up data, without long distance metastasis, no other chronic diseases, and without any treatments before the surgery. The exclusion criteria: patients who suffered from other tumor or other chronic diseases, or died from accidental death or other diseases, lack of pathological and follow-up data, long distance metastasis before the surgery. Ultimately, a total of 206 cases

were eventually enrolled in this study, including 104 males and 102 females, aged 23 to 90 years, median age of 59 years.

### 2.2. Clinical data and follow-up

Clinical data were totally collected from 206 patients with colorectal carcinoma. The clinical data, including gender, age, results of electronic colonoscopy, pathological results, preoperative serum CA125, CEA, CA19-9, hemoglobin (HGB), lymphocyte and post-operative chemotherapy were collected from the electronic medical records of the Second Hospital of Lanzhou University. The follow-up period was from the operative date to the death date, the follow-up period was 5-years post-surgery, and no patients died during follow-up.

### 2.3. Statistical analysis

SPSS 22.0 statistical software was used to analyze all data. Kaplan-Meier survival estimates model were used to assess the correlation of the progression survival (PFS) and overall survival (OS) with gender, age, CEA, CA125, CA199, HGB, white blood cell, lymphatic metastasis, tumor node metastasis stage (TNM

stage) and chemotherapy regimen. Finally, Subgroup analysis was used to assess the correlation between the expression of CEA and CA125 and chemotherapy.  $P < .05$  was considered statistically significant.

### 3. Results

#### 3.1. Figures of electronic colonoscopy and pathology from typical cases and Statistical results

Most of patients come to the hospital for bloody stool. For instance, a patient was detected by colonoscopy for hematochezia, and the result showed that ascending colon tumor, local necrosis, hemorrhage, ulceration (Fig. 1A). The result of pathological biopsy: Moderately differentiated adenocarcinoma (Fig. 1 B); Another case who suffered from hematochezia was detected by colonoscopy, the result showed that rectal malignant tumor (about 5cm from anal verge), it is circumferential hyperplasia with ulceration and local hemorrhage (Fig. 1 C). The result of pathological biopsy: Poorly differentiated adenocarcinoma (Fig. 1 D). The correlations between the OS and age, gender, lymphatic metastasis, TNM stage, pathology grade, chemotherapy regimen, HGB, white blood cell, percentage of neutrophils, percentage of lymphocyte, the expression of CA125, CA199, and CEA in serum of patients with colorectal carcinoma before operation were analyzed by Log-rank test. Results showed that the expression of CA125 and CEA, Lymphatic metastasis, TNM stage, pathology grade, Chemotherapy regimen were significantly associated with the PFS, but it is not related to other clinical factors (Table 1, Fig. 2); and found that the expression of CA125 and CEA, Lymphatic metastasis, TNM stage, pathology grade, Chemotherapy regimen were significantly associated with the OS, but it is not related to other clinical factors (Table 2, Fig. 3).

#### 3.2. Hierarchical analysis for the correlation between the PFS, OS, and chemotherapy regimen and expression of CA125 and CEA in serum of patients with colorectal carcinoma before operation

The statistical results showed that CA125 and or CEA expression was negatively related to the PFS of the post-operative patients, Median PFS was 1162 days in the patients with CA125 and or CEA high expression, and Median PFS was 1505 days in the patients with CA125 and CEA expression ( $\chi^2=13.346$ ,  $P=.001$ ); In patients with low expression of CA125 and CEA, comparing with patients treated with oxaliplatin plus capecitabine (XELOX) and FOLFOX4 chemotherapy, there was no statistical difference about the PFS of patients with colorectal carcinoma. Interestingly, the Median PFS was 1459 days in the patients treated with XELOX, the Median PFS was 1520 days in the patients treated with FOLFOX4 ( $\chi^2=0.038$ ,  $P=.845$ ). However, In patients with high expression of CA125 and or CEA, comparing with patients treated with XELOX and FOLFOX4 chemotherapy, the Median PFS was 1082 days in the patients treated with XELOX, the Median PFS was 1335 days in the patients treated with FOLFOX4 ( $\chi^2=4.547$ ,  $P=.033$ ), the PFS of patients with colorectal carcinoma was statistical difference. It was also found that patients with TNM III-IV were better treated with FOLFOX4 regimen. (Table 3, Fig. 4). Moreover, in patients with low expression of CA125 and CEA, comparing with patients treated with XELOX and FOLFOX4

