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Prognostic Value of Circulating CA19-9 in Colorectal Cancer Patients

Tohru NAKAGOE[1)], Terumitsu SAWAI[1)], Takashi TSUJI[1)], Masaaki JIBIKI[1)], Masayuki OHBATAKE[1)], Atsushi NAKASHIMA[1)], Hiroyuki YAMAGUCHI[1)], Nobuko KUROSAKI[1)], Toru YASUTAKE[1)], Hiroyoshi AYABE[1)], Hiroko MIYASHITA[2)], Kokichi ARISAWA[3)]

1) First Department of Surgery, Nagasaki University School of Medicine, Nagasaki
2) School of Allied Medical Science, Nagasaki University
3) Department of Preventive Medicine and Health Promotion, Nagasaki University School of Medicine

Aims: **We examined the preoperative serum levels of sialyl Lewis^a (CA19-9) and carcinoembryonic antigen (CEA) in 262 colorectal cancer patients, in order to clarify whether or not the prognostic value of CA19-9 after curative surgery is superior to that of CEA.**

Patients and Methods: **The patients were divided into two groups: low or high antigen groups (higher or lower than a selected diagnostic-based cut-off value). For evaluation of the prognostic value of CA19-9 and CEA, the disease-free interval was studied.**

Results: **The disease-free interval of patients with a high serum levels of CA19-9 or CEA was significantly shorter than for those patients with a low serum level of the particular antigen ($P<0.0001$ and $P=0.0009$, respectively). The disease-free interval of patients with stage I/II tumors who had a high CA19-9 level was significantly shorter than in those patients with stage I/II tumors with low CA19-9 levels ($P=0.0020$). In contrast, the disease-free interval of patients with stage I/II tumors who had a low or high CEA level did not differ. Cox s regression analysis revealed that a high serum level of CA19-9 or CEA was an independent predictor for short disease-free interval after curative surgery, separate from stage (Hazard ratio=2.65 or 1.68, respectively, versus a low serum level of each respective antigen).**

Conclusions: **These data suggest that the preoperative serum level of CA19-9 was a stronger prognostic factor after curative surgery than CEA. Furthermore, in contrast to CEA, CA19-9 provides more prognostic information than that obtained by conventional staging methods in patients with stage I/II tumors.**

Address Correspondence: Tohru Nakagoe, M.D.,
First Department of Surgery, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
TEL: +81-95-849-7304 FAX: +81-95-849-7306
E-mail: nakagoe@net.nagasaki-u.ac.jp

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Introduction

Carbohydrate antigen 19-9 (CA19-9) and Carcinoebryonic antigen (CEA) have been well recognized, and are widely used as tumor markers for colorectal caner.[1,2] The structure of CA19-9 was identified by Magnani et al. as a ganglioside-containing sialylated lacto-N-fucopentaose II (sialyl Lewis^a), structurally related to the Lewis^a blood-group substance.[3,4] CA19-9 binds to the endothelial cell-surface receptors E-selectin and P-selectin.[5] Thus, cells expressing CA19-9 adhere to endothelial cells that had been activated by some cytokine.[6] Such molecular function supports the idea that CA19-9 may actually play a role in the adhesion of cancer cells to endothelial cells, resulting in hematogenous metastasis.[6−9] The increased expression of CA19-9 in tumors, as demonstrated by immunohistochemistry, is associated with poor prognosis in colorectal cancer patients after surgery.[10]

Such oncologically-induced carbohydrate modifications, however, may not be limited to the tumor s primary site.[11] Filella et al.[1] reported that the preoperative serum level of CA19-9 provided more prognostic information than could be obtained by conventional staging methods in colorectal cancer patients. In addition, the prognostic significance of CEA was not independent of Dukes classification.[1] However, to date, CEA is the most commonly used tumor maker in patients with the colorectal cancer. It s use as an early diagnostic index for recurrence during follow-up after radical surgery has been well established by several authors.[12−14] Therefore, the aim of this study is to

clarify whether or not the prognostic value of CA19-9 is superior to that of CEA in colorectal cancer patients.

