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Prognostic Value of Pretreatment Serum CA199 in Patients with Locally Advanced Rectal Cancer Treated with CRT Followed by TME with Normal Pretreatment Carcinoembryonic Antigen Levels

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Keywords

Prognostic value · Pretreatment serum carbohydrate antigen199 · Locally advanced rectal cancer · Normal pretreatment carcinoembryonic antigen levels · CRT

Abstract

Background: Elevated pretreatment carcinoembryonic antigen (CEA) levels are related to poor prognosis in patients with locally advanced rectal cancer (LARC) treated with neo-CRT followed by TME. In patients with normal pretreatment CEA levels, the prognostic significance of carbohydrate antigen 199 (CA199) is controversial. ***Objectives:*** The aim of this study was to explore the prognostic value of pretreatment serum CA199 in patients with LARC who had normal pretreatment CEA levels treated with neo-CRT followed by curative surgery. ***Methods:*** A retrospective study of 456 patients with LARC treated with neo-CRT followed by TME between January 2006 and May 2017 was performed. We employed the maximal χ^2 method to determine the CA199 threshold of 9.1 U/mL based on the difference in survival and divided patients into 2 groups. Group 1: patients with pretreatment s-CEA < 5 ng/mL and CA199 ≥ 9.1 U/mL. Group 2: patients with pretreatment s-CEA < 5 ng/mL and CA199 < 9.1 U/mL. Overall survival (OS) across CA199 was assessed using Cox proportional hazard regression models (PS:CEA ≥ 5 ng/mL was seen as elevated). ***Results:*** Multivariate analyses demonstrated that the following factors were significantly related to OS in patients with LARC with normal pretreatment CEA levels: ypT (odds ratio [OR] 1.863, $p = 0.030$), ypN (OR 1.622, $p = 0.026$), and pretreatment CA199 levels (OR 1.886, $p = 0.048$). ***Conclusion:*** Pretreatment CA199 is an independent factor for OS in patients with LARC with normal pretreatment CEA levels, which may reach the clinic to guide individualized decision-making.

Introduction

Carcinoembryonic antigen (CEA) is an acidic glycoprotein first extracted from colon and embryonic organizations by Gold and Freedman in 1965, which plays a role as a contact medium between tumor cells [1]. Carbohydrate antigen 199 (CA199) is an oligosaccharide tumor-associated antigen with a molecular weight greater than 1,000 kD, which functions in adhesion during tumor progression.

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To date, CEA has been recommended by major guidelines to play an important role in diagnosis, staging and risk assessment, treatment and response evaluation, and follow-up of CRC, whereas CA199 has not, albeit its significance in uncovering prognosis and recurrence has been confirmed by some studies [2–7].

With the promotion of a multidisciplinary treatment concept, good local control rate, and lower toxicity, preoperative chemoradiotherapy is more widely used in patients with locally advanced rectal cancer (LARC) compared with postoperative chemoradiotherapy [8–11].

Elevated pretreatment CEA levels are considered to be in accordance with poor prognosis in patients with LARC treated with neo-CRT followed by TME [12–14]. In that case, it means that those with normal pretreatment CEA have better outcomes. However, whether CA199 is predictive of prognosis in this cohort has not been determined. A better understanding of the prognostic value of CA199 is particularly important in patients with LARC treated with preoperative CRT and surgical resection because the result can help to predict outcomes and even feed back to the clinic. Hence, we elucidated the thresholds and explored the prognostic value of pretreatment serum CA199 levels in the above population.

Materials and Methods

Patients and Parameters

We retrospectively analyzed 456 patients who were treated with neo-CRT followed by radical surgery from January 2006 to May 2017 at our institution. They all met the following conditions: (1) histopathologically proven rectal adenocarcinoma; (2) complete clinicopathological data, including sex, age, clinical stage, tumor location, chemotherapy regimen, yp stage, survival status, and surgery style; and (3) serum levels of CEA and CA199 were measured via chemiluminescent immunoassay in the laboratory of our center. We referred to the threshold of 9.1 obtained by the X-tile software to divide patients into 2 groups: group 1 included patients with normal pretreatment s-CEA levels and CA199 ≥ 9.1 U/mL; and group 2 included those with normal pretreatment s-CEA levels and CA199 < 9.1 U/mL.

