Identification of Patients with High-risk Lymph Node-negative Colorectal Cancer and Potential Benefit from Adjuvant Chemotherapy

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Background: Adjuvant chemotherapy is not indicated in lymph node-negative colorectal adenocarcinoma (CRC), even though some cases will present recurrent disease. It is important to identify a subgroup of patients with the highest risk of relapse because of the potential benefit of adjuvant chemotherapy. The objective of this study is to define the prognostic factors and describe a method for the selection of this subgroup.

Methods: A retrospective cohort of 124 patients with lymph node-negative CRC with complete surgical resection was studied. Cox’s proportional hazards model was used to define the prognostic factors associated with CRC-related survival and to develop a method for prediction of recurrence probability.

Results: The cohort included 62 women and 62 men with mean age 55.8 years. The mean follow-up period was 11.7 years. T classification of the primary tumor, differentiation grade, carcinoembryonic antigen level, gender and the presence of neural invasion were significant prognostic factors according to the multivariate analysis (final model P = 0.00001). Using risk ratios for these prognostic factors, we defined a high-risk group of 78 patients and a low-risk group of 46 patients with 24 and 5 recurrences, respectively (recurrence rates of 30.8% and 10.9% respectively, P = 0.011).

Conclusions: Using these factors, a prognostic scale was developed to predict high risk of recurrence in cases of completely resected CRC and to identify them as a subgroup of patients with potential benefit of adjuvant chemotherapy.

Key words: colorectal adenocarcinoma – adjuvant chemotherapy – lymph node-negative – recurrent disease – prognostic factors

INTRODUCTION

The occurrence of colorectal carcinoma (CRC) is common in Western developed countries, but less frequent in developing countries (1). It ranks second among gastrointestinal malignancies in Mexico, after gastric carcinoma, and the mortality rates have shown an increasing trend during the last few decades (2,3).

Radical surgical resection is the only known curative treatment for CRC (4). However, approximately 30% of all resected patients present with a relapse and eventually die. The probability of recurrence and survival after complete resection is dependent on the most important prognostic factors: depth of invasion in the bowel wall and lymph node metastases (4).

Adjuvant treatments have been reported to increase the probability of cure in surgically treated patients with high risk of recurrence (5). Recent randomized controlled trials evaluating adjuvant chemotherapy in CRC have shown reduced recurrence rates and survival benefit in patients with lymph node metastases (6,7). However, there is no consistent evidence that adjuvant chemotherapy is associated with overall improved survival compared with surgery alone in patients with lymph node-negative CRC (8).

Although complications such as bowel perforation, bowel obstruction or invasion of adjacent organs may be markers for high probability of recurrence, this has not been definitely proved. These factors can be used to select patients who may benefit from adjuvant chemotherapy; however, the treatment is
not routinely applied even in cases of important subgroups that eventually present with recurrent disease (8).

The aim of the present study is to define the clinical predictive factors of recurrence and survival in patients with lymph node-negative CRC after radical resection, and to develop a practical multivariate method for the clinical selection of patients with high probability of recurrence, who may be potential candidates for adjuvant chemotherapy.

SUBJECTS AND METHODS

A retrospective cohort study of patients with colon and rectal adenocarcinoma treated at the Instituto Nacional de Cancerología in Mexico City from January 1983 to December 1998 was performed. The inclusion criteria were—subjects of any age and sex, with an endoscopic and histopathological diagnosis of colorectal adenocarcinoma, complete surgical resection (no residual disease: R0) performed at the Institute and complete pathological study of the resected specimen.

The 1997 version of the Tumor–Node–Metastasis staging system of the American Joint Committee on Cancer (TNM-AJCC) was used in the study (9). Only patients with stage I (T1,2, N0, M0) or II (T3,4, N0, M0) were included in the database.

Patients with anal margin tumors and/or histopathology different from that of adenocarcinoma were not included in the study.

Hospital charts were reviewed and clinical variables were recorded. A prospective review of histopathological slides of all lymph nodes and surgical specimens was performed blindly by two pathologists. Lymph node-negative status was defined by the absence of neoplastic cells in one slide stained with hematoxylin and eosin per lymph node. The slide review included confirmation of adenocarcinoma, the depth of invasion through the bowel wall, differentiation degree, presence of vascular invasion that was either venous or lymphatic, presence of neural invasion and confirmation of the lymph node-negative status following the standard recommendations (10).

STATISTICAL ANALYSIS

Univariate analyses using the chi-square test and Kaplan–Meier method were performed with the purpose of selecting those variables associated with recurrence and survival. Survival curves were constructed using the Kaplan–Meier method (11), and the differences were compared using the log-rank method. Follow-up was calculated from the first postoperative day to the last visit recorded in the charts or until CRC-related death. Censored patients were those lost during follow-up and those who died by causes other than CRC. The patients who were lost to follow-up were located and interviewed on phone.

