Verification of a New Clinicopathologic Staging System for Colorectal Adenocarcinoma

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Rectal adenocarcinoma is said to have a poorer outcome than colon adenocarcinoma when compared on the basis of Dukes' staging. However a new staging system, determined by a multivariate analysis of 147 patients with rectal adenocarcinoma, has revealed three other variables significantly related to outcome. Therefore this study analyzed the authors' experience with colonic carcinoma during the same time period as they had studied for rectal carcinoma to determine whether the new staging system is valid for colon carcinoma as well, and, if so, to compare the outcome of patients with colon and rectal carcinoma on the basis of this new staging. A total of 603 patients with 611 colonic adenocarcinoma were operated on at the University of Chicago Medical Center between 1965 and 1981. Two hundred seventy-nine adenocarcinomas (45.7%) were located proximal to the splenic flexure and 332 (54.3%) were located between the splenic flexure and the rectosigmoid. Four hundred sixty-two patients underwent segmental colectomy, 46 subtotal colectomy, 26 total colectomy, 18 proctocolectomy, 5 abdominal-perineal resection, 1 appendectomy, while 20 had local excision of the tumor through colotomy and 25 had permanent diverting stoma as the only procedure. The operative mortality rate was 6.1% in the whole group, but was only 2.7% in the group of potentially curable patients. Complete follow-up was obtained in all patients. To validate a previous staging system for Dukes' B and C rectal adenocarcinoma, the authors investigated the correlation between 5-year survival for colonic carcinoma patients and all relevant variables that they had considered potentially meaningful in the previous study with rectal adenocarcinoma. The resulting multivariate analysis using Cox regression showed that the four variables found previously to be significantly related to outcome for rectal adenocarcinoma patients (stage, race, tumor morphology, and vascular and/or lymphatic microinvasion) were the only four variables significantly ($p < 0.05$) associated with outcome for colonic adenocarcinoma patients. In addition, by using the results of their previous staging system for rectal adenocarcinoma patients, they 'predicted' the 5-year survival rates of the colon adenocarcinoma patients, divided in 16 staging subgroups. In subgroups of at least 15 patients, the rectal staging system predicted the outcome to within 1 to 6 percentage points of the observed outcome of the colonic adenocarcinoma patients. Thus this study validates this staging system, incorporating stage, race, tumor morphology, and microinvasion to predict 5-year survival rate more accurately than Dukes' staging alone for both colon and rectal adenocarcinoma. In addition, when grouped according to this classification, patients with colon carcinoma have the same outcome probabilities as patients with rectal carcinoma.

THE ORIGINAL DUKES' classification has been modified and refined several times[1] in the 50 years following its publication. Although the modified classifications have permitted a more precise prognosis in patients with 'early' cancers confined to the mucosa (stage A), and in patients with more extensive and distant spread (stage D), the remaining patients, who represent the majority of colorectal cancers, are grouped into two large, heterogeneous groups.

In 1988, prompted by our inability to predict accurately the long-term prognosis of an individual patient after resection of a stage B or C rectal carcinoma, we evaluated our experience with rectal carcinoma to identify clinical or pathologic characteristics that influenced outcome.[2] The results of our study on rectal carcinoma revealed that Dukes' staging, race, tumor morphology, and the presence or absence of lymphatic and/or vascular microinvasion significantly influenced patient outcome. By associating these four statistically significant and independent variables, we were able to divide patients with stage B and C rectal adenocarcinoma into 16 subgroups, each with its own more precise prognosis. The present study represents our attempts to validate these results, to extend them to colon carcinoma, and to compare the long-term prognosis

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of patients with colon and rectal carcinoma on the basis of this new staging.

Materials and Methods

Between 1965 and 1981, 603 patients with colonic adenocarcinomas underwent surgical treatment at the University of Chicago Medical Center. The clinical records of all these patients were reviewed and complete follow-up to December 1988 was obtained in all through the Registry of Neoplastic Diseases of the University of Chicago. Data on age, sex, race, tumor location, morphology and size, evidence of local invasion, type of operation, mortality, evidence of local recurrence or distant metastasis, presence of synchronous colonic adenocarcinomas, familial polyposis, and ulcerative or Crohn's colitis were specifically sought in each instance. Tumors were defined as exophytic when they exhibited a polypoid growth pattern protruding into the lumen at least 1 cm; when lacking such characteristic growth pattern, tumors were classified as nonexophytic. Operative deaths were defined as those deaths occurring within 30 days from the time of operation.

