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ORIGINAL ARTICLE – COLORECTAL CANCER

Clinical Significance of CEA and CA19-9 in Postoperative Follow-up of Colorectal Cancer

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ABSTRACT

Background. We evaluated the efficiency of CEA and CA19-9 as tools for diagnosing recurrence in the postoperative surveillance of colorectal cancer.

Materials and Methods. A total of 227 patients who underwent curative resection for colorectal cancer between 1999 and 2003 at our hospital received complete follow-up according to the schedule determined prospectively. Using receiver operating characteristic (ROC) analysis, performance of postoperative values of CEA or CA19-9 for detecting recurrence was assessed.

Results. The sensitivity (1.000) and specificity (0.978) of the postoperative values of CEA in the high preoperative CEA group were very high. Even in the normal preoperative CEA group, the area under the curve (AUC) of the ROC curve of CEA (0.740, 95% confidence interval [95% CI], 0.628–0.852) was significantly larger than 0.5 ($P < 0.001$). The postoperative values of CA19-9 showed high sensitivity (0.833) and specificity (0.900) in the high preoperative CA19-9 group, while the AUC of the ROC curve of the normal preoperative group was as small as 0.510 (95% CI, 0.376–0.644). In the high preoperative CA19-9 group, however, there was no significant difference between the AUC of CA19-9 (0.904, 95% CI, 0.786–1.000) and that of CEA (0.869, 95% CI, 0.744–0.994) ($P = 0.334$).

Conclusions. The measurement of CEA is an efficient way to detect recurrence. The efficiency of measuring CA19-9 for the purpose of detecting recurrence is low, especially in patients with a normal level of preoperative CA19-9. Even in patients with a high preoperative level of CA19-9, CEA might be able to fill the role of CA19-9.

A method for postoperative surveillance of colorectal cancer has not yet been established. Although recently the trend has been to use a high-intensity program, it remains unclear whether a more intensive strategy provides any significant advantages.[1–6] In addition, the cost effectiveness and efficiency of the surveillance are also important.[7–9]

According to the recommendations of the American Society of Clinical Oncology (ASCO) 2006 GI tumor markers guideline update, measurement of postoperative serum carcinoembryonic antigen (CEA) levels should be performed every 3 months for stage II or III disease for at least 3 years if the patient is a potential candidate for surgery or chemotherapy for metastatic disease.[10] As for carbohydrate antigen 19-9 (CA19-9), presently available data are insufficient to recommend its use for postoperative surveillance in colorectal cancer.[11] Often, CA19-9 stays within the normal range in the early stage of recurrence. However, it may be useful to add CA19-9 to the postoperative surveillance tools in colorectal cancer, since CA19-9 can be an indicator of poor prognosis and metastasis.[12–17] Based on these reports, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) recommends that CA19-9 be measured in combination with CEA during postoperative surveillance.[18]

The clinical performance of a laboratory test can be described in terms of diagnostic accuracy. The diagnostic accuracy as a measure of decision performance requires the introduction of the concepts of the sensitivity and specificity of a diagnostic test, but these usually depend on the

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cutoff value. The receiver operating characteristic (ROC) curve is a technique for visualizing and providing a cutoff-independent method for the evaluation of diagnostic tests. ROC analysis can be used as a statistical method to evaluate the performance of diagnostic tests.[19–21] The methodology has recently been adapted to several clinical areas that are heavily dependent on screening and diagnostic tests, laboratory testing, and radiology.[22–25]

In the present study, we used ROC analysis to visually and statistically evaluate the efficiency of CEA and CA19-9 as tools for the diagnosis of recurrence in the postoperative surveillance of colorectal cancer.

MATERIALS AND METHODS

A total of 266 patients underwent curative resection for colorectal cancer of TNM stage I–III between 1999 and 2003 at the Department of Surgery, Saga University Hospital. The patients underwent postoperative examinations according to the follow-up schedule determined prospectively before the beginning of the study. There were 39 patients who received inappropriate follow-up and were excluded from the study. The study involved a total of 227 patients. All the patients provided informed consent, and approval for the study was obtained from the institutional review board of Saga University Faculty of Medicine.

