Carcinoembryonic Antigen and Albumin Predict Survival in Patients With Advanced Colon and Rectal Cancer

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Hypothesis: Patients with stage IV colon or rectal cancer at initial diagnosis have characteristics that will predict subsequent survival time.

Design: Retrospective cohort study.

Setting: Urban county teaching hospital providing tertiary care.

Patients: Patients who came to the study institution with stage IV colon or rectal cancer between 1991-1999.

Main Outcome Measure: Survival duration (days) after diagnosis.

Results: One hundred five patients were identified, with a median survival of 225 days (interquartile range, 72-688 days). Univariate analysis identified carcinoembryonic antigen (CEA) and albumin (ALB) as possible predictors for survival. Classification and regression tree analysis, a form of binary recursive partitioning, was used to identify optimal cut points for CEA (275 ng/mL) and ALB (2.7 g/dL) levels. Based on the cut points, patients were stratified into the following groups: (1) low CEA, high ALB; (2) low CEA, low ALB; (3) high CEA, high ALB; and (4) high CEA, low ALB. The median survival times for the first group and the fourth group were 287 days (interquartile range, 150-851 days) and 39 days (interquartile range, 14-168 days), respectively. A Kaplan-Meier analysis was performed, and a statistically significant difference was identified across all strata ($P = .004$). Additionally, groups 1 and 4 demonstrated the largest overall survival difference ($P < .001$).

Conclusions: Patients with stage IV colon and rectal cancer with a CEA level greater than or equal to 275 ng/mL and an ALB level less than 2.7 g/dL had a significantly shorter survival time. Conversely, patients with an ALB level greater than or equal to 2.7 g/dL and a CEA level less than 275 ng/mL had a longer survival time.

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Colon and rectal cancer is the second leading cause of death from cancer in the United States and is a significant overall health problem. It is estimated that approximately 130,000 patients were diagnosed as having colon and rectal cancer in the year 2000, and approximately 20% to 25% of patients with this disease have evidence of metastases when first diagnosed. Some patients with metastatic disease are ideally treated with aggressive surgical resection, and the survival advantage obtained by the resection of metastatic disease in selected patients has been established. It is well known, however, that patients with stage IV colon and rectal cancer display survival heterogeneity, with some patients exhibiting very short survival. With the availability of successful nonoperative therapy for complicated colon and rectal cancer, including colonic stenting and endoscopic laser therapy, more options are available for treatment. Placement of a colonic stent, for example, may completely relieve the symptoms of obstruction in some patients who would have previously been taken directly to the operating room. The decision to pursue additional therapy may then be decided in an elective manner for some patients with metastatic disease.

If patients with very short life expectancies can be identified at the time of diagnosis, they may benefit by nonoperative palliative therapy with an emphasis on a shortened hospital stay and early return home or referral for hospice care. Conversely, patients who are likely to have a higher probability of a longer survival time may benefit from more aggressive operative management, even if this includes the possibility of a more complicated hospital course. The goal of this study was to identify characteristics of pa-
METHODS

This was a retrospective cohort study conducted at Harbor–University of California–Los Angeles Medical Center, an urban, county, tertiary care teaching hospital that serves a primarily minority indigent population in southern California. Consecutive patients who came to our institution between 1991-1999 and who were diagnosed as having stage IV colon and rectal adenocarcinoma were included. Patients were excluded if they had previously been diagnosed and treated for colon and rectal adenocarcinoma elsewhere or diagnosed as having other histologic tumor types. All patients were identified and categorized using our tumor registry.

Data were collected for each patient, including age, sex, race/ethnicity, initial symptoms (weight loss, symptoms of obstruction, rectal bleeding, pain, and constipation), initial laboratory values (hematocrit and mean corpuscular volume, creatinine, prothrombin time, aspartate aminotransferase, alanine aminotransferase, albumin (ALB), total bilirubin, carcinoembryonic antigen (CEA), alkaline phosphatase, and fibrinogen), and location of the primary tumor and its metastases. Data were also collected from the patients’ hospitalization and included whether an operation was performed and, if so, the type of operation; other treatment, including chemotherapy and radiation; and the histologic and pathologic features of the tumor. Finally, follow-up and survival times were collected from the tumor registry.

