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Clinical Significance of Serum Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 Levels Before Surgery and During Postoperative Follow-Up in Colorectal Cancer

Harunobu Sato[1], Yoshikazu Koide[1], Miho Shiota[1], Hiroshi Takahashi[2], Zenichi Morise[1], Ichiro Uyama[1]

[1]*Department of Surgery, Fujita Health University School of Medicine, Aichi, Japan*

[2]*Department of Medical Statistics, Fujita Health University School of Medicine, Aichi, Japan*

Objective: Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are the most common colorectal cancer markers. We aimed to identify the appropriate clinical conditions for measuring serum CEA and CA19-9 levels before surgery and during follow-up.

Methods: This study included 1275 colorectal cancer patients who were divided into 3 groups according to preoperative CEA levels (group A, ≤5 ng/mL; group B, >5–≤11 ng/mL; group C, >11 ng/mL). Each group was subdivided into 2 groups according to preoperative CA19-9 levels (cutoff level: ≤37 U/mL). Recurrence and survival rates were analyzed.

Results: Recurrence rate, disease-free survival after curative surgery, and prognosis were significantly worse in group A and B patients with high CA19-9 levels. At recurrence, CEA levels showed a greater increase in group B and C patients; CA19-9 levels increased in group A patients with high CA19-9 levels. At recurrence, high serum CA19-9 levels were observed in group A patients with high preoperative serum CA19-9 levels, even if the serum CEA level did not increase. Preoperative CA19-9 levels could predict recurrence and prognosis in groups A and B.

Conclusion: Periodic CA19-9 determination is useful for monitoring recurrence among group A patients with high CA19-9 levels.

Key words: Colorectal cancer – CA19-9 – CEA – Tumor marker – Prognosis

Corresponding author: Harunobu Sato, MD, PhD, Department of Surgery, Fujita Health University, School of Medicine, 1-98 Dengakugakubo, Kustukake-cho, Toyoake, Aichi 470-1192, Japan.
Tel.: 81 562 93 9296; Fax: 81 562 93 8311; E-mail: harsato@hotmail.co.jp

A tumor marker (TM) is a biological substance that is synthesized by neoplastic or embryonic cells and can be measured in body fluids or tissues of patients with cancer. TMs can be important tools for tumor screening, diagnosis, staging, follow-up, treatment response evaluation, and recurrence monitoring.[1] Colorectal cancer (CRCA) is the third leading cause of cancer and the fourth leading cause of cancer mortality worldwide.[2] Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 are well known as the most common TMs of CRCA. CEA, an intracellular adhesion molecule and member of the immunoglobulin superfamily, was first described in 1965 by Gold and Freedman.[3] CA19-9, which was described by Kopowski in 1979,[4] is a mucin-type glycoprotein that is known as a ligand of E-selectin; CA19-9 plays an important role in the adhesion of cancer cells to endothelial cells.[5]

Many studies have shown that elevated preoperative serum CEA or CA19-9 levels were associated with cancer progression, increased risk of recurrence, and poor prognosis in patients with CRCA.[6–9] To date, some studies have been conducted to prove the clinical utility of measuring serum CEA and CA19-9 levels.[10–13] Serum CEA and CA19-9 levels are generally measured before surgery and during postoperative follow-up and are considered useful TMs of CRCA. Based on these reports, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) has recommended that CA19-9 be measured in combination with CEA during postoperative follow-up after curative surgery.[14] Despite this recommendation to measure serum CEA levels, sufficient evidence on the significance of serum CA19-9 measurements is lacking.[15,16] Some guidelines recommend measuring only the serum CEA levels before surgery and during follow-up.[17–19] However, an increased serum CA19-9 level is occasionally the first sign of recurrence. It would be both economically and clinically important to demonstrate the advantage of measuring the serum CA19-9 level in addition to the serum CEA level. However, no previous studies have reported a situation in which useful information was provided by measuring the serum CA19-9 level in addition to the serum CEA level.

This study was designed to identify the information provided by serum CA19-9 measurements and the appropriate clinical situation in which both serum CEA and CA19-9 levels should be measured before surgery and during follow-up.

Patients and Methods

Of the 1353 consecutive patients referred to Fujita Health University for CRCA between 1991 and 2007, 1275 patients (790 men and 485 women; average age, 64.0 years; age range, 23–95 years) in whom both CEA and CA19-9 were measured preoperatively were enrolled in the study. Tumors were located in the colon in 742 patients (58.2%) and in the rectum in 533 patients (41.8%).

