

ORIGINAL ARTICLE

The clinical significance of preoperative serum levels of carbohydrate antigen 19-9 in colorectal cancer

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Purpose: Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are the most frequently used tumor markers in the clinical setting of colorectal cancer (CRC). This study was designed to investigate the correlation between preoperative serum levels of CA 19-9 (pre-CA 19-9) and the clinicopathologic factors of patients with CRC. **Methods:** A study was performed on 333 patients with histologically diagnosed colorectal adenocarcinoma between December 2008 and November 2011, based on prospective collected data. The clinical data such as age, sex, location of tumor, size of tumor, differentiation, depth of tumor (T), lymph node metastasis (N), distant metastasis (M), lymphatic invasion, venous invasion, perineural invasion, stage, and preoperative serum levels of CEA (pre-CEA) and pre-CA 19-9 were obtained. These patients were classified into two groups according to pre-CA 19-9 (CA 19-9 high: >39 U/mL, $n = 61$ [18.3%]; CA 19-9 normal: <39 U/mL, $n = 272$ [81.7%]). **Results:** Sixty-one patients among 333 patients (18.3%) with CRC showed a high pre-CA 19-9. The elevation of pre-CA 19-9 was significantly associated with size of tumor (4.8 ± 0.1 cm vs. 6.1 ± 0.3 cm, $P < 0.001$), right colon cancer ($P < 0.001$), depth of tumor ($P < 0.001$), lymph node metastasis ($P < 0.001$), distant metastasis ($P < 0.001$), perineural invasion ($P = 0.008$), peritoneal seeding ($P < 0.001$), and stage ($P < 0.001$). On multivariate analysis, high pre-CA 19-9 was shown to be independently associated with high pre-CEA, lymph node metastasis, right colon cancer, large tumor size, and peritoneal seeding. There were twelve patients confirmed for peritoneal seeding among 333 patients (3.6%). **Conclusion:** High pre-CA 19-9 in advanced colorectal cancer might provide important information to predict the possibility of peritoneal seeding.

Key Words: Carbohydrate antigen 19-9, Colorectal neoplasms, Peritoneal seeding

INTRODUCTION

Serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are commonly used in colorectal cancer (CRC) clinics. However, their clinical usefulness remains controversial from

diagnostic, prognostic, and surveillance points of view [1]. The American Society of Clinical Oncology guidelines suggest that there is insufficient evidence for using CA 19-9 in the management of patients with CRC [2]. This study was designed to elucidate the efficiency of preoperative serum levels of CA 19-9 (pre-CA 19-9) as a tool

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for the preoperative diagnosis of CRC and to investigate the correlation between pre-CA 19-9 and the clinicopathologic factors of patients with CRC.

METHODS

A total of 333 patients with histologically diagnosed colorectal adenocarcinoma were included in the study group between December, 2008 and November, 2011. Among them, 281 patients underwent curative resection and palliative resection was performed in 52 patients. Pre-CA 19-9 and preoperative serum levels of CEA (pre-CEA) were measured, with CEA > 5.0 ng/mL and CA 19-9 > 39 U/mL being regarded as elevated status. The clinical and pathological characteristics of patients with and without elevated pre-CA 19-9 were compared, as well as those with and without locally advanced cancer or peritoneal seeding. Locally advanced cancer included tumors that are T4N1-2Mx at the time of initial presentation. Peritoneal seeding was diagnosed when visible metastatic lesions had pathologic proof. Obstruction was classified on the basis of clinical endoscopic findings. The situation when endoscopy was not passed and preoperative bowel preparation was possible was regarded as partial obstruction. Complete obstruction was regarded as when flatus could not be passed, and preoperative bowel preparation was impossible. Statistical analysis was carried out using the SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) by Clinical Trial Center, Department of Biostatistics. The clinicopathological variables between the groups were compared using Student t-tests or test for trend. The two groups were compared by cross-table analysis using Pearson's chi-square test. Logistic regression was applied for multivariate analysis to determine any important predictors of high pre-CA 19-9. P-value of less than 0.05 was considered to be statistically significant.