**Table 2**

**The correlation between clinical data and OS of patients with colorectal carcinoma were analyzed by Log-rank test.**

Clinical parameters	Cases	Median OS (days)	Log-Rank $\chi^2$	P
Gender				
male	107	1323	1.202	.273
female	99	1414		
Age				
<59	102	1462	3.376	.066
$\geq 60$	104	1262		
HGB				
<99	47	1381	0.200	.655
$\geq 100$	159	1364		
WBC				
<4	24	1349	0.803	.370
$\geq 4.1$	182	1497		
Percentage of neutrophils				
<70%	111	1422	2.502	.114
$\geq 71\%$	95	1305		
Percentage of lymphocyte				
<40%	187	1365	0.123	.643
$\geq 41\%$	19	1422		
CA125				
<35	165	1415	3.744	.050
$\geq 36$	41	1180		
CA199				
<27	158	1411	1.761	.184
$\geq 28$	48	1244		
CEA				
<3.4	126	1471	4.612	.032
$\geq 3.5$	80	1305		
TNM stage				
I-II	73	1439	4.485	.034
III-IV	133	1275		
Pathology grade				
I-II	122	1452	5.510	.019
III-IV	84	1220		
Lymphatic metastasis				
Positive	96	1464	6.511	.011
Negative	110	1240		
Chemotherapy regimen				
XELOX	128	1321	3.313	.069
FOLFOX4	78	1430		

Whether it is high or not that is based on the normal reference value range of the clinical test result report. A higher than normal reference value is specified as a high expression, and a lower than reference value is specified as a low expression, such as CA125, CA199, CEA and so on. CA125 = carbohydrate antigen125, CA199 = carbohydrate antigen 199, CEA = carcino embryonic antigen, FOLFOX = oxaliplatin, 5-fluorouracil and Calcium folinate, HGB = haemoglobin, PFS = progression-free survival, TNM stage = tumor node metastasis stage, WBC = white blood cell, XELOX = oxaliplatin plus capecitabine.

chemotherapy, there was no statistical difference about the OS of patients with colorectal carcinoma. In patients with high expression of CA125 and CEA, the Median OS was 1457 days in the patients treated with XELOX, the Median PFS was 1531 days in the patients treated with FOLFOX4 ( $\chi^2=0.020$ ,  $P=.889$ ). In patients with high expression of CA125 and or CEA, comparing with patients treated with XELOX and FOLFOX4 chemotherapy, the Median PFS was 1140 days in the patients treated with XELOX, the Median PFS was 1372 days in the patients treated with FOLFOX4 ( $\chi^2=4.349$ ,  $P=.037$ ), the PFS of patients with colorectal carcinoma was statistical difference. It was also found that patients with TNM III-IV were better treated with FOLFOX4 regimen. (Table 4, Fig. 5).

