Lymphangiosis as a Predictor of Outcome in Patients With Primary Diffusely Infiltrative Adenocarcinoma of the Colon and Rectum

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**Objective:** To investigate the relationships between outcome and clinicopathological factors, DNA flow cytometrical characteristics, and postoperative adjuvant therapy in patients with primary diffusely infiltrative colorectal adenocarcinoma.

**Design:** Inception cohort study.

**Setting:** A medical center that offers a mixture of primary, secondary, and tertiary care services.

**Patients:** Among 7035 patients undergoing resection of primary colorectal adenocarcinoma from 1980 to 1996, 37 patients with a pathological diagnosis of primary diffusely infiltrative tumor were selected. All patients had received regular follow-up until February 28, 1998, or until death.

**Main Outcome Measures:** Cancer-specific survival compared by log-rank test and Cox regression model.

**Results:** Univariate analyses revealed tumor stage (stages II-III vs stage IV, \( P = .01 \)) and severity of lymphangiosis (absent/mild vs moderate/severe, \( P = .04 \)) were significant in predicting outcome. A proliferative index of greater than 20% was insignificant (\( P = .08 \)) in predicting outcome. In a Cox regression model, TNM stage and lymphangiosis were independently correlated with a worse outcome. When compared with tumors having less severe lymphangiosis, the odds ratio of death due to cancer in cases of tumors with moderate to severe lymphangiosis was 2.4 (95% confidence interval, 1.0-5.6; \( P = .05 \)).

**Conclusion:** Lymphangiosis and TNM stage were independently predictive of outcome in patients with primary diffusely infiltrative colorectal cancer.


**DIFFUSELY INFILTRATIVE carcinoma mainly spreads beneath the mucosal layer, produces minimal mucosal alterations, and transforms the affected organ into a rigid, contracted tubular structure.** The terms **liminitis plastica**\(^2\) and **scirrhous carcinoma**\(^10,12\) are used interchangeably to describe the same type of disease. Laufman and Saphir\(^2\) first described this type of disease in the colon in 1951. Although diffusely infiltrative carcinoma was originally believed to mainly consist of poorly differentiated or signet ring cell carcinoma, moderate to moderately differentiated tumor has been reported.\(^5,13\) Because of the relative mucosal sparing and varied histologic pattern, diagnosis is based on exclusion of metastasis from cancer of other organs and on its characteristic morphologic appearance. The prognosis of patients with diffusely infiltrative carcinoma is generally reported to be poor.\(^3,13\) Nevertheless, the association between the prognosis of patients and variable factors, including clinicopathological factors, DNA flow cytometrical variables, and postoperative adjuvant therapy, is unknown. This study sought to assess whether any clinicopathological factors, DNA flow cytometrical variables, or postoperative adjuvant therapy correlate with outcome in patients with diffusely infiltrative carcinoma.

**RESULTS**

**CLINICAL FINDINGS**

Among 7035 cases of primary colorectal carcinoma, 37 (0.53%) were of the primary diffusely infiltrative type. Twenty patients (54.1%) were female. The average age at diagnosis was 48.1 years (SD, 18.4 years). Eighteen tumors (48.6%) were located in the rectum. All 37 patients had at least 1 of the following complaints: diarrhea, changes in bowel habits, abdominal pain, or rectal bleeding. None of the 37 patients had a history of chronic ulcerative colitis.
PATIENTS AND METHODS

PATIENTS

A total of 7035 patients underwent resection of primary colorectal adenocarcinoma at Chang Gung Memorial Hospital, Taipei, Taiwan, a privately run medical center, from 1980 to 1996. Thirty-seven of these patients (those with a histologic diagnosis of primary diffusely infiltrative tumor) were selected for study. Signet ring cell rectal adenocarcinoma that was initially suspected to be metastatic was diagnosed in 3 of these patients after vigorous surveillance failed to find another primary origin. Paraffin-embedded tissue blocks of resected specimens from each of the 37 cases were used for DNA analysis and were re-examined by a pathologist (without knowledge of clinical data) to determine pathological features, including histologic grade,14 presence of intracellular or extracellular mucin, resection margin, involvement of lymph nodes, lymphangiosis, and TNM stage.15 Lymphangiosis was scored as negative, mild, moderate, or severe.15 An average of 10 slides were examined per tumor. Clinical and demographic data including tumor location, sex, age, symptoms, and status of follow-up were obtained from medical records and/or the Registry of Colorectal Cancer, Chang Gung Memorial Hospital. Hematogenous spread at diagnosis included metastasis to liver, lung, bone, or peritoneum. Tumors with a lower edge within 15 cm of the anal verge were designated as rectal.

