


Prognostic Impact of Pretreatment Elevated and Normalized Carcinoembryonic Antigen Levels After Neoadjuvant Chemoradiotherapy in Resected Locally Advanced Rectal Cancer Patients

Jianyuan Song ¹⁻³
Zhuhong Chen¹
Daxin Huang¹
Benhua Xu¹⁻³

¹Department of Radiation Oncology, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, People's Republic of China; ²Department of Medical Imaging Technology, College of Medical Technology and Engineering, Fujian Medical University, Fuzhou, Fujian Province, People's Republic of China; ³Fujian Medical University Union Clinical Medicine College, Fuzhou, Fujian Province, People's Republic of China

Purpose: The prognostic significance of pretreatment elevated and normalized CEA after neoadjuvant chemoradiotherapy (nCRT) was evaluated.

Materials and Methods: The characteristics of 951 locally advanced rectal cancer patients with nCRT were retrieved and were analyzed retrospectively. Pretreatment CEA levels were defined as CEA evaluated one week prior to the nCRT. CEA after nCRT was deemed as CEA measured one week before surgery. The normal CEA levels were set at <5 ng/mL. The normal CEA group was defined as patients with normal pretreatment CEA levels. The normalized CEA group was defined as patients with elevated pretreatment CEA levels and normal CEA levels after nCRT. The elevated CEA group was defined as patients with elevated pretreatment CEA levels and elevated CEA levels after nCRT.

Results: Compared with the elevated CEA group, the normalized CEA group was associated with better overall survival (OS) (HR: 0.625, 95%CI: 0.416–0.938, $P=0.022$). There was no difference between the normalized CEA group and the normal CEA group (HR: 1.143, 95% CI: 0.84–1.557, $P=0.395$).

Conclusion: In conclusion, the study indicated that OS of the normalized CEA group and the normal CEA group was better than the elevated CEA group.

Keywords: rectal cancer, locally advanced rectal cancer, LARC, carcinoembryonic antigen, CEA

Introduction

Carcinoembryonic antigen (CEA) as one of the tumor markers was carried out to screen for cancer, predict the survival of cancer, and detect the recurrence of rectal cancer.¹⁻³ The screening value of CEA has been studied.^{1,4,5} The CEA levels were associated with the survival of rectal cancer.⁶ CEA clearance has an intensive relationship with overall survival of metastatic colorectal cancer.⁴ CEA was recommended to monitor the recurrence of rectal cancer.^{7,8} The changes of CEA levels after curative surgery were associated with the survival of rectal cancer.^{9,10} Neoadjuvant chemoradiotherapy (nCRT) and curative resection for locally advanced rectal cancer (LARC) is recommended.^{3,11,12} There were few reports related to prognostic impact of the changes of CEA

Correspondence: Benhua Xu
Department of Radiation Oncology,
Fujian Medical University Union Hospital,
Fuzhou, 350001, People's Republic of
China
Email: benhuaxu@163.com

levels after nCRT in LARC. In the present study, the prognostic significance of pretreatment elevated and normalized CEA after nCRT were assessed.

Materials and Methods

Ethics Statement

In this study, all information was retrospectively extracted in the context of compliance with the ethical standards of the institutional and/or national research committees and the principles of the Declaration of Helsinki. Patients' medical records were analyzed retrospectively. No individual identifiable information was used. Thus, the Fujian Medical University Union Hospital Ethic Review Board considered that the patients' consent was unnecessary. The study was approved by the Fujian Medical University Union Hospital Ethic Review Board (Number: 2020KY066).