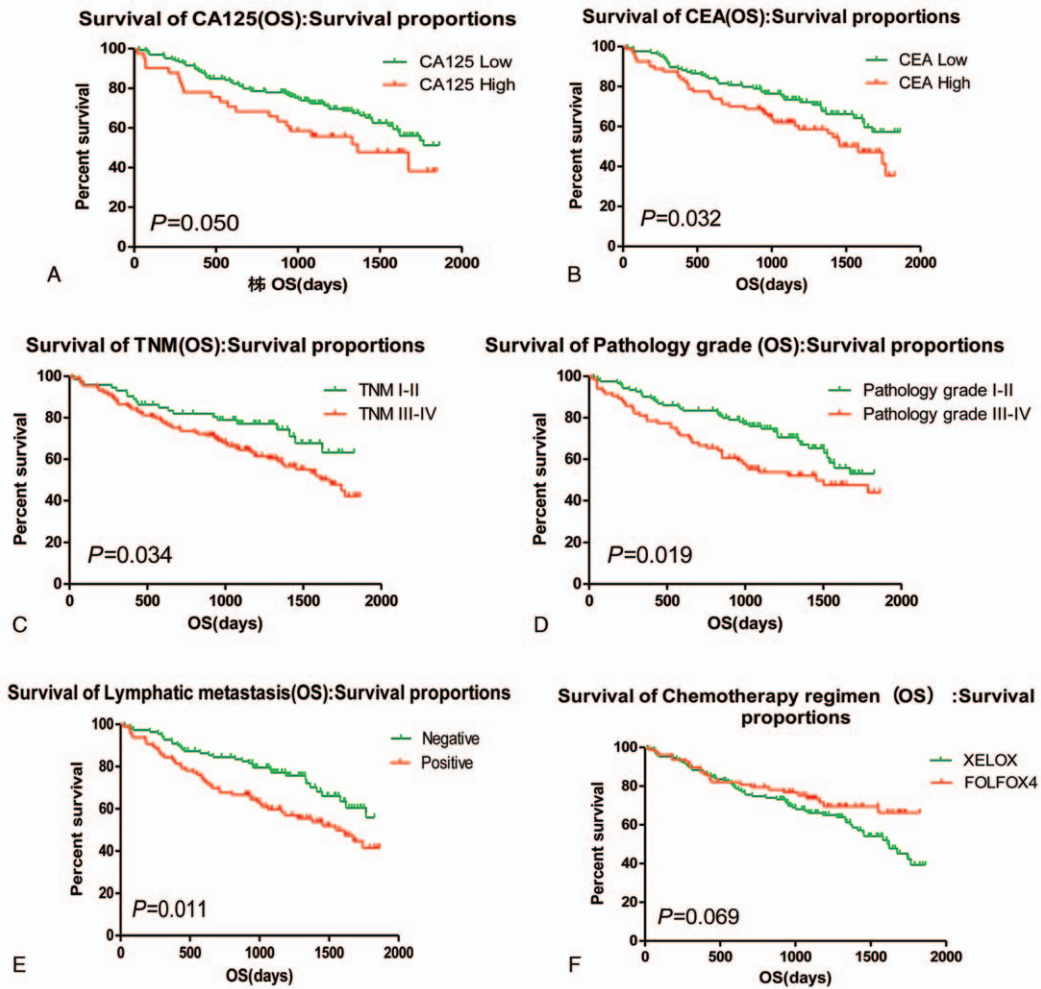


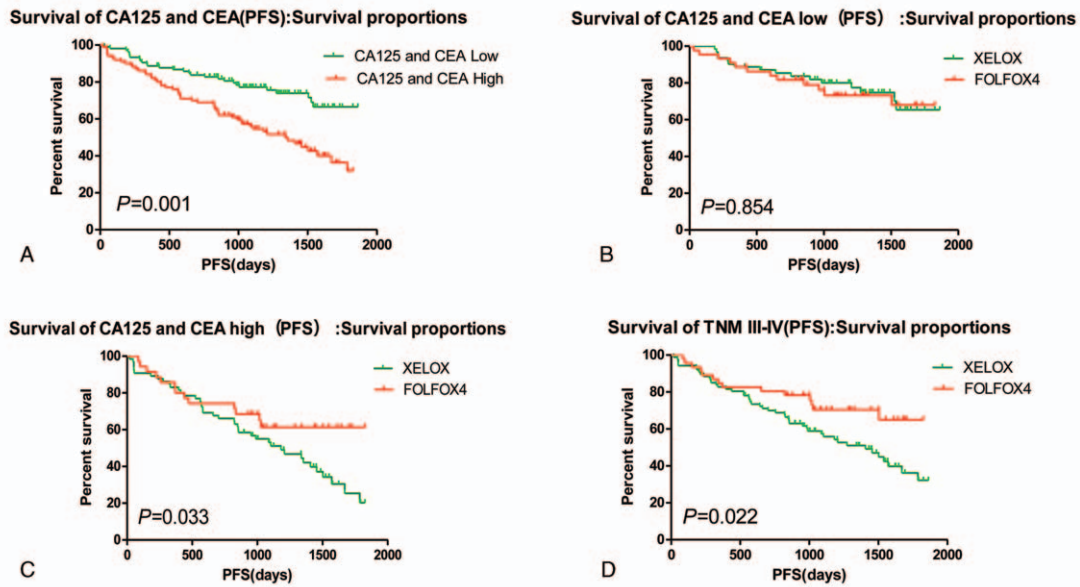
Figure 3. Clinical factors affecting the OS of patients. OS = overall survival.