After curative surgery, postoperative surveillance was performed according to the JSCCR guidelines for the treatment of CRCA.[14] Follow-up consisted of a physical examination and serum CEA and CA19-9 measurements every 3 months for the first 3 years and every 6 months for the next 2 years. Abdominal imaging (ultrasonography and/or computed tomography [CT]) and chest CT were performed every 6 months, and a barium enema study or colonoscopy was performed every 1–2 years for 5 years. Patients were observed for at least 5 years after surgery. Recurrences were confirmed either histologically or radiologically. Oral 5-fluorouracil (5FU) derivatives were administered for 12 months in patients with Dukes' stage B cancer. Bolus infusion of 5FU and leucovorin or UFT (tegafur-uracil) and Uzel (Taiho Pharmaceutical Co Ltd, Tokyo, Japan) were administered for 6 months as adjuvant chemotherapy in patients with Dukes' stage C cancer. Patients with metastatic disease were treated with the current standard therapy in Japan according to the JSCCR guidelines for the treatment of CRCA after 2005[14] or the National Comprehensive Cancer Network clinical practice guideline in oncology before 2005.[17]

Serum CEA and CA19-9 levels were determined via the chemiluminescent enzyme immunoassay at a clinical laboratory (Fujirebio Inc, Tokyo, Japan). A serum CEA level of $\leq$5 ng/mL and a serum CA19-9 level of $\leq$37 U/mL were considered normal. Preoperative serum CEA and CA19-9 levels were examined in all patients within 30 days before surgery. The serum CEA and CA19-9 levels were high in 471 (36.9%) and 308 patients (24.2%), respectively. A receiver operating curve (ROC) was used to determine the appropriate cutoff value of the preoperative serum CEA level for predicting postoperative recurrence in patients with CEA levels >5 ng/mL. Based on this result, all 1275 patients were divided into 3 groups according to the preoperative serum CEA levels. Furthermore, each group was subdivided into 2 groups according to the preoperative serum CA19-9 level.

Clinical outcomes with respect to overall survival and recurrence were retrospectively evaluated among the groups to examine the clinical usefulness of measuring both the serum CEA and CA19-9 levels before surgery. Furthermore, the serum CEA and CA19-9 levels at the time of recurrence were studied in each group to examine the clinical usefulness of measuring both TMs during follow-up. Macroscopic tumor type, lymphatic invasion, and venous invasion were described according to the Japanese classification of CRCA.[20] The median duration of follow-up was 112 months (range, 1.5–231 months). The follow-up duration did not significantly differ among the groups.

Statistical analysis

The Mann-Whitney *U* test or independent *t*-test was used for statistical analysis. Categorical variables were analyzed using the χ^2 test or Fisher's exact probability test. The survival rates were calculated according to the Kaplan-Meier method and were compared using the Peto-Prentice Wilcoxon test.

Data were statistically analyzed using JMP 11 software (SAS Institute Inc, Cary, North Carolina). All data were expressed as number of patients and frequency (%) or median and range. $P < 0.05$ was considered significant.

Results

Cutoff value of preoperative serum CEA level in patients with high preoperative serum CEA level

The area under the curve was 0.599. When the cutoff value for preoperative serum CEA level was defined as 11 ng/dL in patients with CEA levels >5 ng/mL, the sensitivity and specificity of serum CEA level for predicting postoperative recurrence were 65.9% and 54.0%, respectively. Based on this result, all 1275 patients were divided into 3 groups according to the preoperative serum CEA levels. There were 804 patients in group A (serum CEA level ≤5 ng/mL); 201 patients in group B (serum CEA level >5 or ≤11 ng/dL); and 270 patients in group C (serum CEA level >11 ng/dL).

Clinical and pathologic characteristics of groups A, B, and C

Relationships between preoperative serum CA19-9 level and clinicopathologic characteristics of CRCA in groups A, B, and C are shown in Table 1. High preoperative serum CA19-9 levels were detected in 88 patients (10.9%) from group A, in 65 (32.3%) from group B, and in 155 (57.4%) from group C. The number of patients with high serum CA19-9 levels was significantly higher in groups with higher serum CEA levels ($P < 0.01$). With respect to other characteristics, noninfiltrating tumors (macroscopic types 0, 1, and 2) were more frequent in group A and B patients with high serum CA19-9 levels than in those with normal CA19-9 levels. In group C, colon cancer was more frequent in patients with high serum CA19-9 levels than in those with normal serum CA19-9 levels. In group B, well-differentiated adenocarcinoma or moderately differentiated adenocarcinoma was more frequent in patients with normal serum CA19-9 levels than in those with high levels. In group A, T3 or T4 cancer was more frequent among patients with high serum CA19-9 levels than among those with normal levels. In groups A and B, lymph node metastasis was more frequent among patients with high serum CA19-9 levels than among those with normal levels. Finally, in all 3 groups, Dukes' stage D disease was more frequent among patients with high serum CA19-9 levels than among those with normal CA19-9 levels.