Patients and Methods

Preoperative serum levels of CA19-9 and CEA were measured in 262 colorectal cancer patients (155 male and 107 female) who underwent attempted curative resections at Nagasaki University Hospital from January 1990 to December 1995. The median age of patients studied was 65.0 years (range, 23 - 90). Patients with more than one carcinoma of the colon (synchronous or metachronous) were excluded from this study. In the studied patients, there was no evidence of other organ malignancies, and no patients had been given preoperative treatment with anticancer drugs. Patients who died within 30 postoperative days were not included in this study.

One hundred and sixty tumors were localized in the colon and 102 tumors were localized in the rectum. The surgically resected specimens from the 262 colorectal cancer patients were fixed in 10% formaldehyde and embedded in paraffin. The sections of the resected specimens were stained with hematoxylin and eosin. The American Joint Committee on Cancer (AJCC) Classification and Stage grouping was used to classify the tumors.[15] Each tumor was histopathologically classified according to its histology using the World Health Organization criteria presented by Jass and Sobin[16]: 80 tumors were classified as well-differentiated adenocarcinomas, 155 tumors as moderately differentiated adenocarcinomas, 20 tumors as poorly differentiated adenocarcinomas, and 7 tumors as mucinous carcinomas. The 262 patients included 38 patients in stage I, 130 in stage II, and 94 in stage III.

All patients underwent standard follow-up examinations, including laboratory testing every 3 months. The median length of follow-up was 1847 days (range, 72-3154 days). Of the 262 patients, 171 patients are currently alive with no evidence of recurrent disease, while 4 patients are alive with recurrent disease at the time of this writing (i.e. December 1999). Recurrences of colorectal cancer followed by death occurred in 63 patients, and 24 patients died of different diseases with no evidence of colorectal tumor.

Measurement of the serum levels of antigens

In order to detect the presence of circulating cancer markers, blood was obtained from the patients venous circulation after an overnight fast. The blood samples were separated immediately by centrifugation and the remaining blood sera were stored at -80℃ until use. The serum levels of CA19-9 and CEA were measured in the Otsuka Assay Laboratory (Tokushima, Japan) using commercially available radioimmunoassay kits: specifically, the Centocor CA19-9 RIA kit[17] (Centocor, Malvern, PA, USA) and the CEA Roche 2 kit[18] (Nippon Roche K.K., Tokyo, Japan), respectively. The data obtained were based on the simultaneous assay of these two antigens using the same set of sera. The cut-off values recommended by the manufacturers for diagnostic use were 37 U/ml for CA19-9 and 2.5 ng/ml for CEA .[17,18] For each antigen, we classified the patients into two groups: a high antigen group, with a serum antigen concentration greater than the selected cut-off value, and a low antigen group, with less than the cut-off value.

Statistical analysis

For univariate statistical analysis, the χ^2 test or Fisher's exact probability test for categorical data was used. For evaluation of the prognostic value of CA19-9 and CEA, the disease-free interval in the 262 patients was studied. The effect of each variable upon the disease-free interval was calculated according to the Kaplan-Meier method,[19] and differences between survival curves were tested for significance using the log-rank test.[20]

Multivariate analysis was performed with a Cox's proportional hazard regression model in order to assess the effects of different variables on patient.[21] The serum levels of CA19-9 and CEA were compared with the stage that is generally used in colorectal cancer patient management and well-supported in the literature.[15] All tests were two-tailed and a P value of less than 0.05 was considered to be significant.

Results

Comparison of stage between low antigen group and high antigen group

Of the 262 patients, the high antigen groups encompassed the following patients and percentages: 52 (19.9%) for CA19-9 and 92 (35.1%) for CEA. The distribution of CA19-9 and CEA according to the AJCC stage grouping is shown in Table 1. The high CEA group had a more advanced stage than the low CEA group (P=0.0026), although there was no difference in stage between the low CA19-9 group and the high CA19-9 group.

Table 1. Distribution of CA19-9 and CEA according to AJCC stage grouping.

