# The Prognostic Significance of Tumor Location and Bowel Obstruction in Dukes B and C Colorectal Cancer

## Findings from the NSABP Clinical Trials

NORMAN WOLMARK, M.D., H. SAMUEL WIEAND, PH.D., HOWARD E. ROCKETTE, PH.D., BERNARD FISHER, M.D., ANDREW GLASS, M.D., WALTER LAWRENCE, M.D., HARVEY LERNER, M.D., ANATOLIO B. CRUZ, M.D., HERBERT VOLK, M.D., HENRY SHIBATA, M.D., JAMES EVANS, M.D., DAVID PRAGER, M.D., OTHER NSABP INVESTIGATORS

**The present study examines the prognostic significance of tumor location and bowel obstruction in Dukes B and C colorectal cancer. Data were obtained from 1021 patients entered into two randomized prospective clinical trials of the NSABP. Tumor location proved to be a strong prognostic discriminant. Lesions located in the left colon demonstrated the most favorable prognosis. Tumors of the rectosigmoid and rectum had the worst prognosis with the relative risk of treatment failure for the latter being over three fold that of the left colon. When the relative risks associated with tumor location were adjusted for nodal imbalances, the left colon continued to demonstrate the most favorable prognosis. The presence of bowel obstruction also strongly influenced the prognostic outcome. Examination of the data without considering tumor location disclosed that patients with bowel obstruction were at greater risk for treatment failure than those without obstruction. The effect of bowel obstruction was influenced by the location of the tumor. The occurrence of bowel obstruction in the right colon was associated with a significantly diminished disease-free survival, whereas obstruction in the left colon demonstrated no such effect. This phenomenon was independent of nodal status and tumor encirclement, the latter two factors proving to be of prognostic significance independent of tumor obstruction. A multivariate analysis in which the covariate effects of sex, age, nodal status, tumor obstruction, encirclement, and tumor location were adjusted underscored the role of tumor location and obstruction as prognostic discriminants. The results indicate that the definition of prognostic factors can identify patient subsets with unique characteristics.**

*From the National Surgical Adjuvant Breast and Bowel Project (NSABP), Scaife Hall, Pittsburgh, Pennsylvania*

THE CURRENT EFFORT IN SOLID TUMOR adjuvant therapy has indicated that various patient subsets can respond in a heterogeneous manner to identical treatment. These patient subsets are in general characterized by a group of specific host and tumor properties which are of prognostic importance. As a consequence of this demonstration, the delineation of patient subsets on a basis of prognostic discriminants has assumed a greater importance in colorectal cancer. Although tumor location and bowel obstruction have traditionally been regarded as prognostic discriminants, firm information to support this contention has been lacking. Reports analyzing the significance of tumor location have been limited and have produced widely divergent conclusions.[1-5] Several explanations may be entertained to account for this variance. The first consideration is that there has been a general tendency to perceive the large bowel as consisting of only two anatomic regions: the "colon" and rectum. The majority of studies addressing the significance of tumor location has concentrated predominantly on the prognosis of tumors above and below the peritoneal reflection without emphasis on specific anatomic regions of the colon.[6-10] A second possible explanation for the seemingly divergent results obtained in previously performed studies may lie in the failure to consider tumor location in conjunction with other variables which may be of prognostic importance. Should two tumors located at different sites demonstrate a dissimilar disease-free survivorship, the differences observed may not have been due exclusively to tumor location, but may have been a result of a differing proportion of positive nodes or a difference in the mean number of positive nodes. A third confounding influence which has restricted the study of tumor location is the

Supported by USPHS NIH-U10-CA-34212 and an American Cancer Society Grant RC-13.

* See Appendix 1 for contributing participants in Protocol Nos. C-01 and R-01.

Reprint requests: Norman Wolmark, National Surgical Adjuvant Breast and Bowel Project (NSABP) Headquarters, Room 914 Scaife Hall, 3550 Terrace Street, Pittsburgh, Pennsylvania 15261.

Submitted for publication: May 18, 1983.

widespread adherence to certain misconceptions assumed to be based on reliable information, which in actuality cannot be substantiated. As an example, the popular tenet that prognosis of a tumor decreases in direct proportion to the distance from the ileocecal valve cannot be corroborated from published data.

Similar considerations may be applied to the significance of bowel obstruction. In the majority of analyses which have been reported, bowel obstruction has been associated with a poorer prognosis when compared to nonobstructing tumors.[2,11-18] The same analyses usually indicate that bowel obstruction does not occur randomly in the colon but that there is a site predilection. In spite of this observation, investigations of the prognostic effect of obstruction have failed to control for location. In addition, previous studies have rarely associated bowel obstruction with other variables, such as the number of positive nodes and tumor location. Establishing whether bowel obstruction has direct prognostic significance or is simply predictive of another discriminant is of importance in elucidating the behavior of colorectal cancer.

The present study, utilizing a cohort of patients from the randomized prospective clinical trials of the National Surgical Adjuvant Project for Breast and Bowel Cancer (NSABP) was carried out in order to determine the prognostic significance of tumor location and bowel obstruction in Dukes B and C colorectal cancer. The analysis considers the independent effect of tumor location and bowel obstruction on disease-free survival. In addition, findings are presented from a multivariate analysis in which the influence of sex, age, nodes, and lumen encirclement on tumor location and obstruction is addressed.

## Materials and Methods

Data for this analysis were obtained from NSABP protocols C-01 and R-01, two randomized prospective clinical trials designed to determine the efficacy of adjuvant therapy in colorectal cancer. Protocol designs and patient accession have been described in more detail elsewhere.[19] The cohort employed consisted of patients with Dukes B and C carcinoma of the colon and rectum randomized between November 1977 and December 1981. Patients with colon cancer were randomized to receive no further treatment, BCG or chemotherapy consisting of 5 FU, MeCCNU, and Vincristine. Rectal patients were randomized to no further treatment, postoperative radiotherapy, or the same chemotherapy regimen utilized in the colon protocol. Reference to the Dukes classification was according to the classical criteria described in 1932 for carcinoma of the rectum and adapted for use in colonic tumors.[20] Dukes B lesions were characterized by extension of tumor through the muscularis propria into the pericolic adipose tissue without regional lymph node metastases. Dukes C tumors were exemplified by regional node metastases with any depth of tumor penetration.

