RESEARCH ARTICLE

Carbohydrate Antigen 19-9 Levels Associated with Pathological Responses to Preoperative Chemoradiotherapy in Rectal Cancer

Seung-Gu Yeo[1,2], Dae Yong Kim[1]*, Tae Hyun Kim[1], Sun Young Kim[1], Ji Yeon Baek[1], Hee Jin Chang[1], Ji Won Park[1], Jae Hwan Oh[1]

Abstract

Purpose: To investigate whether pretreatment serum carbohydrate antigen 19-9 (CA 19-9) levels are associated with pathological responses to preoperative chemoradiotherapy (CRT) in patients with rectal cancer. Materials and Methods: In total, 260 patients with locally advanced rectal cancer (cT3-4NanyM0) who underwent preoperative CRT and radical surgery were analyzed retrospectively. CRT consisted of 50.4 Gy pelvic radiotherapy and concurrent chemotherapy. Radical surgery was performed at a median of 7 weeks after CRT completion. Pathological CRT response criteria included downstaging (ypStage 0-I) and ypT0-1. A discrimination threshold of CA 19-9 level was determined using a receiver operating characteristics analysis. Results: The median CA 19-9 level was 8.0 (1.0-648.0) U/mL. Downstaging occurred in 94 (36.2%) patients and ypT0-1 in 50 (19.2%). The calculated optimal threshold CA 19-9 level was 10.2 U/mL for downstaging and 9.0 U/mL for ypT0-1. On multivariate analysis, CA 19-9 (≤ 9.0 U/mL) was significantly associated with downstaging (odds ratio, 2.089; 95% confidence interval, 1.189-3.669; P=0.010) or ypT0-1 (OR, 2.207; 95%CI, 1.079-4.512; P=0.030), independent of clinical stage or carcinoembryonic antigen. Conclusions: This study firstly showed a significant association of pretreatment serum CA 19-9 levels with pathological CRT responses of rectal cancer. The CA 19-9 level is suggested to be valuable in predicting CRT responses of rectal cancer cases before treatment.

Keywords: Rectal cancer - CA 19-9 - chemoradiotherapy - response prediction.

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Introduction

Following the sequence transition from postoperative chemoradiotherapy (CRT) to preoperative CRT for locally advanced rectal cancer (LARC), the identification of diverse pathological CRT responses for each patient became feasible after surgery (Charlton et al., 2013; Lee et al., 2013; Lee et al., 2013). The degree of pathological CRT response has a significant relationship with long-term oncologic outcomes in LARC patients (Maas et al., 2010; Yeo et al., 2010; Park et al., 2012; Dou et al., 2014). Biological information obtained from pathological CRT responses may be exploited to develop individualized treatment strategy, including postoperative chemotherapy (Collette et al., 2007). Additionally, if the CRT response can be evaluated accurately before surgery or predicted before CRT, planning of conservative surgery for good responders or CRT intensification for poor responders may become possible (Callender et al., 2010; Yeo, et al., 2010; Dou et al., 2013; Yu et al., 2013).

Research to predict pathological CRT responses in rectal cancer has included clinical, preclinical molecular, and radiological studies (Zeestraten et al., 2012). Several clinical studies have reported pretreatment serum carcinoembryonic antigen (CEA) levels as a significant and independent factor predictive of pathological CRT responses (Yoon et al., 2007; Lee et al., 2013). The carbohydrate antigen 19-9 (CA 19-9), another important serum marker in gastrointestinal malignancies, is known to be associated with colorectal tumor behavior (Reiter et al., 2000). However, the pretreatment serum CA 19-9 concentration has not been investigated previously in terms of an association with CRT response in rectal cancer.

In this study, we assessed pretreatment serum CA 19-9 levels with regard to an association with pathological responses to preoperative CRT in LARC patients.

Materials and Methods

Patients

We retrospectively analyzed 260 LARC (cT3-4N any M0) patients who underwent preoperative CRT and radical surgery at the National Cancer Center (Goyang, Korea) between March 2009 and June 2013. We excluded

*[1]Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, Goyang, [2]Department of Radiation Oncology, Soonchunhyang University College of Medicine, Cheonan, Korea *For correspondence: radiopiakim@hanmail.net*

patients whose data of pretreatment serum CA 19-9 level were not available (n=31) or with distant metastasis at the time of surgery (n=14). This study was approved by the Institutional Review Board of the National Cancer Center, and written informed consent was obtained from each patient before treatments.