Oncologic results of groups A, B, and C

Curative surgery was performed significantly more frequently in patients with normal serum CEA levels than in those with high serum CEA levels (742/804 cases, 92.3% versus 314/471 cases, 66.7%; $P < 0.001$). Recurrence after curative surgery was significantly more frequent among patients with high serum CEA levels than among those with normal levels (28.0% versus 14.2%; $P < 0.001$). Similarly, curative surgery was performed significantly more frequently in patients with normal serum CA19-9 levels than in those with high serum CA19-9 levels (866/967 cases, 89.6% versus 190/308 cases, 61.7%; $P < 0.001$). Recurrence after curative surgery was significantly more frequent in patients with high serum CA19-9 levels than in those with normal serum CA19-9 levels (65/190 cases, 34.2% versus 128/866 cases, 14.8%; $P < 0.001$).

In all the groups, curative surgery was performed more frequently in patients with normal serum CA19-9 levels than in those with high serum CA19-9 levels (Table 2). In groups A and B, recurrence after curative surgery was significantly more frequent in patients with high serum CA19-9 levels than in those with normal serum CA19-9 levels; however, no significant difference in the

Table 1 Clinical and pathologic characteristics of groups A, B, and C

	Group A (n = 804)			Group B (n = 201)			Group C (n = 270)		
CA19-9	Normal (%)	High (%)	*P* value	Normal (%)	High (%)	*P* value	Normal (%)	High (%)	*P* value
n	716	88		136	65		115	155	
Age,y[a]	63.5 (23–95)	66.5 (29–87)	0.26	65.5 (34–91)	63.0 (36–93)	0.33	65.0 (25–86)	62.0 (27–84)	0.38
Gender									
Male	455 (63.5)	41 (46.6)	0	90 (66.2)	41 (63.1)	0.67	74 (64.3)	89 (57.4)	0.25
Female	261 (36.5)	47 (53.4)		46 (33.8)	24 (36.9)		41 (35.7)	66 (42.6)	
Macroscopic type									
Type 0	89 (12.4)	5 (5.7)		5 (3.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Type 1	56 (7.8)	5 (5.7)	0	7 (5.1)	5 (7.7)	0.02	2 (1.7)	6 (3.9)	0.34
Type 2	530 (74.0)	63 (71.6)		115 (84.6)	49 (75.4)		105 (91.3)	133 (85.8)	
Type 3	16 (2.2)	6 (6.8)		4 (2.9)	6 (9.2)		5 (4.3)	6 (3.9)	
Type 4	0 (0.0)	0 (0.0)		0 (0.0)	1 (1.5)		0 (0.0)	0 (0.0)	
Type 5	25 (3.5)	9 (10.2)		5 (3.7)	4 (6.2)		3 (2.6)	10 (6.5)	
Location									
Colon	439 (61.3)	46 (52.3)	0.11	82 (60.3)	37 (56.9)	0.65	48 (41.7)	94 (60.6)	0
Cecum	22 (3.1)	3 (3.4)		5 (3.7)	4 (6.2)		1 (0.9)	4 (2.6)	
A colon	45 (6.3)	6 (6.8)		6 (4.4)	3 (4.6)		8 (7.0)	16 (10.3)	
T colon	43 (6.0)	5 (5.7)		10 (7.4)	2 (3.1)		5 (4.3)	6 (3.9)	
D colon	21 (2.9)	4 (4.5)		6 (4.4)	0 (0.0)		4 (3.5)	6 (3.9)	
S colon	193 (27.0)	19 (21.6)		30 (22.1)	15 (23.1)		15 (13.0)	34 (21.9)	
Rectosigmoid	115 (16.1)	9 (10.2)		25 (18.4)	13 (20.0)		15 (13.0)	28 (18.1)	
Rectum	277 (38.7)	42 (47.7)		54 (39.7)	28 (43.1)		67 (58.3)	61 (39.4)	
Upper rectum	84 (11.7)	10 (11.4)		19 (14.0)	10 (15.4)		16 (13.9)	17 (11.0)	
