Original Article

Prognostic value of CEA and CA19-9 in patients with local advanced rectal cancer receiving neoadjuvant chemoradiotherapy, radical surgery and postoperative chemotherapy

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Background: We aim to investigate the prognostic factors and evaluate the role of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) in local advanced rectal cancer (LARC) patients who received neoadjuvant chemoradiotherapy (neo-CRT), radical surgery and postoperative chemotherapy.

Methods: In total, 197 cases of LARC patients who underwent neo-CRT, total mesorectal excision (TME), and adjuvant chemotherapy were recruited. Serum levels of CEA and CA19-9 were detected both at baseline and after neo-chemoradiotherapy. Multivariate analysis was used to assess correlations between levels of CEA and CA19-9 and patients' prognosis (survival, recurrence, and metastasis). Rates of survival, distant metastasis (DM), and local recurrence (LR) were estimated using Kaplan-Meier survival analysis, the log-rank test, and Cox proportional hazards.

Results: The median follow-up time was 45.3 months, and a cohort of 197 patients was analyzed; 84 (42.6%) patients had elevated baseline CEA levels, 21 (10.7%) patients had elevated baseline CA19-9 levels, and 14 (7.1%) patients had both; 77.4% (65/84) patients with high CEA levels and 76.2% (16/21) with high CA19-9 levels returned to normal after neo-chemoradiotherapy. The Cox regression model suggested that elevated CEA was associated with an increased risk of disease-free survival (DFS) (HR: 2.058, 95% CI: 1.034–4.096, P=0.040) and DM (HR: 2.144, 95% CI: 1.058–4.346, P=0.034). Elevated CA19-9 was identified as an independent prognostic factor, with poorer overall survival (OS) (HR: 2.894, 95% CI: 1.196–7.006, P=0.018) and DFS (HR: 4.533, 95% CI: 2.067–9.940, P<0.001) and increased incidences of LR (HR: 6.139, 95% CI: 1.813–20.783, P=0.004) and DM (HR: 4.052, 95% CI: 1.892–8.678, P<0.001). Besides, combined CEA with CA19-9 was a stronger prognostic predictor. Patients with both high levels of CEA and CA19-9 had the poorest DFS (HR: 8.157, 95% CI: 3.232–20.591, P<0.001) and the highest risk of DM (HR: 8.790, 95% CI: 3.324–23.248, P<0.001).

Conclusions: LARC patients with high levels of CEA or/and CA19-9 at initial treatment have a worse prognosis, even after neo-CRT, subsequent radical resection, and adjuvant chemotherapy. These findings suggest that this subset of patients requires more intensive treatment or additional treatment strategies.

Keywords: Carbohydrate antigen 19-9 (CA19-9); carcinoembryonic antigen (CEA); neoadjuvant chemoradiotherapy (neo-CRT); prognosis; rectal cancer

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Introduction

Neoadjuvant chemoradiotherapy (neo-CRT) combined with radical surgery and postoperative chemotherapy is recommended as the standard treatment of patients with stage II/III rectal cancer (1-3). With the multimodality treatment, the 5-year overall survival (OS) has exceeded 75% (4-6). Although, multidisciplinary treatment of local advanced rectal cancer (LARC) successfully improves outcomes, 5–10% of patients experiencing local recurrence (LR), and up to 30% suffering from distant metastasis (DM) (7,8). Carcinoembryonic antigen (CEA) and Carbohydrate antigen 19-9 (CA19-9) are the most commonly used markers for diagnosis, treatment response assessment, and recurrence monitoring in CRC (9-13). Several studies have shown the prognostic value of CEA/CA19-9 in rectal cancer (14-17). However, few studies explored the correlations between elevated CEA and CA19-9 at initial treatment and prognosis in LARC patients after neo-CRT, total mesorectal excision (TME), and postoperative adjuvant chemotherapy.

Herein, we hypothesized that elevated CEA or/and CA19-9 might indicate poor prognosis in LARC patients after the standard treatment. Thus, we collected serum levels of CEA and CA19-9 at initial therapy and after neo-CRT. Then, we investigated the correlations between elevated CEA and CA19-9 levels before treatment and prognosis (survival, recurrence, and metastasis) in patients with LARC after neo-CRT, TME, and postoperative adjuvant chemotherapy. We committed to finding high-risk prognostic factors in LARC patients after the standard first-line treatment. Moreover, we explored whether the management for the patient population needs improvement.

We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2269).

Methods

Patients

Between June 2011 and September 2015, eligible patients aged at least 18 years, with clinical stage II (T_3-$_4N_0$) or III (T_1-$_4N_1$-$_2$) rectal adenocarcinoma who had a distal tumor border within 12 cm of the anal verge by colonoscopy were retrospectively collected at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China. This study was conducted according to the Declaration of Helsinki (as revised in 2013), and the ethic committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (Project number 20180927-1) approved the study. All patients provided written informed consent before the treatment.

