

Carbohydrate Antigen 19-9 Predicts Synchronous Peritoneal Carcinomatosis in Patients with Colorectal Cancer

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Abstract. *Background:* Colorectal cancer (CRC) with peritoneal carcinomatosis (PC) has the worst prognosis among all types of metastases, but is difficult to diagnose. This study investigated whether preoperative serum carbohydrate antigen (CA) 19-9 level can predict synchronous PC in patients with primary CRC. *Patients and Methods:* The cases of 395 CRC patients who underwent primary lesion resection were retrospectively reviewed. Risk factors were evaluated by uni- and multivariate analyses from clinicopathological data. *Results:* In the univariate analysis, tumor invasion ($p<0.001$), lymph node and hematogenous metastases ($p=0.037$ and $p<0.001$, respectively), and elevated preoperative serum CA19-9 level ($p<0.001$) were associated with synchronous PC, and multiple regression analysis revealed that an elevated preoperative serum CA19-9 level was an independent risk factor for PC (odds ratio=5.03, 95% confidence interval=1.29-19.60, $p=0.020$). *Conclusion:* Elevated preoperative serum CA 19-9 level may be useful in predicting synchronous PC in patients with CRC.

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in males and the second in females worldwide; about 1.4 million new cases and nearly 700,000 deaths from CRC were reported in 2012 (1). Peritoneal carcinomatosis (PC) is not a rare manifestation in the natural course of CRC, and is associated with worse overall survival (2-4). The incidence of synchronous PC in patients with

CRC is 3.6–15% (5-11), despite recent advances in early disease detection. Computed tomography (CT) is used for diagnosing PC; however, small metastatic nodules cannot always be detected by CT (12-15). As such, it is not unusual to find PC during the removal of the primary tumor.

Carbohydrate antigen (CA) 19-9 is a tumor marker often used in combination with carcinoembryonic antigen (CEA) in the management of patients with CRC. A previous study reported that a high preoperative serum CA 19-9 level was independently associated with high preoperative serum CEA level, lymph node metastasis, right colon cancer, large tumor size, and PC (16), suggesting that it provides important information for predicting the occurrence of PC. Another group reported younger age, advanced T-stage, poor differentiation grade, and right-sided tumor as risk factors for the presence of PC at the time of diagnosis (8). However, it is unclear whether the preoperative CA19-9 level is predictive of synchronous PC in patients with CRC.

To address this issue, the present study investigated whether an elevated preoperative serum CA19-9 level can predict synchronous PC in patients with CRC undergoing resection of the primary lesion.

Patients and Methods

Patient population. We retrospectively analyzed 395 patients with pathologically confirmed CRC (clinical stage I–IV), who underwent primary tumor resection with or without metastasectomy between January 2009 and December 2015 at the Department of Surgery, Omori Red Cross Hospital in Tokyo, Japan. Medical charts of all patients included in this study were retrieved from our registry, and clinicopathological data were collected. Factors included in the analyses were age, sex, American Society of Anesthesiologists (ASA) physical status, site of primary tumor, maximum tumor diameter, tumor depth, lymph node metastasis classified according to the Union for International Cancer Control guidelines (17), histology, lymphatic and venous involvement, hematogenous metastasis, PC, and preoperative serum CEA and CA19-9 levels. Patients underwent exploration of the abdominal cavity for macroscopic PC which, if

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present, was classified according to the Japanese Classification of Colorectal Carcinoma edited by the Japanese Society for Cancer of the Colon and Rectum (18). In the classification, peritoneal metastases were categorized into the following three groups according to PC status: P1, metastasis only to adjacent peritoneum; P2, a few metastases of the distant peritoneum; P3, numerous metastases of the distant peritoneum. Serum CEA and CA19-9 values were measured using ARCHITECT i2000 with ARCHITECT CEA or CA19-9 XR reagents, respectively (Abbott Laboratories, Abbott Park, IL, USA). CEA and CA19-9 levels of up to 5.0 ng/ml and 37.0 U/ml, respectively, were taken as upper cut-off values for reference ranges. Patients were divided into two groups: those with and without synchronous PC. Clinical and pathological variables affecting the presence of synchronous PC were compared between the two groups. To investigate the impact of synchronous PC on the survival of patients with CRC, we carried out a subgroup analysis in patients with stage IV disease in which we compared 2-year overall survival rates between patients with and those without PC. The study protocol was approved by the Institutional Review Board of Omori Red Cross Hospital (Approval Number: 15-6).

