Does Serum CA19-9 Play a Practical Role in the Management of Patients With Colorectal Cancer?

Shunji Morita, M.D., Ph.D., Takashi Nomura, M.D., Ph.D., Yukio Fukushima, M.D., Ph.D., Takashi Morimoto, M.D., Ph.D., Nobuaki Hiraoka, M.D., Ph.D., Nobuhiro Shibata, M.D., Ph.D.

Deparment of Surgery, Yao Municipal Hospital, Osaka, Japan

PURPOSE: CA19-9 is often used in combination with carcinoembryonic antigen to manage patients with colorectal cancer, even though there is insufficient evidence to support this use of CA19-9. Carcinoembryonic antigen, by contrast, has been regarded as a better indicator of poor prognosis and recurrence. The purpose of this study is to clarify whether CA19-9 is, in fact, a useful marker in the management of colorectal cancer patients by comparing it with carcinoembryonic antigen. METHODS: A retrospective investigation was done for a consecutive series of 155 patients with colorectal adenocarcinoma who underwent potentially curative surgery between 1995 and 1999. Excluded were patients with postoperative assays performed less than three times for either carcinoembryonic antigen or CA19-9 and those who had developed secondary cancers. Data from 118 patients were analyzed in terms of prediction of prognosis and detection of recurrences. RESULTS: The sensitivities of preoperative CA19-9 and carcinoembryonic antigen were 29.8 percent and 45.3 percent, respectively. In the univariate analysis of preoperative carcinoembryonic antigen and CA19-9 assays in 114 patients, high carcinoembryonic antigen level was significantly associated with poor prognosis (P = 0.0090 by log-rank test). We could not find a significant association between carcinoembryonic antigen and CA19-9 and those who had developed secondary cancers. Data from 118 patients were analyzed in terms of prediction of prognosis and detection of recurrences. RESULTS: The sensitivities of preoperative carcinoembryonic antigen and CA19-9 and carcinoembryonic antigen were 29.8 percent and 45.3 percent, respectively. In the univariate analysis of preoperative carcinoembryonic antigen and CA19-9 assays in 114 patients, high carcinoembryonic antigen level was significantly associated with poor prognosis (P = 0.0090 by log-rank test). We could not find a significant association between carcinoembryonic antigen and CA19-9 and those who had developed secondary cancers. Among 40 patients with recurrences, postoperative elevations of tumor markers were seen in 19 cases for CA19-9 and in 37 for carcinoembryonic antigen throughout the follow-up periods. Sensitivity, specificity, positive predictive value, and negative predictive value were 0.48, 0.88, 0.68, and 0.77, respectively, for CA19-9, and 0.93, 0.88, 0.80, and 0.96, respectively, for carcinoembryonic antigen. In patients with recurrences, the initial postoperative elevation of tumor markers was seen earlier than the detection of recurrence in 68.4 percent of those with CA19-9 elevation and in 67.6 percent of those with carcinoembryonic antigen elevation. There was only one patient with recurrence who had CA19-9 elevation without carcinoembryonic antigen elevation, while 19 recurrent patients had carcinoembryonic antigen elevation without CA19-9 elevation. Multivariate analysis showed a significant risk of carcinoembryonic antigen elevation against recurrence with an odds ratio of 32.0 (P < 0.0001), in contrast to an insignificant association of CA19-9 elevation (P = 0.23). CONCLUSION: We could not find clinical significance to support the use of CA19-9 to predict the prognosis and detect recurrence of colorectal cancer. Because of this, we do not recommend routine use of CA19-9 in staging and surveillance of colorectal cancer patients. [Key words: CA19-9; Carcinoembryonic antigen; Colorectal cancer; Screening; Surveillance; Prognosis; Recurrence]

I t remains unclear whether monitoring tumor markers brings any clinical benefit to treating patients with colorectal cancer. Guidelines for the use of tumor markers in breast and colorectal cancer have been indicated by the American Society of Clinical Oncology (ASCO). These guidelines suggest measuring carcinoembryonic antigen (CEA) levels in colorectal cancer patients during preoperative staging and postoperative surveillance for detecting liver metastases and monitoring treatment, but not for screening.
Eighty percent of surgeons in the United States use CEA routinely in the management of colorectal cancer patients.\(^2\) CEA measurement is likely the most efficient means of early detection of potentially curable recurrent diseases.\(^3,4\) Prompt detection of recurrent disease may lead to curative surgery or palliative chemotherapy, although the survival benefits of monitoring CEA still remain to be clarified.

