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ORIGINAL ARTICLE

CEA levels predict tumor response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer*

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Abstract

Objective The aim of this study was to evaluate the impact of serum carcinoembryonic antigen (CEA) in the prediction of pathological complete response (pCR) in locally advanced rectal cancer (LARC) patients treated with neoadjuvant chemoradiotherapy (nCRT).
Methods A total of 925 LARC patients who underwent nCRT followed by TME between March 2006 and February 2018 were enrolled at Fudan University Shanghai Cancer Center. Using logistic regression models, we investigated the associations between serum CEA levels and pathological complete remission (pCR). Further stratified analyses were performed according to different CEA thresholds.
Results We found that pre-nCRT CEA and post-nCRT CEA were negatively correlated with pCR ($P < 0.001$). Stratified analyses revealed that when the CEA cutoff value was set to 5 ng/mL, 10.6% of patients with post-nCRT CEA levels > 5 ng/mL achieved pCR. Meanwhile, when the CEA cutoff value was set to 10 ng/mL, only 6.8% of the patients with post-nCRT CEA levels > 10 ng/mL achieved pCR.
Conclusion In summary, pre- and post-nCRT CEA levels ≤ 5 ng/mL were favorable predictors of pCR in LACR patients, and the "watch and wait" strategy is not recommended for patients with post-nCRT CEA levels > 10 ng/mL.

Key words: locally advanced rectal cancer (LARC); carcinoembryonic antigen (CEA); neoadjuvant chemoradiotherapy; pathological complete response (pCR)

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Rectal cancer is one of the leading causes of mortality and morbidity worldwide, and its growing incidence reflects the consequences of a modification in lifestyle behaviors [1]. According to NCCN clinical practice guidelines [2], the standard treatment for locally advanced rectal cancer (LARC) includes neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME). However, prior studies have shown inconsistent treatment responses to neoadjuvant CRT, ranging from a pathological complete response (pCR) to the total resistance. Previous studies [3–7] have shown that rectal cancer patients with pCR after neoadjuvant chemoradiotherapy and surgical resection of the primary lesion have better long-term outcomes than patients who lack significant remission or non-remission, and pCR rates of 10%-30% have been reported in some studies [8–10]. However, a method to identify patients who can benefit the most from nCRT remains to be found. This stratification could be used to identify patients in whom "watch and wait" management may be a significant treatment option. "Watch and wait" is a novel alternative to TME after a clinical complete response (cCR) to nCRT with the promise of improved quality of life and comparable cure effect [11]. In addition, the NCCN guidelines suggest that "watch and wait" management may be considered for patients with a cCR and no evidence of residual disease. Therefore, it is important to explore predictive factors of pCR before surgery in LARC patients to support decision-making in organ preservation strategies.

In recent years, a number of studies have explored the importance of pre- and post-nCRT carcinoembryonic antigen (CEA) levels on pCR and come to different conclusions. Some studies [12–15] have reported that a lower pre-treatment CEA level is associated with a higher pCR

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rate, while others have shown that the predictive value is only significant in non-smokers [16–17]. Other studies have shown that a lower pre-nCRT CEA level is not correlated with pCR [18–19], while post-nCRT CEA is negatively correlated with pCR [20–22]. Furthermore, several studies have suggested that patients with elevated pre-nCRT CEA levels may not be suitable for the "watch and wait" strategy [23]. However, only limited research focusing on the correlation between pre- and post-treatment CEA and pCR in the Asian population has been performed. Therefore, this retrospective study was performed to evaluate the predictive value of pre- and post-treatment CEA levels after neoadjuvant chemoradiotherapy in LARC patients. These findings can be used to distinguish LARC patients who are suitable for the "watch and wait" strategy based on the CEA levels.

Materials and methods

Study participants

Between March 2006 and February 2018, a total of 1130 patients with locally advanced rectal cancer received nCRT at Fudan University Shanghai Cancer Center. The inclusion criteria of this study were as follows: (1) distance from the anal verge ≤ 12 cm; (2) histopathological diagnosis of adenocarcinoma; (3) clinical stage T3-4 and/or N+ with MRI or ERUS; (4) no evidence of distant metastasis shown on computed tomography (CT) of the chest and abdomen; (5) receiving a long-course CRT followed by radical resection within 6-10 weeks after the end of CRT; (6) available pre- and post-nCRT CEA data. Pre-nCRT CEA level was defined as the CEA value measured within one week before nCRT, while post-nCRT CEA level is the CEA value measured within one week before surgery.