Enhanced magnetic resonance imaging (MRI) and endorectal ultrasound were used for local staging. A full colonoscopy or rigid proctoscopy and computed tomography (CT) scan of the chest and abdomen were performed before treatment. Positron emission tomography-CT (PET-CT) was recommended to exclude DM if there were suspicious test results. Patients were required to have an Eastern Cooperative Oncology Group performance status ≤1 and adequate hematologic (defined as hemoglobin ≥90 g/L, neutrophils ≥1.5 billion/L, platelets ≥80,000 billion/L), liver function (total bilirubin <2 mg/dL; alanine aminotransferase, aspartate aminotransferase <3× the upper limit of normal), and renal function (creatinine ≤130 μmol/L). Exclusion criteria included the presence of metastatic disease, previously receiving radiotherapy or chemotherapy to the pelvis, the presence of previous or concurrent cancers, or clinically significant cardiac disease.

Treatment

Preoperative radiotherapy consisted of 45–50 Gy administered in 25 fractions delivered with a minimum energy of 6-MV photons. The target delineation criteria refer to the North American Tumor Radiation Therapy Collaborative Group (RTOG) and the European Society of Oncology (ESMO) guidelines. Organs at risk included the small intestine, colon, bladder, and femur head, and corresponding dose limitations were as follows: small intestine D_{max} <52 Gy; colon D_{max} <54 Gy; bladder V_{65} <50%; femur head V_{50} ≤5% (18).

Preoperative concurrent chemotherapy included capecitabine (825 mg/m^2, oral, twice daily) and oxaliplatin (130 mg/m^2 on day 1 and day 22) during radiotherapy. Oral capecitabine was given alone to elderly

patients (age ≥65) or to patients who poorly tolerated combination therapy. One cycle CapeOX or two cycles of mFOLFOX6 chemotherapeutic regimens were given after chemoradiotherapy and before radical surgery.

TME surgery was performed 6-8 weeks after neo-CRT and included low anterior resection (LAR), abdominal-perineal resection (Miles), and Hartmann's procedure. Adjuvant chemotherapy regimens including CapeOX or mFOLFOX6, and the total perioperative treatment were approximately six months. The specific regimens with dosages were as follows: (I) CapeOX: oxaliplatin 130 mg/m^2 IV, day 1, capecitabine 1,000 mg/m^2 twice daily, days 1–14, every 3 weeks; and (II) mFOLFOX6: oxaliplatin 85 mg/m^2 IV day 1, leucovorin 400 mg/m^2 IV, 5-FU 400 mg/m^2 IV bolus on day 1, then 1,200 mg/m^2/d ×2 days continuous infusion, every 2 weeks.

Measurement of tumor markers

Venous blood was collected in the morning before breakfast from all of the subjects. Blood samples were allowed to clot at room temperature for 30 minutes and then centrifuged at 1,000 g for 20 minutes at 4 ℃. The upper phase of the serum was collected, aliquoted, and stored at –80 ℃. Serum CEA and CA19-9 were measured by the electrochemiluminescence immunoassay system Cobas E411 and E601 (Roche, Mannheim, Germany), respectively. The cut-off value is 5 ng/mL of CEA and 37 U/mL of CA19-9, as recommended by the manufacturer. Once the tumor markers increased above the upper limit, reexamination would be performed on the same day. The assays were performed blinded to the retrospective study.

Data collection

A total of 267 eligible patients were retrospectively collected from June 2011 to September 2015. The follow-up deadline was May 2018, and the median follow-up time was 45.3 months (range, 12.0–86.3 months). Serum levels of CEA and CA19-9 at baseline were detected within one week before neo-CRT. In addition, tumor markers 2–3 weeks after neo-CRT and before radical surgery were also collected for analysis. Sixty-five patients were excluded due to incomplete laboratory results for CEA or CA19-9, and five patients were lost to follow-up, leaving 197 patients available for analysis. All patients were treated with neo-CRT, radical surgery 6–8 weeks later, and adjuvant chemotherapy according to NCCN guidelines. The baseline characteristics of patients are shown in (*Table 1*), including gender, age, clinical stage, tumor location, baseline values of CEA and CA19-9, CRM (evaluated by MRI), added oxaliplatin or not to concurrent chemoradiotherapy, type of radical surgery and specific downstaging, including T- and N-downstaging. In addition, clinical staging and corresponding levels of CEA and CA19-9 before and after neo-CRT are shown in (Table S1). Most patients with high levels of CEA or CA19-9 before treatment returned to normal after neo-CRT.