Staging workups involved a digital rectal examination, a complete blood count, a liver function test, measurement of serum CA 19-9 and CEA concentrations, video colonoscopy, chest radiography, computed tomography (CT) scanning of the abdomen and pelvis, and magnetic resonance imaging (MRI) with or without transrectal ultrasonography. 18F-deoxyfluoroglucose positron-emission tomography was performed as required. Locally advanced (cT3-4) resectable disease was determined based primarily on MRI. Positive lymph node involvement was defined as a lymph node ≥ 0.5 cm in the short-axis diameter, observed on CT or MRI. Serum CA 19-9 and CEA levels were measured at the same laboratory using Architect i2000 chemiluminescent microparticle immunoassays (Abbott Laboratories, Abbott Park, IL).

Treatments

Radiotherapy was delivered to the whole pelvis at a dose of 45 Gy in 25 fractions, followed by a 5.4 Gy boost in three fractions within 6 weeks. All patients underwent CT simulation in a prone position for three-dimensional conformal planning. A three-fields plan was used, consisting of a 6-MV photon posterior-anterior field and two 15-MV photon opposed-lateral beams. The prescription dose was specified at the isocenter of the planning target volume. The initial radiation field encompassed a volume that included the gross tumor and mesorectum, presacral space, the entire sacral hollow, and the regional pelvic lymphatics. The superior border was placed at L5/S1, and the inferior border at > 3 cm caudal to the gross tumor. The boost field included the gross tumor volume and mesorectum, with ≥ 2 cm margins in all directions.

Chemotherapy administered concurrently with radiotherapy used one of three regimens: (1) 5-fluorouracil and leucovorin (two cycles of i.v. bolus injections of 5 fluorouracil 400 mg/m^2/d and leucovorin 20 mg/m^2/d for 3 days in the first and fifth weeks of radiotherapy), (2) capecitabine (oral administration of capecitabine 825 mg/m^2 twice daily during radiotherapy without weekend breaks), or (3) tegafur-uracil (UFT) and leucovorin (oral administration of UFT 400 mg/m^2/d and leucovorin 90 mg/m^2/d for 5 days a week during radiotherapy). At median 7 weeks after CRT completion, patients underwent radical proctectomy, including high ligation of the inferior mesenteric vessels and total mesorectal excision.

Evaluation and analysis

After surgery, the pathological tumor stage was determined according to the TNM classification system recommended by the International Union Against Cancer and the American Joint Committee on Cancer, 7th edition. Pathological CRT response criteria included downstaging and ypT0-1. Downstaging was defined as a transition from cStage II-III (cT3-4NanyM0) to ypStage 0-I (ypT0-2N0M0). The ypT0-1, more specified response criterion than downstaging, was adopted because for this status, a local excision may be considered instead of radical surgery.

The discrimination threshold of CA 19-9 level was determined using a receiver operating characteristics (ROC) analysis. The cutoff value of CEA was set at the upper normal limit, 5.0 ng/mL. For analysis of pretreatment variables that are associated with downstaging or ypT0-1, the chi-squared test, Fisher's exact test, or linear-by-linear association was used, depending on the nature of the data. To identify independent factors, a multivariate logistic regression model was constructed including variables that achieved statistical significance in univariate analyses. All statistical tests were two-sided and were performed using the SPSS software (ver. 14.0; SPSS, Chicago, IL, USA). Differences with P values <0.05 were deemed statistically significant.

Results

Patients' characteristics are summarized in Table 1. The study population had a median age of 62 years and 195 (75.0%) patients were male. The cT3 classification covered 93.5% of the patients. The median pretreatment CEA and CA 19-9 levels were 3.6 (0.8-1128.3) ng/mL and 8.0 (1.0-648.0) U/mL, respectively. After CRT, 229 (88.1%), 26 (10.0%), and 5 (1.9%) patients underwent low anterior resection, abdominoperineal resection, and Hartmann's operation, respectively.

Downstaging occurred in 94 (36.2%) patients and ypT0-1 in 50 (19.2%). The calculated optimal threshold of CA 19-9 level was 10.2 U/mL for downstaging (Figure 1) and 9.0 U/mL for ypT0-1 (Figure 2).