RESULTS

Sixty-one patients among 333 patients (18.3%) with CRC showed a high pre-CA 19-9. The Age, gender, body

mass index, American Society of Anesthesiologists score did not differ significantly between patients with normal and high pre-CA 19-9. Patients with high pre-CA 19-9 were significantly more likely to show right side colon cancer and high CEA than patients with normal pre-CA 19-9 (Table 1).

Patients with high pre-CA 19-9 were significantly more likely to show perineural invasion, large tumor size, depth of tumor, lymph node metastasis, distant metastasis, and advanced tumor stage than patients with normal pre-CA 19-9. Differentiation, lymphatic invasion, vascular invasion did not differ significantly between patients with normal and high pre-CA 19-9 (Table 2).

The risk factors for pre-CA 19-9 based on multivariate analysis are shown in Table 3. High pre-CA 19-9 was shown to be independently associated with high pre-CEA (odds ratio [OR], 2.795; P = 0.034), lymph node metastasis (OR, 2.459; P = 0.026), right colon cancer (OR, 0.359; P = 0.019), large tumor size (OR, 1.233; P = 0.012), and peri-

Table 1. The clinical characteristics of patients with colorectal cancer

Variable	CA 19-9: normal (n = 272)	CA 19-9: high (n = 61)	P-value
Age (yr)	63.2 ± 0.7	64.2 ± 1.6	0.524
Male sex	169 (62.1)	37 (60.7)	0.830
Body mass index (kg/m ²)	23.1 ± 0.2	22.5 ± 0.5	0.205
Carcinoembryonic antigen			< 0.001
Normal	180 (66.4)	15 (24.6)	
High	91 (33.6)	46 (75.4)	
ASA score			0.926
I	145 (53.3)	32 (52.5)	
II	101 (37.1)	24 (39.3)	
III	25 (9.2)	5 (8.2)	
IV	1 (0.4)	0 (0)	
Location			0.002
Rectum	64 (23.5)	26 (42.6)	
Left colon	93 (34.2)	22 (36.1)	
Right colon	115 (42.3)	13 (21.3)	
Obstruction			< 0.001
No	184 (67.6)	22 (36.1)	
Partial	82 (30.1)	29 (47.5)	
Complete	6 (2.2)	10 (16.4)	

Values are presented as mean ± standard deviation or number (%). CA 19-9, carbohydrate antigen 19-9; ASA, American Society of Anesthesiologists.

Table 2. The pathologic characteristics of patients with colorectal cancer

Variable	CA 19-9: normal (n = 272)	CA 19-9: high (n = 61)	P-value
Size of tumor (cm)	4.8 ± 0.1	6.1 ± 0.3	<0.001
Differentiation			0.081
Well	45 (16.5)	5 (8.2)	
Moderate	218 (80.1)	52 (85.2)	
Poor	7 (2.6)	3 (4.9)	
Mucinous	2 (0.7)	0 (0)	
Signet-ring cell	0 (0)	1 (1.6)	
Lymphatic invasion			0.058
Negative	225 (82.7)	44 (72.1)	
Positive	47 (17.3)	17 (27.9)	
Vascular invasion			0.060
Negative	232 (85.3)	46 (75.4)	
Positive	40 (14.7)	15 (24.6)	
Perineural invasion			0.008
Negative	206 (75.7)	36 (59.0)	
Positive	66 (24.3)	25 (41.0)	
Depth of tumor			<0.001
Tis	11 (4.0)	2 (3.3)	
T1	34 (12.5)	2 (3.3)	
T2	38 (14.0)	0 (0)	
T3	162 (59.6)	39 (63.9)	
T4	27 (9.9)	18 (29.5)	
Lymph node metastasis			<0.001
N0	162 (59.6)	18 (29.5)	
N1	69 (25.4)	15 (24.6)	
N2	41 (15.0)	28 (45.9)	
Distant metastasis			<0.001
M0	240 (88.2)	40 (65.6)	
M1	32 (11.8)	21 (34.4)	
Peritoneal seeding			<0.001
Negative	269 (98.9)	52 (85.2)	
Positive	3 (1.1)	9 (14.8)	
Stage			<0.001
0	13 (4.8)	2 (3.3)	
I	61 (22.4)	2 (3.3)	
II	85 (31.4)	12 (19.7)	
III	83 (30.5)	24 (39.3)	
IV	30 (10.9)	21 (34.4)	

Values are presented as mean±standard deviation or number (%).

toneal seeding (OR, 6.973; P = 0.022) in multivariate analysis.