	No. of Carcinoma (%)			No. of Carcinoma (%)		
	Low CA19-9 group (n=210)	High CA19-9 group (n=52)	*P* value	Low CEA group (n=170)	High CEA group (n=92)	*P* value
Stage			0.0965			0.0026
I	35 (16.7)	3 (5.8)		34 (20.0)	4 (4.4)	
II	104 (49.5)	26 (50.0)		80 (47.1)	50 (54.4)	
III	71 (33.8)	23 (44.2)		56 (32.9)	38 (41.3)	

Table 2. Prognostic variables for survival in Cox s regression analysis.

Variable	Categories	Hazard ratio	(95% CI*)	*P* value
Stage	I	1		
	II	5.07	0.67-37.99	0.1140
	III	18.81	2.57-137.42	0.0038
Serum CA19-9 status	Low	1		
	High	2.65	1.59-4.41	0.0002
Serum CEA status	Low	1		
	High	1.68	1.02-2.78	0.0410

* CI, Confidence interval.

Comparison of disease-free interval after surgery between low antigen group and high antigen group patients

Figure 1 shows the disease-free interval of patients with colorectal cancer according to the results of preoperative CA19-9 and CEA levels. Patients with high serum levels of CA19-9 and CEA had shorter disease-free intervals than those with low serum levels of those respective antigen ($P<0.0001$ and $P=0.0009$, respectively)

Figures 2 and 3 show the prognostic evaluations of CA19-9 and CEA serum levels subdivided according to AJCC stage grouping. The disease-free interval of patients with stage I/II tumors who had high CA19-9 levels was significantly shorter than that noted in patients with low CA19-9 levels ($P=0.0020$), although the disease-free interval of patients with stage I/II disease who had either low or high CEA levels did not differ. The disease-free interval of patients with stage III disease who had high serum levels of CA19-9 or CEA was significantly shorter than the interval noted in patients with low serum levels of the respective antigens ($P=0.0008$ or $P=0.0019$, respectively).

Prognostic value of serum antigen level

A multivariate Cox's regression analysis was used in order to select the variables having the correlation with disease-free interval. The variables, i.e. serum CA19-9 status or serum CEA status, were each independent prognostic factors for the disease-free interval of patients after curative surgery, separate from stage. The hazard ratios of high serum levels of CA19-9 or CEA versus low serum levels of the respective antigens were 2.65 or 1.68, respectively (Table 2).