Statistical analysis. Associations between the presence of synchronous PC and clinical and pathological parameters were assessed with the Fisher's exact test. Variables that were significant in the univariate analysis were examined in the multivariate analysis with the logistic regression test. Survival analyses were performed with the Kaplan–Meier method and log-rank test. All reported p-values are two-tailed, and those less than 0.05 were considered significant. Data were analyzed using EZR v.1.24 for Windows software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (19).

Results

A total of 231 men (58.5%) and 164 women (41.5%) were included in the study, with a median age of 73 years (range=30-94 years). In total 67 patients (17.0%) had an elevated preoperative serum CA19-9 level. All 395 patients underwent exploration of the abdominal cavity for macroscopic PC and resection of the primary lesion with curative or palliative intent. There were 12 patients (3.0%) with pathologically confirmed synchronous macroscopic PC. There were no significant differences among P1, P2, and P3 groups with respect to preoperative CA19-9 level; we, therefore, divided the 395 patients into two groups, with or without synchronous PC, for subsequent analyses. Demographic and baseline characteristics are summarized in Table I.

A comparison of clinical and pathological outcomes between patients with and without synchronous PC is shown in Table II. In univariate analyses, factors that were significantly associated with synchronous PC were greater tumor depth ($p<0.001$) and number of metastatic lymph nodes ($p=0.037$), presence of hematogenous metastases ($p<0.001$), and elevated preoperative CA19-9 level ($p<0.001$). There were no significant differences in terms of other factors between the two groups.

Results of the multiple logistic regression analysis to identify risk factors associated with synchronous macroscopic PC are shown in Table III. When parameters that were significant in univariate analyses were subjected to multivariate analysis, an elevated preoperative CA19-9 level [odds ratio (OR)=5.03; 95% confidence interval (CI)=1.29-19.60; $p=0.020$] was found to be a significant risk factor for synchronous PC. The presence of hematogenous metastases was also associated with synchronous PC (OR=3.29; 95% CI=0.88-12.30; $p=0.076$).

To assess the impact of synchronous PC on the prognosis of patients with CRC, a subgroup analysis was carried out only on patients with metastatic disease (*i.e.* 50 patients with stage IV CRC). Patients with synchronous PC had worse 2-year overall survival rates than those without synchronous PC (82.6% vs. 33.3%, $p<0.001$) (Figure 1).

Discussion

PC at the time of initial presentation is not uncommon in CRC; the associated refractory ascites, progressive intestinal obstruction, and intractable abdominal pain can negatively impact both survival and quality of life of patients (11). Furthermore, 20-50% of patients with recurrent CRC have metastasis confined to the peritoneal cavity (20), with approximately 30% dying as a result (7). Therefore, confirming the occurrence of PC is critical in CRC. The majority of patients with CRC with synchronous PC have hematogenous metastases and are exclusively treated with palliative care for symptom relief with or without chemotherapy (21). In this study, about 3.0% of patients were diagnosed with synchronous macroscopic PC, an incidence that is slightly lower than the 4.5% reported in the guidelines for treatment of CRC edited by the Japanese Society for Cancer of the Colon and Rectum (6). This was partly because our study did not include patients with stage IV disease who did not undergo primary lesion resection, whereas the data described in the guidelines included such patients. Of the patients with synchronous PC, 50% had other metastatic diseases; only 16.7% of patients underwent curative resection. We found that patients with stage IV CRC with synchronous PC had a significantly worse prognosis than those without synchronous PC, in agreement with previous studies (2-4).

CA19-9 was originally isolated from a human colorectal cancer cell line as a derivative of lacto-*N*-fucopenteose II (sialyl-Lewis[a], hapten of human Lewis[a] blood-group determinant) (22). In this study, the preoperative serum CA19-9 level was elevated in 17% of patients, which is similar to the rates reported in other studies (23, 24). The American Society of Clinical Oncology guidelines state that there is insufficient evidence for using CA19-9 in the management of patients with CRC (25). However, a number

Table I. Patient characteristics.