A concentration of 10.0 or 9.0 U/mL was used as the discrimination threshold of CA 19-9 in the predictive factor analyses. On univariate analysis (Table 2), tumor size, cT classification, CEA, and CA 19-9 showed significant associations with downstaging. Tumor size, cN

Table 1. Patients' Characteristics (n = 260)

Characteristics		No (%)
Age (years)	Median (range)	62 (29-84)
Gender	Male	195 (75.0)
	Female	65 (25.0)
Hemoglobin (g/dL)	Median (range)	12.8 (6.3-17.2)
Distance from anal verge (cm)	Median (range)	5.8 (0-10)
Tumor size (cm)	Median (range)	4.2 (2.0-10.0)
cT classification	cT3	243 (93.5)
	cT4	17 (6.5)
cN classification	cN0	35 (13.5)
	cN1	140 (53.8)
	cN2	85 (32.7)
Histological grade	Low1	245 (96.1)
	High2	10 (3.9)
	Not specified	5
CEA (ng/mL)	Median (range)	3.6 (0.8-1128.3)
CA 19-9 (U/mL)	Median (range)	8.0 (1.0-648.0)
Chemotherapy	5-FU/leucovorin	135 (51.9)
	Capecitabine	58 (22.3)
	UFT/leucovorin	67 (25.8)

*"Abbreviations: CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; 5-FU, 5-fluorouracil; UFT, tegafur-uracil. 1Well or moderately differentiated. 2Poorly differentiated, mucinous cell, or signet ring cell carcinoma

Table 3. Multivariate Analysis of Predictive Factors

	Downstaging			Primary tumor response		
	OR	95% CI	P1	OR	95% CI	P1
CEA (≤5 *vs* >5 ng/mL)	3.21	1.74-5.94	<0.01	2.52	1.14-5.60	0.02
CA 19-9 (≤9 *vs* >9 U/mL)	2.09	1.19-3.67	0.01	2.21	1.08-4.51	0.03
cT classification (cT3 *vs* cT4)	4.77	1.01-22.50	0.05			
cN classification (cN- *vs* cN+)				2.36	1.03-5.41	0.04

"Abbreviations: CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; OR, odds ratio; CI, confidence interval. 1Multivariate logistic regression

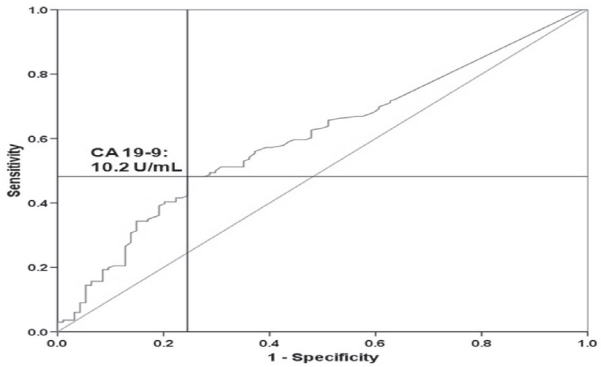

Figure 1. Receiver Operating Characteristic (ROC) Curve of Serum Carbohydrate Antigen 19-9 (CA 19-9) Level Relative to Pathological Downstaging. The area under the ROC curve was 0.605 (p=0.005). A criterion of CA 19-9 level corresponding with the highest Youden Index (0.237) was 10.2 U/mL (sensitivity: 48.2%, specificity: 75.5%)

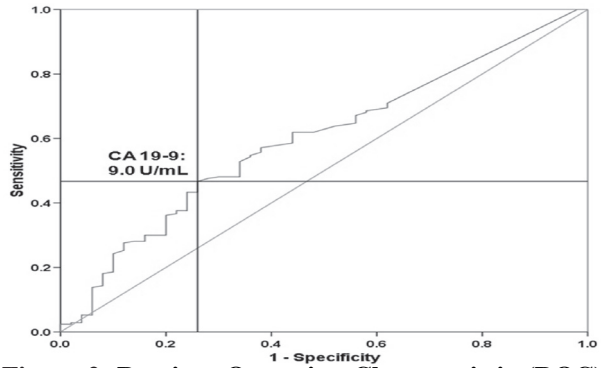

Figure 2. Receiver Operating Characteristic (ROC) Curve of Cerum Carbohydrate Antigen 19-9 (CA 19-9) Level Relative to ypT0-1 Status. The area under the ROC curve was 0.599 (p=0.029). A criterion of CA 19-9 level corresponding with the highest Youden Index (0.207) was 9.0 U/mL (sensitivity: 46.7%, specificity: 74.0%)

classification, histological grade, CEA, and CA 19-9 were significantly associated with ypT0-1. A CA 19-9 level of > 10.0 U/mL or > 9.0 U/mL was a negative predictor of downstaging and ypT0-1. On multivariate analysis (Table 3), cT and cN classifications were predictive factors for downstaging or ypT0-1, respectively. CEA and CA 19-9 (9.0 U/mL, but not 10.0 U/mL) showed independent significance in relation to both downstaging and ypT0-1.