Radiotherapy

The method of radiotherapy has been described in a prior published paper [15, 16]. Regarding target volumes, we set tumor/tumor bed as the gross tumor volume (GTV) based on examinations. Covering all the mesorectum, the pre-sacral soft tissue, internal iliac, and obturator lymphatic drainage area was set as CTV. Techniques to achieve radiotherapy included 3DCRT with a dose of 50.4 Gy in 28 fractions and IMRT with a dose of 50 Gy in 25 fractions. We delivered 45 Gy to the PTV-CTV of all.

Chemotherapy

Three regimens were adopted according to clinical trials in different periods as follows: (1) Capeox (oxaliplatin 130 mg/m^2 ivgtt d1, capecitabine 825 mg/m^2 bid po d1–14). (2) Capecitabine was taken orally at a dosage of 825 mg/m^2 twice daily, during the whole period of radiotherapy. (3) Folfox4 (oxaliplatin 85 mg/m^2 ivgtt d1, leucovorin 200 mg/m^2 ivgtt d1–d2, 5-Fu 400 mg/m^2 ivgtt d1–d2, 5-Fu 1,200 mg/m^2 civ 46 h).

Surgery

Surgery was performed 8–12 weeks after the end of neochemoradiotherapy. All the operations followed the tumor mesorectal excision principle carried out by experienced experts from our center, including APR (abdominoperineal resection) and SSR (sphincter-saving resection).

Adjuvant Chemotherapy

Postoperative adjuvant chemotherapy was recommended 4 weeks after the surgery for appropriate patients by doctors according to postoperative pathology and NCCN guidelines. As a result, 77% of patients received adjuvant chemotherapy, and the remaining patients did not receive adjuvant chemotherapy due to economic reasons, physical reasons, or complications, and so on.

Follow-Up

The frequency of regular outpatient follow-up was once every 3 months within 2 years after curative surgery, once every 6 months in the third to fifth years, and annually thereafter. The follow-up involved regular blood tests, CEA, CA199, chest CT, and abdominopelvic MRI. We also recommended that patients have a colonoscopy once a year.

Data Analysis

We used X-tile software to adapt the maximal χ^2 method to analyze and determine the best cutoff value of 9.1 according to the difference in survival curves, thus dividing the patients into 2 groups as described above. The χ^2 test was employed to compare the clinicopathological baseline between the 2 groups. Overall survival (OS) rates were estimated using the Kaplan-Meier method and the log-rank test. Univariate and multivariate analyses of prognostic factors for OS were carried out using Cox's proportional hazards model. A p value < 0.05 was considered statistically significant. With the help of SPSS software, version 25, we completed the above calculations.

Results

Application of X-Tile for Cutoff Decision and Grouping

X-tile software was applied to determine the cutoff value of pretreatment serum CA199 levels associated with 5-year survival in patients with normal pretreatment CEA levels who were treated with neo-CRT followed by TME. The optimum threshold we obtained was 9.1 U/mL. Therefore, we divided all patients into 2 groups. Group 1: patients with pretreatment s-CEA < 5 ng/mL

Table 1. Clinicopathological characteristics according to CEA and CA199 group

Factor	Group 1	Group 2	*p* value
Gender, *n* (%)			
Male	151 (55.5)	122 (66.3)	0.021
Female	121 (44.5)	62 (33.7)	
Age, years	56±11.2	54±11.3	0.475
Pre-T stage, *n* (%)			
T1, T2	14 (5.1)	12 (6.5)	0.077
T3, T4	257 (94.5)	167 (90.8)	
Tx	1 (0.4)	5 (2.7)	
Pre-N stage, *n* (%)			
N0	37 (13.6)	24 (13.0)	0.863
N+	235 (86.4)	160 (87.0)	
Clinical stage, *n* (%)			
I, II	20 (7.6)	12 (6.8)	0.764
III, IV	244 (92.4)	164 (93.2)	
Tumor location, *n* (%)			
RA	55 (20.4)	44 (24.3)	0.332
RB	214 (79.6)	137 (74.3)	
Induction chemo, *n* (%)			
Yes	97 (35.7)	69 (37.5)	0.460
No	175 (64.3)	115 (62.5)	
Oxaliplatin, *n* (%)			
Yes	97 (35.7)	69 (37.5)	0.689
No	175 (64.3)	115 (62.5)	
Adjuvant chemo, *n* (%)			
Yes	65 (23.9)	39 (21.2)	0.520
No	207 (76.1)	145 (78.8)	
yp-T classification, *n* (%)			
T0	66 (24.4)	55 (30.2)	0.061
T1, T2	90 (33.3)	70 (38.5)	
T3, T4	114 (42.2)	57 (31.3)	
yp-N classification, *n* (%)			
N0	197 (73.0)	150 (82.4)	0.020
N+	73 (27.0)	32 (17.6)	
yp-M classification, *n* (%)			
M0	259 (95.9)	179 (98.4)	0.144
M+	11 (4.1)	3 (1.6)	
yp-stage, *n* (%)			
0	63 (23.3)	51 (28.0)	0.091
I, II	128 (47.4)	97 (53.3)	
III, IV	79 (29.3)	34 (18.7)	
Surgery type, *n* (%)			
APR	34 (12.5)	17 (9.2)	0.278
SSR	238 (87.5)	167 (90.8)	
Follow-up, months	38±22.8	44±24.1	0.778
pCR, %	23.2	27.7	0.270
LVI, *n* (%)			
(+)	13 (4.8)	4 (2.2)	0.208
(−)	272 (95.2)	180 (97.8)	