Follow-up

Patients were followed at 3-month intervals after surgery for two years, at 6-month intervals for the next three years, and once yearly five years later. Evaluations consisted of patient history, physical examination, serum CEA, serum CA19-9, a complete blood count, and blood chemical analysis at every visit. Proctoscopy, abdominal ultrasonography and CT/MRI studies of the abdomen, pelvis, and chest were routinely examined every 6–12 months.

Statistical analysis

Primary endpoints included OS and disease-free survival (DFS). OS was defined as the time from the beginning of neo-adjuvant chemoradiation to death from any cause. DFS was defined as the time from the start of treatment to the first incidence of either LR or DM. Secondary endpoints included DM and LR. DM was defined as any recurrence outside the pelvic cavity, and LR was defined as any recurrence within the pelvic cavity or perineum.

OS, DFS, DM, and LR rates were estimated utilizing the Kaplan-Meier method and the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression. Two-sided P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software package (version 19.0; IBM, Armonk, NY).

Results

We first performed survival and recurrence analyses on all patients (OS, DFS, LR, DM), listing all possible variables, including gender, age, tumor location, CRM (evaluated by MRI), CEA, CA19-9, pathologic complete response (pCR), T-downstage, N-downstage, and adding oxaliplatin to the concurrent chemoradiotherapy regimen.

Table 1 Baseline characteristics of patients

Character	Subtype	Number of cases (%)
Gender	Male	133 (67.5)
	Female	64 (32.5)
Age	Median [range]	60 [29–85]
	<50	25 (12.7)
	50–65	121 (61.4)
	>65	51 (25.9)
Clinical stage	II: $cT_{3-4}N_0M_0$	23 (11.7%)
	III A: $cT_2N_1M_0$	12 (6.1%)
	III B: $cT_{3-4}N_1M_0$	84 (42.6%)
	III B: $cT_2N_2M_0$	4 (2.0%)
	III C: $cT_{3-4}N_2M_0$	74 (37.6%)
Tumor location	<5 cm	73 (37.1)
	5–10 cm	110 (55.8)
	>10 cm	14 (7.1)
CEA (ng/mL)	≤5	113 (57.4)
	>5	84 (42.6)
CA 19-9 (U/mL)	≤37	176 (89.3)
	>37	21 (10.7)
CRM (by MRI)	Involved	62 (31.5)
	Clear	135 (68.5)
CRT with OX	With	162 (82.2)
	Without	35 (17.8)
Type of surgery	Anterior resection	123 (62.4)
	Abdominal-perineal resection	56 (28.4)
	Hartmann	18 (9.1)
Downstage[§]	T-downstage	108 (54.8)
	N-downstage	163 (82.7)

[§], downstage, including T-downstage and N-downstage, means clinical restaging after neo-CRT and before radical surgery compared with clinical staging at initial treatment. CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CRT, neoadjuvant chemoradiotherapy; OX, oxaliplatin; CRM, circumferential resection margin.

Univariate analysis was performed to identify potential significant variables for different endpoints (OS, DFS, LR, and DM) (*Table 2*), using P>0.15 as the exclusion criterion. Multivariate analysis was subsequently performed for OS, DFS, LR, and DM (*Table 3*), which identified independent prognostic risk factors and strongly identified CEA and CA19-9.

Survival and progression analysis

The median follow-up time was 45.3 months (range, 12.0–86.3 months). A total of 28 patients died, and the 3- and 5-year OS rates were 89.1% and 82.7%, respectively. Thirteen patients experienced LR (6.6%), and the 3- and 5-year LR rates were 5.6% and 7.2%, respectively. DM occurred in thirty-eight cases (19.3%), of which twelve cases (31.6%) had liver metastases, and 18 (47.4%) had lung metastases as the first site. The 3- and 5-year DM rates were 18.2% and 20.3%, respectively. Most local or distant progression occurred within three years, and the 3- and 5-year DFS rates were 80.8% and 78%, respectively.

In univariate analysis, potential predictors for OS included gender, CRM, CEA, CA19-9 and pCR. CRM, CEA, CA19-9, pCR, T-downstage, and N-downstage were the potential prognostic factors for DFS. Potential predictors for LR included tumor location, CA19-9, and pCR; CRM, CEA, CA19-9, pCR, and T-downstage were the potential risk factors for DM, respectively.

By adjusting for all known covariates and using COX regression model analysis, only CRM and CA19-9 were independently predictive of OS. CEA, CA19-9, and pCR were the independent prognostic factors for DFS. CA19-9 and tumor location were predictive of LR; CEA, CA19-9, and pCR were the independent risk factors for DM. In addition, LARC patients could not benefit from adding oxaliplatin to neo-CRT in the study.