The postoperative examinations were performed according to the following schedule (Fig. 1). History was taken and a physical examination and measurement of tumor markers were performed every 3 months for the first 3 years and every 6 months during years 4 and 5. Chest X-ray and abdominal computed tomography (CT) were done every 6 months for 5 years, and colonoscopy was performed at 1 and 3 years after surgery. Patients were observed until 5 years after surgery or until recurrence was confirmed. Recurrence was confirmed histologically or radiologically.

The tumor markers assessed in the present study were serum CEA (a latex immunoassay, Mitsubishi Chemical Ltd, Japan, normal $\leq$5.0 ng/ml) and CA19-9 (a latex immunoassay, Mitsubishi Chemical Ltd, Japan, normal $\leq$37 ng/ml). The values of CEA and CA19-9 were referred to as "value-CEA" and "value-CA19-9," respectively. The ratios of the CEA and CA19-9 values at last follow-up or at the diagnosis of recurrence to those 1–3 months after the operation, hereafter referred to as the "ratio-CEA" and "ratio-CA19-9," were calculated to assess the increase in CEA and CA19-9.

Preoperative serum levels of CEA and CA19-9 were examined within 30 days before surgery in all patients. The patients were divided according to the values of CEA or CA19-9 measured preoperatively. Patients with less than 5 ng/ml of preoperative CEA were categorized as the "CEA negative group," and those with 5 ng/ml or more of preoperative CEA were categorized as the "CEA positive group." In the same way, patients with less than 37 ng/ml of preoperative CA19-9 were categorized as the "CA19-9 negative group" and those with 37 ng/ml or more of preoperative CA19-9 were categorized as the "CA19-9 positive group."

The distribution of clinicopathologic factors was analyzed by chi-square test or *t*-test. Diagnostic parameters for CEA and CA19-9 were assessed by ROC curve analyses. The best cutoff values for the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were calculated. The area under the curve (AUC) with the 95% confidence interval (95% CI) and asymptotic significance were also calculated. Statistical analyses were performed using SPSS version 17.0 software (SPSS Inc). *P* values less than 0.05 were considered statistically significant.

The likelihood ratio is defined as the ratio between the probability of a defined test result given the presence of a disease and the probability of the same test result in the absence of the disease. Positive likelihood ratio and negative likelihood ratio are related to the sensitivity and specificity of a test. Tests with positive likelihood ratios higher than 10 are generally considered to be clinically useful tests, while those with positive likelihood ratios lower than 5 are not considered to be useful. Tests with negative likelihood ratios lower than 0.10 are generally considered to be clinically useful tests.[26–28]

FIG. 1 Postoperative follow-up schedule

Year				**1**				**2**				**3**				**4**				**5**
Month	**3**	**6**	**9**	**12**	**3**	**6**	**9**	**12**	**3**	**6**	**9**	**12**	**3**	**6**	**9**	**12**	**3**	**6**	**9**	**12**
Physical examination	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•
CEA, CA19-9	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•
Chest X ray		•		•		•		•		•		•		•		•		•		•
Abdominal CT		•		•		•		•		•		•		•		•		•		•
Total colonoscopy				•								•								

$$\text{Positive likelihood ratio} = \text{sensitivity}/(1 - \text{specificity})$$
$$\text{Negative likelihood ratio} = (1 - \text{sensitivity})/\text{specificity}$$

The asymptotic significance of the AUC of the ROC curve was also calculated to evaluate the performance of the tests in the present study.[29,30] The AUC is always 0.5 or more and ranges between 0.5 and 1.0. If a laboratory test shows a perfect separation of the test values of 2 groups, the AUC is 1.0. If no apparent distributional difference exists between the 2 groups of test values, the AUC is 0.5.