**Table 3**

The correlation between the PFS and the expression of CA125 and CEA in the patients with different chemotherapy regimen.

Hierarchical define	Clinical parameters	cases	Median PFS (d)	Log-Rank $\chi^2$	P
All patients	CA125 and CEA (low)	106	1505	13.346	.001
	CA125 and or CEA (high)	100	1162		
CA125 and CEA(low)	XELOX	62	1459	0.038	.845
	FOLFOX4	44	1520		
CA125 or CEA(high)	XELOX	66	1082	4.547	.033
	FOLFOX4	34	1335		
TNM I-II	XELOX	41	1468	0.223	.637
	FOLFOX4	32	1383		
TNM III-IV	XELOX	87	1192	5.233	.022
	FOLFOX4	46	1418		
Pathology grade I-II	XELOX	70	1381	1.208	.272
	FOLFOX4	52	1460		
Pathology grade III-IV	XELOX	58	1147	1.464	.226
	FOLFOX4	26	1298		

CA125 = carbohydrate antigen125, CA199 = carbohydrate antigen 199, CEA = carcino embryonic antigen , FOLFOX = oxaliplatin , 5-fluorouracil and Calcium folinate, HGB = haemoglobin, PFS = progression-free survival, TNM stage = tumor node metastasis stage, WBC = white blood cell, XELOX = oxaliplatin plus capecitabine.



**Figure 4.** Subgroup analysis: The effect of CA125 and CEA expression on chemotherapy efficacy. CA125 = Carbohydrate antigen125, CEA = carcino embryonic antigen.

**3.3. The results of Cox regression**

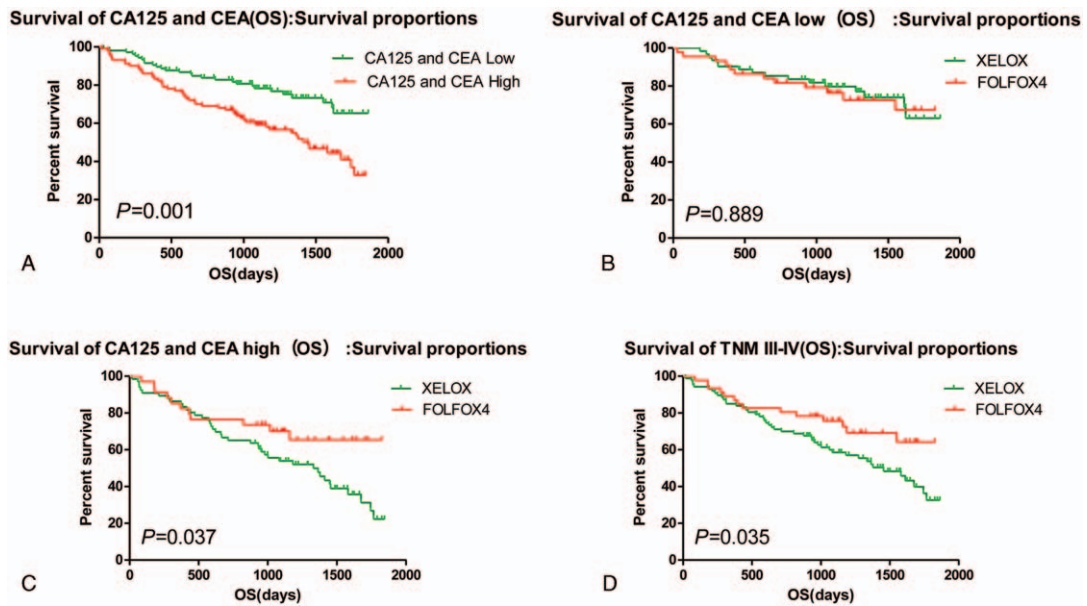
Cox regression is used to analyze the factors that affect the risk of tumor progression and evaluate whether they are independent prognostic factors. Univariate analysis revealed that comparing with the patients with CA125 low, patients with CA125 high had higher tumor progression risk (HR = 1.708, 95% CI: 1.047-2.784,  $P = .32$ ) and comparing with the patients with CEA low, patients with CEA high had higher tumor progression risk (HR = 1.631, 95% CI: 1.057- 2.516,  $P = .27$ ). The result also showed