All data were collected using a closed-response data collection form and entered into an electronic database. These data were then transferred into native SAS format using translational software (DBMSCopy; Conceptual Software, Houston, Tex), and statistical analyses were performed using SAS Version 8.1 (SAS Institute Inc, Cary, NC) and CART Version 4.0 (Salford-Systems, San Diego, Calif).

Descriptive analyses and univariate tests of association were performed, and the Wilcoxon rank sum test, Kruskal-Wallis test, χ² test, or the Fisher exact test was used where appropriate. Classification and regression tree (CART) analysis, a form of binary recursive partitioning, was used during the modeling process to identify optimal values of continuous variables to stratify patients into long and short survival periods. Classification and regression tree analysis is a nonparametric statistical method that is used (1) to explore data by identifying underlying relationships among groups of variables; (2) to detect important and often subtle variable interactions within complex data structures; and (3) to develop robust decision algorithms by determining an optimal method for classifying observations based on a large number of possible predictor variables. It can also be used in a simpler way, as in this study, to find optimal values for continuous variables to create the most homogeneous split within the dataset with respect to short vs long survival time. Survival analyses were performed using the Kaplan-Meier method, and log-rank tests were performed to test survival differences. This study was approved by our institutional review board and the human subjects committee.

RESULTS

One hundred five patients were identified and included. Of these, 54 (51%) were women, 33 (31%) were white, 27 (26%) were African American, 27 (26%) were Hispanic, and 18 (17%) were Asian (Table 1). The median age was 56 years (interquartile range [IQR], 44-62 years), and the median survival time for the entire group was 225 days (IQR, 72-668 days) (Table 2). Weight loss was the most common symptom on initial examination, occurring in 42 patients (40%), while 38 patients (36%) had symptoms of obstruction, 30 (28%) had lower gastrointestinal bleeding, 22 (21%) had pain, and 24 (23%) had of constipation. The patterns of metastatic disease were variable. Fifty-six patients (53%) had metastases limited to the liver, 20 patients (19%) had metastases to both the lungs and the liver, 24 patients (23%) had metastases elsewhere within the peritoneal cavity, and the remaining 5 patients (5%) had metastases confined to the lungs. Forty-two patients (40%) had primary tumors of the left colon. Thirty-two patients (30%) were found to have tumors of the right colon, and an additional 26 patients (25%) had tumors originating in
the rectum. In 5 patients (5%), the location of the primary lesion was undetermined.

During the initial hospitalization, 79 patients (75%) underwent an operation. Most of these procedures were left and right colectomies accounting for 31 (39%) and 23 (29%) of the procedures, respectively. Six (8%) total colectomies were performed, and 10 patients (10%) underwent surgery with an attempt for cure, representing 13% of the operations. An additional 14 laparotomies without major resection (17%) occurred. Five procedures (6%) involved local transanal tumor excision. Additionally, 2 patients (2%) were treated with colonic stenting, and an additional 2 patients (2%) underwent endoscopic laser treatment. Forty-five patients (46%) were subsequently treated with chemotherapy for their metastatic disease, and 18 patients received radiation therapy.

Results of pathologic examination were available for 86 patients (82%). Twenty-nine patients (28%) had G1, or well-differentiated adenocarcinomas, while 38 patients (36%) had G2, or moderately differentiated tumors. Nineteen patients (18%) had G3, or poorly differentiated tumors, and signet ring was noted in 4 patients (4%) on histologic analysis.

