Clinical Significance of Tumor Marker NCC-ST 439 in Large Bowel Cancers

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We examined serum NCC-ST 439 for its significance as a tumor marker of large bowel cancer in 121 patients with primary and 36 with recurrent large bowel cancer. Serum NCC-ST 439 was positive in 27.3 percent of the former and 66.7 percent of the latter. It was false-positive in only 5.6 percent of patients with benign diseases. Positive serum NCC-ST 439 correlated with lymph node and liver metastases. The combination assay for NCC-ST 439, CEA, and CA19-9 was positive in 49.6 percent of the patients with primary tumors and 88.9 percent of those with recurrent tumors; in other words, the diagnostic accuracy improved. The results demonstrated that the determination of serum NCC-ST 439 in large bowel cancer might be useful in cancer staging and that NCC-ST 439, if used in combination with CEA, is particularly useful in diagnosing recurrences because of its improved diagnostic accuracy. [Key words: NCC-ST 439; CEA; CA19-9; Tumor marker; Colorectal cancer]

Yamaguchi A, Kurosaka Y, Ishida T, Nishimura G, Kanno M, Kosaka T, Yonemura Y, Miyazaki I. Clinical significance of tumor marker NCC-ST 439 in large bowel cancers. Dis Colon Rectum 1991;34:921–924.

A variety of tumor markers that help to detect large bowel carcinoma are now available. Among other things, clinical use of carcinoembryonic antigen (CEA) is widespread.[1] CEA is, however, of limited value in early diagnosis of the malignancy, although it is useful in staging its malignant grade or recurrence.[2–4]

Hirohashi *et al.*,[5] on the other hand, have obtained a new monoclonal antibody NCC-ST 439, with the gastric cancer cell strain ST-4 as an immunogen. Immunohistochemical studies revealed that this new antibody is highly tumor-specific and reacts well on pancreatic and large bowel carcinoma, suggesting its usefulness as a tumor marker.[6] The findings evidencing the usefulness of the tumor marker NCC-ST 439 in diagnosing large bowel cancer and the significance of the combination assay for NCC-ST 439, CEA, and CA19-9 are reported in this paper.

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PATIENTS AND METHODS

Subjects included 121 patients with primary large bowel cancer (78 with colon cancer and 43 with rectal cancer), 36 with recurrent large bowel cancer, and 36 with benign diseases, including gastritis, cholecystolithiasis, and large bowel diverticulum. Lymph node metastases were positive in 56 (46.3 percent), and liver metastases were positive in 19 of 121 patients. Twenty-four of the patients had Dukes' A, 34 had Dukes' B, 38 had Dukes' C, and 25 had Dukes' D tumors.

Serum CEA was measured with radioimmunoassay kit using monoclonal antibodies (supplied by Dinabot) and CA19-9, with an enzyme immunoassay (EIA) kit (supplied by Fujirebio). Serum NCC-ST 439 was determined with "sandwich" EIA reagents (supplied by Nippon Kayaku, Tokyo, Japan) using ST-439 antibody adsorption beads and horseradish peroxidase-conjugated ST-439 antibody. The cutoff value of CEA was 5 ng/ml; that of CA19-9 was 37 U/ml; and those of NCC-ST 439 were 4.5 U/ml for all males and for females aged 50 or more years and 7.0 U/ml for females aged under 50 years.

Statistical significance was calculated using the χ^2 test. Differences were deemed significant when P was less than 0.05.

RESULTS

The following positive rates were achieved in patients with primary large bowel cancer: 27.3 percent (33/121) with NCC-ST 439, 41.3 percent (50/121) with CEA, and 26.4 percent (32/121) with CA19-9 (Table 1). The positive rates in the 36 patients with recurrent large bowel cancer were 63.9 percent with CEA, 41.7 percent with CA19-9, and 66.7 percent (24/36) with NCC-ST 439. NCC-ST 439 and CEA showed significantly higher positive rates in the patients with recurrent cancers than did CA19-9. Of the benign-disease group, only

Table 1.
Positive Serum NCC-ST 439, CEA, and CA19–9 Rates in Colorectal Carcinomas and Benign Disease

	No. of Patients	No. of Positives of Each Marker (%)		
		NCC-ST 439	CEA	CA19–9
Colorectal cancer				
Primary	121	33 (27.3%)	50 (41.3%)	32 (26.4%)
Recurrent	36	24 (66.7%)	23 (63.9%)	15 (41.7%)
Benign disease	36	2 (5.6%)	3 (8.3%)	7 (19.4%)

Table 2.
Relationship Between Lymph Node Metastasis and the Positive Rate of each Marker

	No. of Patients	No. of Positives of Each Marker (%)		
		NCC-ST 439	CEA	CA19–9
Lymph node metastasis				
Positive	56	23 (41.1%)	29 (51.8%)	25 (44.6%)
Negative	65	10 (15.4%)	21 (32.3%)	7 (10.8%)

two (5.6 percent) patients with mammary gland fibroma were positive with NCC-ST 439. On the other hand, CEA was positive in 8.3 percent, and CA19-9 was positive in 19.4 percent of the patients with benign diseases.