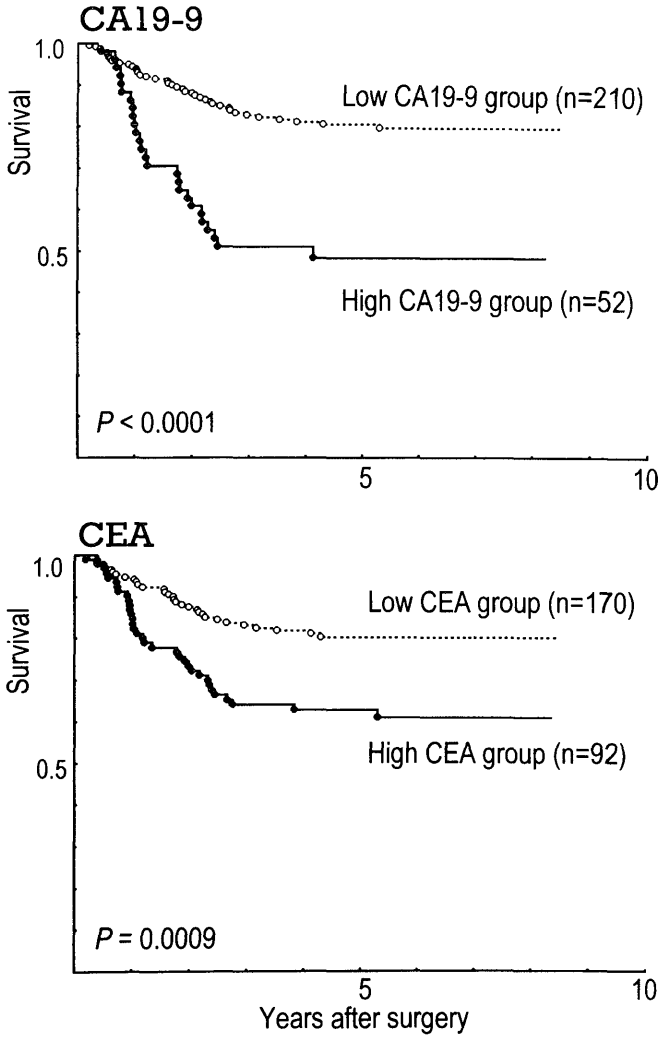

Fig 1. Disease-free interval after curative surgery for patients with colorectal cancer according to preoperative serum levels of CA19-9 (top) and CEA (bottom).

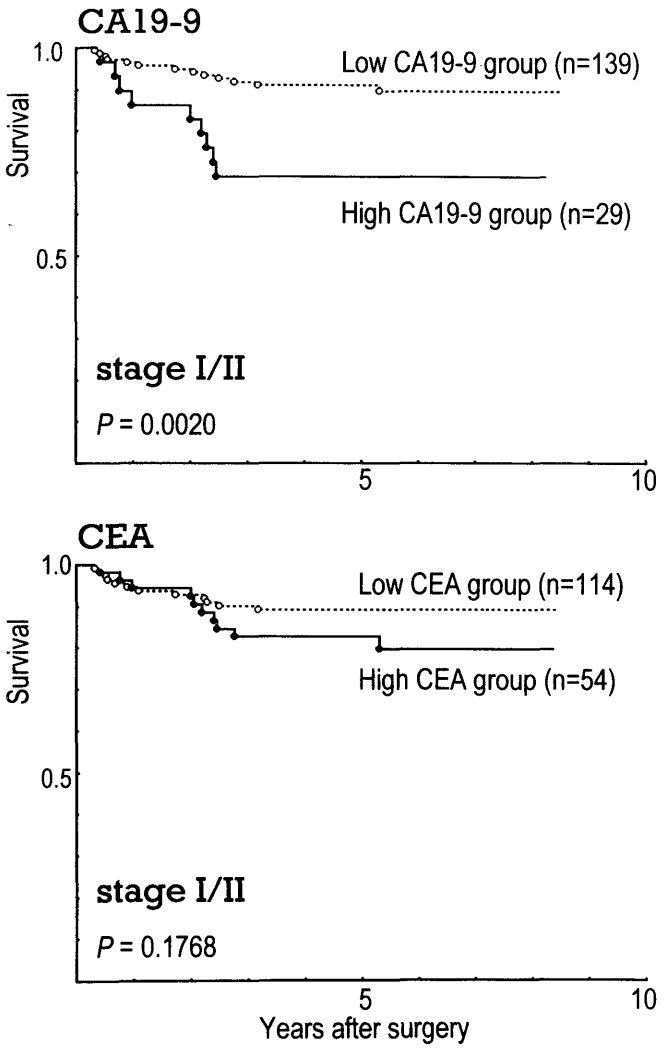

Figure 2. Disease-free interval after curative surgery for patients with stage I/II tumors according to preoperative serum levels of CA19-9 (top) and CEA (bottom).