Survival duration was divided into “long” and “short” groups based on a survival length of 120 days. Univariate testing was performed on all possible predictive variables (Table 3). Alkaline phosphatase, aspartate aminotransferase, total bilirubin, CEA, and ALB were identified as statistically significantly associated with survival. Optimal values for each of these predictor variables were analyzed by CART analysis to predict long or short survival time. Based on this modeling technique, CEA and ALB levels were identified as the best predictors of survival. Based on these cut points, patients were stratified into the following 4 groups based on a CEA level of 275 ng/mL and an ALB level of 2.7 g/dL: (1) low CEA, high ALB; (2) low CEA, low ALB; (3) high CEA, high ALB; and (4) high CEA, low ALB (Tables 1 and 2). All patients were used to generate the CEA and ALB levels, but only 91 patients had values for both CEA and ALB, and were thus stratified. In this group of patients, there were 10 patients (10%) resected with curative intent. Seven (7%) had a CEA level less than 275 ng/mL and an ALB level greater than or equal to 2.7 g/dL. No significant difference in survival was identified when the patients were stratified based on the goal of the operation (P = .3). For this reason, these patients were not excluded from the analysis.

### Table 2. CEA Level, ALB Level, and Survival Time by Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1* (n = 45)</th>
<th>Group 2† (n = 20)</th>
<th>Group 3‡ (n = 14)</th>
<th>Group 4§ (n = 12)</th>
<th>Total (n = 105)††</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA, median (IQR), ng/mL</td>
<td>21 (8-54)</td>
<td>14 (4-75)</td>
<td>953 (606-1860)</td>
<td>2763 (1768-4630)</td>
<td>52 (11-582)</td>
</tr>
<tr>
<td>ALB, median (IQR), g/dL</td>
<td>3.3 (2.8-3.7)</td>
<td>2.4 (2.3-2.5)</td>
<td>3.1 (2.9-3.5)</td>
<td>2.2 (1.9-2.3)</td>
<td>2.8 (2.5-3.5)</td>
</tr>
<tr>
<td>No. of survival days (IQR)</td>
<td>287 (150-851)</td>
<td>277 (66-706)</td>
<td>279 (124-376)</td>
<td>39 (14-168)</td>
<td>225 (72-688)</td>
</tr>
</tbody>
</table>

Abbreviations: ALB, albumin; CEA, carcinoembryonic antigen; IQR, interquartile range.

*ALB ≤ 2.7 g/dL and CEA < 275 ng/mL.
†ALB ≤ 2.7 g/dL and CEA ≥ 275 ng/mL.
‡ALB ≤ 2.7 g/dL and CEA ≤ 275 ng/mL.
§ALB > 2.7 g/dL and CEA ≥ 275 ng/mL.
††The total number of patients studied was 105, but only patients with both ALB and CEA levels were stratified, the total number of patients was 91.

### Table 3. Univariate Statistics for Continuous Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short†</td>
</tr>
<tr>
<td>Age, y</td>
<td>59 (49-63)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>329 (130-538)</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>75 (30-119)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>1.0 (0.6-2.0)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>2.5 (2.2-3.0)</td>
</tr>
<tr>
<td>Carcinoembryonic antigen, ng/mL</td>
<td>338 (15-2245)</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>38 (25-58)</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>13 (12.6-14)</td>
</tr>
<tr>
<td>Mean corpuscular volume, f/L</td>
<td>82 (70-89)</td>
</tr>
<tr>
<td>Fibrinogen, g/dL</td>
<td>342 (233-591)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>34 (28-41)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9 (0.7-1.1)</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert total bilirubin to micromoles per liter, multiply by 17.1; creatinine to micromoles per liter, multiply by 88.4; fibrinogen to micromoles per liter, multiply by 29.41.