There were twelve patients confirmed with peritoneal seeding among 333 patients (3.6%) (Table 4). Four patients with peritoneal seeding were not detected in preoperative radiologic evaluations and had high pre-CA 19-9. The sen-

Table 3. The risk factors for preoperative serum carbohydrate antigen 19-9 based on multivariate analysis

Variable	OR (95% CI)	P-value
pT category		
T1-T2		
T3-T4	2.104 (0.443-9.982)	0.349
pN category		
Negative		
Positive	2.459 (1.114-5.429)	0.026
Distant metastasis		
Negative		
Positive	1.367 (0.557-3.356)	0.495
Lymphatic invasion		
Negative		
Positive	1.035 (0.296-3.617)	0.957
Vascular invasion		
Negative		
Positive	1.046 (0.285-3.844)	0.946
Perineural invasion		
Negative		
Positive	1.244 (0.596-2.597)	0.561
Preoperative CEA		
Normal		
High	2.795 (1.083-7.214)	0.034
Peritoneal seeding		
Negative		
Positive	6.973 (1.326-36.662)	0.022
Location		
Rectum		
Left colon	0.714 (0.332-1.535)	0.388
Right colon	0.359 (0.153-0.843)	0.019
Size of tumor	1.233 (1.047-1.451)	0.012
Obstruction		
No		
Yes	1.266 (0.605-2.651)	0.531

OR, odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen.

sitivity and specificity of preoperative serum CA 19-9 for peritoneal seeding were 75% and 83.8%, respectively. The positive predictive value and negative predictive value of preoperative serum CA 19-9 for peritoneal seeding were 14.8% and 85.2%, respectively (Table 5). The sensitivity and specificity of preoperative serum CEA for peritoneal seeding were 75.0% and 32.4%, respectively. The positive predictive value and negative predictive value of preoperative serum CEA for peritoneal seeding were 4.0% and 96.0%, respectively.

Table 4. The characteristics of patients with peritoneal seeding

No.	Age (yr)	Sex	Location	Pre-CEA	Pre-CA 19-9	Detection	T	N	M	Metastasis	Size (cm)	Obstruction	OP
1	55	Male	Left	3,039.08	>10,000	CT, PET	4	2	1	Liver, lung, peritoneum	6	-	AR
2	42	Male	Rectum	4.08	1,801.35	PET	3	2	1	Peritoneum	6	Partial	LAR
3	73	Male	Right	165.66	294.16	OP	3	1	1	Liver, peritoneum	7	Partial	RHC
4	79	Male	Right	64.63	201.04	OP	4	2	1	Liver, peritoneum	10	-	TC
5	55	Male	Left	325.94	152.42	CT, PET	3	2	1	Peritoneum	7	Complete	APR
6	72	Female	Right	4.90	151.01	OP	4	2	1	Ovary, peritoneum	6	Partial	RHC
7	54	Female	Right	3.48	99.93	OP	3	2	1	Peritoneum	4.5	Partial	RHC
8	35	Male	Left	38.49	98.45	CT	3	1	1	Liver, peritoneum	4.5	Partial	AR
9	63	Male	Right	32.37	57.01	CT	4	2	1	Peritoneum	7	Partial	RHC
10	62	Female	Rectum	664.47	24	CT, PET	3	2	1	Liver, lung, peritoneum	6	Partial	SFC
11	56	Male	Rectum	3.19	9.71	CT, PET	3	2	1	Liver, peritoneum	5.5	-	LAR
12	41	Female	Left	0.86	<2.00	CT	3	0	1	Peritoneum	7.2	Partial	AR

Pre-CEA, preoperative serum levels of carcinoembryonic antigen; Pre-CA 19-9, preoperative serum levels of carbohydrate antigen 19-9; T, tumor; N, node; M, metastasis; OP, operation; CT, computed tomography; PET, positron emission tomography; AR, anterior resection; LAR, low anterior resection; RHC, right hemicolectomy; TC, total colectomy; APR, abdominoperineal resection; SFC, splenic flexure colectomy.