This analysis does not include tumors which, because of metastatic disease or continguous involvement, extended beyond the scope of curative operative resection. As a result of the classification utilized, all negative node tumors described herein were characterized by transmural tumor penetration. A rectal tumor was defined by protocol as any lesion which required opening the pelvic peritoneum in order to define the distal extent of the tumor. A rectosigmoid lesion was one which was located at the distal most sigmoid colon and did not require the opening of the pelvic peritoneum in order to ascertain the distal clinical tumor margin. Patients with rectal tumors were treated with either anterior resection or abdominoperineal resection with the operative conduct for all patients determined by the protocol. Seven hundred and sixty patients with carcinoma of the colon and 261 patients with carcinoma of the rectum were available with follow-up information in whom tumor location was documented and reviewed by the NSABP statistical office. One hundred and forty patients were designated as having bowel obstruction based on preoperative clinical evaluation and, of these, 50 patients were treated with a preliminary diverting colostomy. The average time on study was 29 months.

Two varieties of statistical analyses were carried out. In the first instance, each putative prognostic discriminant was examined separately and treated as an independent variable. Use was made of the Mantel-Haenszel statistic in order to test the differences in disease-free survival between two or more groups. In general, when the Mantel-Haenszel statistic is discussed, reference is made to the two group test, and whenever a p-value is provided, it is two-sided. Another measure which was utilized and may be as important as the p-value when dealing with prognostic factors was the relative risk of treatment failure. Whenever the Mantel-Haenszel statistic was used for comparison of two groups, the observed and expected number of treatment failures were computed. Letting O1 (E1) and O2 (E2) be the number of observed (expected) failures in groups 1 and 2, respectively, the relative risk of group 1 to group 2 was defined by (O1/E1)/(O2/E2). If this value was equal to one, the two groups had "equivalent" prognoses; whereas a relative risk greater than one indicated that the prognosis of group 1 was worse than that of group 2, and a relative risk less than one indicated that the prognosis of group 1 was better than that of group 2. If the relative risk was two, for example, a patient from group 1 was roughly twice as likely to fail as a patient from group 2 (hence the expression relative risk of group 1 to group 2).

The second statistical method which was utilized in the examination of obstruction and location as prognostic factors was the Weibull Model. Statistical models based on the Weibull distribution are capable of adjusting for covariate effects. The mathematics involved in the model are described elsewhere,[21,22] but the model allows regression analysis with treatment failure as the dependent variable and the putative prognostic factors as independent variables. The coefficient obtained utilizing this method is therefore adjusted for the other covariates. All covariates have been treated as binary (0, 1) and, in the model presented, the baseline hazard or "control" consists of patients with the following characteristics: (1) obstruction, 0 = nonobstructing tumors, 1 = obstructing tumors; (2) sex, 0 = male, 1 = female; (3) age, 0 = <60, 1 = ⩾60; (4) nodes (1–4) and nodes (⩾5), 0 = other number of positive nodes, 1 = number of positive nodes given in parenthesis; (5) encirclement, 0 = less than half the circumference involved, 1 = greater or equal to half the circumference involved; and (6) location, 0 = left colon, 1 = given location.

Just as in linear regression analysis, there is a coefficient associated with each factor which can be standardized to obtain a p-value using normal tables. This p-value is a measure of how important the term is to the model, which is an indicator of how important the corresponding factor is as a prognosticator.

## Results

### *Tumor Location*

Tumors were initially categorized in nine separate anatomic regions of the large bowel and the per cent distribution according to location is illustrated in figure 1. Rectosigmoid tumors have been included with the sigmoid in this illustration because of the small number of patients in the former category. Maintaining these anatomic locations presented a problem in that too few patients were available in some categories to permit conclusive analysis. Accordingly, an analysis was carried out in order to determine which of the categories could be grouped together in order to achieve sufficient sample size. Criteria for grouping categories mandated that each region within the group had a similar prognosis and was contiguous anatomically. The initial analysis compared the relative risks of treatment failure of the nine original anatomic categories to the sigmoid colon (the largest single group) without adjusting for any other factors. Table 1 depicts the relative risks for the nine individual categories as well as the grouped locations. The individual relative risks for the transverse colon, splenic flexure, and descending colon were similar, thus enabling the formation of the major group designated "left colon." Similarly the cecum, ascending colon, and hepatic flexure were grouped and designated "right colon." The initial categories of sigmoid and rectum had sufficient patient numbers and differing relative risks, thus not requiring grouping; whereas, the rectosigmoid warranted independent designation in spite of the small sample size in order to enable subsequent comparisons. The combining of categories resulted in five major grouped locations, which are used in subsequent analyses.