Lower rectum	191 (26.7)	28 (31.8)		35 (25.7)	16 (24.6)		50 (43.5)	43 (27.7)	
Proctus	2 (3.6)	4 (4.5)		0 (0.0)	2 (3.1)		1 (0.9)	1 (0.6)	
Histology									
Well	459 (64.1)	46 (52.3)	0.06	74 (54.4)	30 (46.2)	0.01	70 (60.9)	78 (50.3)	0.39
Moderately	225 (31.4)	34 (38.6)		57 (41.9)	26 (40.0)		36 (31.3)	60 (38.7)	
Poorly	9 (1.3)	1 (1.1)		1 (0.7)	4 (6.2)		3 (2.6)	8 (5.2)	
Mucinous	16 (2.2)	5 (5.7)		4 (2.9)	4 (6.2)		4 (3.5)	9 (5.8)	
Others	7 (1.0)	2 (2.3)		0 (0.0)	1 (1.5)		2 (1.7)	0 (0.0)	
Invasion depth									
Tis	51 (7.1)	5 (5.7)		0 (0.0)	1 (1.5)		1 (0.9)	1 (0.6)	
T1	125 (17.5)	4 (4.5)		9 (6.6)	0 (0.0)	0.84	2 (1.7)	0 (0.0)	
T2	115 (16.1)	13 (14.8)		7 (5.1)	6 (9.2)		4 (3.5)	3 (1.9)	
T3	197 (27.5)	30 (34.1)		59 (43.4)	25 (38.5)		44 (38.3)	48 (31.0)	
T4a	196 (27.4)	27 (30.7)	0.01	57 (41.9)	25 (38.5)		44 (38.3)	70 (45.2)	0.08
T4b	24 (3.4)	6 (6.8)		4 (2.9)	6 (9.2)		15 (13.0)	26 (16.8)	
Unknown	8 (1.1)	3 (3.4)		0 (0.0)	2 (3.1)		5 (4.3)	7 (4.5)	
Lymphatic invasion									
ly0	112 (15.6)	11 (12.5)	0.92	7 (5.1)	3 (4.6)	0.46	3 (2.6)	2 (1.3)	0.25
ly1	299 (41.8)	39 (44.3)		55 (40.4)	23 (35.4)		34 (29.6)	38 (24.5)	
ly2	261 (36.5)	29 (33.0)		68 (50.0)	30 (46.2)		63 (54.8)	87 (56.1)	
ly3	22 (3.1)	5 (5.7)		5 (3.7)	5 (7.7)		5 (4.3)	9 (5.8)	
Unknown	22 (3.1)	4 (4.5)		1 (0.7)	4 (6.2)		10 (8.7)	19 (12.3)	
Venous invasion									
v0	433 (60.5)	45 (51.1)	0.09	48 (35.3)	21 (32.3)	0.68	37 (32.2)	36 (23.2)	0.10
v1	206 (28.8)	33 (37.5)		66 (48.5)	27 (41.5)		41 (35.7)	67 (43.2)	
v2	53 (7.4)	6 (6.8)		19 (14.0)	12 (18.5)		27 (23.5)	30 (19.4)	
v3	4 (0.6)	0 (0.0)		2 (1.5)	1 (1.5)		0 (0.0)	3 (1.9)	
Unknown	20 (2.8)	4 (4.5)		1 (0.7)	4 (6.2)		10 (8.7)	19 (12.3)	
Lymph node metastasis									
N0	482 (67.3)	41 (46.6)	0	67 (49.3)	18 (27.7)	0	39 (33.9)	37 (23.9)	
N1	153 (21.4)	17 (19.3)		43 (31.6)	21 (32.3)		34 (29.6)	46 (29.7)	
N2	48 (6.7)	17 (19.3)		13 (9.6)	11 (16.9)		24 (20.9)	35 (22.6)	
N3 / N4	26 (3.6)	10 (11.4)		10 (7.4)	13 (20.0)		10 (8.7)	24 (15.5)	0.10

Table 1 Continued

	Group A (n = 804)			Group B (n = 201)			Group C (n = 270)		
CA19-9	Normal (%)	High (%)	*P* value	Normal (%)	High (%)	*P* value	Normal (%)	High (%)	*P* value
Unknown	7 (1.0)	3 (3.4)		3 (2.2)	2 (3.1)		8 (7.0)	13 (8.4)	
Dukes' classification									
A	250 (34.9)	18 (20.5)		11 (8.1)	3 (4.6)		5 (4.3)	1 (0.6)	
B	223 (31.1)	22 (25.0)		56 (41.2)	14 (21.5)		33 (28.7)	25 (16.1)	
C	204 (28.5)	35 (39.8)		52 (38.2)	30 (46.2)		50 (43.5)	46 (29.7)	
D	36 (5.0)	12 (13.6)	0	16 (11.8)	17 (26.2)	0.01	26 (22.6)	83 (53.5)	0
Unknown	3 (0.4)	1 (1.1)		1 (0.7)	1 (1.5)		1 (0.9)	0 (0.0)	

[a]Median (range).

frequency of recurrence with respect to the serum CA19-9 level was observed in group C (Table 2). In all groups, no significant differences were observed in the recurrence site and time interval from surgery to recurrence with respect to the serum CA19-9 level.