Table 5. The characteristics of patients with peritoneal seeding

No.	Metastatic pattern				Follow-up duration (mo)	Prognosis
	Peritoneum	Liver	Ovary	Lung		
1	Isolated nodule	Multiple	-	Multiple	13	Dead
2	Isolated nodule	-	-	-	20	Progressive disease
3	Localized seeding	Multiple	-	-	6	Dead
4	Localized seeding	Single	-	-	26	Stable disease
5	Generalized seeding	-	-	-	2	Dead
6	Isolated nodule	-	Ovarian and adnexal seeding	-	15	Dead
7	Isolated nodule	-	-	-	38	Progressive disease
8	Generalized seeding	Single	-	-	28	Partial response
9	Localized seeding	-	-	-	-	Follow-up loss
10	Generalized seeding	Multiple	-	Multiple	19	Progressive disease
11	Localized seeding	Multiple	-	-	21	Progressive disease
12	Localized seeding	-	-	-	16	Complete remission

DISCUSSION

CA 19-9 is a predominant carbohydrate antigen that was defined from the culture medium of a CRC cell line [3]. Serum CEA and CA 19-9 are commonly used as classical tumor markers in CRC patients [4]. But Yamashita and Watanabe [1] suggested that pre-CEA and pre-CA 19-9 do not show satisfactory sensitivity as screening (diagnostic) markers in CRC. The utility of CA 19-9 as a diagnostic marker in colorectal cancer is limited in a number of ways. First, patients with negative Lewis blood group antigen cannot synthesize CA 19-9, and therefore it is not used as a serologic marker in these individuals, who make up about

10% of the population. Second, patients with benign biliary tract disease can have levels up to 400 U/mL, with 87% having concentrations higher than 70 U/mL. Significant numbers of patients with pancreatitis, either acute or chronic, also have elevated levels. Third, besides pancreatic cancer, CA 19-9 levels are also elevated in patients with other cancers, including those of the biliary tree (95%), stomach (5%), liver (hepatocellular carcinoma, 7%), and lung (13%). For CRC, CA 19-9 levels add little clinically useful information to determine CEA levels [5]. The low diagnostic power of CA 19-9 may be due to a high proportion of colorectal cancer patients having the Lewis (a-b-) phenotype, who cannot synthesize these markers

[6]. The overall reported incidences of high pre-CA 19-9 range from 10.6% to 24.4% [7-11]. In our study, there were 61 patients (18.3%) with high pre-CA 19-9 among 333 patients. The American Society for Clinical Oncology recommends that the present data are insufficient to recommend CA 19-9 for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with CRC [12].

Nevertheless, the clinical significance of pre-CA 19-9 is still controversial. Morita et al. [13] did not recommend routine use of CA 19-9 in staging and surveillance of CRC, because they could not find clinical significance to support the use of pre-CA 19-9 to predict the prognosis and detect recurrence of CRC [13]. In contrast, Nakagoe et al. [7] advocated that high pre-CA 19-9 may serve as a useful marker in identifying patients with node-negative CRC at high risk for recurrence after surgery [7]. The discrepancy is considered to be derived from the difference in size of the study and distribution of tumor stage in each study population. In another multivariate analysis showed tumor progression on chemotherapy ($P < 0.0001$), elevated preoperative serum CA 19-9 ($P < 0.0001$), number of resected metastases ($P < 0.001$), and the number of lines of chemotherapy ($P < 0.04$), but not the type of first line treatment, were independently associated with decreased survival [14]. We have concentrated on the significance of pre-CA 19-9 for CRC staging. In this study, high pre-CA 19-9 was shown to be independently associated with high pre-CEA, lymph node metastasis, right colon cancer, large tumor size, and peritoneal seeding.