CEA is an independent predictor of DFS and DM

In the univariate analysis, elevated baseline CEA was associated with reduced OS (5-year, 73.6% *vs*. 89.8%, P=0.014), DFS (5-year, 68.6% *vs*. 85.7%, P=0.002), and DM (30.2% *vs*. 12.1%, P=0.001) (*Table 2*). Kaplan-Meier curves showed a comparison of the OS, DFS, LR, and DM for the elevated and normal CEA levels before treatment in LARC patients with neo-CRT, radical surgery, and adjuvant chemotherapy (*Figure 1A*,*B*,*C*,*D*). Multivariate analysis suggested patients with elevated CEA were associated with a decreased DFS [hazard ratio (HR): 2.058, 95% confidence interval (CI): 1.034–4.096, P=0.040] and a higher risk of DM (HR: 2.144, 95% CI: 1.058–4.346, P=0.034) (*Table 3*).

Table 2 Univariate analysis of the effects of different characteristics on 5-year OS, 5-year DFS, DM, and LR

Characteristic	Subtype	N	OS		DFS		DM		LR	
			%	P	%	P	%	P	%	P
Gender	Male	133	78.3	0.072*	76.4	0.208	22.1	0.197	6.8	0.858
	Female	64	91.1		82.1		15.4		7.9	
Age	<50	25	88	0.854	84	0.764	16.0	0.847	4	0.804
	50–65	121	82		78		20.0		7.4	
	>65	51	82.3		76.5		21.6		8	
CRM (by MRI)	+	62	74.5	0.024*	67.7	0.012*	31.1	0.013*	11.3	0.174
	–	135	89.5		83.1		15.1		5.6	
Tumor location (cm)	<5	73	79.5	0.519	73	0.401	23.8	0.549	13.6	0.041*
	5–10	110	85		82.1		17		2.7	
	>10	14	75		78.6		21.4		7.1	
CEA (ng/mL)	≤5	113	89.8	0.014*	85.7	0.002*	12.1	0.001*	6.2	0.378
	>5	84	73.6		68.6		30.2		8.4	
CA19-9 (IU/mL)	≤37	176	86.2	<0.001*	82.1	<0.001*	15.9	<0.001*	5.7	0.006*
	>37	21	45.8		47.6		52.4		19	
Neo-CRT with OX	With	162	83.2	0.404	78.1	0.923	19.8	0.897	6.8	0.572
	Without	35	82.8		80		20		8.6	
pCR	Yes	69	90.4	0.071*	92.8	0.001*	7.2	0.002*	2.9	0.144*
	No	128	79		70.9		26.5		9.4	
T-downstage[§]	Yes	108	83.5	0.888	85.2	0.034*	13.9	0.044*	6.5	0.955
	No	89	82.5		70.5		26.7		7.7	
N-downstage[§]	Yes	163	83.2	0.520	82.1	0.064*	18.2	0.221	6.4	0.584
	No	34	80.6		64.6		28.2		11.1	

*, indicate P<0.15. [§], downstage, including T-downstage and N-downstage, means clinical restaging after neo-CRT and before radical surgery compared with clinical staging at initial treatment. OS, overall survival; DFS, disease-free survival; LR, local recurrence; DM, distant metastasis; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; neo-CRT, neoadjuvant chemoradiotherapy. OX, oxaliplatin; CRM, circumferential resection margin; pCR, pathologic complete response; CI, confidence interval; T, tumor; N, lymph node.

The results indicated that CEA was an independent prognostic risk factor of DFS and DM for LARC patients.

CA19-9 is an independent predictor of OS, DFS, LR, and DM

Compared with normal baseline CA19-9 values, patients with elevated CA19-9 values showed reduced OS (5-year, 45.8% *vs*. 86.2%, P<0.001) and DFS (5-year, 47.6% *vs*. 82.1%, P<0.001), along with higher risk of LR (19% *vs*. 5.7%, P=0.006) and DM (52.4% *vs*. 15.9%, P<0.001) (*Table 2*). Kaplan-Meier curves comparing the OS, DFS, LR, and DM of LARC patients with elevated and normal baseline CA19-9 levels after receiving neo-CRT, radical surgery, and adjuvant chemotherapy (*Figure 2A*,*B*,*C*,*D*).

The Cox regression model also suggested reduced OS (HR: 2.894, 95% CI: 1.196–7.006, P=0.018), DFS (HR: 4.533, 95% CI: 2.067–9.940, P<0.001), and increased incidence of LR (HR: 6.139, 95% CI: 1.813–20.783, P=0.004) and DM (HR: 4.052, 95% CI: 1.892–8.678, P<0.001) in LARC patients with elevated baseline CA19-9 levels (*Table 3*). Therefore, the results above indicated that

Table 3 Multivariable analysis of different characteristics on 5-year OS, DFS, LR, DM