Group 1: CEA < 5 ng/mL and CA199 ≥ 9.1 ng/mL. Group 2: CEA < 5 ng/mL and CA199 < 9.1 ng/mL. Induction chemo, induction chemotherapy; Adjuvant chemo, adjuvant chemotherapy; APR, abdominoperineal resection; SSR, sphincter-saving resection; LVI, lymph-vascular invasion.

and CA199 ≥ 9.1 U/mL. Group 2: patients with pretreatment s-CEA < 5 ng/mL and CA199 < 9.1 U/mL.

Clinicopathological Characteristics of the Patients

The detailed parameters of the clinicopathological characteristics collected in our study are shown in Table 1. There were 456 patients enrolled in total: 273 were male and 183 were female. The proportion of male patients in each group was higher than that of female patients (group 1 55.5 vs. 44.5%, and group 2 66.3 vs. 33.7%), with a significant difference between the 2 groups. Age, pretreatment T stage, pretreatment N stage (N0/N+), pretreatment clinical stage, tumor location, receipt of induction chemotherapy or not, employing an oxaliplatin-based regimen, use of adjuvant chemotherapy or not, ypT, M stage, rate of pCR, rate of SSR, status of lymph-vascular invasion, and follow-up time did not differ significantly between the 2 groups. The median age was 56 ± 11.2 and 54 ± 11.3 years. Interestingly, the rate of ypN+ decreased from 27.0 to 17.6% from group 1 to group 2. Similarly, we observed the same trend for the proportion of ypT3–4 in each group from 42.2 to 31.3%. Of note, group 2 obtained the most satisfying pCR rate, namely, 27.7%.

The Pretreatment CA199 Level Is of Prognostic Value in Patients with LARC with Normal Pretreatment CEA Levels for OS

As shown in Figure 1, the survival curves of group 1 and group 2 diverged significantly. The 5-year OS rate was 91.9% in group 1 and 95.1% in group 2. In the Cox hazard model, univariate and multivariate analyses were employed to evaluate the significance of the pretreatment serum CA199 level as an independent prognostic factor. As shown in Table 2, sex, age, SSR, tumor location, use of oxaliplatin, adjuvant chemotherapy, clinical stage, preT stage, and preN stage did not strongly influence OS. Within our groupings, ypT stage, ypN stage, ypM stage, pCR rate, status of lymph-vascular invasion, and receiving induction chemotherapy or not were associated with OS. The *p* values were 0.000, 0.000, 0.000, 0.048, and 0.010, respectively. In the multivariate analysis, with normal pretreatment CEA levels, CA199 ≥ 9.1 U/mL was significantly correlated with poor OS (HR = 0.530, 95% CI: 0.280–1.003, $p = 0.048$). At the same time, patients with more advanced ypT stage and ypN+ had shorter survival times (ypT stage: HR = 1.863, 95% CI: 1.246–2.787, $p = 0.030$) (ypN stage: HR = 1.622, 95% CI: 1.060–2.482, $p = 0.026$). However, status of lymph-vascular invasion, induction chemotherapy, ypM0, and pCR did not contribute to better OS.