Discussion

In this study, we analyzed 260 LARC patients managed with preoperative CRT and radical surgery, and showed that pretreatment CA 19-9 level was an independent predictive marker of pathological CRT response. Upper

Table 2. Univariate Analysis of Predictive Factors

	Downstaging		Primary tumor response	
	ypStage 0-I	ypStage II-III	ypT0-1	ypT2-4
	94 (36.2)	166 (63.8)	50 (19.2)	210 (80.8)
Age (y)				
≤ 60	45 (36.9)	77 (63.1)	22 (18.0)	100 (82.0)
> 60	49 (35.5)	89 (64.5)	28 (20.3)	110 (79.7)
P1	0.82		0.65	
Gender				
Male	72 (36.9)	123 (63.1)	36 (18.5)	159 (81.5)
Female	22 (33.8)	43 (66.2)	14 (21.5)	51 (78.5)
P	0.66		0.59	
Hemoglobin (g/dL)				
≤ 12.5	37 (31.6)	80 (68.4)	16 (13.7)	101 (86.3)
> 12.5	55 (39.0)	86 (61.0)	32 (22.7)	109 (77.3)
P	0.22		0.06	
Distance from anal verge (cm)				
< 5.0	49 (41.9)	68 (58.1)	14 (19.4)	58 (80.6)
≥ 5.0	45 (31.5)	98 (68.5)	36 (19.1)	152 (80.9)
P	0.08		0.96	
Tumor size (cm)				
≤ 4.2	56 (42.9)	75 (57.3)	34 (26.0)	97 (74.0)
> 4.2	38 (29.5)	91 (70.5)	16 (12.4)	113 (87.6)
P	0.03		<0.01	
cT classification				
cT3	92 (37.9)	151 (62.1)	50 (20.6)	193 (79.4)
cT4	2 (11.8)	15 (88.2)	0	17 (100)
P	0.03		0.05	
cN classification				
cN-	17 (48.6)	18 (51.4)	13 (37.1)	22 (62.9)
cN+	77 (34.2)	148 (65.8)	37 (16.4)	188 (83.6)
P	0.1		<0.01	
Histological grade				
Low2	85 (34.7)	160 (65.3)	42 (17.1)	203 (82.9)
High3	6 (60.0)	4 (40.0)	6 (60.0)	4 (40.0)
P	0.17		<0.01	
CEA (ng/mL)				
≤ 5.0	76 (45.8)	90 (54.2)	41 (24.7)	125 (75.3)
> 5.0	18 (19.1)	76 (80.9)	9 (9.6)	85 (90.4)
P	<0.01		<0.01	
CA 19-9 (U/mL)				
≤ 10.0	70 (44.9)	86 (55.1)	37 (23.7)	119 (76.3)
> 10.0	24 (23.1)	80 (76.9)	13 (12.5)	91 (87.5)
P	<0.01		0.03	
CA 19-9 (U/mL)				
≤ 9.0	66 (44.3)	83 (55.7)	37 (24.8)	112 (75.2)
> 9.0	28 (25.2)	83 (74.8)	13 (11.7)	98 (88.3)
P	<0.01		<0.01	
Chemotherapy				
5-FU/Leucovorin	45 (33.3)	90 (66.7)	27 (20.0)	108 (80.0)
Capecitabine	22 (37.9)	36 (62.1)	9 (15.5)	49 (84.5)
UFT/Leucovorin	27 (40.3)	40 (59.7)	14 (20.9)	53 (79.1)
P	0.31		0.99	
CRT-surgery interval (weeks)				
≤ 7	55 (41.4)	78 (58.6)	30 (22.6)	103 (77.4)
> 7	39 (30.7)	88 (69.3)	20 (15.7)	107 (84.3)
P	0.07		0.16	

*Abbreviations: CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; UFT, tegafur-uracil. 1Chi-squared test, Fisher's exact test, or linear-by-linear association. 2Well or moderately differentiated. 3Poorly differentiated, mucinous cell, or signet ring cell carcinoma

limit of CA 19-9 level, which is associated with favorable pathological CRT response, was found to be 9.0 U/mL. In addition to CEA level, previously known as a significant predictor of pathological CRT responses in LARC (Yoon et al., 2007; Lee, et al., 2013), CA 19-9 was newly found to be another tumor marker closely associated with CRT response, independently of CEA level or clinical stage.