CA19-9 is a widely used tumor marker for colorectal cancer in clinical practice. According to a nationwide surveillance study by questionnaire conducted by the Japan Research Society of the Colon and Rectum in 2002, more than 95 percent of surgeons in Japan routinely monitor CEA in follow-up of patients with colorectal cancer. More than 80 percent of surgeons also use other tumor markers, represented by CA19-9, for postoperative surveillance of colorectal cancer. The guidelines from the ASCO, however, suggest that insufficient evidence exists for using CA19-9 in management of colorectal cancer.\(^1\) Several authors have described the prognostic significance of CA19-9.\(^5-9\) There are also reports indicating the possible usefulness of CA19-9 in monitoring recurrences,\(^10-15\) whereas others have shown contradictory results.\(^16-20\) We describe a retrospective study investigating whether CA19-9 plays a significant role in the management of colorectal cancer patients in terms of prediction of prognosis and detection of recurrence.

**PATIENTS AND METHODS**

Between January 1991 and December 1999, 155 patients with histologically confirmed colorectal adenocarcinoma underwent potentially curative surgery at Yao Municipal Hospital. Because we required at least three postoperative assays to judge the postoperative elevation of tumor marker in this study, we excluded 34 patients for whom there were less than three postoperative measurements of either CA19-9 or CEA. Three patients who developed secondary cancers during the follow-up period were also excluded from study; 118 patients remained for the study. The median follow-up period was 1,476 days. There were 59 males and 59 females with a mean age of 63 ± 10 years (± standard deviation). The stage of each patient was determined according to TNM classification, yielding 34, 30, 44, and 10 patients in Stages I, II, III, and IV, respectively. Colon and rectal cancers were found in 73 and 45 patients, respectively.

During the follow-up period, 997 and 1,145 assays were done for CA19-9 and CEA, respectively. In other words, CA19-9 and CEA were measured a mean of once per 173 and 151 days, respectively.

Blood samples of the patients were sent to Otsuka Assay Laboratories (Tokushima, Japan) or Mitsubishi Kagaku Bio-Chemical Laboratories (Tokyo, Japan) and the serum concentrations of CEA and CA19-9 were determined by the immunosassays. Postoperative elevation of CA19-9 or CEA was defined as two consecutive elevations beyond the cutoff value to exclude transient elevations. During the study, the cutoff value we used for CEA was altered from 2.5 to 5.0 ng/ml when we changed the assay from an immunoradiometric assay to a chemiluminescent immunoassay. The cutoff value of CA19-9 remained the same (37 units/ml) throughout the study. We thus adopted the ratio of the measured value to the cutoff value as an index when comparing the absolute values of the tumor markers between patients or between assays.

Patients were followed up with routine examinations, including measurement of tumor markers (every 3 to 6 months), ultrasonography or computed tomographic scan (every 6 to 12 months), colonoscopy (6 to 12 months after surgery), and chest x-ray (every year). Recurrence was diagnosed from comprehensive evaluation of all medical findings, not just from the results of tumor marker assays.

Statistical analysis was performed with StatView® 5.0 (Abacus Concepts, Berkeley, CA). To compare survival between the two groups we used the Kaplan-Meier method with log-rank test. The Cox proportional hazards model was also used in a multivariate study. Comparisons of factors other than survival in the two groups were done either by chi-squared test or Student’s t-test. A P value of less than 0.05 was considered statistically significant.

**RESULTS**

Preoperative Serum Levels of CA19-9 and CEA and Prognosis

Prognostic values of preoperative measurement of CA19-9 and CEA in 114 patients were assessed. Preoperative values were not available for CA19-9 in three patients and for CEA in one patient. Preoperative markers were above the cutoff levels for CA19-9 in 34 patients (29.8 percent) and for CEA in 53 patients (45.3 percent). Patients were divided into two groups according to whether they had high (above the cutoff value) or normal preoperative levels. Prog-