Patients and Clinical Parameters

The database of our institution was reviewed. The data of LARC patients was retrieved, who were treated with nCRT and curative surgery from September 2006 to October 2017. TNM was used on the basis of The Union for International Cancer Control (UICC) eighth edition. The information relating to characteristics of patients and tumor were collected, including age, gender, CEA levels, postneoadjuvant TNM (ypTNM), clinical TNM (cTNM), the total number of retrieved lymph node (TLN), surgery, the neoadjuvant radiotherapy regimen, the nCRT regimens, consolidation chemotherapeutic regimens, adjuvant chemotherapy and the interval between neoadjuvant therapy and surgery. Pretreatment CEA levels were defined as CEA evaluated one week prior to the nCRT. CEA after nCRT was deemed as CEA measured one week before surgery. The normal CEA levels were set at <5 ng/mL. The normal CEA group was defined as patients with normal pretreatment CEA levels. The normalized CEA group was defined as patients with elevated pretreatment CEA levels and normal CEA levels after nCRT. The elevated CEA group was defined as patients with elevated pretreatment CEA levels and elevated CEA levels after neoadjuvant chemoradiotherapy. A history and physical examination, including endoscopic ultrasonography and magnetic resonance imaging, was carried out to define clinical T and N stages. The exclusion criteria were as follows: (a) histologically proven signet-ring cell carcinoma or other carcinoma; (b) age at diagnosis <18 years;

(c) previous or concurrent other malignancies; (d) patients with inadequate clinicopathological information; (e) presence of unresectable cancer; (f) previous history of chemotherapy or pelvic radiation.

Neoadjuvant Chemoradiotherapy and Surgery

In the capecitabine regimen, patients received capecitabine with 825 mg/m² twice daily, day 1–14, every 21 days one cycle. In the oxaliplatin plus leucovorin and 5-fluorouracil 5-FU (FOLFOX4) regimen, patients received oxaliplatin with 85 mg/m², day 1, leucovorin with 200 mg/m², day 1–2, 5-FU with 400 mg/m², days 1–2, 600 mg/m², days 3–4, every 14 days one cycle. In the capecitabine plus oxaliplatin (CapeOX) regimen, patients received oxaliplatin with 130 mg/m², day 1, capecitabine with 825 mg/m² twice daily, days 1–14, every 21 days one cycle. In the modified oxaliplatin plus leucovorin and 5-FU (mFOLFOX6) regimen, patients received oxaliplatin with 85 mg/m², day 1, leucovorin 400 mg/m², day 1, 5-FU 400 mg/m², day 1, 1200 mg/m², day 2–3, every 14 days one cycle. The 5-FU-based nCRT includes FOLFOX4 and mFOLFOX6 regimens. The nCRT was initiated at the beginning of radiotherapy. The planning target volume (PTV) of clinical target volume was treated with 45 Gy. The PTV of gross tumor volume was treated with 50.4 Gy in 3-dimensional conformal radiotherapy (3DRT) cohort or 50 Gy in intensity-modulated radiation therapy (IMRT) cohort. The resection was performed 6–12 weeks after nCRT. The operation was carried out on the basis of the tumor-specific mesorectal excision or total mesorectal excision principle. The excision was completed by abdominoperineal resection (APR) or other resection.

Follow-up

The frequency of regular follow-up was once every three months within the first two years, once every six months in the next three years, and annually thereafter.

Data Analysis

The differences between the variable groups were analyzed with the Pearson's chi-squared test or Student's *t*-test. The interval between neoadjuvant therapy and surgery was dichotomized for OS before the log rank test by using optimal cutoff values determined by the "surv_cutpoint" function of the "survminer" R package. The survival-analyses were performed using the Kaplan–Meier method

Table I Baseline Characteristics of Rectal Cancer Patients

Variables	All Patients (n=951)(%)
Gender	
Female	330 (34.7)
Male	621 (65.3)
Age (years) (mean SD)	55.2 (11.4)
cT classification	
cT1	1 (0.1)
cT2	51 (5.4)
cT3	355 (37.3)
cT4	544 (57.2)
cN classification	
Negative	98 (10.3)
Positive	853 (89.7)
Pretreatment CEA (ng/mL) (mean SD)	13.44 (45.41)
Neoadjuvant chemotherapy	
CapeOx	245 (25.8)
Capecitabine	549 (57.7)
5-FU based	157 (16.5)
Neoadjuvant radiotherapy	
3DRT	309 (32.5)
IMRT	642 (67.5)
Consolidation chemotherapy	
NO	632(66.5)
CapeOx	35(3.7)
Capecitabine	261(27.4)
5-Fu based	23(2.4)
Postoperative chemotherapy	
NO	214 (22.5)
CapeOx	102 (10.7)
Capecitabine	4 (0.4)
5-FU based	631 (66.4)
Surgery	
NO APR	845 (88.9)
APR	106 (11.1)
TLN (mean SD)	12.8 (7.5)
CEA after nCRT (ng/mL) (mean SD)	4.2 (14.72)
ypT classification	
ypT0	197 (20.7)
ypT1	56 (5.9)
ypT2	239 (25.1)
ypT3	396 (41.7)
ypT4	63 (6.6)