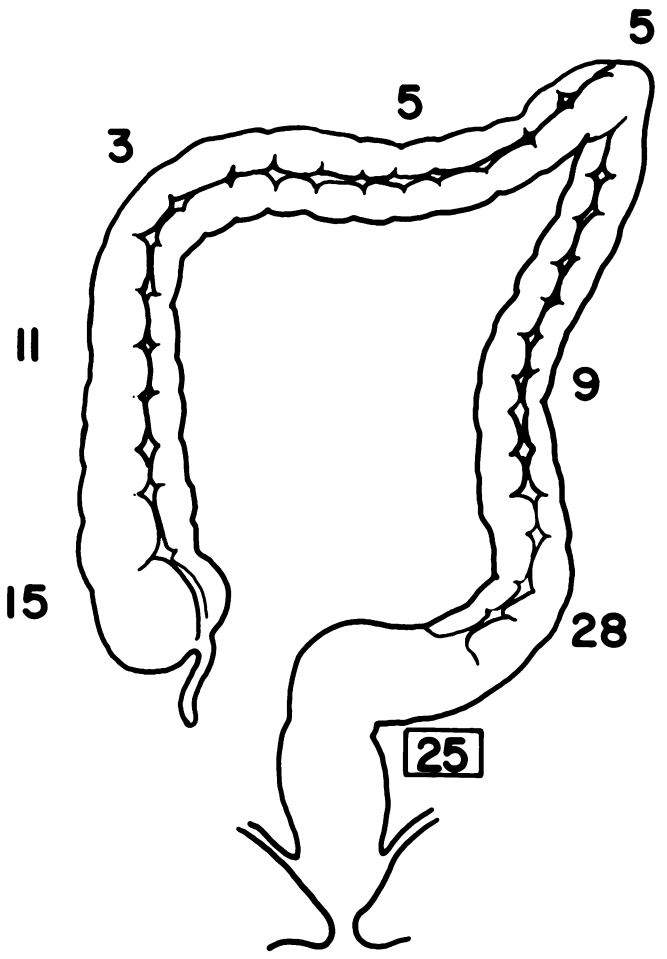


FIG. 1. Per cent distribution of 1021 Dukes B and C colorectal cancers according to location (rectosigmoid tumors have been included with the sigmoid).

Life table analysis for the six individual anatomic categories that were combined to form the left and the right colon groups are depicted in figure 2A. It is evident that the transverse colon, splenic flexure, and descending colon (left colon) all had similar disease-free survival distributions. The cecum, ascending colon, and hepatic flexure (right colon), although similar to each other, had disease-free survival distributions different from the categories comprising the left colon.

TABLE 1. *Tumor Location and Risk of Treatment Failure*

| Location | No. | Risk Relative to Sigmoid | Grouped Location | No. | Risk Relative to L Colon | p Value *vs.* R Colon | Sig. | Rectosig. | Rectum |
|---|---|---|---|---|---|---|---|---|---|
| Transverse colon | 49 | .53 | | | | | | | |
| Splenic flexure | 45 | .63 | Left colon | 184 | 1.00 | .005 | .06 | .002 | .00005 |
| Descending colon | 90 | .61 | | | (1.00)* | (.02) | (N.S.) | (.008) | (.0001) |
| Cecum | 151 | 1.11 | | | | | | | |
| Asc. colon | 106 | 1.06 | Right colon | 294 | 1.88 | | N.S. | N.S. | .0005 |
| Hepatic flex. | 37 | 1.06 | | | (1.71) | | (N.S.) | (N.S.) | .005 |
| Sigmoid | 246 | 1.00 | Sigmoid | 246 | 1.56 | | | .05 | .0005 |
| | | | | | (1.49) | | | (.08) | (.005) |
| Rectosig. | 36 | 1.82 | Rectosig. | 36 | 2.82 | | | | N.S. |
| | | | | | (2.59) | | | | (N.S.) |
| Rectum | 261 | 2.09 | Rectum | 261 | 3.22 | | | | |
| | | | | | (2.59) | | | | |

* Data presented in parentheses have been adjusted for nodal imbalances. N.S. = not significant; sig = sigmoid; and rectosig = rectosigmoid.

Utilizing the defined five grouped locations, relative risks were computed, now employing the left colon as a basis for comparison, since this was the group which proved to have the best prognosis. The relative risk for the left colon was significantly smaller than that for the other four groups (Table 1). The relative risk for a rectal tumor was 3.22 times that of a left colon lesion ($p = .00005$). The relative risk for a right colon tumor was significantly greater than the left colon ($p = .005$) but smaller than the rectum ($p = .0005$). The relative risk for the sigmoid colon was greater than the left colon ($p = .06$) and smaller than the rectum ($p = .0005$). No significant differences in relative risk were apparent when the rectosigmoid (lesions above the peritoneal reflection) were compared with the rectum (lesions below the peritoneal reflection).

Disease-free survival for the five grouped categories are depicted in figure 2B and illustrate the magnitude of the differences imparted by tumor location.

The data presented thus far were obtained by combining the three randomized arms in the colon and rectum protocols. The propriety of utilizing such methodology was addressed by examining the relative risks of treatment failure for each of the three randomized treatment categories. The data are depicted in Table 2 for each blinded treatment arm. For the rectum, the radiotherapy arm has been placed in the column corresponding to the BCG-treated cohort in the colon. The results indicated that the