To compare the performance between the tests, the areas under 2 ROC curves were statistically compared using the method reported by Hanley and McNeil[21] P value was calculated using a critical ratio Z defined by:

$$Z = (\text{AUC1} - \text{AUC2}) \Big/ \left(\sqrt{\text{SE}_1^2 + \text{SE}_2^2 - 2r\ \text{SE}_1\ \text{SE}_2} \right)$$

RESULTS

Of 227 patients, 62 showed recurrence by the end of the follow-up period. The distribution of the clinicopathological characteristics of patients with or without recurrence is shown in Table 1. There were no significant differences in age, sex, tumor location, or histology between the groups. However, significantly higher numbers of recurrences were observed in patients with higher clinical stages. The average preoperative values of CEA and of CA19-9 did not differ significantly between the groups. When divided by the usual cutoff values, significantly higher numbers of recurrences were observed in the CEA-positive group compared with the CEA-negative group. On the other hand, there was no significant difference in the numbers of patients showing recurrence between the CA19-9-positive group and the CA19-9-negative group. As for the postoperative levels of tumor markers at the end of follow-up or at recurrence, the average values of CEA and CA19-9 were significantly different between the groups.

The overall best cutoff values were 4.5 for value-CEA and 2.0 for ratio-CEA (Fig. 2, Table 2). At these cutoff values, the sensitivities were 0.690 and 0.724, the specificities were 0.945 and 0.712, the positive predictive values were 0.827 and 0.452, and the negative predictive values were 0.891 and 0.875, respectively. The AUCs for value-CEA and ratio-CEA were 0.840 (asymptotic significance $P < 0.001$) and 0.729 (asymptotic significance $P < 0.001$), respectively, but the former was significantly larger than the latter ($P = 0.013$).

When divided by preoperative levels of CEA, the best cutoff values of value-CEA were 4.5 in the CEA negative group and 5.9 in the CEA positive group (Fig. 3; Table 3). At these cutoff values, the sensitivity (0.471 vs. 1.000), specificity (0.957 vs. 0.978), positive predictive value (0.773 vs. 1.000), and negative predictive value (0.857 vs. 1.000) in the CEA-positive group were all higher than those in the CEA-negative group. The positive and negative likelihood ratios in the CEA-positive group were 45.45 and 0, respectively. The AUCs for value-CEA of the CEA-negative and CEA-positive groups were 0.740 (asymptotic significance $P < 0.001$) and 0.990 (asymptotic significance $P < 0.001$), respectively. When compared between the groups, the AUC for value-CEA in the CEA-positive group was significantly larger than that in the CEA-negative group ($P < 0.001$).

The overall best cutoff values were 38.0 for value-CA19-9 and 2.21 for ratio-CA19-9 (Fig. 4; Table 4). At these cutoff values, the specificity was as high as 0.969 in each of them. However, the sensitivities of both value-CA19-9 and ratio-CA19-9 were as low as 0.333 and 0.356, respectively. The AUC of value-CA19-9 (0.587) was slightly larger than that of ratio-CA19-9 (0.553), but neither AUC was significantly different from 0.5 (asymptotic significance $P = 0.082$ for value-CA19-9 and $P = 0.293$ for ratio-CA19-9).

Value-CA19-9 showed high sensitivity (0.833) and specificity (0.900) at the best cutoff value of 38.5 in the CA19-9-positive group (Fig. 5; Table 5). In the CA19-9-negative group, however, the sensitivity was very low (0.333) at the best cutoff value of 27.5, although the specificity was high (0.901). The AUC in the CA19-9-positive group was as high as 0.904 (asymptotic significance $P < 0.001$), while that of the CA19-9-negative group was 0.510 (asymptotic significance $P = 0.857$). The difference between them was significant ($P < 0.001$).