(Continued)

Table I (Continued).

Variables	All Patients (n=951)(%)
ypN classification	
ypN0	693 (72.9)
ypN1	192 (20.2)
ypN2	66 (6.9)
Pathologic stage	
0	184 (19.3)
I	240 (25.3)
II	269 (28.3)
III	258 (27.1)
Interval (weeks) (±SD)	9 (±1.9)

Abbreviations: CEA, carcinoembryonic antigen; 3DRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; APR, abdominoperineal resection; TLN, the total number of retrieved lymph nodes; nCRT, neoadjuvant chemoradiotherapy.

with the log rank test. Multivariate analysis were examined by the Cox proportional hazards model. Statistical analysis were performed with R software 3.6.2 and the SPSS software 25.0 (IBM Corporation, Armonk, NY, USA). *P*-value <0.05 was considered statistically significant.

Results

Clinical Characteristics

In total, the characteristics of 951 LARC patients with nCRT were collected. Among the patients, 621 (65.3%) were male, and 330 (34.7%) were female. The mean age was 55.2 years. The mean of pretreatment CEA level was 13.44 ng/mL. The mean of CEA level after nCRT was 4.2 ng/mL. One hundred and eighty-four patients (19.3%) achieved pCR. There are 531 patients, 303 patients and 117 patients in the normal CEA group, normalized CEA group, and elevated CEA group, respectively. The percentage of male in normal CEA group, normalized CEA group and elevated CEA group was 59.5%, 21.3% and 78.6% separately. The mean age of the normal CEA group, normalized CEA group, and elevated CEA group was 54.6 years, 55.4 years and 58.3 years, respectively. The percentage of clinical positive lymph node in the normal CEA group, normalized CEA group, and elevated CEA group was 87.4%, 92.1% and 94% respectively. The percentage of pathologic stage III in the normal CEA group,

Table 2 Baseline Characteristics of Different CEA Group

Variables	Normal CEA (n=531) (%)	Normalized CEA (n=303) (%)	Elevated CEA (n=117) (%)	P-value
Gender				<0.001
Female	215 (40.5)	90 (29.7)	25 (21.4)	
Male	316 (59.5)	213 (21.3)	92 (78.6)	
Age (years) (mean SD)	54.6 (11.2)	55.4 (11.7)	58.3 (10.9)	0.008
cT classification				0.366
cT1	1 (0.2)	0 (0)	0 (0)	
cT2	30 (5.6)	15 (5)	6 (5.1)	
cT3	206 (38.8)	105 (34.6)	44 (37.6)	
cT4	294 (55.4)	183 (60.4)	67 (57.3)	
cN classification				0.026
Negative	67(12.6%)	24(7.9%)	7(6%)	
Positive	464(87.4%)	279(92.1%)	110(94%)	
Pretreatment CEA (ng/mL)(mean (SD))	2.43(1.19)	17.30(22.87)	53.38(115.41)	<0.001
Neoadjuvant chemotherapy				0.303
CapeOx	127 (23.9)	84 (27.7)	34 (29.1)	
Capecitabine	313 (59)	168 (55.5)	68 (58.1)	
5-FU based	91 (17.1)	51 (16.8)	15 (12.8)	
Neoadjuvant radiotherapy				0.24
3DRT	161 (30.3)	109 (36)	39 (33.3)	
IMRT	370 (69.7)	194 (64)	78 (66.7)	
Consolidation chemotherapy				0.649
NO	351 (66.1)	200 (66)	81 (69.2)	
CapeOx	15 (2.8)	15 (5)	5 (4.3)	
Capecitabine	153 (28.8)	79 (26.1)	29 (24.8)	
5-FU based	12 (2.3)	9 (3)	2 (1.7)	
Adjuvant chemotherapy				0.347
NO	121 (27.8)	60 (19.8)	33 (28.2)	
CapeOx	57 (10.7)	33 (10.9)	12 (10.3)	
Capecitabine	4 (0.8)	0	0	
5-FU based	349 (65.7)	210 (69.3)	72 (61.5)	
Surgery				0.413
NO APR	471 (88.7)	266 (87.8)	108 (92.3)	
APR	60 (11.3)	37 (12.2)	9 (7.7)	
TLN (mean SD)	12.7 (7.0)	12.8 (8.0)	13.8 (8.8)	0.324
CEA after nCRT (ng/mL)(mean (SD))	2.40 (2.73)	2.70 (1.12)	16.33 (39.6)	<0.001
ypT classification				<0.001
ypT0	141 (26.6)	42 (13.9)	14 (12)	
ypT1	37 (6.9)	15 (4.9)	4 (3.4)	
ypT2	156 (29.4)	68 (22.4)	15 (12.8)	
ypT3	170 (32)	153 (50.5)	73 (62.4)	
ypT4	27 (5.1)	25 (8.3)	11 (9.4)	

