


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

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**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.<sup>1-3</sup> The screening value of CEA has been studied.<sup>1,4,5</sup> The CEA levels were associated with the survival of rectal cancer.<sup>6</sup> CEA clearance has an intensive relationship with overall survival of metastatic colorectal cancer.<sup>4</sup> CEA was recommended to monitor the recurrence of rectal cancer.<sup>7,8</sup> The changes of CEA levels after curative surgery were associated with the survival of rectal cancer.<sup>9,10</sup> Neoadjuvant chemoradiotherapy (nCRT) and curative resection for locally advanced rectal cancer (LARC) is recommended.<sup>3,11,12</sup> There were few reports related to prognostic impact of the changes of CEA

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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/m<sup>2</sup> 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/m<sup>2</sup>, day 1, leucovorin with  $200$  mg/m<sup>2</sup>, day 1–2, 5-FU with  $400$  mg/m<sup>2</sup>, days 1–2,  $600$  mg/m<sup>2</sup>, days 3–4, every 14 days one cycle. In the capecitabine plus oxaliplatin (CapeOX) regimen, patients received oxaliplatin with  $130$  mg/m<sup>2</sup>, day 1, capecitabine with  $825$  mg/m<sup>2</sup> 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/m<sup>2</sup>, day 1, leucovorin  $400$  mg/m<sup>2</sup>, day 1, 5-FU  $400$  mg/m<sup>2</sup>, day 1,  $1200$  mg/m<sup>2</sup>, 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 1** 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 1** (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<br>(n=531) (%) | Normalized CEA<br>(n=303) (%) | Elevated CEA<br>(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<br>(n=531) (%) | Normalized CEA<br>(n=303) (%) | Elevated CEA<br>(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  $\geq 5$  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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15</sup> Du et al demonstrated that there were no significant differences in overall survival, disease-free survival in the interval of  $\geq 8$  weeks group and the interval of  $<8$  weeks group.<sup>16</sup> 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

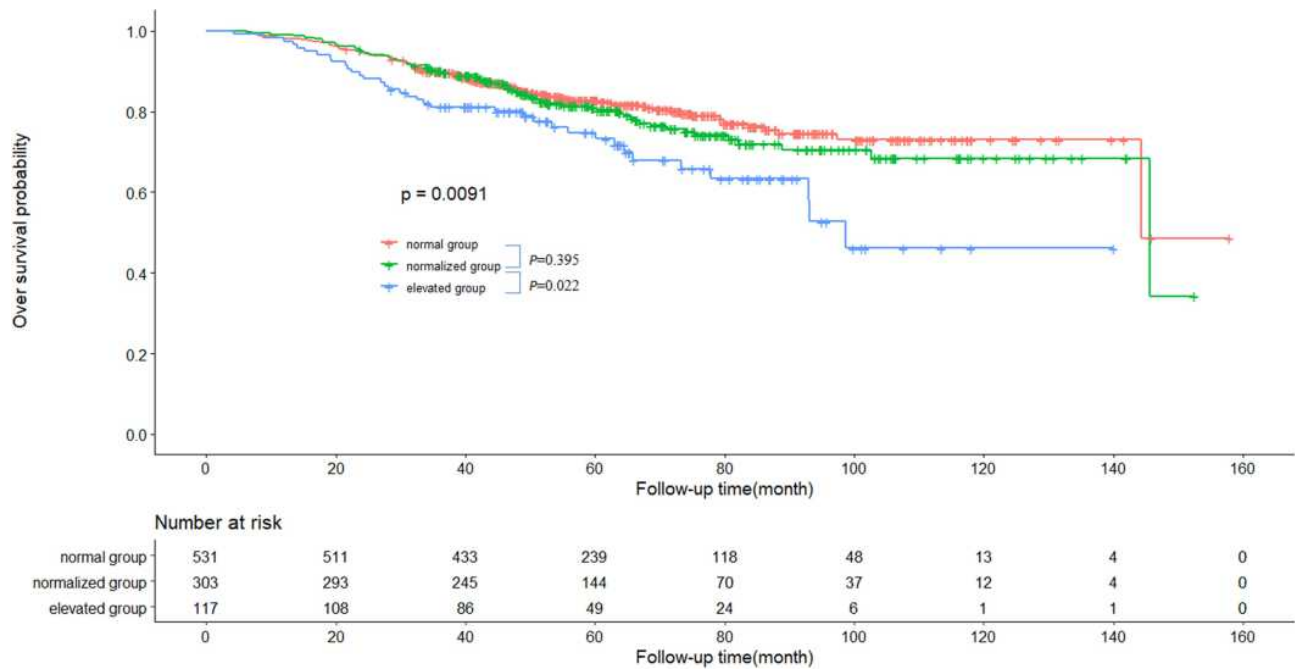
**Table 3** Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival

| 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   |

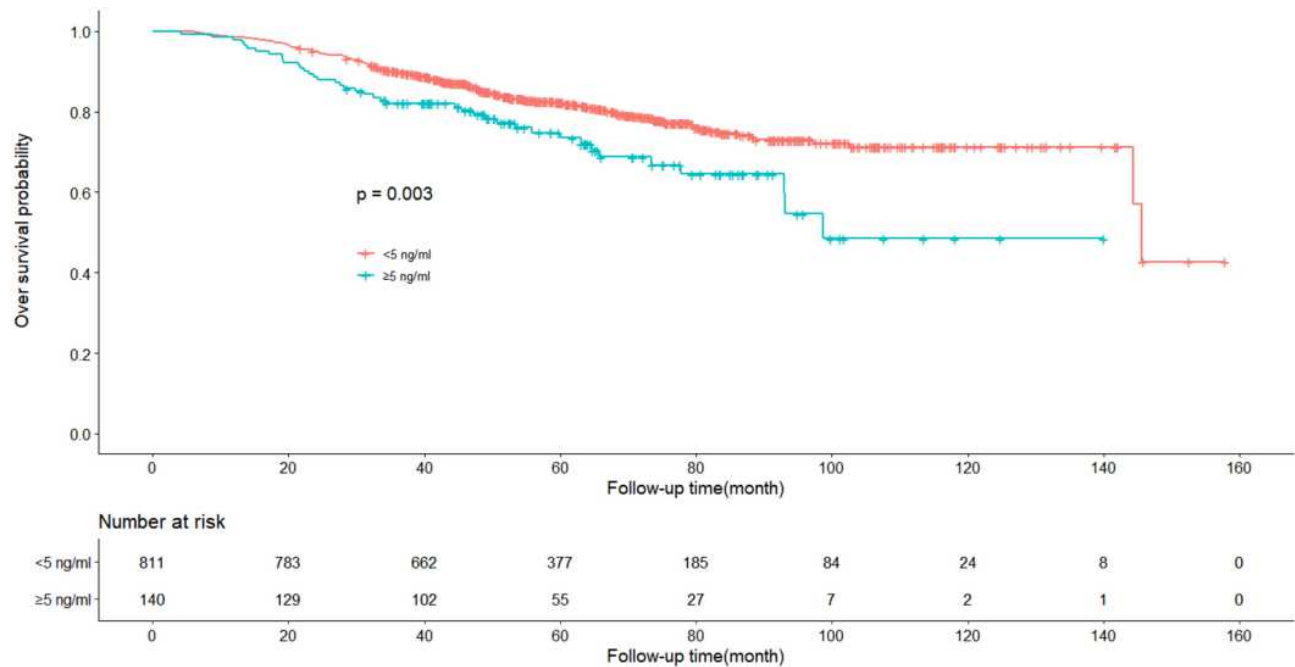
**Abbreviations:** 3DRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; APR, abdominoperineal resection; TLN, the total number of retrieved lymph nodes; CEA, carcinoembryonic antigen.

for locally advanced rectal cancer.<sup>17,18</sup> Our retrospective data illustrated consolidation chemotherapy did not impact the oncological outcomes of patients. And

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.<sup>19–21</sup> 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.<sup>22–26</sup> Serum CEA level is one of the significant predicting factors, which can reflect responses to nCRT



in locally advanced rectal cancer.<sup>22,27</sup> Pretreatment higher CEA level is associated with worse overall survival and disease-free survival of stage I to III rectal cancer.<sup>25</sup> Preoperative serum CEA elevation is correlated with worse outcomes of T1N0M0 rectal cancer.<sup>26</sup> As part of a follow-up regimen, CEA is also recommended by the National Comprehensive Cancer Network (NCCN) to detect tumor recurrence.<sup>12</sup> Prognostic significance of preoperative and early postoperative serum CEA was reported.<sup>23</sup> Some studies have published that CEA after nCRT is in connection with response and prognosis of rectal cancer.<sup>27–30</sup> Song et al showed that posttreatment CEA level was significantly correlated with downstaging.<sup>27</sup> 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.<sup>28</sup> 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.<sup>30</sup> 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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