Radiotherapy and/or fluorouracil-based chemotherapy had been performed within 4 to 6 weeks of resection. All patients had received regular follow-up with serum carcinoembryonic antigen testing, physical examinations every 3 to 6 months, annual chest x-ray, abdominal computed tomography (or sonography of liver), and colonoscopic examinations until February 28, 1998, or until death. Cancer-related death was defined as death due to metastatic disease or treatment of the disease.

DNA FLOW CYTOMETRY

DNA flow cytometrical analysis was performed as previously described.16 The prepared tissue samples were analyzed with a FACS Analyzer (Becton Dickinson, San Jose, Calif). A DNA histogram was generated using a computer with CellFIT Cell-Cycle Analysis software (Version 2.02; Becton Dickinson). The nondiploid histogram included aneuploid and tetraploid histograms. A high proliferative index was defined as 20% or more nuclei in the S and G2M phases. An unfavorable cell kinetic profile included nondiploid histograms and histograms with a high proliferative index.17

STATISTICAL ANALYSIS

Differences in the clinicopathological variables were compared in 2 groups using the Student t, χ2, or Fisher exact test. Survival curves were constructed by the Kaplan-Meier method18 and were compared by the log-rank test.19 A 95% confidence interval (CI) was obtained using the Greenwood formula.20 Survival time was measured in months. The Cox multiple regression analysis was used to adjust simultaneously for all covariates.21 The end point was cancer-related death (cancer-specific survival). The survival time was 0 months for postoperative death. The type I error was set at 0.05. All analyses were performed using the statistical package SPSS for Windows, release 6.0 (SPSS Inc, Chicago, Ill).

PATHOLOGICAL FEATURES

Macroscopically, all the 37 lesions showed a palpable appearance with a stenotic lumen and a rigid, thickened wall in the long segment. The average tumor size was 8.3 cm (SD, 2.3 cm; range, 5-15 cm) in axial length and 4.1 cm (SD, 1.1 cm; range, 2-7 cm) in transverse length. The ratio of axial to transverse length was 2.2 (SD, 0.8; range, 1-5). Nineteen tumors had a flattened and finely granular mucosal surface with tiny diffuse ulcerations or a cobblestone, edematous mucosa without obvious ulceration. The mucosa was spared from tumor involvement. Eighteen tumors had a single ulcer that varied in size (ranging from 1-4 cm in the axial length), usually located in the center of the lesion. The margins of these ulcers were not elevated. Their remaining peripheral portions were covered by intact, atrophic, or edematous mucosa. Diffuse infiltration through all layers of the wall with sparing of the mucosal layer and into the surrounding tissues was observed in all cases. Microscopically, cancer cells were composed of moderately to poorly differentiated cells. Twenty-one patients (57%) had intracellular (signet ring cell) or extracellular mucin-producing tumors. Eighteen (49%) tumors had moderate to severe lymphangiosis (Figure 1). Frequently, overlying mucosa of the lesion was not involved by tumor cells (Figure 2).

SURVIVAL ANALYSIS

Three patients (8.1%) had stage II tumors (2 with transmural invasion and 1 with contiguous organ involvement), 7 (18.9%) had stage III tumors, and 27 (73.0%) had stage IV tumors. One patient died of sepsis 2 weeks after surgery. The overall median cancer-specific survival time was 12 months (SE, 1 month; 95% CI, 11-13 months). Univariate analyses (Table) revealed tumor stage (stages II-III vs stage IV, P=.01) and severity of lymphangiosis (absent/mild vs moderate/severe, P=.04; Figure 3) were significant in predicting outcome. Proliferative index (low vs high, P=.08) was not correlated with prediction of outcome. All 3 of these variables were entered into the Cox regression model. Stage IV tumor and moderate to severe lymphangiosis were associated with a worse outcome. When compared with tumor stages II to III, the odds ratio of death from cancer for stage IV was 3.9 (93% CI, 1.4-10.6; P=.007). When compared with tumors of less severe lymphangiosis, the odds ratio of death from cancer in cases of tumors with moderate to severe lymphangiosis was 2.4 (95% CI, 1.0-5.6; P=.05).