(Continued)

Table 2 (Continued).

Variables	Normal CEA (n=531) (%)	Normalized CEA (n=303) (%)	Elevated CEA (n=117) (%)	P-value
ypN classification				0.047
ypN0	400 (75.3)	217 (71.6)	76 (65)	
ypN1	97 (18.3)	68 (22.5)	27 (23)	
ypN2	34 (6.4)	18 (5.9)	14 (12)	
Pathologic stage				<0.001
0	130 (24.5)	41 (13.5)	13 (11.1)	
I	158 (29.7)	68 (22.5)	14 (12)	
II	112 (21.1)	108 (35.6)	49 (41.9)	
III	13 (24.7)	86 (28.4)	41 (35)	
Interval (weeks) (±SD)	9 (±1.8)	9 (±1.9)	8.6 (±1.9)	0.397

Abbreviations: CEA, carcinoembryonic antigen; 3DRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; APR, abdominoperineal resection; TLN, the total number of retrieved lymph nodes.

normalized CEA group, and elevated CEA group was 24.7%, 28.4% and 35%, respectively. The patients in the elevated CEA group were male, older, with the status of more clinically positive lymph node, more postneoadjuvant advanced tumor stage ($P<0.05$). There are no differences in gender, clinical stage T, the total number of retrieved lymph node, surgery regimens, the neoadjuvant radiotherapy regimen, the neoadjuvant chemotherapeutic regimens, consolidation chemotherapeutic regimens, adjuvant chemotherapy and the interval between neoadjuvant therapy and surgery between the normal CEA group, normalized CEA group, and elevated CEA group ($P>0.05$). The median follow-up period for all eligible patients was 57 (range: 4–158) months. The detail characteristics were showed in Tables 1 and 2.

Factors Affecting Overall Survival of Resected Locally Advanced Rectal Cancer with Neoadjuvant Chemoradiotherapy

Univariate analyses demonstrated that pathologic stage ($P<0.001$) and CEA classification were significantly associated with overall survival (OS) ($P=0.010$). Age, gender, TLN, surgery, radiotherapy regimens, chemotherapeutic regimens, consolidation chemotherapy, adjuvant chemotherapy and the interval were not significantly associated with OS. Multivariate analyses revealed that pathologic stage was an independent prognostic factor (Table 3). The survival curves showed differences of CEA classification. Compared with elevated CEA group, normalized CEA group was associated with better OS

(HR: 0.625, 95%CI: 0.416–0.938, $P=0.022$). There are no differences between the normalized CEA group and normal CEA group (HR: 1.143, 95%CI: 0.84–1.557, $P=0.395$) (Figure 1). Compared with patients with normal CEA levels after nCRT, patients with CEA ≥ 5 ng/mL got worse OS (HR: 1.663, 95%CI: 1.18–2.344, $P=0.003$) (Figure 2).