In the CA19-9-positive group, the efficacy for measuring a tumor marker was compared between value-CEA and value-CA19-9 (Fig. 6; Table 6). The best cutoff values were 3.0 for value-CEA and 38.5 for value-CA19-9. At these cutoff values, the sensitivities (0.833 vs. 0.833) and specificities (0.800 vs. 0.900) were high for both value-CEA and value-CA19-9. The AUCs of both value-CEA (0.869 asymptotic significance $P = 0.001$) and value-CA19-9 (0.904 asymptotic significance $P < 0.001$) were significantly larger than 0.5. Although the AUC of value-CA19-9 was slightly larger that that of value-CEA, there was no significant difference between them in the CA19-9-positive group ($P = 0.334$).

DISCUSSION

Using ROC analysis, the performance of the tumor markers as diagnostic tests in the postoperative surveillance of colorectal cancer was compared visually and statistically in the present study. For detecting recurrence, value-CEA was more efficient than ratio-CEA, and value-CEA in the CEA-positive group was more efficient than

TABLE 1 Clinicopathological characteristics of the patients who underwent curative resection for colorectal cancer

	All ($n = 227$)	Recurrence (+) ($n = 62$)	Recurrence (−) ($n = 165$)	P value
Age	65.2 ± 10.8	63.7 ± 10.2	65.5 ± 11.1	0.661
Sex				
Male	129	39	90	0.257
Female	98	23	75	
Location				
Colon	138	32	106	0.082
Rectum	89	30	59	
Stage				
I	34	6	28	0.011
II	94	19	75	
III	99	37	62	
Histology				
Well and mode	205	54	151	0.316
Poorly, others	22	8	14	
Preoperative CEA				
Value	7.25 ± 14.4	9.5 ± 16.3	6.4 ± 13.5	0.149
<5 ng/ml (negative)	155	36	119	0.032
≥5 ng/ml (positive)	72	26	46	
Preoperative CA19-9				
Value	24.4 ± 3.8	35.7 ± 100.7	20.1 ± 28.2	0.071
<37 ng/ml (negative)	192	49	143	0.215
≥37 mg/ml (positive)	35	13	22	
CEA at evaluation[a]				
Value	4.6 ± 7.2	11.1 ± 11.4	2.2 ± 1.5	<0.001
CA19-9 at evaluation[a]				
Value	32.3 ± 133.2	85.1 ± 250.6	12.9 ± 11.3	<0.001

[a] End of follow-up or recurrence

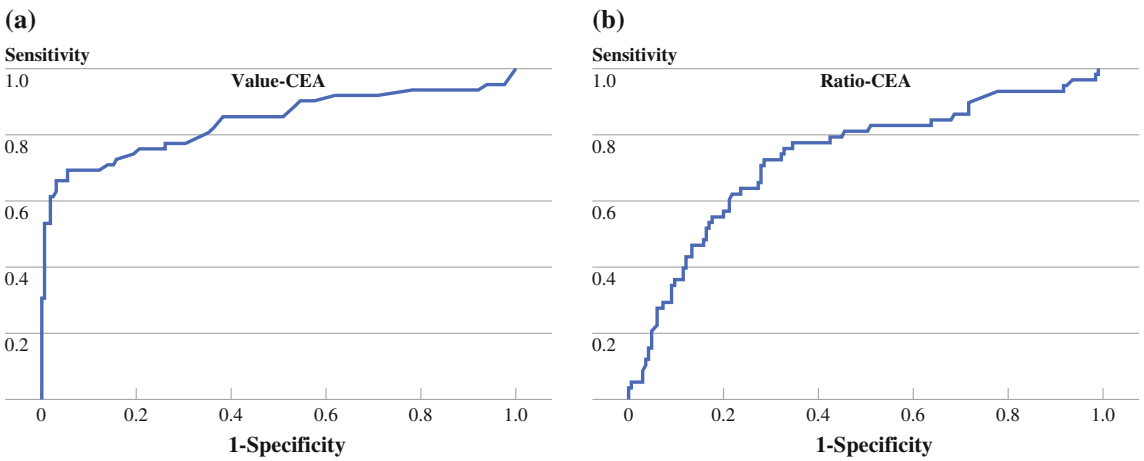

FIG. 2 ROC curves of value-CEA and ratio-CEA. **a** Value-CEA. **b** Ratio-CEA

that in the CEA-negative group. The diagnostic efficiency of value-CA19-9 and that of ratio-CA19-9 did not differ significantly from chance results.