The relationship between nodal metastases and the positive rate of each marker was also examined (Table 2). The positive rates with NCC-ST 439, CEA, and CA19-9 in 65 patients without nodal metastases were as low as 15.4 percent, 32.3 percent, and 10.8 percent, while the rates in the patients with nodal metastases were as high as 41.1 percent, 51.8 percent, and 44.6 percent, respectively. Especially, patients with metastases to the para-aortic lymph nodes showed extremely high (83 percent) positive rates with both NCC-ST 439 and CEA.

In patients with primary large bowel cancer, positive rates with NCC-ST 439 by stage of disease were 0 percent (0/24 patients) in Dukes' A, 17.6 percent (6/34) in Dukes' B, 26.3 percent (10/38) in Dukes' C, and 68.0 percent (17/25) in Dukes' D stage (Table 3). CEA positive rates were 20.8 percent in Dukes' A, 35.3 percent in Dukes' B, 39.5 percent in Dukes' C, and 72.0 percent in Dukes' D, and CA19-9 positive rates were 8.3 percent in A, 8.8 percent in B, 34.2 percent in C, and 56.0 percent in D. The noncurative factors for the 25 Dukes' D patients comprised hepatic metastases (for 19 patients), peritoneal dissemination (for 4), and pulmonary metastases (for 2). In the 19 patients with hepatic metastases, the positive rates with NCC-ST 439, CEA, and CA19-9 were 78.9, 78.9, and 57.9 percent, respectively (Table 4).

Table 3.
Correlation of the Positive Rate of Each Marker with Dukes' Staging

Dukes' Stage	No. of Patients	No. of Positives of Each Marker (%)		
		NCC-ST 439	CEA	CA19–9
A	24	0 (0.0%)	5 (20.8%)	2 (8.3%)
B	34	6 (17.6%)	12 (35.3%)	3 (8.8%)
C	38	10 (26.3%)	15 (39.5%)	13 (34.2%)
D	25	17 (68.0%)	18 (72.0%)	14 (56.0%)

The 36 patients with recurrent large bowel cancer were classified by type of recurrence: 18 patients had hepatic metastases, 8 had pulmonary and brain metastases, 2 had peritoneal dissemination, and 8 had local or lymph node recurrence. The NCC-ST 439 and CEA positive rates in the patients with liver recurrence were high (66.7 and 61.1 percent, respectively), although the CA19-9 positive rate was modest (41.7 percent) (Table 5). Additionally, NCC-ST 439 was positive in 62.5 percent of the patients with brain or lung metastases, 50 percent of the patients with peritoneal dissemination, and 75 percent of the patients with local or nodal recurrence.

Of the 121 patients with primary large bowel cancer, only 22 (18.2 percent) were positive with all three markers. Sixty (49.6 percent) were positive with at least one marker. Among the 36 patients with recurrent cancer, 32 (88.9 percent) were pos-

Table 4.
Comparison of the Positive Rate of Each Marker with Liver Metastases

Liver Metastases	No. of Patients	No. of Positives of Each Marker (%)		
		NCC-ST 439	CEA	CA19–9
Positive	19	15 (78.9%)	15 (78.9%)	11 (57.9%)
Negative	102	18 (17.6%)	35 (34.3%)	21 (20.6%)

Table 5.
Positive Rate of Each Marker in Patients with Recurrent Large Bowel Cancers

Type of Recurrence	No. of Patients	No. of Positives of Each Marker (%)		
		NCC-ST 439	CEA	CA19–9
Hematogenous				
Liver metastases	18	12 (66.7%)	11 (61.1%)	7 (38.9%)
Lung or brain metastases	8	5 (62.5%)	5 (62.5%)	3 (37.5%)
Local or lymph node metastases	8	6 (75.0%)	5 (62.5%)	3 (37.5%)
Peritonitis carcinomatosa	2	1 (50.0%)	2 (100.0%)	2 (100.0%)

Table 6.
Combination of Test Findings in Patients with Primary and Recurrent Colorectal Cancers

	Primary Colorectal Cancer	Recurrent Colorectal Cancer
NCC-ST 439 + CEA	53/121 (43.8%)	32/36 (88.9%)
NCC-ST 439 + CA19–9	42/121 (34.7%)	27/36 (75.0%)
CEA + CA19–9	58/121 (47.9%)	25/36 (69.4%)
NCC-ST 439 + CEA + CA19–9	60/121 (49.6%)	32/36 (88.9%)

itive with the combination assay using all three markers (Table 6), and sensitivity for the combination of NCC-ST 439 and CEA was also 88.9 percent. This suggests that combination assays might be of considerably high diagnostic accuracy.