Univariate Cox’s proportional hazards (CPH) models were fitted in order to select those variables that are associated with CRC-related survival.

The independent variables used in the analyses were age, sex (female 0, male 1), tumor location (colon 0, rectum 1), tumor perforation (no 0, yes 1), bowel obstruction (no 0, yes 1), perioperative transfusion (no 0, yes 1), hemoglobin level, basal serum albumin level, absolute lymphocyte count, preoperative carcinoembryonic antigen (CEA) (≤ 2.9 ng/ml 0, ≥ 3 ng/ml 1), differentiation grade of the tumor (well 1, moderately 2, poorly 3), T classification (1, 2, 3, 4), tumor size (product of two major diameters in cm²), venous invasion (no 0, yes 1), lymphatic invasion (no 0, yes 1) and neural invasion (no 0, yes 1).
The selection of CEA cut-off point was defined as 3 ng/ml by receiver operating characteristic analysis, using the absence or presence of recurrent disease as the dependent variable.

The independent variables with a probability of 0.2 or less in univariate analysis were used in the multivariate models. Risk ratios (RR) with 95% confidence intervals (CI) were calculated as a measure of association using the CPH model (12). Multivariate model selection was performed using Akaike’s information criterion (AIC). We checked the assumptions of proportionality of hazards using the proposed tests (13).

SPSS version 10 (1999) software (SPSS, Inc., Chicago, IL, USA) and Splus2000 (Math Soft, Inc., Seattle, WA, USA) were used for the computations.

RESULTS

A total of 124 patients were studied (62 women and 62 men) with mean age of 55.8 years (SD 14.9). Seventy-nine patients (63.7%) suffered from colon carcinoma and 45 (36.3%) from rectal carcinoma.

Surgical resections performed were right and right-extended colectomy in 45 cases (36.3%), left colectomy in 14 (11.3%), anterior and anterior-low resection of recto-sigmoid in 23 (18.5%) and abdominoperineal resection in 42 (33.9%). Operative morbidity was recorded in 36 cases (29%) with no operative mortality.

Thirty-six (80%) patients with rectal cancer received adjuvant pelvic radiotherapy and eight received 5-fluorouracil as a sensibilisation agent.

Only 29 patients (23.4%) presented recurrence during the follow-up period of this study. Location in the colon was associated with 16 recurrences (20.3%) and location in the rectum with 13 recurrences (28.9%) (non-significant difference [NSD]). Locoregional, distant or both recurrences were recorded in 8, 5 and 3 patients with colon carcinoma and 8, 3 and 2 patients with rectal carcinoma, respectively (NSD).

Table 1 shows the association between independent variables and recurrence. Other variables (tumor size, tumor perforation, bowel obstruction, lymphocyte count and hemoglobin level) did not show significant association with the event of recurrence or CRC-related death and were not considered for further analysis.

Median preoperative CEA in patients without and with recurrence was 3.2 and 8.8 ng/ml, respectively ($P = 0.038$).
The mean follow-up period of the cohort was 11.7 years (range 10.4–13; 95% CI). The 5- and 10-year survival for the group with recurrence were 34.1% and 0%, respectively; those for the group without recurrence were both 100% (P = 0.00001).

Patients with T1, T2, T3 and T4 disease presented 100%, 87.8%, 68.2% and 34.8% 10-year survival rates, respectively. Figure 1 depicts the survival curves by T classification, differentiation degree, CEA and neural invasion.

Table 2 shows the 5-year survival rates and mean survival times by prognostic factor (by T classification, by differentiation degree, by gender, by neural invasion and by preoperative CEA). Other non-significant factors were omitted.

In the multivariate analyses of variables shown in Tables 1 and 2, prognostic factors that significantly predict the event of time to the CRC-related death were T classification, differentiation degree, preoperative CEA, sex and presence of neural invasion. The final model presented a log likelihood (LL) of 185.96 (P < 0.0001), and estimators are depicted in Table 3. These variables were also tested for interaction effects and found non-significant. Adjustment for location on the colon or rectum had no significant effect on the results of the final model.

Using the RR for these prognostic factors (Table 3), we defined a high-risk group of 78 patients which included patients with T4 tumors, those with T3 tumors and poor differentiation and those with T3 tumors plus moderate differentiation and any of the minor prognostic factors (females, neural invasion and CEA ≥ 3 ng/ml). All other patients (46 cases) represented the low-risk group. Survival curves for the high-risk group compared to those of the low-risk group are shown in Fig. 2.

The low- and high-risk groups presented 5 and 24 recurrences, respectively (10.9% and 30.8% recurrence rates respectively; P = 0.011).

**DISCUSSION**

CRC is a treatable and often curable disease (1,4). Surgery is the only curative treatment, but it is frequently complicated by recurrence depending on two major prognostic factors: the level of invasion of the tumor through the bowel wall and the presence of lymph node metastases.