Discussion

The American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used algorithm in clinical practice. Currently, the individual survival of rectal cancer is usually predicted using the TNM staging system.¹³ In our study, the TNM staging system is an independent prognostic factor. Surgery is conventionally performed approximately six to eight weeks after nCRT. Ryan et al showed that minimum eight-week interval from the end of nCRT to TME increases pCR and downstaging rates, and improves recurrence-free survival without compromising surgical morbidity.¹⁴ Gambacorta et al reported that the best time to achieve pCR in LARC is at 10 weeks and that the lengthening of interval is not detrimental concerning survival outcomes.¹⁵ Du et al demonstrated that there were no significant differences in overall survival, disease-free survival in the interval of ≥ 8 weeks group and the interval of <8 weeks group.¹⁶ The study also provided evidence of the fact that the interval did not impact patient outcomes. The consolidation chemotherapy demonstrated the improvement in the downstaging rate

Table 3 Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival

Variables	No. of Patients	Univariate Analysis			Multivariate Analysis		
		HR	95%CI	P-value	HR	95%CI	P-value
Gender							
Female	330	1			1		
Male	621	1.019	0.763–1.361	0.897	0.949	0.706–1.275	0.728
Age (years)				0.47			0.298
<50	279	1			1		
50–59	317	1.036	0.727–1.477	0.843	1.153	0.804–1.654	0.438
≥60	355	1.213	0.864–1.703	0.264	1.328	0.928–1.902	0.121
Neoadjuvant chemotherapy				0.536			0.662
CapeOx	245	1			1		
Capecitabine	549	0.848	0.616–1.169	0.314	0.817	0.527–1.267	0.367
5-FU based	157	0.833	0.550–1.263	0.391	0.96	0.628–1.469	0.851
Neoadjuvant radiotherapy							
3DRT	309	1			1		
IMRT	642	0.918	0.689–1.225	0.562	1.013	0.73–1.405	0.938
Consolidation chemotherapy							
NO	632	1			1		
YES	319	0.903	0.675–1.209	0.494	0.788	0.544–1.141	0.208
Adjuvant chemotherapy							
NO	121	1			1		
YES	830	1.167	0.817–1.668	0.397	1.186	0.818–1.721	0.368
Surgery							
NO APR	845	1			1		
APR	106	1.092	0.719–1.660	0.680	1.112	0.72–1.717	0.632
TLN							
<12	437	1			1		
≥12	514	1.153	0.873–1.522	0.316	1.071	0.803–1.428	0.64
Pathologic stage				<0.001			<0.001
0	184	1			1		
I	240	1.134	0.668–1.925	0.641	1.1	0.645–1.875	0.726
II	269	1.949	1.210–3.139	0.006	1.767	1.083–2.882	<0.001
III	258	2.904	1.828–4.613	<0.001	2.705	1.682–4.348	<0.001
CEA group				0.010			0.115
Normal	531	1			1		
Normalized	303	1.138	0.836–1.550	0.412	1.01	0.735–1.387	0.951
Elevated	117	1.800	1.230–2.634	0.002	1.494	1.002–2.226	0.049
Interval (weeks)							
<8.9	438	1			1		
≥8.9	513	0.785	0.589–1.047	0.099	0.83	0.606–1.138	0.248

Abbreviations: 3DRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; APR, abdominoperineal resection; TLN, the total number of retrieved lymph nodes; CEA, carcinoembryonic antigen.

for locally advanced rectal cancer.^{17,18} Our retrospective data illustrated consolidation chemotherapy did not impact the oncological outcomes of patients. And nCRT, adjuvant chemotherapy remains a future prospective, randomized trial is necessary to evaluate it. In locally advanced rectal cancer with nCRT, adjuvant chemotherapy remains