In groups A and B, the disease-free survival after curative surgery was significantly worse in patients with high serum CA19-9 levels than in those with normal serum CA19-9 levels; however, no significant difference in disease-free survival after curative surgery was observed among group C patients with high and normal serum CA19-9 levels (Fig. 1).

The 5-year survival rates after curative surgery were 84.2% in group A, 78.7% in group B, and 63.2% in group C. The prognosis after curative surgery was significantly worse in groups with higher serum CEA levels (group A versus group B, $P = 0.04$; group B versus group C, $P = 0.02$). The 5-year survival rates after curative surgery were 84.0% and 60.2% among patients with normal and high preoperative serum CA19-9 levels, respectively. The prognosis after curative surgery was significantly better in patients with normal preoperative serum CA19-9 levels than in those with high preoperative serum CA19-9 levels ($P < 0.001$).

Similarly, in groups A and B, the prognosis after curative surgery was significantly worse in patients with high serum CA19-9 levels than in those with normal serum CA19-9 levels; however, no significant difference in prognosis after curative surgery was observed among group C patients with high and normal serum CA19-9 levels (Fig. 2). Together, group A and group B patients accounted for 85.3% of all CRCA patients who were treated with curative surgery (Fig. 3a). Group A patients with high preoperative serum CA19-9 levels accounted for

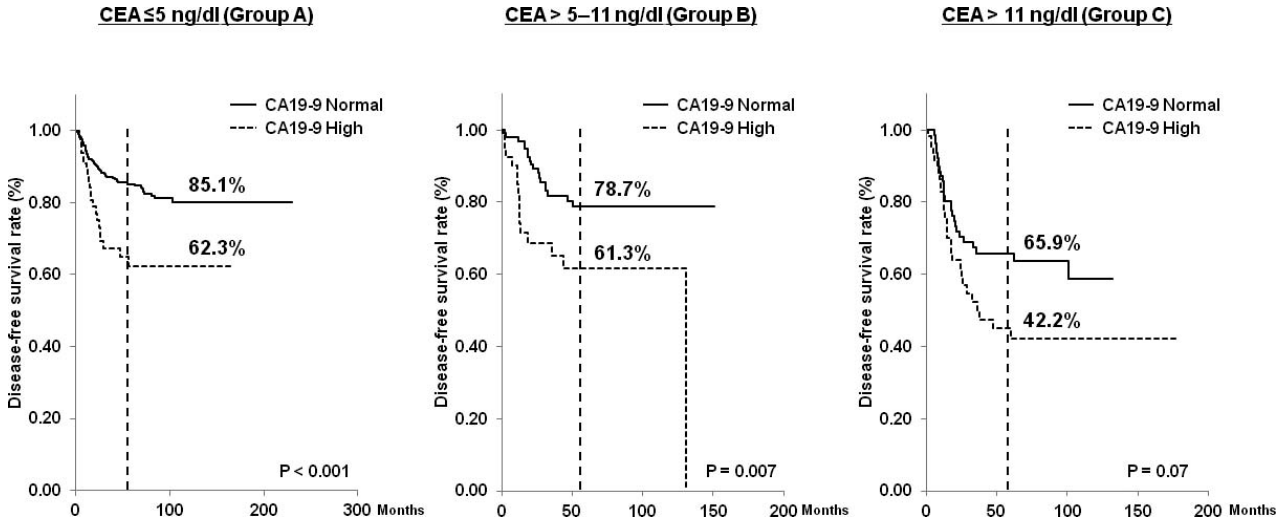

Fig. 1 Disease-free survival according to preoperative serum CEA and CA19-9 levels after curative surgery.

Table 2 Curability and recurrence according to preoperative serum CEA and CA19-9 levels

CEA	CA19-9	n	Curative surgery		*P*	Recurrence		*P*
Group A (≤5 ng/mL)	Normal	716	668	(93.3%)	0	84	(12.6%)	0.0002
	High	88	74	(84.1%)		21	(28.4%)	
Group B (>5 to ≤11 ng/mL)	Normal	136	113	(83.1%)	0.04	18	(15.9%)	0.02
	High	65	46	(70.8%)		15	(32.6%)	
Group C (>11 ng/mL)	Normal	115	85	(73.9%)	0	26	(30.6%)	0.16
	High	155	70	(45.2%)		29	(41.4%)	

7.0% of all CRCA patients treated with curative surgery (Fig. 3b).