The CEA is a complex glycoprotein with a molecular weight of 20,000, which is associated with the plasma membrane of tumor cells, and it may be released into the blood. It is often overexpressed by colorectal adenocarcinomas. Lokich et al. reported that CEA clearance occurred in 2 phases.[31] The first-phase decline of 63%–89% in circulating CEA levels immediately following tumor removal

TABLE 2 Comparison of the diagnostic parameters between value-CEA and ratio-CEA

	Value-CEA	Ratio-CEA
Best cutoff value	4.5	2.0
Sensitivity	0.690	0.724
Specificity	0.945	0.712
Positive predictive value	0.827	0.452
Negative predictive value	0.891	0.875
Positive likelihood ratio	12.54	2.51
Negative likelihood ratio	0.33	0.39
AUC	0.840	0.729
95% CI	0.766–0.914	0.649–0.810
Asymptotic significance	$P < 0.001$	$P < 0.001$
P value (a vs. b)	0.013	

TABLE 3 Comparison of the diagnostic parameters between the CEA-negative group and the CEA-positive group

	CEA-negative	CEA-positive
Best cutoff value	4.5	5.9
Sensitivity	0.471	1.000
Specificity	0.957	0.978
Positive predictive value	0.773	1.000
Negative predictive value	0.857	1.000
Positive likelihood ratio	10.95	45.45
Negative likelihood ratio	0.55	0.00
AUC	0.740	0.990
95% CI	0.628–0.852	0.971–1.000
Asymptotic significance	$P < 0.001$	$P < 0.001$
P value (a vs. b)	< 0.001	

may reflect the fact that the plasma CEA is in dynamic equilibrium with the tumor CEA. The kinetics of the second-phase decline of CEA is variable and may be related to the quantitative circulating pool or to pathophysiologic processes influencing CEA metabolism or secretion in the liver. The CA19-9 is a predominant carbohydrate antigen that was defined from the culture medium of a colorectal cancer cell line. It is a high-molecular-weight (200,000–5 million) glycolipid derived from a monoclonal antibody isolated from mice.[32] It has been used as a tumor marker in gastrointestinal cancers. Also, it is elevated in some patients with nonmalignant diffuse lung diseases and jaundice in the absence of a tumor because of biliary obstruction. Its half-life in serum is 1 day but can vary from less than 1 day to 3 days. Yoshimasu et al. analyzed the disappearance curves for serum tumor marker levels after resection of intrathoracic malignancies.[33] They reported that the average half-life of CA 19-9 was 0.5 days in the first compartment and 4.3 days in the second.

Korner et al. reported that ratio-CEA and value-CEA were useful for detecting recurrence in colorectal cancer using ROC analysis, although they did not perform a direct comparison of ratio-CEA to value-CEA.[34] In the present study, however, value-CEA was demonstrated to be more efficient than ratio-CEA by a statistical comparison of the AUCs of their ROC curves. The best cutoff value of ratio-CEA was 3.0 in their paper, while it was 2.0 in ours. The low cutoff value decreased the specificity, resulting in a decrease of accuracy. This might be a reason for the difference between the studies. Ratio-CEA might be useful to detect recurrence in patients with normal levels of CEA, since ratio-CEA showed higher sensitivity than value-CEA at the best cutoff values in both studies.