Of 19 patients with colon tumor, 18 had data regarding the status of chemotherapy. Eleven had received chemotherapy while 7 had not. The outcome was not related to the adjuvant therapy. The respective me-
Median survival was 13 months (95% CI, 8-18 months) for patients who received chemotherapy and 14 months (95% CI, 8-20 months) for those who did not ($P=.86$). Of 18 patients with rectal cancer, 7 (including 1 postoperative death) had no adjuvant therapy, 6 had single-modality chemotherapy, 2 had single-modality radiotherapy, and 3 had combined chemotherapy and radiotherapy. Chemotherapy (with or without radiotherapy) was associated with a longer survival time ($P=.007$). The median survival was 14 months (95% CI, 5-23 months) for patients who received chemotherapy and 6 months (95% CI, 4-8 months) for those who did not. Radiotherapy was not associated with a better outcome. The respective median survival for patients with radiotherapy and those without was 14 and 10 months ($P=.83$). The survival times for the 3 patients who received combined chemotherapy and radiotherapy was 14, 30, and 72 months, respectively. Six of 9 patients with rectal cancer who received chemotherapy had stage IV tumors, compared with 6 of 8 patients who did not receive chemotherapy ($P=.71$). Adjusted by stage in a Cox regression model, chemotherapy was still important in predicting outcome. The likelihood of death due to cancer in patients who did not receive chemotherapy was 5 times greater than for those who received chemotherapy (95% CI, 1.5-15.3; $P=.009$).

**COMMENT**

Among the clinicopathological and DNA flow cytometrical variables studied, only tumor stage and lymphangiosis were important in predicting outcome of patients with primary diffusely infiltrative colorectal cancer. The odds of death for patients with a stage IV tumor was 4-fold compared with those with a less advanced tumor. The risk of death for patients with a tumor of moderate to severe lymphangiosis was 2.4 times that of patients with a tumor of milder lymphangiosis. The median survival was 11 months (95% CI, 9-13 months) for patients with moderate to severe lymphangiosis compared with 14 months (95% CI, 10-18 months) for patients with milder lymphangiosis ($P=.04$). In the study of Nakahara et al, the median survival time was 7 months for 11 patients with moderate to severe lymphangiosis, compared with 24.5 months for 20 patients with milder lymphangiosis. The median survival was 14 months (95% CI, 5-23 months) for patients who received chemotherapy and 6 months (95% CI, 4-8 months) for those who did not ($P=.83$). The survival times for the 3 patients who received combined chemotherapy and radiotherapy was 14, 30, and 72 months, respectively. Six of 9 patients with rectal cancer who received chemotherapy had stage IV tumors, compared with 6 of 8 patients who did not receive chemotherapy ($P=.71$). Adjusted by stage in a Cox regression model, chemotherapy was still important in predicting outcome. The likelihood of death due to cancer in patients who did not receive chemotherapy was 5 times greater than for those who received chemotherapy (95% CI, 1.5-15.3; $P=.009$).
months for 4 patients with mild lymphangiosis. The degree of lymphatic permeation is also reported to be an important prognostic factor in patients with other morphologic types of stage III rectal tumor.22

In the present study, 37 (0.53%) of 7035 cases with primary colorectal carcinoma were the primary diffusely infiltrative type. This incidence is similar to that of the series of Nakahara (0.64%).13 Twelve (32.4%) moderately differentiated tumors were found in 37 cases. The reported incidence of moderately differentiated tumor varied from 25% to 52%.9,13 The wide variation may be due to a small sample size of each study. The average age of the 37 patients was 47.4 years in the current study—10 years younger than those with other morphologic types of colorectal cancer.16 The earlier age at diagnosis of cancer may be due to more rapid tumor progression and/or different pathogenesis. Although Anderson and Hansen6 found chronic ulcerative colitis in 25% of reviewed cases, both our study and the study of Nakahara et al13 found no chronic ulcerative colitis in cases of primary diffusely infiltrative tumor. This may be explained by the higher prevalence of chronic ulcerative colitis in the Western countries than in Asia.23 Some patients with long-standing chronic ulcerative colitis may develop colorectal carcinoma,24 which tends to be infiltrative and scirrhous.25

The grave prognosis of patients with primary diffusely infiltrative colorectal cancer is well documented.3,4,11,26 Radical resection was not possible in 73% of our patients because of disseminated disease or extensive locoregional invasion. This finding of late diagnosis is in accordance with other studies.4,11,26 In an earlier study of 538 stage III tumors, we also found that the odds of death for patients with such tumors was 11-fold that of patients with other morphologic types of tumors.25 The average duration of symptoms of 3.1 months prior to diagnosis and the higher prevalence of cases with stage IV disease at the time of diagnosis in the current study suggest that the grave prognosis of primary diffusely infiltrative colorectal cancer is caused by both the higher aggressiveness of these tumors and the insidious nature of their growth, which causes minimal symptoms until an advanced stage is reached.

It is interesting that postoperative chemotherapy prolonged the median survival time in patients with rectal tumors, but not in those with colon tumors. The causes of differential response to chemotherapy between colon and rectal cancers are not known.

In conclusion, both lymphangiosis and tumor stage were the independent factors in determining outcome in patients with diffusely infiltrative colorectal cancer. Our results also suggest that fluorouracil-based postoperative chemotherapy might provide a better chance for survival in patients with diffusely infiltrative rectal cancer.

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