Histologic slides and archival paraffin blocks were retrieved for confirmation of diagnosis, determination of histologic type, stage, degree of tumor differentiation, and presence of vascular and/or lymphatic microinvasion by one pathologist (R. Goldberg) who was unaware of the patients's clinical course. Lymphatic microinvasion was defined as the presence of tumor within an endothelial lined space lacking a smooth muscle coat; the same finding was defined as vascular microinvasion if the endothelial line space was surrounded by a smooth muscle layer. Tumors were staged according to the Astler-Coller modification of Dukes' classification.[3]

Data regarding the occurrence of distant metastases, the incidence of local recurrence, and presence of tumor extension through the bowel wall were analyzed by the Kruskal–Wallis analysis of variance (ANOVA),[4] considering each independent variable individually.

To validate the clinical pathologic staging described for potentially curable rectal adenocarcinoma by us in 1988[2] and extend it to colonic adenocarcinoma, we analyzed the 5-year survival of the patients with colonic adenocarcinoma as we did for those with rectal adenocarcinoma. All references to patients with rectal adenocarcinoma refer to our previously described cohort of 250 patients with rectal adenocarcinoma operated on at the University of Chicago Medical Center from 1965 to 1981.[2]

A logistic regression analysis was used, with the dependent variable being 5-year survival. Our previously reported techniques[2] for estimation of parameters and confirmation of assumptions were repeated for this analysis. The same independent variables considered in our previous analysis with rectal adenocarcinoma patients were entered into the multivariate analysis: age (both as a continuous variable and divided into three groups (less than 40 years, between 40 and 59 years, and more than 60 years)*, sex, race, Dukes' stage, tumor morphology (exophytic *versus* nonexophytic), mucin production, and the presence or absence of vascular and/or lymphatic microinvasion. In addition we also considered location of the tumor along the colon (cecum, ascending with hepatic flexure, transverse with splenic flexure, descending, sigmoid, and rectosigmoid).

In addition, to determine whether patients with colon cancer had similar 5-year survival probabilities to patients with rectal cancer when all four variables significant for survival were considered, we 'predicted' the outcome of the colonic carcinoma patients based on the results of the previous model using rectal adenocarcinoma patients alone for each of the 16 subgroups and compared the results to the corresponding observed outcomes of colonic carcinoma patients.

Results

Clinical Findings

Of the 603 patients, 291 were men and 312 were women. Mean age at the time of operation was 64.4 years, with a range from 15 to 93 years. The 603 patients considered had a total of 611 adenocarcinomas. Of these, 279 (45.7%) were located proximal to the splenic flexure and 332 (54.3%) between the splenic flexure and the rectosigmoid (Fig. 1). Twenty patients had associated ulcerative colitis, three patients Crohn's colitis, and four familial polyposis. Thirty-three patients presented with a total obstruction and 14 with an open perforation.

The location of the tumor within the colon and presence of synchronous tumors or associated conditions influenced the type of operation that was performed. One patient underwent an appendectomy, 462 patients a segmental colectomy, 46 a subtotal colectomy, 26 a total colectomy, 18 a protocolectomy, 5 an abdominal perineal resection, while 20 had a local excision of the tumor through a colotomy and 25 a permanent diverting stoma as the only procedure.

Follow-up analysis revealed that 37 patents (6.1%) died in the immediate postoperative period. Of these only one third (n = 13) had a potentially curable adenocarcinoma, for a mortality rate of 2.7% in this group of patients. Furthermore the operative mortality rate decreased markedly during the period reviewed (Fig. 2).

Table 1 compares the distribution, by tumor stage, of

* Note that in the previous publication, age was entered as a continuous variable and dichotomized at 40 years.