Relationship between recurrence and serum CEA and/or CA19-9 levels

At the time of recurrence, high serum CEA levels were detected in 41.9% (44/105 cases) of group A patients, in 75.8% (25/33 cases) of group B patients, and in 80.0% (44/55 cases) of group C patients. A high serum CEA level at the time of recurrence was significantly more frequent in groups with higher preoperative serum CEA levels ($P = 0.0001$). Furthermore, a high serum CA19-9 level at the time of recurrence was significantly more frequent in patients with high preoperative serum CA19-9 levels than in those with normal preoperative serum CA19-9 levels (41/65 cases, 63.1% versus 39/130 cases, 30.0%; $P = 0.0001$). On the other hand, no significant relationship was observed between preoperative serum CEA and CA19-9 levels at the time of recurrence. However, 81.0% of patients with high preoperative serum CA19-9 levels in group A also had high serum CA19-9 levels at the time of recurrence (Table 3). Even among patients with normal serum CEA levels at the time of recurrence, 80.0% of group A patients with high preoperative serum CA19-9 levels also had high serum CA19-9 levels at the time of recurrence. A high serum CA19-9 level at the time of recurrence was significantly more frequent in patients with high preoperative serum CA19-9 levels than in those with normal preoperative CA19-9 levels and in those with normal serum CEA levels at the time of recurrence ($P = 0.0001$ for both groups); however, no similar significant differences were observed in groups B and C (Table 4).

Discussion

TMs have been used in cancer series for tumor screening, diagnosis, and classification, as well as in prognostication and monitoring for recurrence and metastasis.[1] Many studies have been conducted to determine the clinical usefulness of CEA and CA19-9, which are widely used for these purposes in the context of CRCA. Most of these studies, which included a few hundred patients at the most, appeared to indicate a significant correlation between these TMs and advanced-stage disease.[6–9] In addition, it has been reported that treatment outcomes were worse in patients with high preoperative serum CEA level than

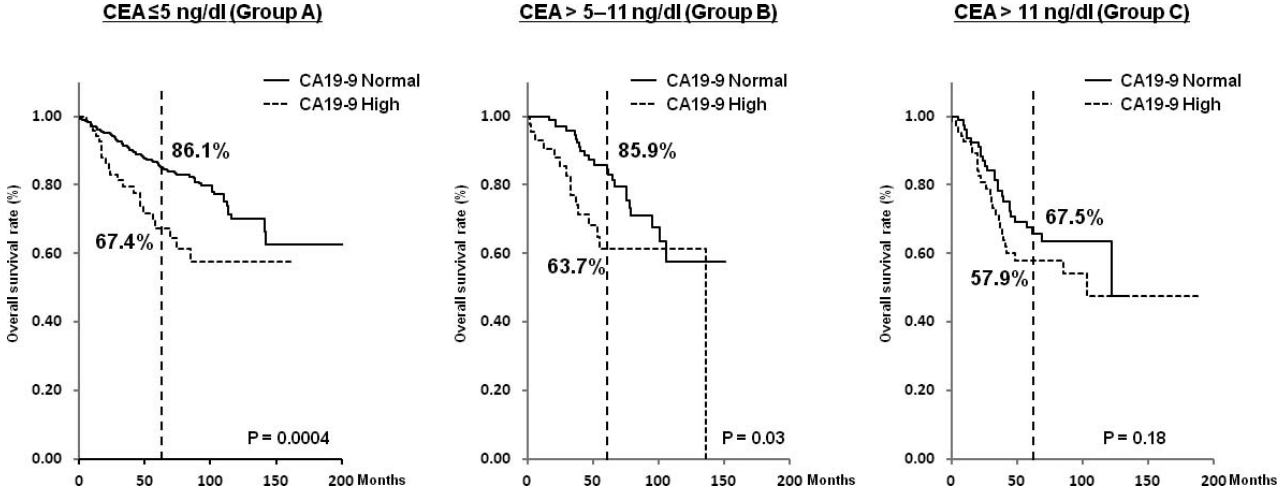

Fig. 2 Overall survival according to preoperative serum CEA and CA19-9 levels after curative surgery.