Variable	
Median age (range), years	73 (30-94)
Gender, n (%)	
Female	164 (41.5)
Male	231 (58.5)
ASA physical status, n (%)	
I	32 (8.1)
II	296 (74.9)
III	67 (17.0)
Site of tumor, n (%)	
Right colon	129 (32.7)
Left colon	191 (48.3)
Rectum	75 (19.0)
Maximum tumor diameter, median (range), mm	45 (8-185)
Tumor depth, n (%)	
T1	52 (13.2)
T2	47 (11.9)
T3	237 (60.0)
T4	50 (14.9)
Lymph node metastasis, n (%)	
N0	229 (58.0)
N1	115 (29.1)
N2	51 (12.9)
Histology, n (%)	
Differentiated	377 (95.4)
Undifferentiated	18 (4.6)
Lymphatic involvement, n (%)	
Absent	116 (29.4)
Present	279 (70.6)
Venous involvement, n (%)	
Absent	354 (89.6)
Present	41 (10.4)
Hematogenous metastasis, n (%)	
Absent	351 (88.9)
Present	44 (11.1)
Peritoneal metastasis, n (%)	
P0	383 (97.0)
P1	5 (1.2)
P2	5 (1.2)
P3	2 (0.5)
Stage*	
I	79 (20.0)
II	142 (36.0)
III	124 (31.4)
IV	50 (12.6)
Median CEA (range), ng/dl	4.2 (0.5-6245)
Median CA19-9 (range), U/ml	10.3 (<2-5846)

ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9. *Union for International Cancer.

Table II. Association between clinicopathological factors and peritoneal carcinomatosis by univariate analysis.

Variable	Peritoneal carcinomatosis, n (%)		p-Value
	Absent	Present	
Age			
<75 Years	212 (55.4)	8 (66.7)	0.56
≥75 Years	171 (44.6)	4 (33.3)	
Gender			
Female	160 (41.8)	4 (33.3)	0.77
Male	223 (58.2)	8 (66.7)	
ASA physical status			
I, II	319 (83.3)	10 (83.3)	1.00
III	64 (16.7)	2 (16.7)	
Site of tumor			
Right colon	121 (31.6)	8 (66.7)	0.057
Left colon	188 (41.1)	3 (25.0)	
Rectum	74 (19.3)	1 (8.3)	
Maximum tumor diameter (mm)			
<50	215 (56.1)	4 (33.3)	0.15
≥50	168 (43.9)	8 (66.7)	
Tumor depth			
T1-3	331 (86.4)	5 (41.7)	<0.001
T4	52 (13.6)	7 (58.3)	
Lymph node metastasis			
N0, 1	342 (89.3)	8 (66.7)	0.037
N2	41 (10.7)	4 (33.3)	
Histology			
Differentiated	366 (95.6)	11 (91.7)	0.43
Undifferentiated	17 (4.4)	1 (8.3)	
Lymphatic involvement			
Absent	115 (30.0)	1 (8.3)	0.19
Present	268 (70.0)	11 (91.7)	
Venous involvement			
Absent	345 (90.1)	9 (75.0)	0.12
Present	38 (9.9)	3 (25.0)	
Hematogenous metastasis			
Absent	345 (90.1)	6 (50.0)	<0.001
Present	38 (9.9)	6 (50.0)	
CEA			
<5 ng/dl	222 (58.0)	5 (41.7)	0.38
≥5 ng/dl	161 (42.0)	7 (58.3)	
CA19-9			
<37 U/ml	324 (84.6)	4 (33.3)	<0.001
≥37 U/ml	59 (15.4)	8 (66.7)	

ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

of studies have demonstrated the clinical significance of CA19-9 in CRC (23, 24, 26, 27). Serum CA19-9, especially a high preoperative level, was found to be an important predictor of disease recurrence (23, 26), and an elevated CA19-9 level was correlated with peritoneal recurrence after

curative resection of CRC (23, 24). The preoperative CA19-9 level may also be useful for predicting the prognosis of patients with stage IV CRC (27). In this study, an elevated preoperative CA19-9 level was the only significant risk factor for synchronous PC in patients with CRC.

Table III. Association between clinicopathological factors and peritoneal carcinomatosis by multivariate analysis.

Variable	OR	95% CI	p-Value
Tumor depth: T4 vs. T1-3	3.11	0.79-12.20	0.11
Lymph node metastasis: N2 vs. N0,1	1.60	0.38-6.65	0.52
Hematogenous metastasis: Present vs. absent	3.29	0.88-12.30	0.076
CA19-9: ≥ 37 vs. < 37 U/ml	5.03	1.29-19.60	0.020

OR, Odds ratio; CI, confidence interval; CA19-9, carbohydrate antigen 19-9.