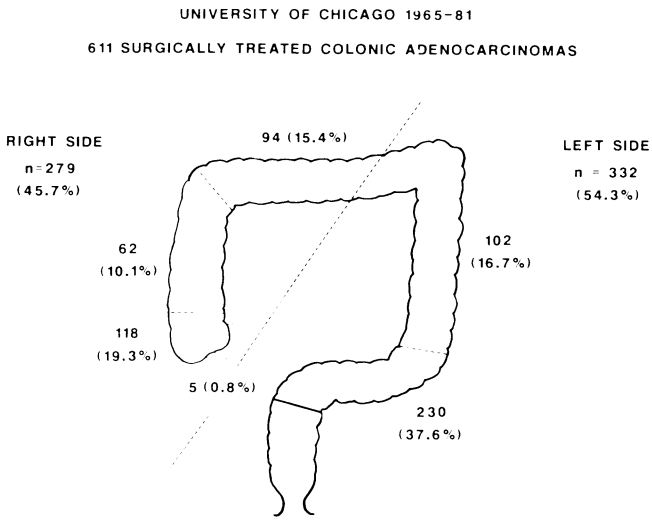

FIG. 1. Location of 611 colonic adenocarcinomas in 603 patients surgically treated at the University of Chicago between 1965 and 1981.

colon adenocarcinomas to that of our previously described rectal adenocarcinoma patients. The distributions among classes A, B, C, and D were comparable between groups. However, within stage B, there was a smaller percentage of B_1 tumors and a higher percentage of B_2 tumors among patients with colon cancer compared to those with rectal cancer.

Ten patients had another synchronous tumor, which was an adenocarcinoma in eight cases and a carcinoid in two. Synchronous adenocarcinomas were found, therefore, in 1.3% of patients. There were six cases of synchronous Dukes' B_1 and B_2 adenocarcinomas, one case of synchronous B_2 and C_2, and one case of synchronous C_1 and C_2. Patients with synchronous adenocarcinomas were considered only once in our analysis and were grouped under the higher stage lesion.

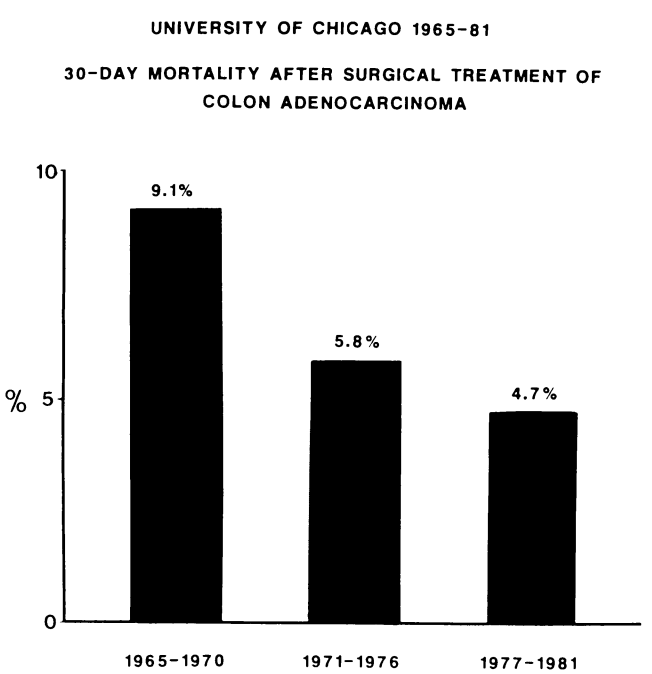

FIG. 2. Operative mortality rate in 603 patients with colon adenocarcinoma surgically treated at the University of Chicago between 1965 and 1981.