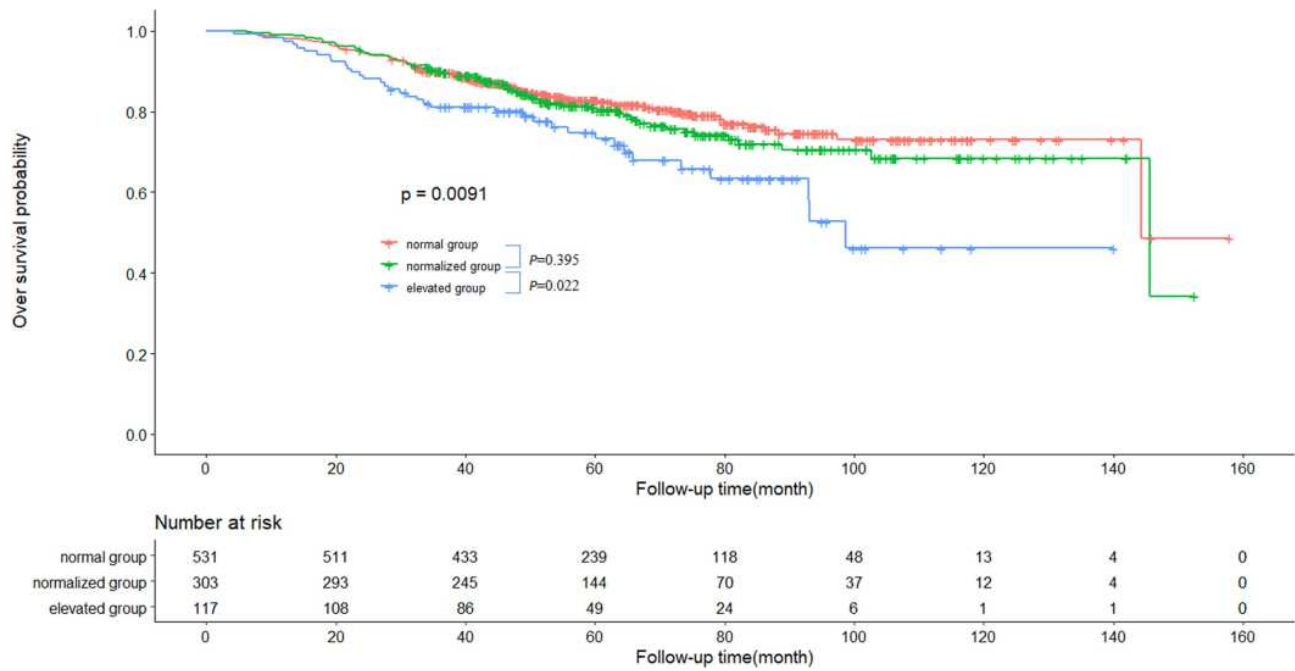


Figure 1 Overall survival curves for the normal CEA group, normalized CEA group and elevated CEA group.