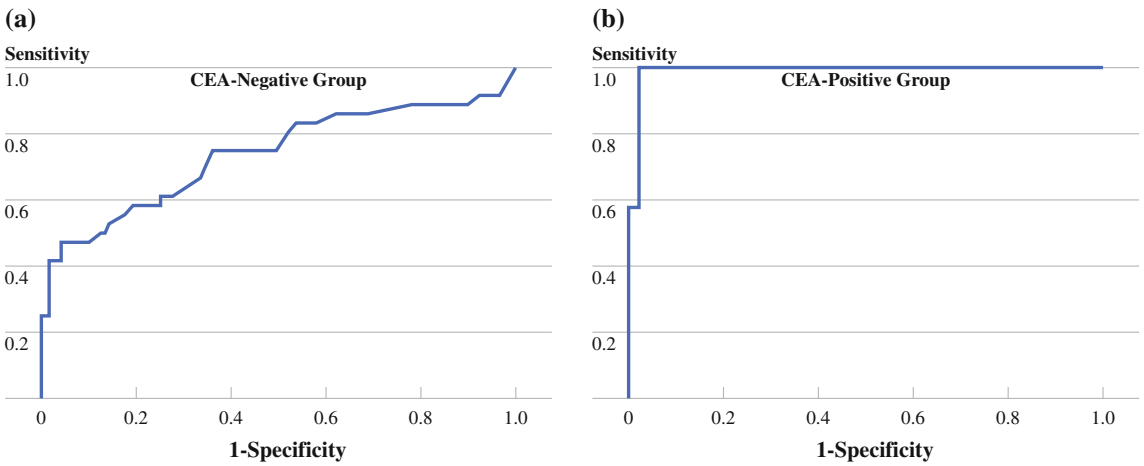

FIG. 3 ROC curves of the CEA-negative group and the CEA-positive group. **a** CEA-negative group. **b** CEA-positive group

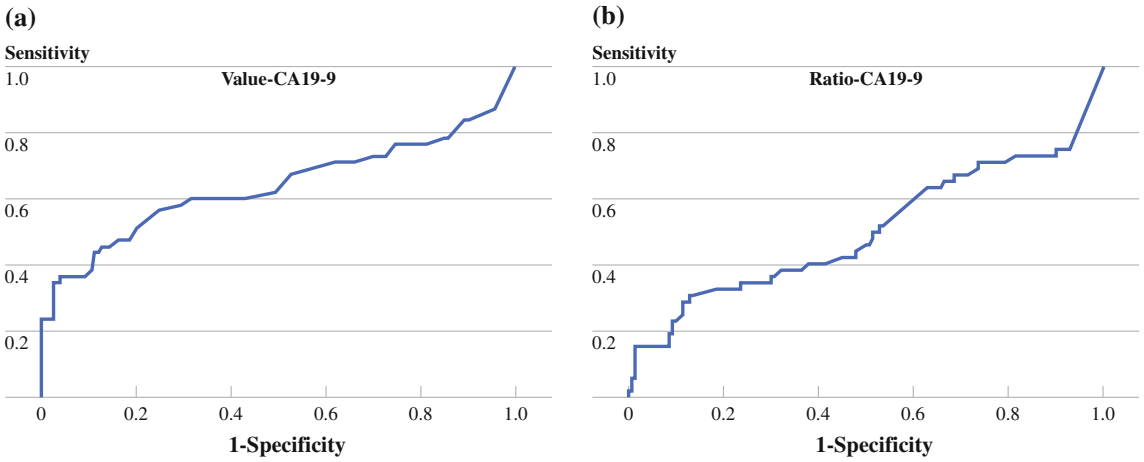

FIG. 4 ROC curves of value-CA19-9 and ratio-CA19-9. **a** Value-CA19-9. **b** Ratio-CA19-9

TABLE 4 Comparison of the diagnostic parameters between value-CA19-9 and ratio-CA19-9

	Value-CA19-9	Ratio-CA19-9
Best cutoff value	38.0	2.21
Sensitivity	0.333	0.356
Specificity	0.969	0.969
Positive predictive value	0.826	0.471
Negative predictive value	0.789	0.762
Positive likelihood ratio	10.74	11.48
Negative likelihood ratio	0.69	0.66
AUC	0.587	0.553
95% CI	0.468–0.706	0.444–0.661
Asymptotic significance	$P = 0.082$	$P = 0.293$
P value (a vs. b)	0.295	