TABLE 1. *Tumor Stage for Colonic and Rectal Adenocarcinoma*

Dukes' Stage	Colon (n = 611)		Rectum* (n = 250)	
A	52	8.5%	25	10%
B_1	37	6.1%	32	12.8%
B_2	218	35.7%	55	20.8%
C_1	—	—	5	2.0%
C_2	173	28.3%	62	24.0%
D	131	21.4%	71	28.4%

* Patients described in detail in previous publication.[2]

Five- and ten-year actuarial survival rates classified by the modified Dukes' staging and exclusive of perioperative deaths are summarized in Table 2 for the colonic adenocarcinoma patients, as well as for our rectal adenocarcinoma patients. Overall patients with colon cancer, when stratified by stage, had higher percentages of 5- and 10-year survival compared to comparably stratified patients with rectal cancer. The differences were most marked when comparing outcomes for stages B_1 and B_2. For example colon adenocarcinoma patients classified as stage B_1 had 100% 5-year survival compared to only 69% for stage B_1 rectal cancer. Figure 3 illustrates the survival curves, based on tumor stage, following the resection of potentially curable colonic adenocarcinomas.

The local recurrence rate after resection of a Dukes' B or C adenocarcinoma was lower among colon carcinoma patients, 7.5% (31 patients), compared to 12% among rectal carcinoma patients. This is also consistent with the finding for both colon and rectal cancers that the more distal the original tumor arose, the higher was the incidence of local recurrence. For tumors of the cecum, the

TABLE 2. *Five- and 10-year Actuarial Survival Rates*

Dukes' Stage	Colonic Adenocarcinoma* 5 Years (%)	Colonic Adenocarcinoma* 10 Years (%)	Rectal Adenocarcinoma 5 Years (%)	Rectal Adenocarcinoma 10 Years (%)
A	100	100	100	†
B_1	100	95.3	68.8	59.4
B_2	82.7	72.4	55.8	44.2
C	49.1	39.5	42.9	25.4
D	3.7	1.5	2.8	†

* Patients with synchronous lesions are grouped with the higher grade lesion (see text).

† Ten-year actuarial survival rate not reported in previous publication.[2]