Table 2. Univariate and multivariate analyses of prognostic factors for overall survival

	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
Gender	0.638	0.378–1.078	0.093			
Age	1.009	0.985–1.033	0.468			
Pre-T	1.302	0.984–1.722	0.065			
Pre-N	1.072	0.947–1.213	0.275			
yp-T	1.865	1.444–2.409	0.000	1.863	1.246–2.787	0.030
yp-N	2.490	1.795–3.455	0.000	1.622	1.060–2.482	0.026
yp-M	5.587	2.522–12.377	0.000	2.259	0.901–5.661	0.082
pCR	0.270	0.108–0.675	0.005	2.163	0.497–9.406	0.304
Surgery	0.893	0.383–2.087	0.795			
Group	0.444	0.242–0.813	0.009	0.530	0.280–1.003	0.048
Tumor location	0.982	0.505–1.908	0.956			
Oxaliplatin	1.737	0.990–3.049	0.054			
Induction chemo	0.136	0.190–0.985	0.048	0.157	0.021–1.146	0.068
p-Stage	0.823	0.296–2.292	0.710			
Adjuvant chemo	0.577	0.312–1.068	0.080			
LVI	3.384	1.346–8.503	0.010	1.058	0.316–3.543	0.927

Oxaliplatin, it means the chemotherapy regimen is oxaliplatin or not; Adjuvant chemo, adjuvant chemotherapy; Induction chemo, induction chemotherapy; LVI, lymph-vascular invasion.

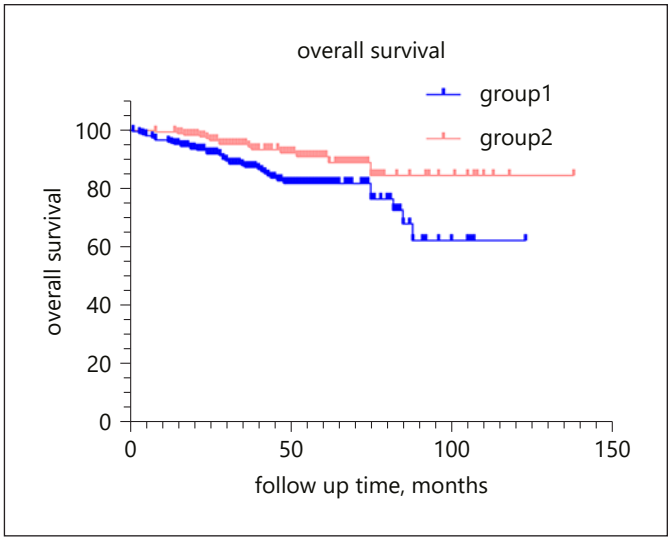

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Fig. 1. Kaplan-Meier analysis of overall survival of group 1 and group 2 patients.

Discussion

When comparing the baseline data, we found that there was a significant difference in sex between groups. Fortunately, in univariate analysis, it was proven that the factor was not of great prognostic value for OS. Some studies have indicated that pretreatment elevated CEA levels can function as a predictor of poor prognosis in patients with LARC [12–14]. In the research of Engineer et al. [12], OS was inferior in patients with pre-CRT CEA levels ≥5 ng/mL. Similarly, in another study by Lee et al. [14], patients in the CEA < 5 ng/mL group had better 5-year disease-free survival (DFS) than did those with CEA ≥ 5 ng/mL. We know that tumor cells containing a high density of CEA are inclined to be resistant to radiation [17].

With respect to pretreatment CA199, its prognostic value in patients with LARC remains controversial. Some studies are for it, while some are not. Wang et al. [17] investigated 310 patients with colorectal cancer only receiving surgery and found that high preoperative CA199 levels were associated with tumor AJCC stage (p = 0.023) and poor prognosis. Similarly, Busbug retrospectively analyzed 172 patients who underwent potentially curative resection of colorectal cancer [18]. The results were that, in comparison with pretreatment CA199 levels, survival time was longer in the CA199-negative group, which elucidated its important prognostic value. Mauri's paper published the conclusion that the serum CA199 value functioned as one of the most significant prognostic factors in patients with advanced colorectal cancer treated