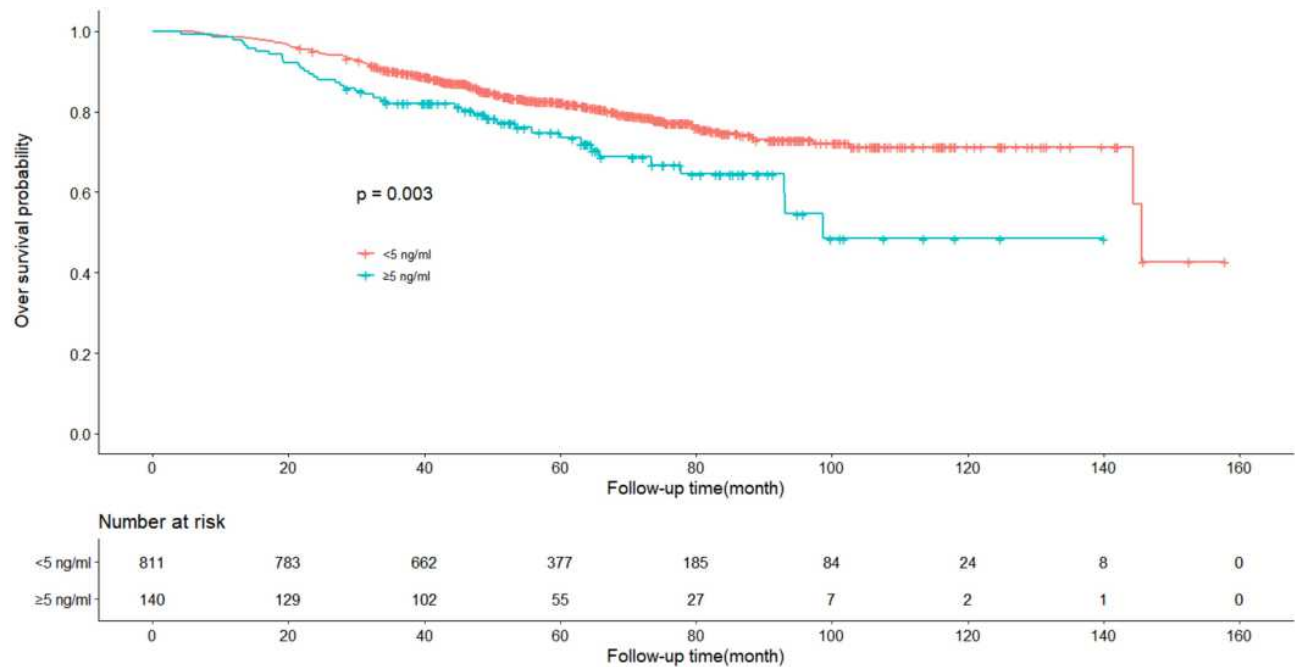


Figure 2 Overall survival curves for patients with the different CEA levels after neoadjuvant chemoradiotherapy.

controversial.^{19–21} The controversy is largely reflected by the differences in the strength of the recommendation from international clinical guidelines. Our retrospective data showed that adjuvant chemotherapy is not beneficial to patients who have received nCRT.

CEA is one of the commonly used tumor biomarkers in rectal cancer. CEA has been recommended to predict tumor response following nCRT and outcomes of rectal cancer.^{22–26} Serum CEA level is one of the significant predicting factors, which can reflect responses to nCRT

in locally advanced rectal cancer.^{22,27} Pretreatment higher CEA level is associated with worse overall survival and disease-free survival of stage I to III rectal cancer.²⁵ Preoperative serum CEA elevation is correlated with worse outcomes of T1N0M0 rectal cancer.²⁶ As part of a follow-up regimen, CEA is also recommended by the National Comprehensive Cancer Network (NCCN) to detect tumor recurrence.¹² Prognostic significance of preoperative and early postoperative serum CEA was reported.²³ Some studies have published that CEA after nCRT is in connection with response and prognosis of rectal cancer.^{27–30} Song et al showed that posttreatment CEA level was significantly correlated with downstaging.²⁷ Perez et al supported the idea that postchemoradiotherapy CEA levels <5 ng/mL has correlation with better clinical response, pathologic response, overall survival and disease-free survival.²⁸ In this study, the data also illustrated that postchemoradiotherapy CEA levels <5 ng/mL has better overall survival. Huh et al showed that postchemoradiotherapy CEA level was an independent prognostic factor for overall survival.³⁰ In our study, the CEA levels was associated with age, ypT classification, cN classification, ypN classification, pathologic stage. However, few studies reported prognostic significance of pretreatment serum CEA and the CEA levels following nCRT, especially for pretreatment of elevated and normalized CEA after nCRT. In this study, in comparison with the elevated CEA group, the patients in the normalized CEA group had better outcomes. There are no differences in the outcomes between the normalized CEA group and the normal CEA group.

However, the study has some limitations. Firstly, the study has selection bias of retrospective analysis, in which some factors associated with survival were unavailable, such as smoking status, genetic alterations, lymphovascular invasion and so on. Furthermore, due to the data being relatively small, large-scale investigations are necessary. Moreover, the study is based on a single institution, more institutions are necessary for external validations.

Conclusion

In conclusion, the study revealed that OS of the normalized CEA group and the normal CEA group was better than in the elevated CEA group.

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Disclosure

The authors report no conflicts of interest in this work.

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