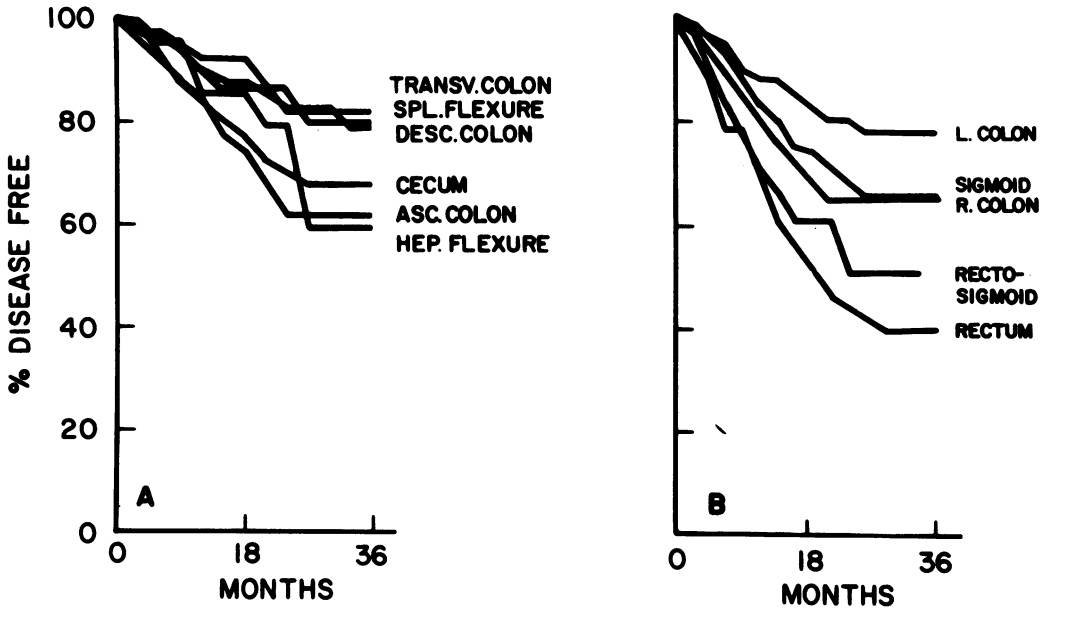


FIG. 2. Disease-free survival according to tumor location: (A) initial anatomic categories; and (B) grouped locations.

qualitative order of the relative risks of treatment failure for the four locations (the rectosigmoid having been excluded because of small patient numbers) was the same in all three treatment groups. The quantitative differences observed may have been due in part to a differing effect of treatment at specific locations.

The previous analyses did not take into account possible imbalances in the distribution of positive nodes within the various anatomic categories. An analysis of nodal distribution (not presented) indicated that there were some imbalances relative to the presence and number of positive nodes in the various locations ($p = .003$). As a consequence of this finding, a two group comparison was carried out for location, this time stratifying on the basis of 0, 1–4 and ≥5 positive nodes. The relative risk of treatment failure, adjusted for nodal imbalances is presented in parenthesis in Table 1. The major differences in relative risks attributed to tumor location were, therefore, not a result of nodal imbalances, although some of the differences in prognosis between the left colon and other locations were of slightly lower magnitude following nodal adjustment.

TABLE 2. *Tumor Location and Risk of Treatment Failure for Each Treatment Category*

| Location | Risk Relative to L Colon in Each Treatment Category | | |
|---|---|---|---|
| | A | B | C |
| L. Colon | 1.00 | 1.00 | 1.00 |
| R. Colon | 1.28 | 2.56 | 2.17 |
| Sigmoid | 1.11 | 2.13 | 1.67 |
| Rectum | 2.63 | 3.85 | 3.70 |

### *Bowel Obstruction*

The anatomic distributions of the 140 patients with Dukes B and C colon cancers with bowel obstruction are depicted in figure 3. The descending colon had the highest incidence of bowel obstruction, accounting for 21% of all documented cases with obstruction. The proportion of all Dukes B and C tumors at a given location which demonstrated obstruction was greater for the splenic flexure and descending colon, accounting for 37 and 26 per cent, respectively, of all lesions at the two locations. In contrast, only 16% of sigmoid tumors presented with bowel obstruction and these tumors accounted for 17% of all obstructing lesions at that location.

The treatment failure risk for obstructing colonic tumors relative to nonobstructing colonic tumors without consideration of location was 1.91 ($p = .005$). There was a variability in the relative risk of treatment failure for obstructing tumors, which was determined by anatomic location (Table 3). In the right colon, a patient with obstruction had an estimated risk of treatment failure three times that of a nonobstructed patient. In contrast, obstructed patients with tumors of the left colon and sigmoid had a relative risk not significantly greater than that of nonobstructed patients. The estimated risk from obstruction in the relatively few patients with rectosigmoid tumors was 4.40, ($p = .01$).

Life table analysis for obstructing and nonobstructing lesions unadjusted for positive nodes are depicted in figure 4. Significant differences relative to disease-free survival between obstructing and nonobstructing lesions were apparent for all patients ($p = .0007$) and patients with right colon tumors ($p = .00003$). No significant differences, however, were apparent when obstructing tumors of the left colon were compared with nonobstructing lesions at the same location. There were too few patients located in the rectosigmoid to perform meaningful disease-free survival comparisons and the differences observed for sigmoid tumors did not approach statistical significance.

An examination of the nodal distribution indicated that within each anatomic group no significant imbalance

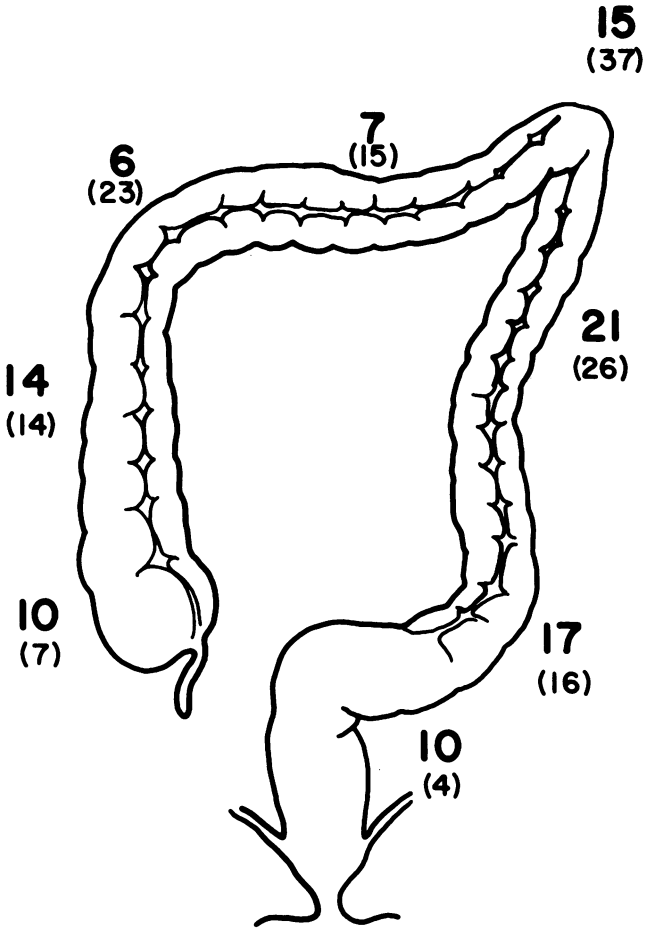


FIG. 3. Per cent distribution of 140 obstructing colorectal cancers according to location. Bold-faced numerals represent the proportion of obstructing lesions as per cent of the total number of obstructing colorectal tumors. Numerals in parentheses indicate the percentage of all tumors (obstructing and nonobstructing) presenting with obstruction at the designated location.