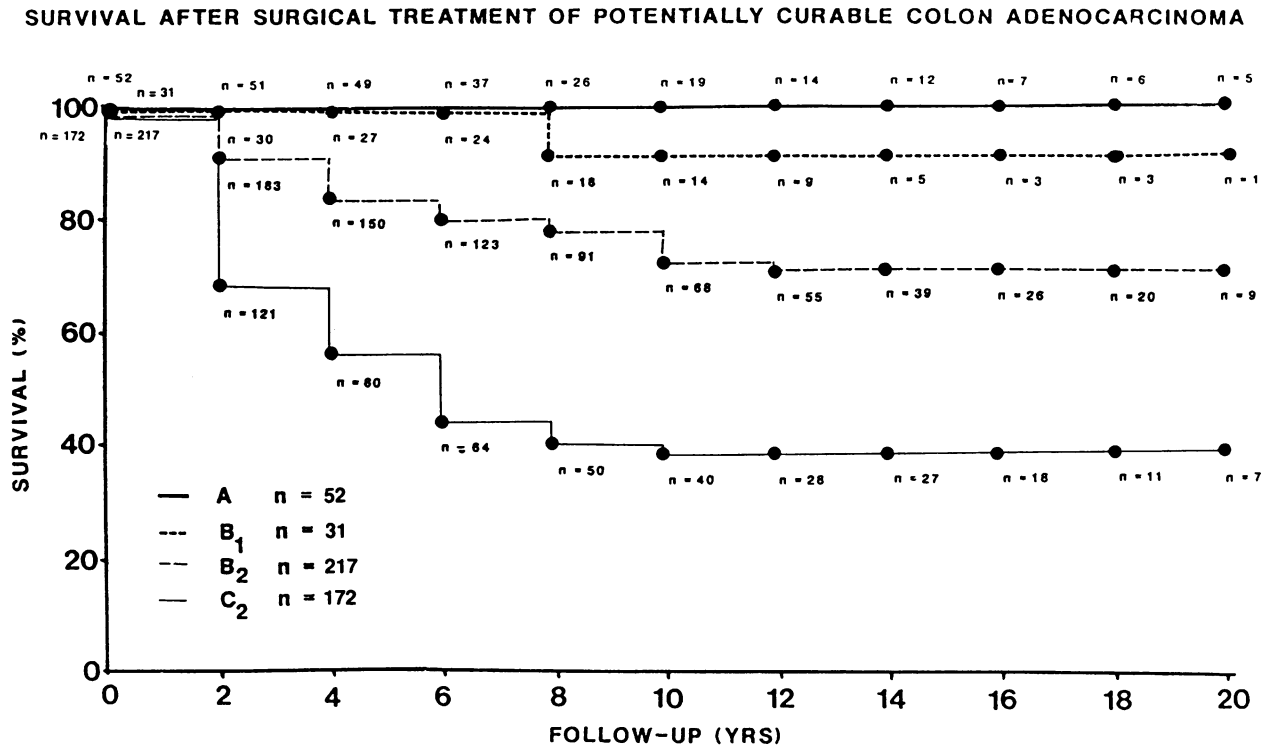

FIG. 3. Survival rates by Dukes' stage based on life table analysis calculated for patients after surgical treatment of potentially curable colon adenocarcinoma at the University of Chicago between 1965 and 1981. Patients who died of intercurrent disease were censored at the time of the last known follow-up.

incidence was 4.8%, compared to 7.3% for tumors of the ascending colon, 8.6% for tumors of the transverse and descending colon, and 9.4% for tumors of the sigmoid and rectosigmoid. The local recurrence rate for colon adenocarcinomas was 1.9% for Dukes' A, 6.3% for Dukes' B, and 9.8% for Dukes' C tumors. One half the recurrences were clinically evident by 2 years and 8 months, and 50% of patients died by 3.5 years. The survival rates, based on life table analysis, were 40.5% at 5 years and 21.6% at 10 years.

Distant metastasis developed in 149 patients (32.5%). Their 5-year survival rate, according to the stage of original tumor, was 100% for Dukes' A and B_1 adenocarcinomas, 30.6% for Dukes' B_2, and 15.3% for Dukes' C_2 tumors. In the 81 cases in which the involved site was known, the liver was the single organ involved in 43 cases (29% of patients with metastasis and 7.1% of all patients). The likelihood of developing a distant metastasis was found to be significantly proportional to the stage of the original tumor, 3.6% at stage A and B_1, 22.7% at stage B_2, and 57.6% at stage C_2 ($p < 0.001$, ANOVA). Vascular and/or lymphatic microinvasion was significantly associated with the development of metastasis; 54.8% of patients with this characteristic developed distant metastasis, as compared with 24.9% of patients without microinvasion ($p < 0.01$, ANOVA). Tumors with a nonexophytic growth pattern also developed distant metastasis significantly more frequently than did exophytic tumors (47.8% *versus* 25.9%, respectively; $p < 0.01$, ANOVA).

There was evidence of extension through the bowel wall in 391 patients (82.8%) of the 472 with colonic adenocarcinomas without intraoperative evidence of distant metastasis. Our analysis revealed that the presence of vascular and/or lymphatic microinvasion was associated with a significantly greater incidence of such tumor extension: 95.6% of patients with microinvasion exhibited such evidence, compared with 77.7% of patients without microinvasion ($p < 0.05$, ANOVA). Furthermore a significantly larger percentage of patients with nonexophytic tumors experienced invasion through the bowel wall, compared with those with exophytic tumors (94.9% *versus* 76.6%; $p < 0.05$, ANOVA).

Model Validation

A multivariate logistic regression analysis was performed using the data from the colon adenocarcinoma patients on whom a potentially curative procedure was

TABLE 3. *Factors Influencing 5-year Survival Rate After 'Curative' Resection of Colon Adenocarcinoma According to the Logistic Regression Analysis*