that comparing with the patients with CA125 and CEA low, patients with CA125 and or CEA high had higher tumor progression risk (HR = 2.356, 95% CI: 1.492–3.722,  $P = .001$ ); patients with negative lymphatic metastasis vs patients with and positive lymphatic metastasis, the latter is at higher risk of tumor progression (HR = 1.750, 95% CI: 1.127–2.716,  $P = .013$ ), patients with pathology grade I-II colorectal carcinoma vs patients with pathology grade III-IV colorectal carcinoma, the latter is at higher risk of tumor progression (HR = 1.671, 95% CI:

**Table 4**  
The correlation between the OS and the expression of CA125 and CEA in the patients with different chemotherapy regimen.

Hierarchical define	Clinical parameters	cases	Median OS (d)	Log-Rank $\chi^2$	P
All patients	CA125 and CEA(low)	106	1519	12.964	.001
	CA125 and or CEA(high)	100	1214		
CA125 and CEA(low)	XELOX	62	1475	0.020	.889
	FOLFOX4	44	1531		
CA125 or CEA(high)	XELOX	66	1140	4.349	.037
	FOLFOX4	34	1372		
TNM I-II	XELOX	41	1496	0.047	.829
	FOLFOX4	32	1430		
TNM III-IV	XELOX	87	1229	4.469	.035
	FOLFOX4	46	1432		
Pathology grade I-II	XELOX	70	1425	1.550	.213
	FOLFOX4	52	1491		
Pathology grade III-IV	XELOX	58	1171	1.173	.279
	FOLFOX4	26	1314		

CA125 = carbohydrate antigen125, CA199 = carbohydrate antigen 199, CEA = carcino embryonic antigen , FOLFOX = oxalipatin, 5-fluorouracil and Calcium folinate, HGB = haemoglobin, PFS = progression-free survival, TNM stage = tumor node metastasis stage.



**Figure 5.** Subgroup analysis: The effect of CA125 and CEA expression on chemotherapy efficacy. CA125 = Carbohydrate antigen125, CEA = carcino embryonic antigen.

1.083–2.578,  $P=.020$ ), patients with TNM I-II colorectal carcinoma vs patients with TNM III-IV colorectal carcinoma, the latter is at higher risk of tumor progression (HR = 1.661, 95% CI: 1.012- 2.728,  $P=.045$ ); Multivariate analysis showed that

CA125 and CEA are not an independent prognostic factor (HR = 1.629, 95% CI: 0.991–2.680,  $P=.54$  for CA125; HR = 1.476, 95% CI: 0.949–2.294,  $P=.74$  for CEA), When CA125 and CEA are combined, their predictive effect is enhanced, and it is an