It was interesting to find that high pre-CA 19-9 level was a predictive marker of peritoneal seeding before surgery. This kind of correlation between CA 19-9 and peritoneal seeding has been reported by some authors. Liu et al. [15] reported that depth of bowel wall invasion, lymph node metastasis, serum CEA level, and CA 19-9 level are risk factors for peritoneal metastasis in colorectal cancer. Yang et al. [10] suggested that CA 19-9 (> 34.6 U/mL), pT4 and age (< 59 years) were significant risk factors of positive peritoneal dissemination. Park et al. [8] reported postoperative serum CA 19-9 elevation was better related to peritoneal recurrence than to liver metastasis. Especially, Yang et al. [10] advocated that if the cutoff for CA 19-9 were set at 135 U/mL, the positive prediction rate for positive

peritoneal dissemination from cytological study would reach 45%. Peritoneal metastasis is involved in approximately 10% to 15% of patients with colorectal cancer at time of initial presentation (synchronous metastasis) and in 20% to 50% of patients who develop recurrence (metachronous metastasis). In our study, there were twelve patients confirmed for peritoneal seeding among 333 patients (3.6%). Four patients with peritoneal seeding were not detected in preoperative radiologic evaluations and had high pre-CA 19-9. The extent pattern of hepatic or ovarian metastasis in these patients were 1 multiple hepatic metastasis, 1 single hepatic metastasis, 1 ovarian and adnexal metastasis. The peritoneal seeding patterns of this group were 2 isolated nodule and 2 localized seeding. The sensitivity and specificity of pre-CA 19-9 for peritoneal seeding were 75% and 83.8%. The positive predictive value and negative predictive value of pre-CA 19-9 for peritoneal seeding were 14.8% and 85.2%.

The mechanism of peritoneal seeding is generally accepted that most of the free tumor cells are sloughed from the primary tumor, but some might have come from other sources, for example, lymph nodes, ovary, or liver [10]. In our study, nine patients with obstruction (75%) had a peritoneal seeding (Table 4). But the risk of obstruction did not reach statistical significance on multivariate analysis for peritoneal seeding. Yang et al. [10] speculated that tumor invasion to peritoneal mesothelial cells might stimulate the expression of CA 19-9 with another possibility being that tumor cells with expression of CA 19-9 might have higher behavior ability of peritoneal metastasis pathway. Differentially expressed in tumor cells, CA 19-9 was a ganglioside-containing sialylated lacto-N-fucopentaose II (sialyl Lewis), structurally related to the Lewis blood group-related carbohydrate structure [16]. Metastases showed a stronger expression than primary tumors and when the tumors were divided according to stage, sialyl Lewis showed a lower expression in Dukes' A and B tumors than in more advanced stages [17]. These structures are of increasing interest since they may function as adhesion molecules; adhesion of tumor cells to the endothelial cell of blood vessels may be mediated by an interaction between sialyl Lewis and E-selectin [18] and tumor cell induced platelet aggregation [19]. Therefore, it was thought

that the mechanism associated with colorectal cancer expressing pre-CA 19-9 might have a higher possibility of peritoneal seeding. High pre-CA 19-9 might be associated with advanced colorectal cancer including peritoneal recurrence and lung metastasis. Lin et al. [9] reported that CA 19-9 may be a prognostic factor for CRC patients with normal CEA levels and an aggressive follow-up protocol for lung metastasis should be used for these patients.

But this study had limitations in its results because the incidences of high pre-CA 19-9 were low (18.3%). Therefore, to make up for low incidence of pre-CA 19-9, the combination of data of pre-CA 19-9 and pre-CEA, as in Nozoe et al's [20] and Park et al's [8] study, should be more important in the future.

In conclusion, high pre-CA 19-9 level was shown to be independently associated with high pre-CEA, lymph node metastasis, right colon cancer, large tumor size, and peritoneal seeding of colorectal cancer. High pre-CA 19-9 might provide the important information needed to predict the subsequently possible peritoneal seeding of tumors not detected in radiologic examination and help the decision to treat patients of CRC. Patients with high pre-CA 19-9 should be warned of the possibility of peritoneal seeding and intraperitoneal chemotherapy. Long-term follow up including recurrence and survival rate should be required in order to provide prognostic information.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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