DISCUSSION

CEA has been a tumor marker and an indispensable tool in diagnosing large bowel cancer since Gold and Freedman[7] reported it in 1965. However, with recent advances in extraction techniques of tumor-associated antigens and in monoclonal antibody-manufacturing technology,[8] many other tumor markers have become available. One such tumor marker is NCC-ST 439, reported by Hirohashi *et al.*[5] This tumor marker is a monoclonal antibody obtained by using ST-4, a cell line derived from poorly differentiated stomach cancer and transplanted in nude mice, as an immunogen. ST-439 reacted with various cancers and some normal tissues including salivary glands, bronchial glands, liver cell membrane, and squamous epithelium of the esophagus. Sandwich EIA detected large amounts of NCC-ST 439 antigens in extracts of colon cancer tissues, while the antigen in normal colon mucosa was undetectable.[6] In a report on their immunohistochemical study, Watanabe *et al.*[6] stated that NCC-ST 439 reacts on large bowel tumors at a 98.8 percent rate, suggesting that NCC-ST 439 is a useful marker of large bowel tumors.

In general, a good tumor marker should have a high sensitivity and specificity but a low false positivity. The NCC-ST 439 positive rate in healthy persons was as low as 5.0 percent (47/942 subjects) according to Ohkura *et al.*[9] In our study, the CA19-9 false-positive rate in benign diseases was 19.4 percent, and the NCC-ST 439 positive rate in the patients with benign diseases was 5.6 percent. This indicates that NCC-ST 439 is a tumor marker with a higher specificity than CA19-9.

Positive serum CEA, CA19-9, and NCC-ST 439 were seen in 41.3, 26.4, and 27.3 percent of the patients with primary large bowel cancer, respectively. By stage of cancer, the NCC-ST 439 positive rate was high in Dukes' C and D (26.3 and 68.0 percent, respectively) and less than 20 percent in Dukes' A and B. This finding suggests that this marker may be of limited value in the early diagnosis of the malignancy as compared with CEA and CA19-9.

It is now believed that CEA provides a means of monitoring the malignant grade and the extent of spread of large bowel cancer and that it is useful in estimating the prognosis of the disease.[10,11] Lewi *et al.*[12] reported that estimations of preoperative CEA levels are of limited value in predicting a poor prognosis following curative resection for colorectal carcinoma. Hostetter *et al.*[13] stated that CEA did not stimulate proliferation of colorectal cancer but appeared to be a cofactor for metastasis, possibly as an adhesion factor. On the other hand, it is reported that, in cancer of the stomach, the presence of NCC-ST 439 in tissue is associated with the stage and prognosis of disease.[14] In our study, positive serum NCC-ST 439 had no bearing on histologic findings. The NCC-ST 439 positive rate in the patients with lymph node metastases was 41.1 percent, compared with 15.4 percent in those with negative nodes. The rate in the patients with liver metastases was 78.9 percent, compared with 17.6 percent in those without liver metastases. This finding suggests that NCC-ST 439, like CEA, may provide a means of monitoring the extent of spread of large bowel cancer and may become a potential marker for preoperative estimation of lymph node or liver metastases.

A variety of tumor markers are now used in the follow-up of patients who undergo curative resection for large bowel cancer. Among other things, CEA is said to be useful in the diagnosis of recurrence. Diagnostic accuracy with NCC-ST 439 in our 36 patients with recurrent cancer was 66.7 percent (24/36 patients), which was higher than with CEA and CA19-9. Especially, the NCC-ST 439 positive rate was high in patients with hematogenous metastases, including those to the liver, lung, and brain. Although the number of cases investigated was small, 75 percent of local and nodal recurrences could be detected with NCC-ST 439; hence, it was supposed that NCC-ST 439 would be more effective in diagnosing recurrence during the observation period following the operation.

We also examined the effectiveness of the combination assay for CEA, CA19-9, and NCC-ST 439. Of the patients with primary large bowel cancers, 43.3 percent could be diagnosed. The fact that serum NCC-ST 439 alone was positive in five patients and that the diagnostic accuracy of the combination assay was 88.9 percent in the 36 patients with recurrent cancer appeared to be of great clinical value.

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