Characteristic	Subtype	P	HR value	95% CI
OS	Gender	0.331	0.608	0.223–1.658
	CRM (+)	0.021*	1.659	0.763–3.609
	CEA	0.298	1.561	0.675–3.609
	CA19-9	0.018*	2.894	1.196–7.006
	pCR	0.224	1.851	0.686–4.996
DFS	CRM (+)	0.278	1.444	0.743–2.805
	CEA	0.040*	2.058	1.034–4.096
	CA19-9	<0.001*	4.533	2.067–9.940
	pCR	0.007*	4.366	1.497–12.737
	T-downstage§	0.231	1.589	0.745–3.390
	N-downstage§	0.058	0.472	0.217–1.025
DM	CRM (+)	0.367	1.372	0.690–2.725
	CEA	0.034*	2.144	1.058–4.346
	CA19-9	<0.001*	4.052	1.892–8.678
	pCR	0.008*	4.345	1.480–12.758
	T-downstage§	0.407	1.385	0.641–2.990
LR	CA19-9	0.004*	6.139	1.813–20.783
	Tumor location	0.021*	0.280	0.095–0.827
	pCR	0.188	2.758	0.609–12.489

*, indicate P<0.05, suggesting that these variables are independent risk factors for OS, DFS, DM, and LR. §, downstage, including T-downstage and N-downstage, means clinical restaging after neo-CRT and before radical surgery compared with clinical staging at initial treatment. OS, overall survival; DFS, disease-free survival; LR, local recurrence; DM, distant metastasis; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; neo-CRT, neoadjuvant chemoradiotherapy; CRM, circumferential resection margin; pCR, pathologic complete response; HR, hazard ratio; T, tumor; N, lymph node.

CA19-9 levels before treatment were a powerful predictor of OS, DFS, LR, and DM in LARC patients after receiving neo-CRT, radical surgery, and adjuvant chemotherapy.

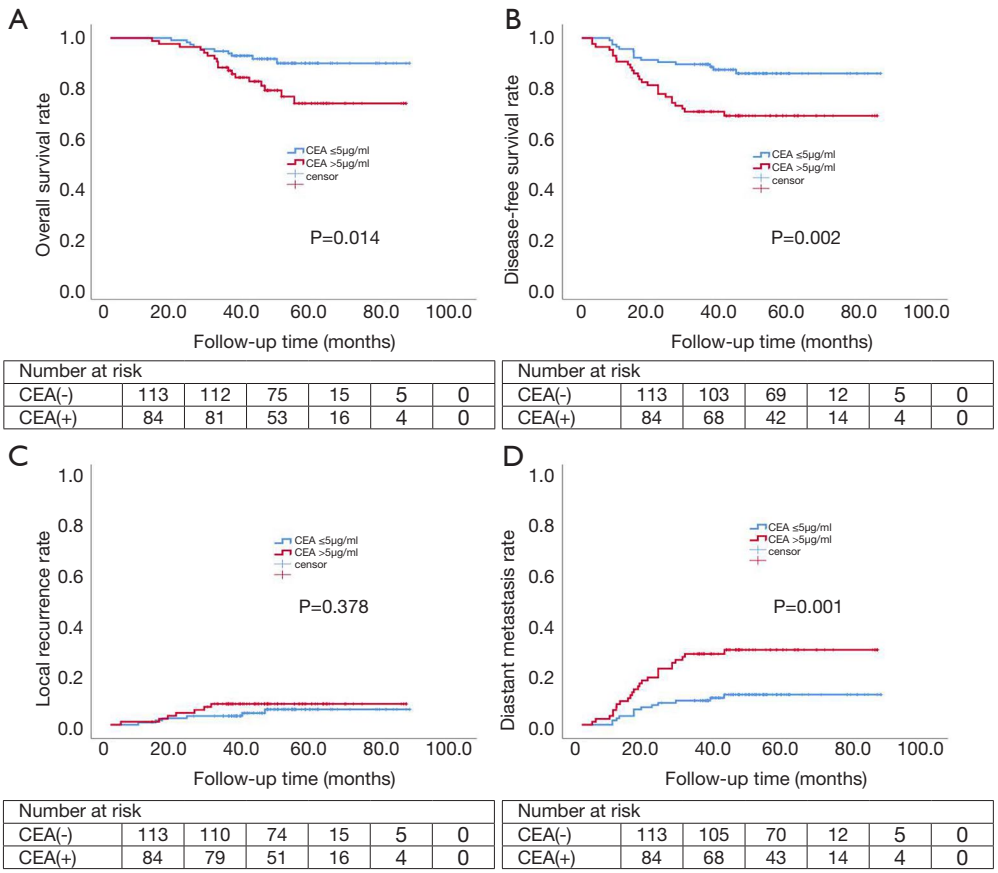
Combined CEA with CA19-9 is a stronger predictor of OS, DFS, LR, and DM

To investigate whether combining CEA and CA19-9 could strongly predict the prognosis of patients. We divided the patients into four groups: (A) normal levels of CEA and CA19-9 (n=106); (B) elevated CEA and normal levels of CA19-9 (n=71); (C) normal levels of CEA and elevated levels of CA19-9 (n=6); (D) high levels of both CEA and CA19-9 (n=14).