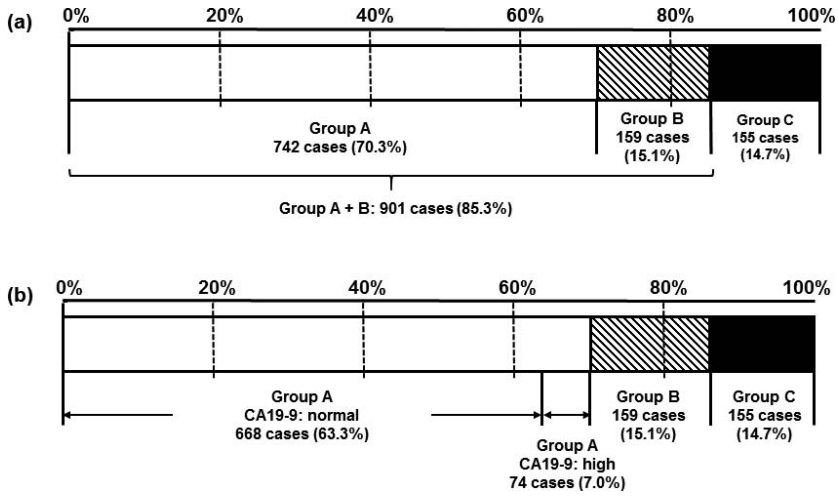

Fig. 3 Ratio of group A, group B, and group C. (a) Patients with preoperative serum CEA levels ≤11 ng/dL, in whom the preoperative CA19-9 level could efficiently predict recurrence and prognosis, occupied 85.3% of all patients. (b) Patients classified as group A and having high preoperative serum CA19-9 levels, in whom periodic CA19-9 detection after curative surgery is considered useful for monitoring recurrence, occupied 7.0% of all patients.

in patients with normal CEA level.[19–21] In the present study, which included more than 1000 patients, the treatment outcomes were significantly worse among patients with higher preoperative serum CEA levels and among those with high preoperative serum CA19-9 levels. Furthermore, patients with high preoperative serum CEA level were classified into 2 groups according to treatment outcomes. However, our results showed that preoperative serum CEA level may be used as a substitute for preoperative serum CA19-9 levels in terms of prediction of recurrence and prognosis, in accordance with a previous report.[16]

Another previous report suggested that preoperative serum CA19-9 level was a prognostic factor for CRCA patients with normal preoperative serum CEA levels.[22] We compared the clinicopathologic characteristics and treatment outcomes of 2 groups of CRCA patients who were divided according to the preoperative serum CA19-9 level, with each group classified by treatment outcome on the basis of the preoperative serum CEA level, to clarify the clinical usefulness of preoperative serum CA19-9 level with respect to the serum CEA level. Significant differences were observed between patients with high and normal serum CA19-9 levels with respect to sex and invasion depth in group A and with respect to macroscopic type, histology, and lymph node metastasis in groups A and B. Furthermore, significant differences in the frequency of distant metastases were observed between patients with high and normal CA19-9 levels, regardless of the preoperative serum CEA level. In addition, significant differences were observed between curative surgery-treated patients in groups A and B with high and normal serum CA19-9 levels in terms of the frequency of recurrence and

Table 3 Serum CA19-9 levels before surgery and at the time of recurrence according to preoperative serum CEA level in patients with curative surgery

Preoperative CA19-9	Recurrence	CA19-9 at the recurrence		
		Normal	High	Unknown
All				
Normal	128 cases	83 (64.9%)	39 (30.5%)*	6 (4.7%)
High	65 cases	20 (30.8%)	41 (63.1%)*	4 (6.2%)
Group A				
Normal	84 cases	60 (71.4%)	20 (23.9%)*	4 (4.8%)
High	21 cases	2 (9.5%)	17 (81.0%)*	2 (9.5%)
Group B				
Normal	18 cases	9 (50.0%)	8 (44.5%)	1 (5.6%)
High	15 cases	6 (40.0%)	9 (60.0%)	0 (0.0%)
Group C				
Normal	26 cases	14 (53.9%)	11 (42.3%)	1 (3.9%)
High	29 cases	12 (41.4%)	15 (51.7%)	2 (6.9%)

*$P = 0.00001$.