Treatment

All the patients underwent intensity-modulated radiation therapy (IMRT) ranging from 44 to 55 Gy in 20 to 25 fractions, concurrent with capecitabine-based chemotherapy, including capecitabine alone, capecitabine plus oxaliplatin, and capecitabine plus irinotecan. A TME was performed 6-10 weeks after completion of CRT. The pathological evaluation was defined according to the 8th American Joint Committee on Cancer (AJCC) Manual [24]. PCR was defined as complete regression of both the primary lesion and the regional lymph nodes.

Statistical analysis

Patient's demographic and clinical-pathological features, including age, gender, Body Mass Index (BMI), distance from the anal verge, clinical T- and N-stage, pathological T- and N-stage after TME, CRT regimen, type of surgery, and CEA values of pre- and post-CRT were retrieved from the patient's medical records.

Continuous variables were reported as mean and standard deviations, and categorical variables were shown as frequencies or percentages. Fisher's exact and Pearson's chi-square tests were used to determine correlations between categorical variables. Logistic regression models identified the predictors of endpoint pCR. For all analyses, a P-value of < 0.05 was considered significant. Statistical analyses were performed using SPSS 26.0 software.

Results

Baseline characteristics

A total of 925 patients were recruited for this retrospective study (Fig. 1 and Table 1). Overall, 29 patients (3.1%) had a clinical T2 primary tumor, 748 (80.9%) had a clinical T3 primary tumor, and 148 (16%) had a clinical T4 primary tumor. Further, 64 patients (6.9%) had a clinical N0 and 861 (93.1%) had a clinical N+, indicating lymphatic metastasis. Tumor pathological staging after TME was evaluated, and 194 patients (21.0%) achieved pCR, as shown in Table 2. Serum CEA levels were collected at two different time periods, one week before nCRT and one week before surgery. In total, 408 patients had pre-nCRT CEA levels greater than 5 ng/mL, while 217 patients had post-nCRT CEA levels greater than 5 ng/mL, while 103 patients had levels > 10 ng/mL.

Multivariate analysis of pCR

A logistic regression model was used to analyze the potential factors influencing pCR (Table 3). The findings revealed that patients with pre-nCRT CEA levels ≤ 5 ng/mL were more likely to achieve a pCR (RR = 0.596, P < 0.001). Similarly, post-nCRT CEA levels were negatively correlated with the pCR rate (RR = 0.438, P < 0.001). Other factors, including age, sex, BMI, clinical T-category, clinical N-category, and distance from the anal verge, were not significantly associated with pCR.

Stratified analysis of the effect of CEA after nCRT on pCR

The 5 ng/mL and 10 ng/mL cutoff values were set to stratify the patients based on their post-nCRT CEA level. There were 217 patients with CEA greater than 5 ng/mL (Table 4), whose pCR rate was 10.6%. Among the remaining 708 patients, 24.2% achieved pCR. There were 103 patients with CEA greater than 10 ng/mL (Table 4), in whom only 6.8% achieved pCR, while the corresponding rate was 22.7% in the remaining patients. The differences in complete response rate between subgroups were statistically significant.