TABLE 3. *Tumor Obstruction and Risk of Treatment Failure*

| Location | Obstructed | Failed | Nonobstructed | Failed | Risk Obst. *vs.* Nonobst. | p-Value |
|---|---|---|---|---|---|---|
| Right colon | 32 | 17 | 257 | 52 | 2.98 | .000003 |
| Left colon | 46 | 7 | 134 | 18 | 1.35 | N.S. |
| Sigmoid | 43 | 10 | 201 | 39 | 1.49 | N.S. |
| Rectosigmoid | 4 | 3 | 31 | 9 | 4.40 | .01 |

existed in obstructed and nonobstructed patients (p = .26). Significant differences in disease-free survival were evident for obstructed and nonobstructed patients with negative nodes (p = .009) or 1–4 positive nodes (p = .01, Fig. 5). There were too few obstructed patients with ≥5 positive nodes to enable analysis of disease-free survival in this subset.

The effect of obstruction on disease-free survival did not differ significantly among the three treatment categories, enabling the combination of the three patient groups.

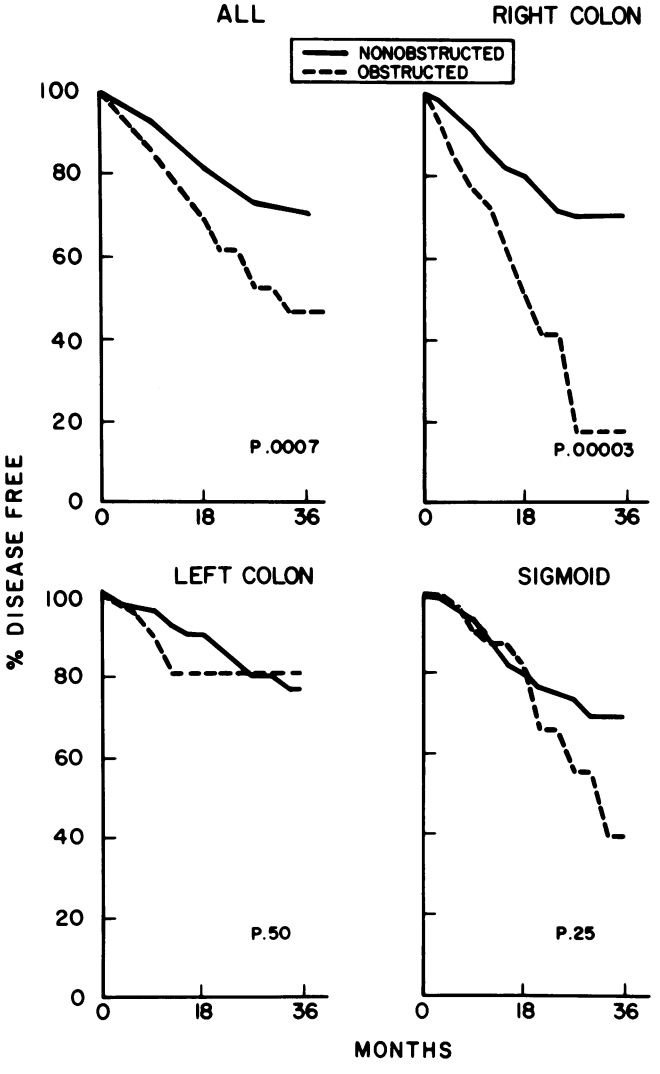


FIG. 4. Disease-free survival of obstructing and nonobstructing tumors according to location.

### *Tumor Encirclement*

A final question which seemed of interest when dealing with bowel obstruction was the relationship between the proportion of lumen encirclement and bowel obstruction. A tumor was considered to be encircling if the proportion of lumen involvement exceeded or equalled one-half the circumference. Nonobstructing tumors served as a baseline and the results obtained are depicted in Table 4. Both obstruction and encirclement appeared to function as prognostic factors, and neither factor completely explained the effects of the other. For example, the estimated risk for encircled nonobstructing tumors relative to nonencircled, nonobstructing tumors was 1.96 (p = .02) indicating that encirclement is important and independent of obstruction. Similarly, the estimated risk for obstructing encircled lesions relative to nonobstructing encircled tumors was 1.76 (p = .0005), emphasizing the importance of obstruction independent of encirclemnt.

### *Multivariate Analysis of Tumor Location and Obstruction*

In order to adjust for the covariate effects of putative prognostic discriminants, a multivariate analysis employing a Weibull regression model was performed. The prognostic factors considered in the model included sex, age, nodal status, obstruction, lumen encirclement, and tumor location. The value of the coefficient, the standardized coefficient and the p-value for the standardized coefficient for all patients are shown in Table 5. The results indicated that obstruction and tumor location continued to serve as significant prognostic discriminants, even after the covariate effects of the other prognostic factors had been adjusted. The positive node categories of 1–4 and ≥5 each served as strong prognostic discriminants, as did tumor encirclement independent of bowel obstruction.