Variable	Beta Coefficient	Standard Error	p Value
Stage			
B (n = 197)	+1.42	0.26	<0.00001
C (n = 151)			
Race			
White (n = 190)	+0.49	0.26	<0.05
Black (n = 158)			
Tumor morphology			
Exophytic (n = 231)	+0.65	0.26	<0.02
Nonexophytic (n = 117)			
Vascular–lymphatic microinvasion			
Absent (n = 252)	+0.92	0.28	<0.001
Present (n = 96)			

performed. Eight patients with synchronous colonic adenocarcinomas and 64 patients with missing data were excluded from this analysis. The patient outcome variable was the 5-year survival rate, while the independent variables were the relevant variables entered into the previous model for rectal carcinoma.[2] Table 3 summarizes the results of the analysis on colonic adenocarcinoma, listing those variables found to be significantly associated with 5-year survival (*i.e.*, those variables with statistically significant coefficients in the model). The results of the multivariate analysis produced the same four variables found previously to be related significantly to survival for rectal adenocarcinoma patients: Dukes' stage (B compared to C), race (white compared to black), tumor morphology (exophytic compared to nonexophytic), and the absence or the presence of vascular and/or lymphatic microinvasion. By categorizing patients by the four characteristics, 16 subgroups emerge with varying prognoses (Fig. 4). Among these groups, white patients with Dukes' stage B, exophytic adenocarcinoma without microinvasion have the best prognosis, while black patients with stage C, nonexophytic tumors with microinvasion have the worst prognosis.

Because our results demonstrated that, classified by Dukes' stage alone, colon cancer patients have better survival rates than rectal carcinoma patients, we wanted to determine if this difference would be maintained using our more precise staging. To do so, we 'predicted' the 5-year survival rates of each of the 16 subgroups of colon adenocarcinoma patients based on the results of the staging system for rectal carcinoma patients and compared them to the corresponding observed rates for the colon patients. Table 4 displays the results. In subgroups of at least 15 patients, the rectal staging system predicted the