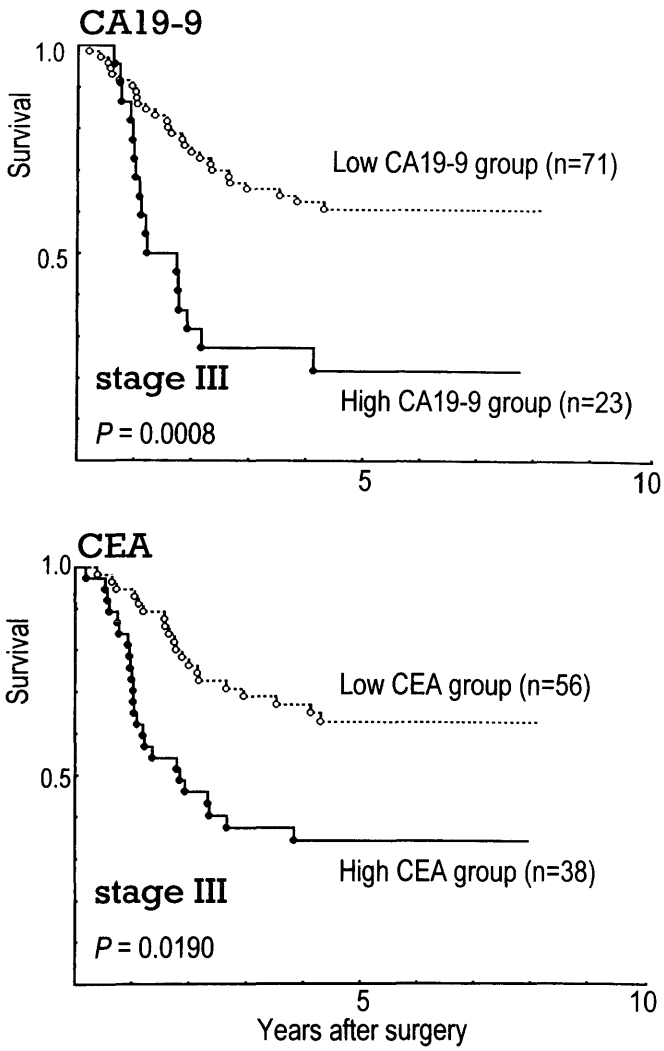

Figure 3. Disease-free interval after curative surgery for patients with stage III tumors according to preoperative serum levels of CA19-9 (top) and CEA (bottom).

Discussion

The current study reveals that preoperative serum level of CA19-9 is a stronger prognostic factor after curative surgery than the preoperative serum level of CEA. In particular, the preoperative serum level of CA19-9 in patients with stage I/II tumors provided additional information for allocating these patients into groups of either low or high risk of recurrence, in contrast to serum levels of CEA.

The prognostic value of the preoperative serum CA19-9 level has been reported in patients with colorectal cancer.[1,22,23] Filella et al.[1] reported the prognostic value of CA19-9 and CEA based on the disease-free interval after curative surgery in 162 colorectal cancer patients. The prognostic value of these serum markers are as follows: (i) CA19-9 provides more prognostic information than conventional staging methods (Dukes classification). In patients with Dukes C tumors, additional information is obtained for the allocation of these patients into groups of either low or high risk of recurrence; (ii) the prognostic significance of CEA is not independent of Dukes classification, according to multivariate analysis.

The current study also reveals that CA19-9 provides more prognostic information than conventional staging methods. In fact, the preoperative serum levels of CA19-9 in patients with stage I/II or III tumors provides additional information for allocating these patients into groups of recurrence risk (either low or high risk). However, in the report of Filella et al.,[1] the prognostic value of CA19-9 in patients with Dukes B tumors is not revealed. The difference between the current study and Filella et al. s report [1] may be due

to the number of patients studied. A total of 168 patients with stage I/II tumors in our series represents 82 patients more than in the Filella et al. s report.[1)]

In the AJCC Cancer Staging Manual, serum CEA level, as well as stage and histologic type, is proposed as an independent prognostic factor for colorectal cancer patients.[15)] Many studies supported this proposal .[2,24,25)] The current study also reveals that the preoperative serum level of CEA is an independent prognostic factor after curative surgery, separate from stage. Filella et al.[1)] has reported that the prognostic significance of CEA is not independent of Dukes classification, according to multivariate analysis. We feel that small number of patients in the Filella et al. s report[1)] may explain the difference between two studies.

In conclusion, the preoperative serum level of CA19-9 was a stronger prognostic factor after curative surgery than the serum CEA level. In addition, CA19-9 provides more prognostic information than is otherwise obtained by conventional staging methods.

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