After CEA, CA 19-9 is the most widely investigated gastrointestinal tumor marker. The CA 19-9 assay measures a tumor-related mucin that contains the sialylated Lewis a pentasaccharide epitope, lacto-N-fucopentose II. CA 19-9 is produced by adenocarcinomas of the pancreas, stomach, gall bladder, colon, ovary, and lung (Duffy, 1998). CA 19-9 has become an established marker for pancreatic cancer, but not for colorectal cancer. The American Society of Clinical Oncology guidelines suggest that there is insufficient evidence for using CA 19-9 in the management of patients with colorectal cancer (Locker et al., 2006). However, there have been reports describing the prognostic significance of CA 19-9 in colorectal cancer patients. In a study including 495 patients, the prognostic impact of preoperative CA 19-9 was found to be independent of both Dukes' stage and CEA concentration. Furthermore, CA 19-9 was a stronger prognostic factor than CEA and predicted outcomes in the Dukes' B-C subgroup (Reiter et al., 2000). Some researchers suggested that CA 19-9 should be used in combination with CEA to increase the sensitivity in detecting recurrence of colorectal cancer (Chen et al., 2005; Nozoe et al., 2006; Lin et al., 2012). Yet, this tumor marker has not been definitely evaluated in rectal cancer patients managed with preoperative CRT. Although the odds ratio was lower than CEA, CA 19-9 demonstrated independent significance as a predictor of pathological CRT response in this study.

Many studies have reported that a pathological complete response after preoperative CRT was associated with a favorable long-term outcome of rectal cancer patients (Maas et al., 2010; Yeo, et al., 2010; Park et al., 2012; Dou et al., 2014). In addition, our group previously showed that when the most important prognostic factor (ypN status) is the same as ypN0, minimal residual disease in the primary tumor (ypT1-2N0) was suggested not to confer a significantly different prognosis compared with a pathological complete response (ypT0N0) (Moon et al., 2012). The pathological complete response occurred in 26 (10%) patients in the present study. Although the statistical significance of CA 19-9 in association with pathological complete response alone was not detected, CA 19-9 was significantly associated with downstaging, which included both ypT0N0 and ypT1-2N0.

The mainstay of surgical therapy for LARC remains the low anterior resection or the abdominoperineal resection. However, mortality and significant morbidity risks are associated with a radical resection (Paun et al., 2010). Some patients are unwilling to undergo anus-sacrificing surgery or are unfit for a radical operation because of a co-existing medical illness. The alternative option of a transanal full-thickness local excision may be favored for selected patients who exhibit marked tumor regression following CRT. Although this strategy remains experimental, several studies have reported favorable long-term outcomes (Callender et al., 2010; Yeo, et al., 2010; Yu et al., 2013). The underlying key rationale includes the correlation between radiosensitivity and the low aggressiveness of rectal cancer (Maas et al., 2010; Yeo, et al., 2010; Park et al., 2012), and the correlation between the radiosensitivity of the primary tumor and that of mesorectal lymph node disease (Kim et al., 2006). The ypT0-1 status is usually regarded as a possible candidate for an observational strategy after local excision, whereas ypT2 or ypT3 is usually followed by a salvage total mesorectal excision (Yeo, et al., 2010). Clinical workups performed at post-CRT but immediately before surgery have limitations in accurately estimating remnant disease status due to CRT-induced inflammation, edema, and fibrosis (Guillem et al., 2013). Our finding that the tumor markers, CEA and CA 19-9, were associated with ypT0-1 status may help to improve the accuracy of candidate selection for conservative surgery after CRT.

Instead of conservative surgery, patients who are expected to have poor CRT responses may be preferentially included in clinical trials. Ongoing clinical trials to develop more effective preoperative strategies for LARC patients address newer chemotherapeutics, targeted agents, induction chemotherapy, and novel radiotherapy methods (Malik et al., 2010; Rodel et al., 2010; Landry et al., 2013; Passoni et al., 2013). The endpoint in these trials is frequently a pathological CRT response. Risk stratification has depended mostly on MRI findings (Taylor et al., 2011), but the current study of tumor marker concentrations may be helpful in improving selection of high-risk patients.

This study had some limitations. The first is the retrospective nature of the analysis, which could result in selection bias. Second, the upper limit of normal CA 19-9 for healthy subjects has been defined by the cutoff value of 37.0 U/mL (Duffy, 1998), but only 15 (5.8%) patients had abnormal levels using this cutoff and no significant association existed between them and downstaging or ypT0-1. The discrimination threshold in the present study (9.0 U/mL) was determined using ROC analysis; however, it should be validated in different cohorts of LARC patients.

In conclusion, this study showed a significant and independent association of pretreatment serum CA 19-9 levels with pathological CRT responses of LARC. Our results indicate that the pretreatment CA 19-9 level warrants further investigation with regard to developing tailored multimodal therapy for LARC patients.

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