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Prognostic impact of carcinoembryonic antigen and carbohydrate antigen 19-9 in stage IV colorectal cancer patients after R0 resection

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ABSTRACT

Background: Although preoperative carcinoembryonic antigen (pre-CEA) and carbohydrate antigen 19-9 (pre-CA 19-9) are reportedly prognostic indicators for colorectal cancer (CRC), the prognostic roles of postoperative CEA (post-CEA) and CA 19-9 (post-CA 19-9) shortly after surgery have not been clarified in patients with curatively resected stage IV CRC. The aim of this study was to evaluate the predictive abilities of post-CEA and post-CA 19-9.

Methods: A total of 129 consecutive patients who had stage IV CRC and underwent R0 resection were retrospectively analyzed. Pre-CEA and post-CEA and CA 19-9 levels were measured within 1 mo before and 3 mo after surgery, respectively. Relapse-free survival (RFS) and overall survival were estimated using the Kaplan–Meier method, and multivariate analysis was performed using the Cox proportional hazards model.

Results: Pre-CEA was elevated (≥5.0 ng/mL) in 73.6% of the patients and remained elevated after surgery in 32.7% of the patients. Elevated post-CA 19-9 (≥50 U/mL) was observed in 9.5% of the patients. Neither elevated pre-CEA nor elevated pre-CA 19-9 was significantly associated with RFS but both elevated post-CEA and elevated post-CA 19-9 were associated with markedly reduced RFS ($P = 0.0002$ and $P = 0.0004$, respectively). When considered in combination, post-CEA and post-CA 19-9 significantly stratified RFS and was an independent predictive factor for recurrence ($P = 0.0035$), as was lymphatic invasion ($P = 0.0015$). Post-CA 19-9 was the only evident independent predictive factor for overall survival ($P = 0.0336$).

Conclusions: In patients with stage IV CRC who underwent curative resection, the combination of post-CEA and post-CA 19-9 at 3 mo after surgery was a potent prognostic indicator for recurrence.

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Introduction

Approximately 25% of patients with colorectal cancer (CRC) have metastasis to one or more organs at the time of diagnosis.[1] Although these cases are classified as stage IV, which has the worst outcomes of all stages, complete surgical resection of both the primary lesion and distant metastases reportedly contributes to long survival times.[2] Thus, radical operations are currently performed in about one-fourth of patients with stage IV CRC,[2,3] and cases in which neoadjuvant chemotherapy enables complete resection of the metastasis are increasing alongside advances in anticancer drugs.[4] However, the recurrence rate remains higher in patients with stage IV CRC who receive complete resection than those patients with other disease stages.[5,6] Accordingly, predictions of relapse risk in these patients are important to the treatment strategy after surgery. Lymph node metastasis, peritoneal invasion, primary tumor location, and other factors have been reported to be associated with recurrence in patients with stage IV disease;[2,7] yet, no definite predictive marker for recurrence has been established because stage IV includes a wide variety of cancer statuses, ranging from solitary liver metastasis to metastasis in multiple organs.

Preoperative carcinoembryonic antigen (pre-CEA) and carbohydrate antigen 19-9 (pre-CA 19-9) are two major tumor markers for CRC.[8-10] CEA level is known to increase at the time of recurrence in many cases and is therefore used widely as a marker for postoperative surveillance in CRC.[11-13] Pre-CEA and pre-CA 19-9 elevation have associations with recurrence[7,14-19] suggesting the potential applicability of these markers as predictive factors. However, the roles of pre-CEA and pre-CA 19-9 have not been established fully in patients with stage IV disease, and the roles of CEA and CA 19-9 shortly after surgery have not been investigated previously. No study has compared the predictive abilities of these markers, as measured both preoperatively and postoperatively. Under the hypothesis that postoperative levels of these markers reflect the microscopic residual cancer and consequently may be superior to preoperative markers for predicting cancer recurrence, we investigated the prognostic impacts of CEA and CA 19-9 in patients who had stage IV disease, received curative resection, and had a high risk of recurrence.

Patients and methods

Patients

For this retrospective study, data were collected on 129 consecutive patients who had stage IV CRC with simultaneous distant metastasis, and who underwent surgical R0 resection between July 2004 and May 2014 at The University of Tokyo Hospital. Patients were excluded if they had Lynch syndrome, inflammatory bowel disease, or concomitant primary cancer in extracolic organs at the operation. All enrolled patients had synchronous distant metastasis at the time of the primary operation, and received macroscopically complete resection of the primary and metastatic cancer, as achieved by one-stage or two-stage surgery. The histopathology of each resected specimen was analyzed postoperatively, and the pathologic tumor-node-metastasis classification and staging were determined according to the classification established by the American Joint Committee on Cancer.[20] Serum CEA and CA 19-9 levels were measured within 1 mo before and at least every 1-3 mo after surgery. CEA levels $\geq$5.0 ng/mL and CA 19-9 levels $\geq$50 U/mL were defined as high CEA and high CA 19-9, respectively, according to the normal ranges of these markers at our institution. Postoperative surveillance was performed using computed tomography scans (every 6-12 mo) and colonoscopy (every 1-2 y), in addition to the measurement of CEA and CA 19-9. The study protocol was approved by the Ethics Committee of the University of Tokyo.

Statistical analysis

The associations between primary metastatic organs and tumor markers were analyzed using chi-square tests. Relapse-free survival (RFS) and overall survival (OS) were estimated using the Kaplan–Meier method and compared between groups using log-rank tests. Multivariate Cox proportional hazards analyses were also performed, including variables with $P < 0.1$ in the univariate analyses within the multivariate model. For all analyses, survival times were calculated from the date of complete resection. All statistical analyses were performed using the statistical software program JMP Pro 11.0 software (SAS Institute Inc, Cary, NC). P values < 0.05 were defined as statistically significant.

Results

The clinicopathologic characteristics of the 129 patients enrolled in the present study are summarized in Table 1. Pre-CEA levels were high in 73.6% of the patient cohort, of whom only 32.7% had CEA that remained high after surgery. High pre-CA 19-9 (32.0%) was less common than pre-CEA high and decreased to 9.5% postoperatively. Table 2 presents the associations between post-CEA, post-CA 19-9, their combination, and preoperative clinicopathologic variables. Post-CEA only showed a significant association with age, post-CA 19-9 only showed a significant association with histologic types, and double-high status showed no significant association with any of the preoperative variables. The magnitudes of pre-CEA and post-CEA levels showed no correlation ($r = 0.02698$, $P = 0.7797$; data not shown), while the magnitudes of pre-CA 19-9 and post-CA 19-9 showed a weak correlation ($r = 0.2969$, $P = 0.0022$; data not shown). In more than half (58.5%) of the patients with high pre-CEA, CEA levels normalized. Similarly, CA 19-9 normalized in most (67.7%) of the patients with high pre-CA 19-9.

The liver was the most frequent organ of metastasis (75.2%), followed by the peritoneum (16.3%) and lungs (7.8%). Metastases were resected simultaneously in 56.6% of the patients, and postoperative chemotherapy was administered to 60.5% of the patients. Table 3 presents the associations between the metastatic organs and the elevation of each tumor marker. Pre-CEA levels were high in most patients with liver metastasis (84.2%). In contrast, high pre-CEA was less