## Discussion

The importance of defining prognostic discriminants in solid tumors has been underscored by the results forthcoming from adjuvant therapy clinical trials. The information obtained, particularly from breast cancer, has

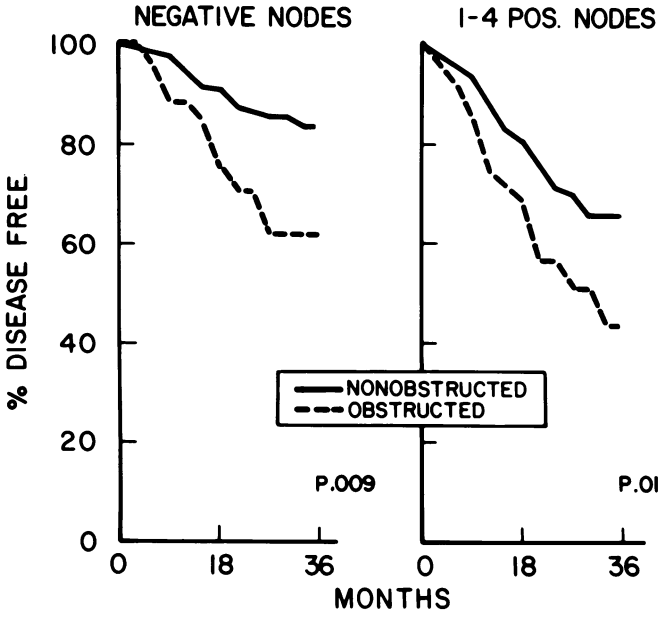


FIG. 5. Disease-free survival of obstructing and nonobstructing tumors according to nodal status.

demonstrated that subsets of patients may have a widely heterogeneous response to identical adjuvant therapy. It may be conjectured that all patients with colorectal cancer will similarly not behave in a uniform manner relative to chemotherapeutic response. As a consequence, the analysis of adjuvant therapy data for "all" colorectal patients without considering specific prognostic factors disregards the putative heterogeneity of the disease. The identification of biological subsets in colorectal cancer is in large part contingent on the elucidation of prognostic discriminants. Although tumor location has been associated with prognosis in colorectal cancer, there is a general tendency to regard tumors arising in the colon above the peritoneal reflection as a single entity. It is not unreasonable to postulate that those factors which determine the predilection of a tumor for a specific location may also have resulted in a tumor at that location which has distinct properties and, hence, may have a unique response to adjuvant therapy.

The results presented herein indicate that tumor location is indeed a strong prognostic discriminant. Left colon tumors had a better prognosis than tumors in any other location including the rectum. Tumors of the rectosigmoid and rectum had the worst prognosis, with the relative risk of treatment failure for the latter being over threefold that of the left colon. This phenomenon could not be explained on the basis of nodal imbalance at the specific location analyzed. When the node adjusted relative risk for rectal tumors was compared to other locations, the rectum continued to demonstrate the highest risk of treatment failure for all regions except the rectosigmoid. The node adjusted relative risk for the rectum and rectosigmoid was similar. Although the conclusions based on this latter finding are limited by the small sample size of rectosigmoid patients, at least in this analysis, no prognostic significance could be attributed to the presence or absence of serosa. The assessment of tumor location in a multivariate analysis in which the effect of sex, age, nodes, and tumor encirclement was adjusted disclosed that tumor location served as an important prognostic discriminant. The findings underscore the heterogeneous behavior of colon cancers based on anatomic location and emphasize the inherent danger in regarding colonic tumors as a single uniform disease process. This observation may be relevant to the analysis of adjuvant therapy response which should be performed according to specific anatomic region and not simply according to whether serosa is present or absent, and supports the propriety of stratifying patients according to tumor location.

TABLE 4. *Relative Risk of Treatment Failure for Obstructed and/or Encircled Patients Relative to Nonobstructed, Nonencircled Colon Patients*

| Group | Pts. | Failed | Risk | p-Value *vs.* (2) | p-Value *vs.* (3) |
|---|---|---|---|---|---|
| (1) Nonobstructed, nonencircled | 116 | 14 | 1.00 | .02 | .0001 |
| (2) Nonobstructed, encircled | 363 | 77 | 1.96 | | .0005 |
| (3) Obstructed, encircled | 101 | 33 | 3.27 | | |

The presence of bowel obstruction also proved to be a strong prognostic discriminant. Obstruction was most likely to occur in the descending colon; however, the splenic flexure demonstrated the greatest proportion of obstructed tumors in that 37% of all tumors presenting at that location manifested signs and symptoms of obstruction. The effect of bowel obstruction on disease-free survival was influenced by the anatomic location of the tumor. The occurrence of bowel obstruction in the right colon was associated with a significantly diminished dis-

TABLE 5. *Regression Coefficients, Standardized Coefficients, and Associated p-Values for Weibull Model Fit to Disease-free Survival*

| | Coefficient | Standard Coefficient | p |
|---|---|---|---|
| Sex | −.05 | −.34 | .72 |
| Age | −.23 | 1.49 | .14 |
| Nodes (1–4) | .89 | 4.57 | .0001 |
| Nodes (5+) | 1.55 | 7.08 | .0001 |
| Obstruction | .63 | 3.12 | .002 |
| Encirclement | .68 | 3.34 | .0008 |
| Right colon* | .86 | 3.31 | .001 |
| Sigmoid | .45 | 1.65 | .10 |
| Rectosigmoid | 1.73 | 3.60 | .0004 |
| Rectum | 1.19 | 4.32 | .0001 |
| Weibull K | 1.39 | 4.55 | .0001 |

* Locations are relative to the L colon.