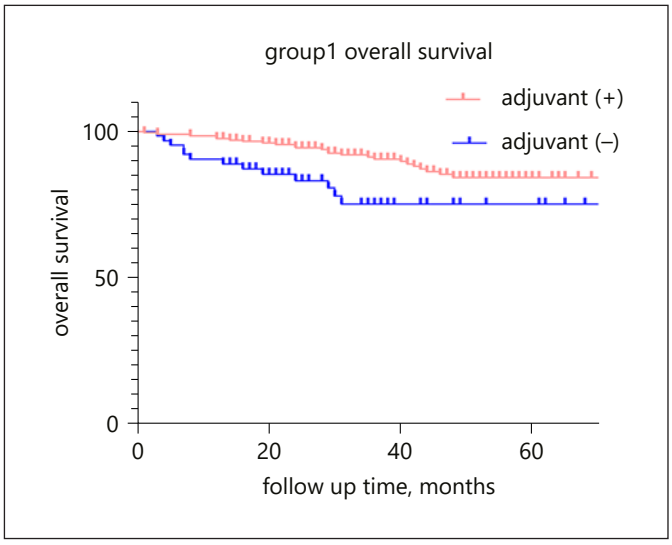

Fig. 2. Kaplan-Meier analysis of overall survival of group 1 patients with and without adjuvant chemotherapy.

by chemotherapy with an obvious difference in survival time between groups (CA199 < 37 U/mL: 30.0 months vs. CA199 ≥ 37 U/mL: 10.3 months) [19]. Morita could not find evidence to confirm the value of CA199 in predicting the prognosis and detecting the recurrence of colorectal cancer [20]. Webb's findings also support Morita's idea, namely, that CA199 had no prognostic significance. Apparently, the above analysis was based on the inclusion of patients with colorectal cancer, and the treatment methods were different [21]. However, Zhang's research was similar to ours, in which 303 patients with LARC with neo-CRT were reviewed. In univariate and multivariate analyses, elevated CA199 (>35 U/mL) was significantly related to poor OS ($p = 0.003$), DFS ($p = 0.001$), and distant metastasis-free survival ($p = 0.039$), and patients could benefit from adjuvant chemotherapy in OS and DFS [22].

A previous study from our center demonstrated that pretreatment CEA and pretreatment CA199 could reflect responses to CRT therapy because the pCR rate revealed long-term oncological outcomes to some extent [15]. However, we did not previously perform a survival-related analysis due to the follow-up time being too short, so we explored this further in the present research. To our knowledge, our study is the first to use the maximal χ^2 method to determine the cutoff point of the pretreatment CA199 level, which is different from other methods [23]. Shin et al. [24] revealed that preoperative CA199 was associated with 5-year DFS and OS in patients with advanced rectal cancer. This was the population that we focused on, and we are pleased to have the largest cohort so far. In the patients with normal pretreatment CEA levels who achieved better outcomes, we confirmed that pretreatment CA199 was an independent prognostic factor ($p = 0.048$). Also, it is worth noting that what we set as a threshold 9.1 U/mL, which was less than the lower limit of normal value, reduced the gap and overturned the conventional wisdom that a test was meaningful if it was above the lower limit of normal. As an adhesion molecule, CA199 plays a role in tumor progression, which may help to explain what we revealed in our study [25]. It should be added that most patients received adjuvant chemotherapy, and we were surprised that adjuvant chemotherapy led to a better OS in group 1 patients (Fig. 2), similar to Zhang's study results [22].

Nevertheless, our study has some limitations. First, all data are from our single institution's database. As a retrospective study, data deletion is inevitable. However, based on our large sample, the interference caused by such data loss to the results should be negligible. Unfortunately, due to the lack of data, we did not explore the clearance pattern of CA199, which shows the changing trend during treatment. Also, there was a big pity that no complete data on TME grade and status of tumor budding were available since no sound pathological system was established at that time. Thus, it may be necessary to conduct a prospective trial to realize it.

Conclusion

We utilized the minimum p value method to select 9.1 U/mL as the critical value of CA199, thus dividing patients with normal pretreatment CEA levels into 2 groups. The results showed that pretreatment CA199 was an independent factor affecting prognosis.

Statement of Ethics

Although patients' consents were not specifically obtained for this analysis, all information was retrospectively extracted in the context of compliance with the ethical standards of the institutional and/or national research committees and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Patient medical records were analyzed retrospectively, with no individual patient identifiable information used. Thus, the Fujian Medical University Union Hospital Ethic Review Board deemed patients' consents unnecessary.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Author Contributions

B.X. and D.H. contributed to the conception and design of this study. D.H. drafted the manuscript. Q.L. and J.S. participated in the acquisition and statistical analysis of the data and the interpretation of the results. Q.L. and J.S. assisted with the interpretation of the results. All authors revised the manuscript for intellectual content.

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