Recently, Park et al. reported that the significance of postoperative measurement of CEA is different depending on the preoperative levels of CEA.[35] This is often experienced in clinical settings. Almost all patients with a high level of preoperative CEA show increased levels of CEA when their colorectal cancers recur, but this increase is observed less often in patients with normal levels of preoperative CEA. In the present study, the postoperative measurement of CEA was very efficient for patients with a high level of preoperative CEA. This was clearly demonstrated by the ROC curve in Fig. 3b, the AUC of which was 0.990, and also by the high positive likelihood ratio (45.45) with a low negative likelihood ratio (0.00). On the other hand, postoperative measurement of CEA was less efficient for patients with a normal level of preoperative CEA, as demonstrated by the smaller AUC (0.740) in the CEA-negative group. Even in this CEA-negative group, however, the measurement of CEA seemed to be useful since the AUC of this group was significantly higher than the chance results.

The low efficiency of CA19-9 seems to be mainly the result of low sensitivity. At our best cutoff value, the

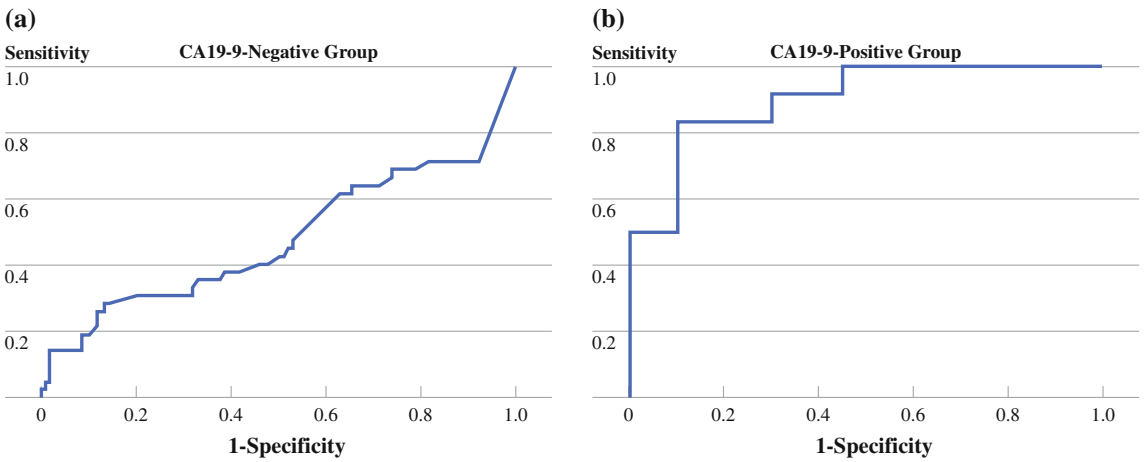

FIG. 5 ROC curves of the CA19-9-negative group and CA19-9-positive group. **a** CA19-9-negative group. **b** CA19-9-positive group

TABLE 5 Comparison of the diagnostic parameters between the CA19-9-negative group and the CA19-9-positive group

	CA19-9-negative	CA19-9-positive
Best cutoff value	27.5	38.5
Sensitivity	0.333	0.833
Specificity	0.901	0.900
Positive predictive value	0.560	0.833
Negative predictive value	0.790	0.869
Positive likelihood ratio	3.36	8.33
Negative likelihood ratio	0.74	0.19
AUC	0.510	0.904
95% CI	0.376–0.644	0.786–1.000
Asymptotic significance	$P = 0.857$	$P < 0.001$
P value (a vs. b)	< 0.001	

TABLE 6 Comparison of the diagnostic parameters between value-CEA and value-CA19-9 in the CA19-9-positive group