ease-free survival, whereas the presence of obstruction in the left colon (the most frequent site of occurrence) was associated with no such effect. The demonstration that this finding could not be accounted for by a disproportionate occurrence of positive nodes and the documentation that both histologically positive node and negative node tumors with obstruction had a worse prognosis than patients without obstruction in the same nodal groups warrant further comment. The effect of obstruction on prognosis cannot be explained simply by an association of a higher incidence of positive nodes. The results obtained from the multivariate analysis leads to the conclusion that obstruction is a strong prognostic discriminant independent of nodal status. The disclosure that bowel obstruction in the right colon had a greater negative impact on disease-free survival than it did in the left colon is equally enigmatic. It has been suggested that, in order for a tumor to cause obstruction in the right colon, it must be of much larger size than an obstructing tumor in the left colon thereby accounting for the observed differences. Evidence that this explanation is unlikely may be derived from our previous analyses in which tumor size *per se* was shown to be of no prognostic significance.[19,23] It must be emphasized that this present analysis includes only those patients surviving the operation in whom the tumor was resectable for cure (Dukes B and C). The discrepancies in the disease-free survival attributable to bowel obstruction were therefore not due to an increased incidence of postoperative sequelae unrelated to treatment failure. The influence of bowel obstruction could not be accounted for by the degree of lumen encirclement, since encirclement proved to be of prognostic significance independent of tumor obstruction. The contribution of encirclement was not related to the presence or absence of positive nodes or the number of positive nodes.

It should be emphasized that the patient cohort utilized for this analysis was one selected by the eligibility criteria of the clinical trials, and therefore, may or may not be representative of the general population with colorectal cancer. Moreover, it is not a certainty that, particularly for tumor location, the data presented reflect the natural history that could be anticipated from a cohort receiving no therapy. Although the qualitative order of relative risks for each location was the same in all three treatment arms, it is possible that the quantitative differences evident may be due in part to a differing effect of treatment at specific locations. Despite these differences, the prognostic importance of tumor location and bowel obstruction has been demonstrated by the analysis. It is noteworthy that the average time on study for patients contributing to this analysis was 29 months. Although this represents a short follow-up interval, particularly when contrasted with the more conventional 5- and 10-year intervals employed, it must be emphasized that this analysis was not carried out to provide long-term natural history data, but rather to characterize prognostic discriminants.

## References


1. Spratt JS Jr, Spjut HJ. Prevalance and prognosis of individual clinical and pathologic variables associated with colorectal carcinoma. Cancer 1967; 20:1976–1985.
2. Copeland EM, Miller LD, Jones RS. Prognostic factors in carcinoma of the colon and rectum. Am J Surg 1968; 116:875–881.
3. Watson FR, Spratt JS, Jr, LeDuc RJ. Analysis of variance and covariance for colorectal adenocarcinomas in man as a logical prelude to "staging." J Surg Oncol 1976; 8:155–163.
4. Evans JT, Vanna J, Aronoff BL, et al. Management and survival of carcinoma of the colon: results of a national survey by the American College of Surgeons. Ann Surg 1978; 188:716–720.
5. Malcolm AW, Perencevich NP, Olson RM, et al. Analysis of recurrence patterns following curative resection for carcinoma of the colon and rectum. Surg Gynecol Obstet 1981; 152:131–136.
6. Kirklin JW, Dockerty MB, Waugh JM. The role of the peritoneal reflection in the prognosis of carcinoma of the rectum and sigmoid colon. Surg Gynecol Obstet 1949; 88:326–331.
7. Stearns MW, Binkley GE. The influence of location on prognosis in operable rectal cancer. Surg Gynecol Obstet 1953; 96:368.
8. Dwight RW, Higgins GA, Keehn RJ. Factors influencing survival after resection in cancer of the colon and rectum. Am J Surg 1969; 117:512–522.
9. Berge T, Ekelund TBG, Mellner C, et al. Carcinoma of the colon and rectum in a defined population. Acta Chir Scand 1973; 438:11–86.
10. Goodwin JD, Brown CC. Some prognostic factors in survival of patients with cancer of the colon and rectum. J Chronic Dis 1975; 28:441–454.
11. Cole PP. The intramural spread of rectal cancer. Br Med J 1913; 1:431–433.
12. Coller FA, Kay EB, MacIntyre RS. Regional lymphatic metastasis of carcinoma of the rectum. *Surgery* 1940; 8:294.
13. Nickell DF, Dockerty MB. The five-year survival rate in cases of completely obstructing annular carcinoma of the descending colon and sigmoid; a pathologic study. Surg Gynecol Obstet 1948; 87:519.
14. Grinnell RS. The spread of carcinoma of the colon and rectum. Cancer 1950; 3:641–652.
15. Dunning EJ, Jones TE, Hazard JB. Carcinoma of the rectum. A study of factors influencing survival following combined abdominoperineal resection of the rectum. Ann Surg 1951; 133:166–173.
16. Wilder TC, Dockerty MB, Waugh JM. A clinicopathologic study of obstructing carcinomas of the right portion of colon. Surg Gynecol Obstet 1961; 113:353.
17. Chang WY, Burnett WE. Complete colonic obstruction due to adenocarcinoma. Surg Gynecol Obstet 1962; 114:353.
18. Minister JJ. Comparison of obstructing and nonobstructing carcinoma of the colon. Cancer 1964; 17:242.
19. Wolmark N, Cruz I, Redmond CK, et al. Tumor size and regional lymph node metastasis in colo-rectal cancer—a preliminary analysis from the NSABP clinical trials. Cancer 1983; 51:1315–1322.
20. Dukes CE. The classification of cancer of the rectum. J Pathol Bact 1932; 35:323–332.
21. Kalbfleisch J, Prentice PL. The statistical analysis of failure time data. New York: John Wiley and Sons, 1980.
22. Miller RG Jr. Survival Analysis. New York: John Wiley and Sons, 1981.
23. Wolmark N, Fisher ER, Wieand HS, et al. The relationship of depth of penetration and tumor size to the number of positive nodes in Dukes C colorectal cancer. Cancer 1983, May 1984.