Previous studies have shown that the sensitivity of CT in detecting peritoneal implants is influenced by lesion size (12, 14); small nodules (<0.5 cm) were visualized by CT with only 11% sensitivity (14). In the present study, 50% of patients with PC were identified as having no PC in the preoperative CT evaluation, but had high preoperative CA19-9 level; two of the patients had multiple hepatic metastases, one had multiple hepatic and lung metastases, and the others had PC alone. The sensitivity and specificity of an elevated preoperative CA19-9 level for detecting synchronous PC were 67% and 85%, respectively; the positive and negative predictive values were 14% and 99%, respectively; and the accuracy was 84% (data not shown). These results suggest that the preoperative CA19-9 level may be useful in predicting synchronous PC in patients with CRC; in fact, several reports indicate that it may have predictive value for identifying PC in patients with gastric cancer (28-30).

CA19-9 (sialyl-Lewis[a]) expressed on tumor cells has been implicated in the mechanisms underlying distant metastasis and peritoneal spread (31-36). Tumor metastasis is similar to leukocyte trafficking in that tumor cells circulating in the blood extravasate and populate new tissues using the same types of adhesion molecule (32, 33). In cancer cell lines expressing sialyl-Lewis[x] and/or sialyl-Lewis[a], tumor cell adhesion to the endothelium expressing E-selectin was correlated with the expression level of sialyl-Lewis, an E-selectin ligand (34). Furthermore, tumor cells activate platelets that express P-selectin, which interacts with sialyl-Lewis; P-selectin-dependent tumor cell adhesion to platelets leads to tumor cell aggregation and microembolism (35). Thus, interaction of CA19-9 with selectins is important in hematogenous metastasis. With regards to peritoneal seeding, CA19-9 expressed by pancreatic adenocarcinoma cells was shown to interact with E-selectin constitutively expressed on human mesothelial and endothelial cells in the peritoneum. The interaction of pancreatic adenocarcinoma cells expressing CA19-9 with E- and P- selectins was demonstrated by dynamic flow assays and flow cytometry, with CA19-9 shown to be the main E-selectin ligand. In addition, peritoneal metastasis was reduced in E- and P-

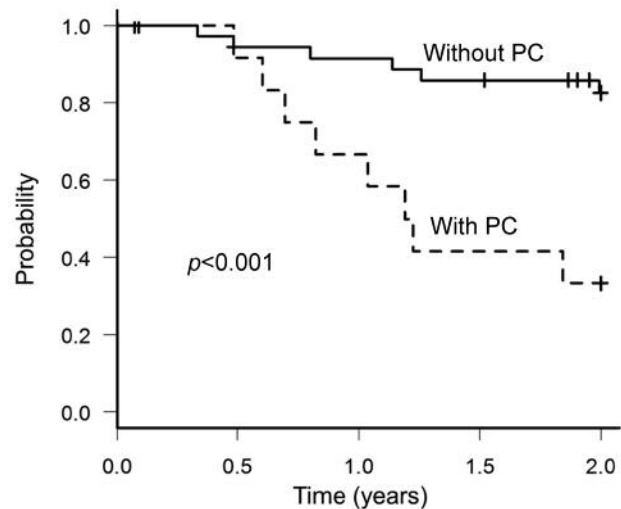


Figure 1. Survival curves of patients with stage IV colorectal cancer who underwent resection of the primary lesion. Kaplan-Meier estimates of the 2-year overall survival of patients with and without peritoneal carcinomatosis (PC) are shown.

selectin double knockout mice compared to wild-type mice in a xenograft model (36).

There were caveats and limitations to this study. The serum CA19-9 level is influenced by factors besides PC; individuals with a Lea-b-phenotype (*i.e.* lacking the Lewis antigen glycosyltransferase) are unable to synthesize CA19-9 (5-10% of the population) (37, 38), while those with benign biliary tract disease, acute or chronic pancreatitis, and malignancies including pancreatic, biliary tree, stomach, liver, or lung cancer can exhibit an elevated CA19-9 level (5). Furthermore, this study is limited by its retrospective design and small sample size, and was carried out at a single institution; additional studies with larger populations are, therefore, required to confirm our findings.

In conclusion, the results presented here indicate that the preoperative serum CA19-9 level is a useful indicator of synchronous PC. This can inform postoperative treatment strategies and is useful for predicting the prognosis of patients with CRC.

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