**Table 5**

**The results of Cox regression.**

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age		.060		
<60	reference			
≥60	0.658 (0.425–1.018)			
Gender		.274		
female	reference			
male	0.782 (0.504–1.215)			
CA125		.032*		.054*a
<35	reference		reference	
≥36	1.708 (1.047- 2.784)		1.629 (0.991–2.680)	
CEA		.027*		.074*a
<3.4	reference		reference	
≥3.5	1.631 (1.057- 2.516)		1.476 (0.949–2.294)	
CA125 and CEA		.001*		.001*b
CA125 and CEA (low)	reference		reference	
CA125 or CEA (high)	2.356 (1.492- 3.722)		2.309 (1.462–3.649)	
Lymphatic metastasis		.013*		.019*b
Positive	reference		reference	
Negative	1.750 (1.127- 2.716)		1.697 (1.093- 2.636)	
Pathology grade		.020*		.030*c
I-II	reference		reference	
III-IV	1.671 (1.083- 2.578)		1.621 (1.049- 2.505)	
TNM stage		.045		.051*d
I-II	reference		reference	
III-IV	1.661 (1.012- 2.728)		1.641 (0.935- 2.540)	

<sup>a</sup>The variables (Lymphatic metastasis, CA125 and CEA) were tested in a multivariate analysis.

<sup>b</sup>The variables (Lymphatic metastasis,combined CA125 and CEA) were tested in a multivariate analysis.

<sup>c</sup>The variables (Pathology grade, CA125 and CEA) were tested in a multivariate analysis.

<sup>d</sup>The variables (TNM stage, CA125 and CEA) were tested in a multivariate analysis.

CA125 = carbohydrate antigen125, CA199 = carbohydrate antigen 199, CEA = carcino embryonic antigen, TNM stage = tumor node metastasis stage.

independent prognostic factor (HR=2.309, 95% CI: 1.462–3.649,  $P=.001$ ). and also found that Lymphatic metastasis, TNM stage and pathology grade are an independent prognostic factors (HR=1.697, 95% CI: 1.093– 2.636,  $P=.19$  for Lymphatic metastasis; HR=1.621, 95% CI: 1.049– 2.505,  $P=.30$  for pathology grade; HR=1.641, 95% CI: 0.935– 2.540,  $P=.51$  for TNM stage). (Table 5).

#### 4. Discussion

At present, the treatment of colorectal cancer has made some progress. However, the mortality of patients with colorectal carcinoma is still high. Therefore, it is urgent to optimize the current treatment methods to reduce the mortality of patients with colorectal carcinoma. Research on tumor markers is also a means to improve the efficiency of tumor diagnosis and treatment in clinical work.<sup>[18]</sup> The application of molecular markers means that tumor prognosis assessment is no longer a limit to clinical pathological parameters, research on biomarkers has main 2 parts, including the prognosis of patient with carcinoma and guiding the treatment. The intervention of some tumor related markers could promote anti-tumor effects, this is so-called “targeted therapy” which provides a new method for tumor management.<sup>[9]</sup> Study showed that CA125 and CEA play an important role in the diagnosis and treatment of colorectal carcinoma.<sup>[19]</sup> The results of this study also showed that the expression of CA125 and CEA had a negative correlation with the OS of patients with colorectal carcinoma.

Recently, CEA and CA125 are widely used in clinical laboratory, but they are mainly used to monitor the recurrence of tumors. There are few reports on the application of CEA and CA125 in clinical chemotherapy. The results of this study showed that the prognosis of patients with colorectal carcinoma was poor, especially these patients with high expression of CEA and CA125 in serum. In patients with normal CA125 and CEA, there was no significant difference in OS, whether it is A or B regimen. However, the median OS was shorter in patients receiving XELOX chemotherapy, and longer in patients receiving FOLFOX chemotherapy than in patients with CA125 or (and) CEA over-expression. The result of this study has some guiding significance for the prognosis evaluation and chemotherapy plan of postoperative patients with colorectal carcinoma.

#### Author contributions

**Conceptualization:** Jie Mao, Peng Du, Zhi-Bin Cheng.

**Data curation:** Peng Du, Han-teng Yang, Huan Hu, Shi-Yao Wang, Xia Wu.

**Formal analysis:** Jie Mao, Peng Du, Huan Hu, Shi-Yao Wang.

**Funding acquisition:** Jie Mao, Zhi-Bin Cheng.

**Methodology:** Peng Du, Han-teng Yang, Huan Hu, Shi-Yao Wang.

**Writing – original draft:** Peng Du.

**Writing – review & editing:** Jie Mao, Zhi-Bin Cheng.

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