## Appendix 1

*Participants in Protocol Nos. C-01 and R-01*

| *Institution* | *Principal Investigator* |
|---|---|
| Albany Regional Cancer Center, New York, NY | Thomas Cunningham |
| Albert Einstein College of Medicine, New York, NY | Herbert Volk |
| Albert Einstein Medical Center, Philadelphia, PA | Stanley Levick/Ajit Desai |
| Allentown Hospital, Allentown, PA | David Prager |
| Baptist Memorial Hospital, Pensacola, FL | Allan Patton |
| Berkshire Medical Center, Pittsfield, MA | Jesse Spector/Harvey Zimbler |
| Billings Interhospital Oncology Project, MT | David Myers |
| Boston University, Boston, MA | Merrill Feldman |
| Bowman Gray School of Medicine, NC | John Michael Sterchi |
| Brentwood Hospital, Warrensville Heights, OH | B. L. Horvat |
| Bryn Mawr Hospital, Bryn Mawr, PA | Thomas G. Frazier |
| Camden-Clark Memorial Hospital, WV | Nikunj Shah |
| City of Hope Medical Center, Duarte, CA | Jose J. Terz |
| Denver General Hospital, Denver, CO | George Moore |
| Downstate Medical Center, SUNY (state?) | Bernard Gardner |
| Ellis Fischel State Cancer Hospital, MO | William Kraybill |
| Geisinger Medical Center, Danville, PA | James Evans |
| Good Samaritan Hospital, Lexington, KY | William Meeker |
| Gulf Coast Community Hospital, Panama City, Panama | William Gregory Bruce |
| Harbor General Hospital, Torrance, CA | David State/M. Michael Shabot |
| Highland Hospital, Rochester, NY | Sidney Sobel |
| Hotel-Dieu, Montreal, CA | Andre Robidoux |
| Hotel-Dieu, Quebec City, Canada | Louis Dionne |
| Jewish General Hospital, Montreal, Canada | Richard Margolese |
| Kaiser Permanente, Portland, OR | Andrew Glass |
| Kaiser Permanente, San Diego, CA | Thomas Campbell |
| Letterman Army Medical Center, CA | David Gandara |
| Louisiana State University, New Orleans, LA | Isidore Cohn/Robert Beazley |
| Louisiana State University, Shreveport, LA | Don M. Morris |

*Participants in Protocol Nos. C-01 and R-01*

| *Institution* | *Principal Investigator* |
|---|---|
| Manitoba Cancer Foundation (state?) | David Bowman |
| Marshfield Clinic, Wisconsin, IL | James L. Hoehn |
| Medical College of Virginia, VA | Walter Lawrence |
| Medical College of Wisconsin, IL | William Donegan |
| Memorial Cancer Research Foundation, CA | David Plotkin |
| Michael Reese Hospital, Chicago, IL | Richard Desser |
| Michigan State University, East Lansing, MI | Leif Suh land |
| Montefiore Hospital ≤ Medical Center, New York, NY | Richard Rosen |
| Montreal General Hosptial | John MacFarlane |
| Mount Sinai Hospital, Milwaukee, WI | Jules Lodish |
| Mount Sinai Medical Center, Cleveland, OH | Richard Bornstein/ Jeffrey L. Ponsky |
| Naval Regional Medical Center, Oakland, MD | Michael A. Crucitt |
| Naval Regional Medical Center, San Diego, CA | Jim Guzik |
| Pennsylvania Hospital, Philadelphia, PA | Harvey Lerner |
| Royal Victoria Hospital, Montreal, Canada | Henry Shibata |
| Rush Presbyterian-St. Luke's Medical Center, IL | Janet Wolter/ Steven Economou |
| South Nassau Communities Hospital, New York, NY | Nicholas LiCalzi |
| St. Joseph Hospital, Lancaster, PA | H. P. DeGreen |
| St. Luc Hospital, Montreal, Canada | Roger Poisson/ Sandra Legault-Poisson |
| St. Luke's Hospital, Kansas City, KA | Paul Koontz |
| St. Mary's Hospital, Grand Rapids, MI | Andre Jubert |
| St. Michael's Hospital, Toronto, Canada | Leon Mahoney |
| St. Vincent's Hospital, Indiana | John Cavins |
| St. Vincent's Hospital, New York, NY | Thomas Nealon |
| Tom Baker Cancer Centre, Calgary (state?) | L. Martin Jerry |
| Trumbull Memorial Hospital, Warren, OH | Jerome Stanislaw |
| Tulane University, New Orleans, LA | Carl Sutherland |
| University of California, San Diego, CA | Yosef Pilch |
| University of Florida, JHEP, FL | Neil Abramson |
| University of Hawaii | Noboru Oishi/ Robert Oishi |

**Appendix 1 (*Continued*)**

*Participants in Protocol Nos. C-01 and R-01*

| *Institution* | *Principal Investigator* |
|---|---|
| University of Iowa, IA | Peter Jochimsen |
| University of Louisville, KY | Joseph Allegra |
| University of Maryland, MD | E. George Elias |
| University of Massachusetts, Worchester, MA | Mary Costanza/ Michael Wertheimer |
| University of North Carolina, NC | Robert Capizzi |
| University of Pittsburgh, OH | Bernard Fisher |
| University of Texas, San Antonio, TX | A. B. Cruz/ J. Bradley Aust |
| University of Vermont | Roger Foster |
| VA Medical Center, Boston, MA | Waun Hong |

*Participants in Protocol Nos. C-01 and R-01*

| *Institution* | *Principal Investigator* |
|---|---|
| Valley Hospital, Ridgewood, NY | Hugh Auchincloss |
| Washington Regional Medical Center, AR | James H. Bledsoe |
| West Suburban Hospital, Oak Park, IL | Everett Nicholas |
| West Virginia University, Morgantown, WV | Alvin Watne |
| White Memorial Medical Center, Los Angeles, CA | Matthew Tan |
| Wilmington Medical Center, DE | Robert Frelick |
| Wuesthoff Memorial Hospital, Rockledge, FL | Edward W. Knight |