Kaplan-Meier analysis showed that patients in group D had significant reduced OS (5-year 44.9% *vs.* 91.3%) and DFS (5-year 35.7% *vs.* 86.9%) and higher risks of LR (14.3% *vs.* 5.6%) and DM (64.3% *vs.* 10.9%) than those in group A (*Figure 3A*,*B*,*C*,*D*). The median OS and the median DFS for group D were 49.3 months (95% CI: 28.802–69.798), and 16.2 months (95% CI: 5.750–26.650), respectively. Besides, the Cox regression model also showed that patients in group D had the poorest DFS (HR: 8.157, 95% CI: 3.232–20.591, P<0.001) and the highest risk of DM (HR: 8.790, 95% CI: 3.324–23.248, P<0.001).

Discussion

CEA and CA19-9 are the most commonly used tumor markers in gastrointestinal cancer for diagnosis, treatment



Number at risk						
CEA(-)	113	112	75	15	5	0
CEA(+)	84	81	53	16	4	0

Number at risk						
CEA(-)	113	103	69	12	5	0
CEA(+)	84	68	42	14	4	0

Number at risk						
CEA(-)	113	110	74	15	5	0
CEA(+)	84	79	51	16	4	0

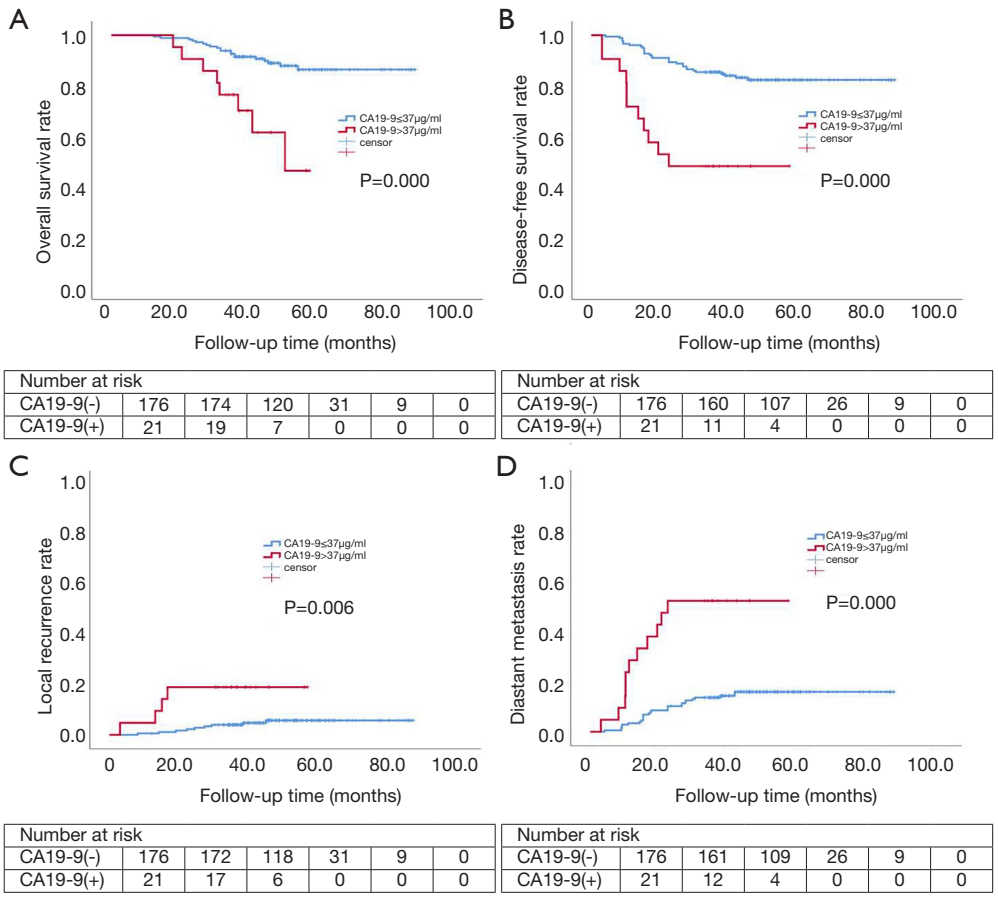
Number at risk						
CEA(-)	113	105	70	12	5	0
CEA(+)	84	68	43	14	4	0

Figure 1 Kaplan-Meier curves comparing the elevated and normal CEA in LARC patients with neo-CRT, radical surgery, and adjuvant chemotherapy. (A) Overall survival; (B) disease-free survival; (C) local recurrence; (D) distant metastasis. LARC, local advanced rectal cancer; CEA, carcinoembryonic antigen. CEA (–): CEA ≤5 ng/mL; CEA (+): CEA >5 ng/mL.