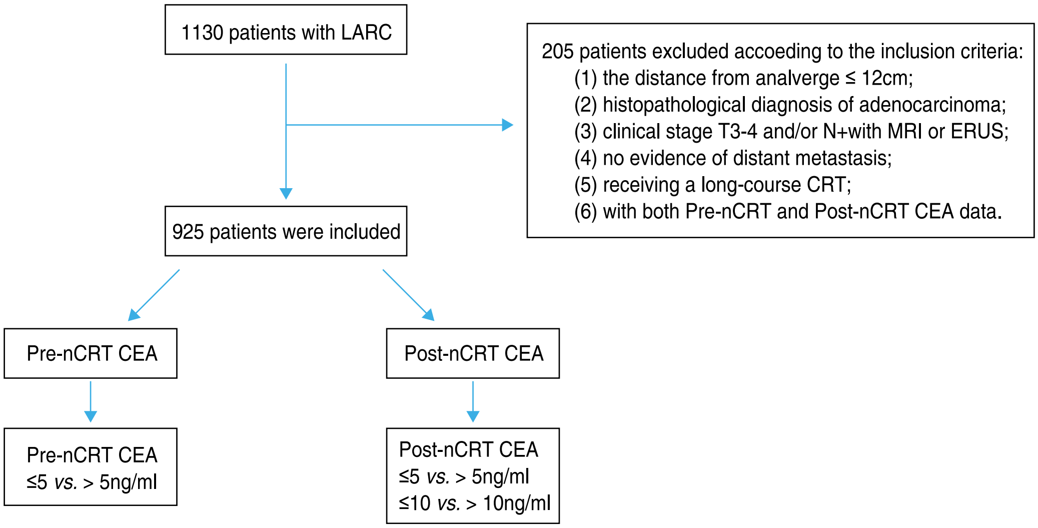

Fig. 1 Stages of this research. Between March 2006 and February 2018, a total of 1130 patients with locally advanced rectal cancer received nCRT at Fudan University Shanghai Cancer Center. In this period, 925 patients met the inclusion criteria for this retrospective analysis, with available pre- and post-nCRT CEA levels.

Discussion

In this study, CEA expression levels were significantly associated with pCR in LARC patients, indicating their use in predicting patient response to nCRT. Patients with pre-nCRT CEA level > 5 ng/mL had a lower pCR (P < 0.001). Similarly, a higher post-nCRT CEA level was negatively correlated with higher pCR (CEA cutoff value set to 5 ng/mL, RR = 0.438, P < 0.001; CEA cutoff value set to 10 ng/mL, RR = 0.300, P < 0.001, respectively). The pCR rate of patients with CEA level > 5 ng/mL was 10.6%, while the pCR rate of the remaining patients with CEA level ≤ 5 ng/mL was 24.2%. Meanwhile, patients with a CEA level greater than 10 ng/mL had a very low pCR rate of 6.8%, while that in the remaining patients was 22.7%. There was no significant correlation between age, sex, BMI, clinical T-category, clinical N-category, and location from the anal verge with pCR.

In this study, the 21.0% pCR rate obtained is consistent with data reported in other studies (10%–30%) [8–10]. CRT and TME result in a poor-quality of life due to adverse reactions to TME. The idea of the "watch and wait" method was first proposed by Habr-Gama [11] and is based on the idea that treatment strategy for LARC patients should be chosen based on the stages after neoadjuvant therapy. Studies have shown that LARC patients who received cCR after chemoradiotherapy have better long-term follow-up results with a "watch and wait" strategy. However, other studies have reported that only 36% of patients clinically evaluated as cCR achieve pCR after surgery. Therefore, precise diagnosis of cCR patients is important. Herein, we performed a large sample study to explore the predictive ability of curative characteristics of nCRT treatment efficacy and to define predictive factors of complete remission.

Recently, studies have discussed the correlation between CEA and treatment evaluation in rectal cancer. Joye I *et al.* [15] reports that the pre-treatment CEA mean level is statistically significant with pCR to nCRT (P = 0.04). Yinuo Tan *et al.* [13] reported that the pCR rate was 22% in patients with pre-treatment CEA levels < 5 ng/mL and 18% in patients with pre-treatment CEA levels ≥ 5 ng/mL. Kleiman *et al.* [19] demonstrate that post-CRT CEA levels are significantly lower in LARC patients with pCR (1.7 *vs.* 2.4 mg/L, P < 0.01). These studies indicate that both pre- and post-CRT CEA levels are strong predictors of achieving pCR in LARC. Similarly, we found that low pre- and post-nCRT CEA levels are significant predictors of pCR. Furthermore, when stratified according to the post-nCRT CEA level (10 ng/mL), the difference in pCR rate between subgroups is significant (6.8% *vs.* 22.7%). Therefore, the "watch and wait" strategy is not recommended if the LARC patients' post-nCRT CEA level is greater than 10 ng/mL after chemoradiotherapy.

Fewer studies have combined the predictive value of the CEA level with the "watch and wait" strategy. This has been associated with a lack of accuracy and sensitivity of CEA in predicting the efficacy of nCRT in LARC. Other studies have identified other predictors of the curative effect of nCRT in LARC. Monguzzi L *et al.* [25] reported that the apparent diffusion coefficient (ADC) value of magnetic resonance diffusion-weighted imaging (DW-MRI) could be used to predict the pathological grade of nCRT. Jia H *et al.* [26] reported a panel of metabolites used to predict pathological response to nCRT in LARC. Zhang J *et al.* [27] also found that the LARC assigner 3 classification

Table 1 Baseline characteristics.