	Value-CEA	Value-CA19-9
Best cutoff value	3.0	38.5
Sensitivity	0.833	0.833
Specificity	0.80	0.90
Positive predictive value	0.647	0.833
Negative predictive value	0.888	0.869
Positive likelihood ratio	4.17	8.33
Negative likelihood ratio	0.21	0.19
AUC	0.869	0.904
95% CI	0.744–0.994	0.786–1.000
Asymptotic significance	0.001	<0.001
P value (a vs. b)	0.334	

overall sensitivity of CA19-9 was 0.333 while the specificity was 0969. Only 19 of 62 patients with recurrence showed levels exceeding the cutoff value for CA19-9 (normal ≤37 ng/mL), although 41 of these 62 patients showed levels exceeding the cutoff value for CEA (normal ≤5.0 ng/mL). Several papers have emphasized that CA19-9 is useful for postoperative surveillance in colorectal cancer.[14,36,37] This conclusion was based on the finding that the prognosis of patients with high preoperative levels of CA19-9 was poor and that most such patients showed increased levels of CA19-9 when the disease recurred. However, these facts do not directly support the efficiency of the measurement of CA19-9 for postoperative surveillance in colorectal cancer. Our analysis also showed that the sensitivity of CA19-9 in the CA19-9-positive group was relatively high, 0.833, at the best cutoff value. In this CA19-9-positive group, the sensitivity of CEA was also 0.833 at its best cutoff value, and there was no statistical difference in the AUCs between CA19-9 and CEA. Therefore, even in the CA19-9-positive group, it might not be necessary to measure CA19-9 if CEA is used for postoperative surveillance. At least there is no need to measure CA19-9 postoperatively in the CA19-9-negative group.

In the postoperative surveillance of colorectal cancer, CEA values are efficient for detecting recurrence, especially in patients with a high level of preoperative CEA. Ratio-CEA might be useful for detecting recurrence in patients not showing levels of CEA exceeding the cutoff value. There is little reason to measure CA19-9 as a diagnostic tool for recurrence, especially in patients with a normal level of preoperative CA19-9. Even in patients with a high level of CA19-9, CEA might be able to replace CA19-9 as a postoperative surveillance tool.

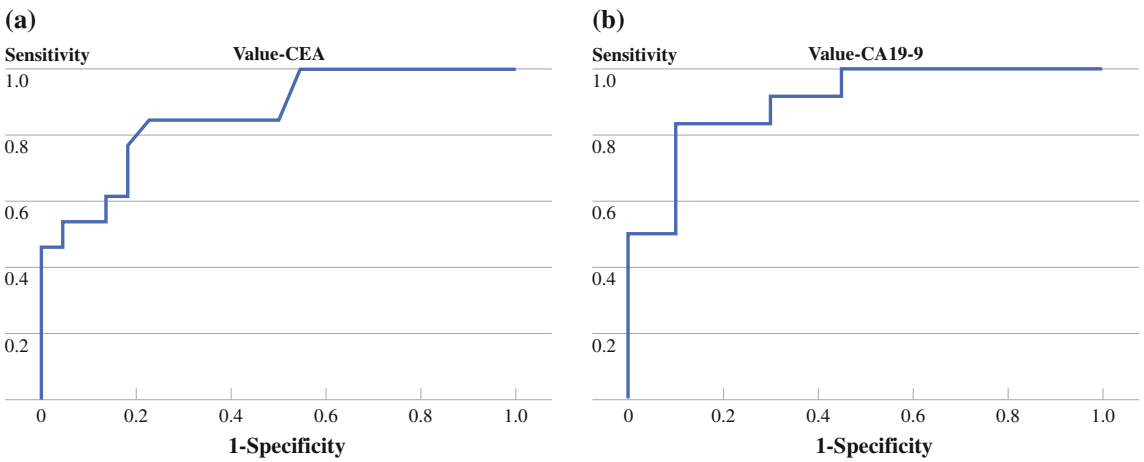

FIG. 6 ROC curves of value-CEA and value-CA19-9 in the CA19-9-positive group. **a** Value-CEA. **b** Value-CA19-9

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