assessment, recurrence monitoring, and prognostic evaluation (9-17,19-24). However, in patients with local advanced rectal cancer, CEA and CA19-9 have not been used for clinical decision making. In this study, we found elevated CEA and CA19-9 indicate a poor prognosis, especially for patients with high levels of CA19-9. Although they had received neo-CRT, TME, and postoperative adjuvant chemotherapy, despite most patients with high levels of CEA or CA19-9 at initial treatment returned to normal after neo-CRT. We demonstrated that elevated CEA and CA19-9 are high-risk prognostic factors in LARC patients after the standard first-line therapy.

For LARC patients received neo-CRT, TME, and adjuvant chemotherapy, the available data from our study revealed that the 5-year OS rate was 82.7%. The survival result was substantially consistent with other randomized trials, which reported rates of approximately 78–81.3% (4,25). Univariate analysis suggested that elevated CEA was not significantly correlated with LR (P=0.378), but indicated declined OS, DFS, and DM. Multivariate analysis further showed that elevated CEA is an independent risk factor for DFS and DM. Kim *et al.* also found CEA was an independent prognostic factor for DFS (P=0.004) in rectal cancer (26). Restivo *et al.* demonstrated that CEA was predictive of DM in local advanced rectal cancer (OR 2.107; 95% CI: 1.313–3.383; P=0.002) (27).

For patients diagnosed with rectal cancer, CEA was detected as one of the initial evaluation. However, the significance of CA19-9 has not been clear. Zhang *et al.* reported CA19-9 was the most significant prognostic factor rather than CEA in LARC patients after receiving neo-CRT and radical surgery (17). However, 28% of patients without postoperative chemotherapy in that study. Rectal cancer patients staged as AJCC II/III and all underwent



Number at risk						
CA19-9(-)	176	174	120	31	9	0
CA19-9(+)	21	19	7	0	0	0

Number at risk						
CA19-9(-)	176	160	107	26	9	0
CA19-9(+)	21	11	4	0	0	0

Number at risk						
CA19-9(-)	176	172	118	31	9	0
CA19-9(+)	21	17	6	0	0	0

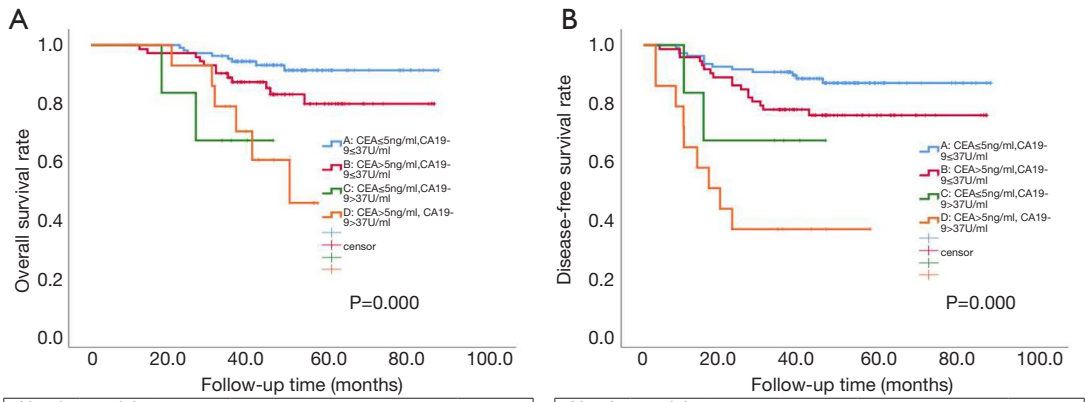
Number at risk						
CA19-9(-)	176	161	109	26	9	0
CA19-9(+)	21	12	4	0	0	0

Figure 2 Kaplan-Meier curves comparing the elevated and normal CA19-9 in LARC patients with neo-CRT, radical surgery, and adjuvant chemotherapy. (A) Overall survival; (B) disease-free survival; (C) local recurrence; (D) distant metastasis. LARC, local advanced rectal cancer; CA19-9, carbohydrate antigen 19-9. CA19-9(–): CA19-9 ≤37 U/mL; CA19-9 (+): CA19-9 >37 U/mL.

rigid first-line standard treatment were included for analysis, we found that in addition to the elevated CA19-9, which indicated extremely poor prognosis, the more important thing is that elevated CEA is also a predictor of DFS and DM, and combined CEA with CA19-9 is a better prognostic predictor. Even though these tumor markers decreased significantly after treatment (Table S1), and conventional imaging examinations have ruled out distant metastases before treatment. Herein, we recommend CA19-9 should be routinely included in the initial assessment in addition to CEA for patients diagnosed with local advanced rectal cancer. More intensive treatment or additional treatment strategies may be required, including intensified preoperative chemotherapy, the addition of targeted therapy to preoperative treatment, adjustment of postoperative chemotherapy to preoperative to strengthen systemic control, or genetic testing to select suitable treatment options.