Items	*n*	%
Total	925	100.0
Age (years)		
≤ 55	440	47.6
> 55	485	52.4
Sex		
Male	634	68.5
Female	291	31.5
BMI		
< 18	38	4.1
18–25	640	69.2
≥ 25	208	22.5
Unknown or missing	39	4.2
Clinical T-categary		
cT2	29	3.1
cT3	748	80.9
cT4	148	16.0
Clinical N-categary		
cN0	64	6.9
cN+	861	93.1
Location from anal verge (cm)		
≤ 5	501	54.2
> 5	424	45.8
CRT regimen		
Cap + RT	354	38.3
CapOx + RT	295	31.9
CapIri + RT	276	29.8
Pre-nCRT CEA level[a]		
≤ 5	517	55.9
> 5	408	44.1
Post-nCRT CEA level[b] (cutoff = 5)		
≤ 5	708	76.5
> 5	217	23.5
Post-nCRT CEA level[b] (cutoff = 10)		
≤ 10	822	88.9
> 10	103	11.1

Note:
[a] Pre-nCRT CEA level was defined as the CEA value within one week before nCRT.
[b] Post-nCRT CEA level was defined as the CEA value within one week before surgery.
Abbreviation: BMI, Body Mass Index; CRT, chemoradiotherapy; RT, radiotherapy; N+, lymphatic metastasis.

could predict outcomes in LARC patients, and tumors identified as low-risk based on this classification had a better prognosis.

This study had several limitations. First, this retrospective study used data from only a single cancer center, which may have led to selection bias. Second, we only reported a correlation between CEA levels and a pCR, but other associated serum tumor markers were not completely collected. Lastly, our study did not analyze the prognosis of patients who chose nonsurgical treatment based on the CEA value.

Table 2 Surgical type and pathological results.

Items	*n*	%
Total	925	100.0
Surgery		
Miles	415	44.9
Dixon	458	49.5
Hartmann	52	5.6
pCR		
Yes	194	21.0
No	731	79.0
ypT		
ypT0	215	23.2
ypT1	33	3.6
ypT2	246	26.6
ypT3	413	44.6
ypT4	18	1.9
ypN		
ypN0	587	63.5
ypN1	263	28.4
ypN2	75	8.1

Note: yp, pathological staging after neoadjuvant therapy.

Table 3 Relative risk for pCR.

Items	RR	*P* value
Age (> 55 *vs.* ≤ 55)	0.867	0.277
Sex (Female *vs.* Male)	0.976	0.858
BMI (≥ 25 *vs.* < 25)	1.250	0.261
Clinical T (cT4 *vs.* cT2-3)	0.958	0.970
Clinical N (cN+ *vs.* cN0)	1.039	0.977
Location from anal verge (> 5 cm *vs.* ≤ 5cm)	0.958	0.755
Pre-nCRT CEA level (> 5 *vs.* ≤ 5)	0.596	< 0.001
Post-nCRT CEA level (> 5 *vs.* ≤ 5)	0.438	< 0.001
Post-nCRT CEA level (> 10 *vs.* ≤ 10)	0.300	< 0.001

Note: RR, risk ratio

Table 4 Correlation between Post-nCRT CEA level and pCR.

Items	PCR		Non-PCR		*P* value
	n	%	*n*	%	
Using 5 ng/mL as Cut-off value of CEA					< 0.001
≤ 5 ng/mL	171	24.2	537	75.8	
> 5 ng/mL	23	10.6	194	89.4	
Using 10 ng/mL as Cut-off value of CEA					< 0.001
≤ 10 ng/mL	187	22.7	635	77.3	
> 10 ng/mL	7	6.8	96	93.2	

Note: CEA refers to Post-nCRT CEA.

Conclusion

This study demonstrated that high serum CEA level is an independent predictor for a lower rate of pCR in locally advanced rectal cancer patients. This could facilitate patient selection and aid clinicians to identify patients who may benefit most from watch-and-wait strategies. However, further prospective, randomized large-scale studies are warranted to combine predictive factors to develop a multi-factor prediction model with a more accurate prediction of complete remission.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

Data availability statement

Not applicable.