*Data are given as median (interquartile range) unless otherwise indicated.
†Survival time of fewer than 120 days.
‡Survival time of greater than 120 days.
The median survival times for group 1 and group 4 were 287 days (IQR, 150-851 days) and 39 days (IQR, 14-168 days), respectively. Group 2 and group 3 demonstrated intermediate survival times of 277 days (IQR, 66-277 days) and 279 days (IQR, 124-376 days), respectively (Table 2). A statistically significant difference was identified across all strata after survival analysis (Figure) \( (P = .004) \). The largest overall survival difference was demonstrated between group 1 and group 4 \( (P < .001) \) (Table 4). Survival at 6 months was only 25% (95% confidence interval [CI], 0%-50%) for patients in group 4 compared with a 6-month survival of 64% (95% CI, 39%-89%), 63% (95% CI, 41%-83%), and 66% (95% CI, 50%-80%) for those in groups 3, 2, and 1, respectively.

This study evaluated patients with advanced colon and rectal cancer in an attempt to identify characteristics present on admission that could stratify a patient’s survival into distinct categories. As nonoperative interventions become increasingly available to the practitioner, predicting an estimated survival duration for the patient with metastatic disease may be important for making the right decision between operative and nonoperative palliative procedures. Our study found a significantly shorter survival time in patients with high CEA and low ALB levels.

Previous studies have focused on stratifying patients with metastatic colon or rectal cancer based on prognosis. A study from the University of Chicago identified 120 patients with stage IV colon and rectal cancer who underwent laparotomy. This study attempted to delineate factors associated with decreased survival to select patients who would benefit most from a more aggressive approach. The authors showed that patients older than 65 years or those who exhibited carcinomatosis or extensive bilobar involvement of the liver had a poorer prognosis. They reported a median survival of 14 months, but included only patients who underwent laparotomy. This may reflect a selection bias, as some patients with a very poor prognosis were likely excluded. This report supported results from prior studies that showed a benefit from the resection of metastatic disease in selected patients. The discussion section of this article also articulated the need to identify a subset of patients with limited survival time. Patients who had greater than 50% of their livers replaced with cancer and those with more poorly differentiated tumors were found to have a significantly shorter survival time in an additional review of patients with incurable colon cancer by Liu et al.12

Carcinoembryonic antigen is a family of related glycoproteins first isolated in 1965. Elevated plasma levels of CEA have been shown to be associated with a number of malignancies, including those in the colon and rectum, breast, pancreas, and lung. Despite this relationship, CEA has not proven useful in the screening of asymptomatic individuals because of its low sensitivity and specificity. Current clinical use of CEA has been largely confined to surveillance after colon and rectal cancer resection to allow early identification of recurrence. Levels of CEA at the time of diagnosis have been shown to be associated with survival of patients with colon and rectal cancer in a number of retrospective studies.13-17

<table>
<thead>
<tr>
<th>Group</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (high albumin†, low CEA‡) vs 4 (low albumin§, high CEA¶)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 (low albumin, low CEA) vs 4 (low albumin, high CEA)</td>
<td>.02</td>
</tr>
<tr>
<td>3 (high albumin, high CEA) vs 4 (low albumin, high CEA)</td>
<td>.04</td>
</tr>
<tr>
<td>1 (high albumin, low CEA) vs 3 (high albumin, high CEA)</td>
<td>.06</td>
</tr>
<tr>
<td>2 (low albumin, low CEA) vs 3 (high albumin, high CEA)</td>
<td>.58</td>
</tr>
<tr>
<td>1 (high albumin, low CEA) vs 2 (low albumin, low CEA)</td>
<td>.69</td>
</tr>
</tbody>
</table>

*No Bonferroni correction was made.
†‡>2.7 g/dL.
§=275 ng/mL.
¶≤275 ng/mL.