It is widely accepted that adjuvant chemotherapy increases the probability of cure in surgically treated patients with positive lymph nodes (7).

Although subgroups of patients with stage II colon cancer may be at a higher risk of recurrence, there is no consistent evidence that adjuvant 5-fluorouracil-based chemotherapy is associated with overall improved survival compared with surgery alone (8). Thus, it is very important to define which group of patients with lymph node-negative CRC may benefit from adjuvant chemotherapy.
The inability to detect a survival advantage of patients with lymph node-negative CRC after adjuvant chemotherapy in randomized clinical trials is due to the low recurrence rate. Therefore, the sample size required to detect subtle survival differences is extremely large, because most of the patients will have good outcome and will not receive the benefit. A randomized clinical trial including only patients with node-negative CRC and high probability of recurrence will require a smaller sample size to detect such survival differences.

In this study, we describe a cohort of 124 patients with lymph node-negative CRC in an attempt to define prognostic factors for the selection of this subgroup.

We found an overall recurrence rate of 23.4%, which constitutes an extremely high rate for a group of patients with lymph node-negative CRC, contrasting with the recurrence rate of 7.3% reported in the Memorial Sloan-Kettering Cancer Center (14). A possible explanation for this might be a varied prevalence of prognostic factors. T1 and T2 stages were more prevalent in Harrison’s series; however, we report more cases in T3 and T4 stage and we also have a longer follow-up time.

While most reports include only patients in stage II CRC, in this study we investigated the prognostic factors in lymph node-negative CRC stages I and II.

The reason for including patients with T1 and T2 disease (with lower probability of recurrence), apart from having more patients for the multivariate analysis, was to obtain a clear dose–response effect on the most important known prognostic factor (Tables 1 and 2). Every study aiming to describe prognostic factors requires adjustment to definitely proven predictive factors such as T classification.

Many reports describe clinical, biochemical, pathological and molecular markers that predict recurrence and can be used to identify patients with high-risk stage II CRC (14, 15, 16, 17, 18, 19, 20, 21 and 22).

Male gender, bowel obstruction, pericolic organ invasion and less than 14 uninvolved nodes in a surgical specimen were identified as poor prognostic markers in stage II CRC (15). In another report, several clinical and histological factors did not predict outcome in lymph node-negative colon cancer patients. However, TNM stage and preoperative CEA predicted survival by multivariate analysis and identified a subgroup of patients with poor prognosis, who could benefit from adjuvant treatment (14). This cohort study of 572 cases with T1-4 colon carcinoma had a relatively short follow-up period, with a median of 35 months (14). We also found an important association between T classification and preoperative CEA level with the event of recurrence or survival.

The detection of micrometastases in lymph nodes has been reported to identify patients with stage II CRC at a high risk of recurrence. In a study of 192 lymph nodes from 26 patients with stage II CRC, using a CEA-specific nested reverse-transcriptase polymerase chain reaction, a correlation was found between the presence of micrometastases and survival (16). These results have been supported by other authors (17). In addition, the number of micrometastases detected by immunohistochemistry and the level of affected lymph nodes have been associated with recurrence (18).

Conversely, a report of 900 lymph nodes from 55 patients with stage II colon carcinoma stated that nodal micrometastases detected by immunohistochemical staining with cyto-
keratin were not useful for identifying stage II patients at higher risk of relapse (19).

A variety of molecular markers have been studied in CRC. However, only some of them correlated with survival in Dukes B stage patients (20,21,22).

These studies have common disadvantages: small sample size, short follow-up period and lack of statistical adjustment with the T classification and other important histopathological and clinical factors.

Recently, the concept of high-risk stage II CRC has been used in the design of randomized phase III trials. This concept is based on classical clinical criteria (invasion of adjacent organs or perforation), which have not been definitely validated by scientific observations (23).

In the present study, we have described five prognostic factors that can be used to calculate the risk of recurrent disease and survival in CRC. We propose a gradation system for selecting patients with higher probability of recurrence.

On the basis of the risk ratios derived from our data, we determined T classification and differentiation grade as major prognostic factors. Preoperative CEA level (3 ng/ml or more), sex (females) and neural invasion represent minor factors.

The highest risk corresponds to patients with the following criteria: 1) T4 tumors associated or not with the presence of other prognostic factors, 2) T3 and poorly differentiated tumors and 3) T3 with moderate differentiation plus any one of three minor prognostic factors. It is probable that T1 and T2 disease corresponds to low risk even in the presence of other prognostic factors.

This simple method should be validated in different cohorts of patients with stage I and II CRC to be used prospectively. Only after that, patients who are enrolled in randomized clinical trials designed to evaluate adjuvant chemotherapy for node-negative CRC should be selected based on this strategy.

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References