Ethical approval

It has passed the ethical examination of our hospital.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33.
2. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN Guidelines Insights: Rectal Cancer, Version 6.2020. J Natl Compr Canc Netw. 2020;18(7):806-815.
3. Belluco C, Forlin M, Olivieri M, et al. Long-term outcome of rectal cancer with clinically (EUS/MRI) metastatic mesorectal lymph nodes treated by neoadjuvant chemoradiation: role of organ preservation strategies in relation to pathologic response. Ann Surg Oncol. 2016;23(13):4302-4309.
4. Hasan S, Renz P, Wegner RE, et al. Microsatellite instability (MSI) as an independent predictor of pathologic complete response (PCR) in LIDB) Analysis. Ann Surg. 2020;271(4):716-723.
5. Hu Y, Wei J, Chang H, et al. The high pCR rate of sandwich neoadjuvant treatment in locally advanced rectal cancer may translate into a better long-term survival benefit: 5-year outcome of a Phase II clinical trial. Cancer Manag Res. 2018;10:4363-4369.
6. Jalilian M, Davis S, Mohebbi M, et al. Pathologic response to neoadjuvant treatment in locally advanced rectal cancer and impact on outcome. J Gastrointest Oncol. 2016;7(4): 603-608.
7. Petrelli F, Coinu A, Cabiddu M, et al. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. Eur Urol. 2014;65(2):350-357.
8. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835-844.
9. Zeng W, Liang J, Wang Z, et al. Clinical parameters predicting pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. Chin J Cancer. 2015;34(10):468-474.
10. Zhu J, Liu F, Gu W, et al. Concomitant boost IMRT-based neoadjuvant chemoradiotherapy for clinical stage II/III rectal adenocarcinoma: results of a phase II study. Radiat Oncol. 2014;9:70.
11. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711-718.
12. Peng H, Wang C, Xiao W, et al. Analysis of Clinical characteristics to predict pathologic complete response for patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. J Cancer. 2018;9(15):2687-2692.
13. Tan Y, Fu D, Li D, et al. Predictors and risk factors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer: a population-based analysis. Front Oncol. 2019;9: 497.
14. Tomono A, Yamashita K, Kanemitsu K, et al. Prognostic significance of pathological response to preoperative chemoradiotherapy in patients with locally advanced rectal cancer. Int J Clin Oncol. 2016; 21(2):344-349.
15. Joye I, Debucquoy A, Fieuws S, et al. Can clinical factors be used as a selection tool for an organ-preserving strategy in rectal cancer? Acta Oncol. 2016;55(8):1047-1052.
16. Wallin U, Rothenberger D, Lowry A, et al. CEA – a predictor for pathologic complete response after neoadjuvant therapy for rectal cancer. Dis Colon Rectum. 2013;56(7):859-868.
17. Yang J, Ling X, Tang W, et al. Analyses of predictive factors for pathological complete remission in neoadjuvant therapy for locally advanced rectal cancer. J BUON. 2019;24(1):77-83.
18. Kalady MF, Campos-Lobato LFD, Stocchi L, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg. 2009;250(4):582-589.
19. Kleiman A, Al-Khamis A, Farsi A, et al. Normalization of CEA levels post-neoadjuvant therapy is a strong predictor of pathologic complete response in rectal cancer. J Gastrointest Surg. 2015;19(6):1106-1112.
20. Armstrong D, Raissouni S, Hiller JP, et al. Predictors of pathologic complete response after neoadjuvant treatment for rectal cancer: a multicenter study. Clin Colorectal Cancer. 2015;14(4):291-295.
21. Kim HJ, Choi G, Park JS, et al. Clinical significance of thrombocytosis before preoperative chemoradiotherapy in rectal cancer: predicting pathologic tumor response and oncologic outcome. Ann Surg Oncol. 2015;22(2):513-519.
22. Perez RO, Juliao GPS, Habr-Gama A, et al. The role of carcinoembriogenic antigen in predicting response and survival to neoadjuvant chemoradiotherapy for distal rectal cancer. Dis Colon Rectum. 2009;52(6):1137-1143.
23. Probst CP, Becerra AZ, Aquina CT, et al. Watch and wait? – Elevated pretreatment CEA Is associated with decreased pathological complete response in rectal cancer. J Gastrointest Surg. 2016;20(1): 43-52.
24. Amin MB, Greene FL, Edge SB, et al. The eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA Cancer J Clin. 2017;67(2): 93-99.
25. Monguzzi L, Ippolito D, Bernasconi DP, et al. Locally advanced rectal cancer: value of ADC mapping in prediction of tumor response to radiochemotherapy. Eur J Radiol. 2013;82(2):234-240.
26. Jia H, Shen X, Guan Y, et al. Predicting the pathological response to neoadjuvant chemoradiation using untargeted metabolomics in locally advanced rectal cancer. Radiother Oncol. 2018;128(3):548-556.

27. Zhang J, Shen L, Deng Y, et al. A novel LARCassigner3 classification predicts outcomes in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy: a retrospective training and validation analysis. Cancer Manag Res. 2019;11:4153-4170.

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