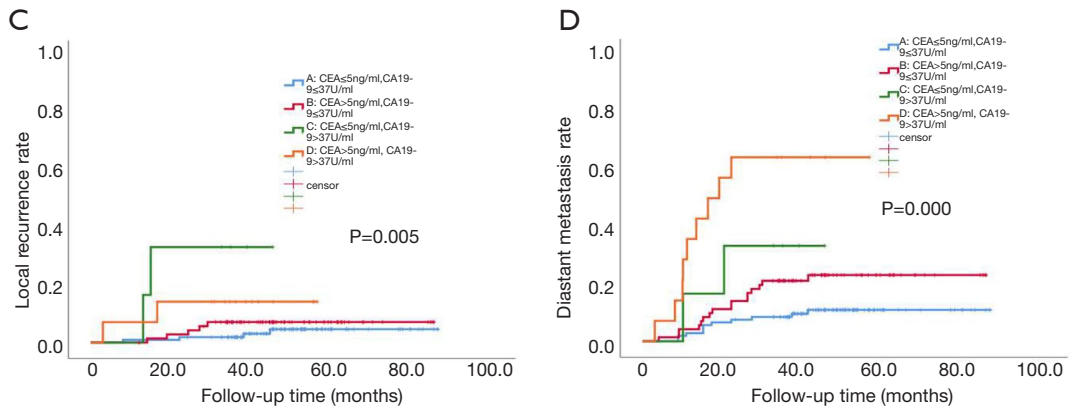
In our retrospective study, MRI-involved CRM was an independent risk factor for OS. It was consistent with the result of the MERCURY trial, where MRI-involved CRM showed a decreased OS in comparison with MRI-clear CRM (HR: 1.97, 95% CI: 1.27–3.04, P<0.01) (28). However, we didn't observe that patients with MRI-involved CRM had a higher risk of LR. It may because part of patients in the MERCURY trial without neoadjuvant treatment. Besides, we also explored the role of oxaliplatin to neo-CRT. The COX regression model suggested it did not improve local or systemic control significantly. Though, it has been reported in previous well-known phase III randomized clinical trials (RCT) (29-31).

There are some limitations in our study. Although we carried out an explicit enter criterion, a retrospective study with the possibility of involving in confounding



Number at risk						
A	107	107	75	15	5	0
B	70	68	45	16	4	0
C	6	5	1	0	0	0
D	14	13	6	0	0	0

Number at risk						
A	107	99	69	12	5	0
B	70	62	38	14	4	0
C	6	4	1	0	0	0
D	14	6	3	0	0	0



Number at risk						
A	107	106	74	15	5	0
B	70	67	44	16	4	0
C	6	4	1	0	0	0
D	14	12	6	0	0	0

Number at risk						
A	107	100	70	12	5	0
B	70	62	39	14	4	0
C	6	5	1	0	0	0
D	14	6	3	0	0	0

Figure 3 Kaplan-Meier curves comparing the elevated CEA/CA19-9 in LARC patients with neo-CRT, radical surgery, and adjuvant chemotherapy. (A) Overall survival; (B) disease-free survival; (C) local recurrence; (D) distant metastasis. LARC, local advanced rectal cancer; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9. (A) CEA ≤5 ng/mL, CA19-9 ≤37 U/mL; (B) CEA >5 ng/mL, CA19-9 ≤37 U/mL; (C) CEA ≤5 ng/mL, CA19-9 >37 U/mL; (D) CEA >5 ng/mL, CA19-9 >37 U/mL.

factors may result in potential bias. Besides, we formulated strict inclusion in order to reduce interfering factors. Only patients who are accurately staging as AJCC II/III preoperatively and receiving standard neo-CRT combined with TME and postoperative chemotherapy are eligible for further researches, which in turn to limit the sample size, especially for patients with elevated CA19-9. We will expand the sample size for further research. Reanalysis using existing tumor markers or updated data from tumor markers derived from tumor specimens would be of interest in the future.

Conclusions

To summarize, LARC patients with high levels of CEA or/and CA19-9 before treatment exhibit worse prognosis, despite receiving subsequent radical resection and existing standard adjuvant chemotherapy. Additional studies are

warranted to further determine the clinical significance of CEA and CA19-9 in rectal cancer. Still, these findings suggest that this patient population needs more intensive treatment or additional treatment strategies.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The retrospective study was approved by the ethic committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (Project number 20180927-1). Informed consent was taken from all the patients.

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