Table 4 Serum CA19-9 level at the time of recurrence in the patients with normal serum CEA level at the time of recurrence CEA level in patients with curative surgery

Preoperative CA19-9	Recurrence	CA19-9 at the recurrence		
		Normal	High	Unknown
All				
Normal	49 cases	44 (89.8%)	5 (10.2%)*	0 (0.0%)
High	19 cases	8 (42.1%)	11 (57.9%)*	0 (0.0%)
Group A				
Normal	43 cases	40 (93.0%)	3 (7.0%)*	0 (0.0%)
High	10 cases	2 (20.0%)	8 (80.0%)*	0 (0.0%)
Group B				
Normal	4 cases	2 (50.0%)	2 (50.0%)	0 (0.0%)
High	3 cases	2 (66.7%)	1 (33.3%)	0 (0.0%)
Group C				
Normal	2 cases	2 (100%)	0 (0.0%)	0 (0.0%)
High	6 cases	4 (66.7%)	2 (33.3%)	0 (0.0%)

*$P = 0.00001$.

prognosis; Dukes' stage D cases were excluded from that analysis. By dividing patients with high serum CEA levels into 2 groups according to CA19-9 levels, the present study found that a preoperative serum CEA level of $\leq$11 ng/mL could effectively predict recurrence and prognosis. In contrast, an earlier study conducted by Lin *et al* only analyzed patients with normal preoperative serum CEA levels.[22] In addition, the follow-up intensity may depend on the preoperative serum CA19-9 level, and accordingly, the preoperative measurement of serum CA19-9 was recommended for 85.3% of all CRCA patients treated with curative surgery.

Following curative surgery, the main goal of follow-up was to improve the prognosis through the detection of early relapse. However, follow-up procedures can be expensive; therefore, intensive follow-up must be justified by sufficient evidence. The serum levels of TMs, such as CEA or CA19-9, have been measured to determine and prove their clinical utility for the early detection of CRCA recurrence during postoperative follow-up. Previous authors have reported the clinical utility of serum CEA levels during the postoperative follow-up of curative surgery-treated CRCA patients.[23,24] For example, the reported sensitivity and specificity of serum CEA with respect to recurrence in nonselected groups varied from 61% to 88% and from 77% to 96%, respectively, whereas the sensitivity and specificity of serum CA19-9 varied from 28% to 80% and from 71%to 97%, respectively.[25] Furthermore, high serum CEA or CA19-9 levels were often reported at the time of recurrence in patients with high preoperative serum CEA or CA19-9 levels.[26] In the present study, the serum levels of both CEA and CA19-9 exhibited similar behavior, as described previously.

In our study, the serum CEA level at the time of recurrence was high in approximately 79% of patients with high preoperative serum CEA levels, despite the fact that only nearly 42% of patients with normal preoperative serum CEA levels had high serum CEA levels at the time of recurrence. On the other hand, nearly 63% of patients with high preoperative serum CA19-9 levels also had high levels at the time of recurrence. In addition, even if serum CA19-9 and CEA levels were periodically measured during follow-up, only 35%–52% of patients had high serum CA19-9 levels at the time of recurrence, regardless of the preoperative serum CEA level. These results suggested that periodic serum CEA measurements alone are sufficient for monitoring recurrence, although Yang *et al* reported a potentially significant advantage of CA19-9 over CEA in patients with higher preoperative serum CA19-9 levels (cutoff, 42 U/mL).[25] However, in our study, 81% of patients with high preoperative serum CA19-9 levels also had high levels at the time of recurrence, even if the preoperative serum CEA level was normal. Furthermore, even if the serum CEA level was normal at the time of recurrence, the serum CA19-9 level was high at the time of recurrence in 80% of patients with a high preoperative serum CA19-9 level and normal preoperative serum CEA level.

Furthermore, periodic serum CA19-9 detection was considered useful for the recurrence surveillance of patients with high preoperative serum CA19-9 levels and normal preoperative normal serum CEA levels. In a study by Lin *et al*, patients with high serum CA19-9 levels were reported to account for 8.1% of all curative surgery-treated patients with CRCA[22]; this population accounted for 7.0% of all such cases in the present study. As a result, periodic measurement of serum CA19-9 levels was recommended for 7%–8% of all curative surgery-treated CRCA patients. This selection of cases for CA19-9 monitoring is expected to enable an economically and clinically superior follow-up schedule.

The present study was limited by its retrospective and single-institute cohort design. Nevertheless, we believe that the results of the present study will play an instructive role in clinical practice. It will be necessary to conduct prospective multicenter studies with a larger series of patients with CRCA to analyze the efficacy of routine serum CA19-9 detection.

In conclusion, preoperative serum CA19-9 detection effectively predicted recurrence and prognosis in patients who had been diagnosed as candidates for curative surgery by preoperative examination and had serum CEA levels $\leq$11 ng/mL. Periodic measurement of serum CA19-9 levels is considered useful for monitoring recurrence in patients with high preoperative serum CA19-9 levels and normal preoperative serum CEA levels.

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