Harrison et al15 from Memorial Sloan-Kettering examined 572 patients with node-negative colon cancer. They found a significant association between preoperative CEA level and survival on review of a prospectively maintained database in which all patients underwent a curative resection. Patients were stratified by CEA levels of 5 ng/mL, 10 ng/mL, and 20 ng/mL, and all of the cutoffs above 5 ng/mL predicted a poor outcome. Multivariate analysis demonstrated a relationship between overall stage and preoperative CEA level; however, patients with stage III and IV disease were not included in this study. Preoperative CEA level was found to be an independent prognostic factor in another study that examined 218 patients who underwent potentially curative operations for colon and rectal cancer.16 Last, a study from Korea17 analyzed more than 2000 patients and found that preoperative CEA level had a statistically significant relationship with survival among all patients, including those with metastatic disease who were undergoing surgery for colon and rectal cancer. When CEA levels were measured in patients with all stages of colon and rectal cancer, patients with metastatic disease were found to have higher levels of CEA when compared with patients with lesser disease.18 A mean level of 102 ng/mL...
was reported for patients with Dukes stage D colon cancer compared with 23 ng/mL, 6 ng/mL, and 4 ng/mL for patients with stage C, B, and A colon cancer, respectively.

Our study, looking only at patients with stage IV disease, used a CEA cutoff point of 275 ng/mL, which is comparatively high. The median CEA level was 52 ng/mL (IQR, 11-582 ng/mL) for all patients in our study, and it is likely that the higher CEA level seen in the patients in group 4 reflects a larger overall tumor burden. Patients in group 3 also demonstrated an elevated CEA level, although the median CEA level in this group was somewhat lower than that in group 4. The median survival in this group, however, was much greater than that seen in group 4. The difference between these groups was their ALB levels, with median ALB levels of 3.1 g/dL and 2.2 g/dL for group 3 and 4, respectively.

Serum ALB levels have recently been studied in a group of male patients with locally advanced or metastatic cancer.20 The investigators examined 40 patients with a variety of cancers, including esophagus, stomach, pancreas, colon and, non-small cell lung cancer. Levels of ALB were found to be correlated with percentage of ideal body weight and extent of reported weight loss. This study purports that the rate of ALB synthesis has been shown to be the same in cancer patients as in healthy patients. An explanation for the hypoalbuminemia seen in cancer patients with cachexia, proposed by these authors, is that lower levels of ALB are indicative of an ongoing systemic response that causes the loss of these proteins. A statistically significant inverse relationship between C-reactive protein, an acute-phase protein, and level of ALB was identified in these patients, lending support to this theory.

This may help to explain why low ALB levels, when combined with high CEA levels, were associated with a significantly decreased survival time in our study patients. Patients in group 4 likely had a higher degree of tumor burden as reflected by their high CEA levels. A low ALB level, at the very least, likely reflects some type of systemic compromise. Whether this is specifically from an activation of the systemic inflammatory response system or a result of nutritional depletion secondary to the existence of a metabolically active tumor is not known.

Appropriate treatment of patients with stage IV colon and rectal cancer may optimize survival time and quality of life. Patients who have minimal disease and favorable prognostic features, possibly including low CEA and high ALB levels, may warrant aggressive surgical resection both for cure and in some cases, palliation. Colon and rectal cancer is a somewhat atypical oncologic disease where radical surgery may be justified for palliation in selected patients.20 This selection of patients should be based largely on the potential for a longer survival time, as it would be unfortunate to perform radical surgery for palliation on a patient with a very short survival time. Patients with significant tumor burden and expected short survival time, possibly as reflected by high CEA and low ALB levels, may be more appropriately considered for more conservative operative therapy or nonoperative management. Patients with short expected survival durations may also benefit from earlier hospice referrals.

A significant survival difference was demonstrated when our patients were stratified based on initial CEA and ALB levels. Patients with CEA levels greater than or equal to 275 ng/mL and ALB levels less than 2.7 g/dL exhibited significantly decreased survival times. Our study was limited by the number of patients within each group; an evaluation of the predictive value of CEA and ALB in a larger population may be warranted. These data may aid the physician in determining the appropriate counseling and optimal treatment for patients with advanced colon and rectal cancer.

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REFERENCES