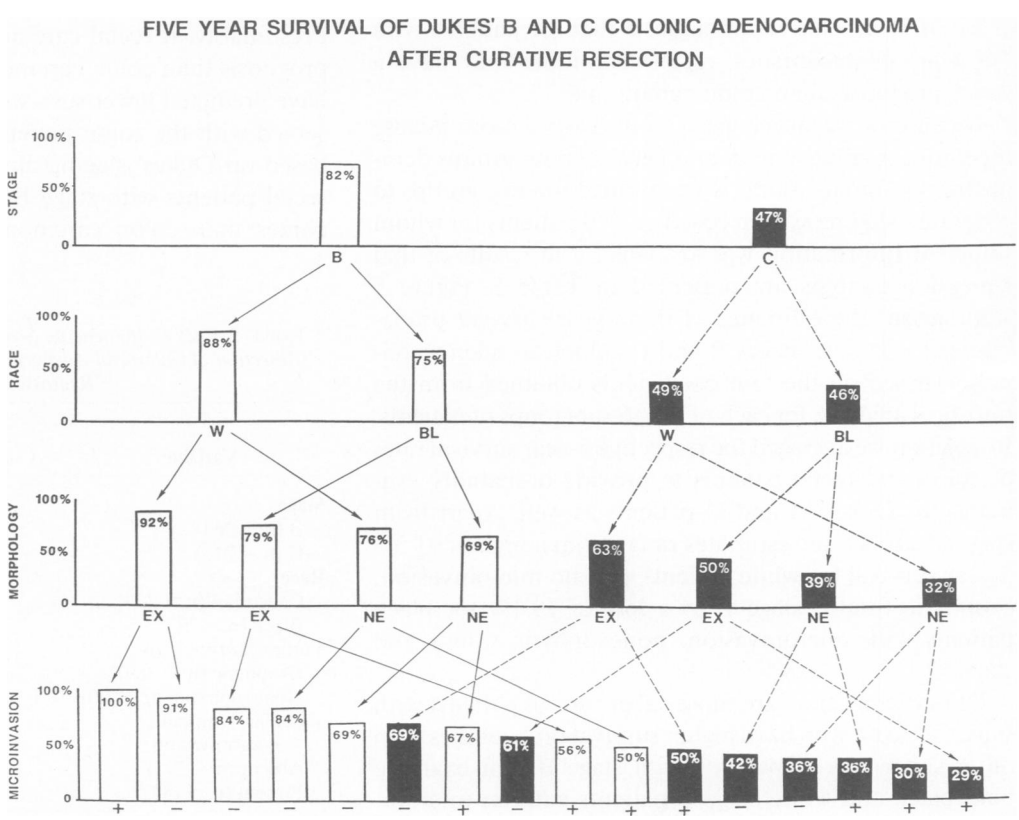

FIG. 4. Refinement of prognostic value of Dukes' classification in estimating 5-year survival probability. Estimates of 5-year survival probabilities, obtained from logistic regression, are shown for 16 different groups of patients. The groups were divided on the basis of those factors (stage, microinvasion, tumor type, and race) believed to have a significant effect on mortality rates. Survival estimates of patients for which all these attributes are known are given at the bottom of the figure. The estimates in the higher levels, for which one or more attributes are not known, were calculated by weighing the estimated probabilities in the constituent groups by those group frequencies in the sample analyzed. Thus these estimates are specific to samples approximately the same composition as the sample considered here. Only the survival estimates given at the bottom can be generalized to accommodate population with other compositions.

TABLE 4. *Predicted and Observed 5-year Survival Rates of 16 Subgroups Based on Staging System, Using Rectal Adenocarcinoma Data to Predict Survival and Colon Adenocarcinoma Data to Observe It*

Stage	Race	Morphology	Micro-invasion	n	Predicted 5-year Survival	Observed 5-year Survival
B	White	Exophytic	−	78	92%	91%
B	White	Exophytic	+	43	85%	84%
B	White	Nonexophytic	−	10	81%	100%
B	White	Nonexophytic	+	19	80%	84%
B	Black	Exophytic	−	29	75%	69%
B	Black	Exophytic	+	9	66%	56%
B	Black	Non-exophytic	−	26	66%	69%
B	Black	Non-exophytic	+	6	59%	50%
C	White	Exophytic	−	31	59%	61%
C	White	Exophytic	+	14	51%	50%
C	White	Nonexophytic	−	14	52%	36%
C	White	Nonexophytic	+	6	40%	67%
C	Black	Exophytic	−	17	33%	29%
C	Black	Exophytic	+	12	32%	42%
C	Black	Nonexophytic	−	20	26%	30%
C	Black	Nonexophytic	+	14	14%	36%

outcome to within 1 to 6 percentage points of the observed outcome of the colonic cancer patients. The greatest difference was noted for the subgroup with the worst prognosis (blacks with stage C, nonexophytic adenocarcinoma with microinvasion). For that group, the predicted value for the 5-year survival was 14% compared to an observed value of 36%. This result suggests that for patients with the worst characteristics, rectal carcinoma may have a worse prognosis than colon carcinoma.

Because our goal has been to develop a more precise predictive staging system, and because both groups demonstrated similar results, we combined the two groups to generate a staging system based on 479 patients for whom sufficient information was available. The results of that regression analysis are presented in Table 5. Figure 5 summarizes the estimates of the 5-year survival probabilities for Dukes' stages B and C colorectal adenocarcinoma, based on the four coefficients obtained from the statistical analysis, for each of the 16 subgroups of patients. In addition we averaged the respective 5-year survival rates of colon and rectal patients to provide probability estimates for Dukes' A and D patients as well. Apart from stages A and D, the estimates range from a high of 91.3% 5-year survival for white patients with no microinvasion, exophytic tumor, stage B to a low of 19.1% for black patients with microinvasion, nonexophytic tumor and stage C.

Of particular note are those subgroups of patients with stage C disease who have higher survival probabilities than other subgroups of patients with stage B. For example both black and white stage C patients without microinvasion and with exophytic tumors have greater survival probabilities than those with stage B disease who have microinvasion and nonexophytic tumors.

Discussion

The present study represents our attempt to validate the results obtained in our initial study on rectal carcinoma. We chose to evaluate patients with colon carcinoma who underwent surgery during the same time period and by the same surgeons at the University of Chicago Medical Center. This group of patients provided us with the opportunity to explore whether our staging, like the Dukes' classification, was valid for colon adenocarcinoma as well as rectal carcinoma, and if so, whether the two sites varied in their prognosis, when controlled for the four significant variables.

The resulting multivariate analysis revealed that the four variables found previously to be significantly related to outcome for rectal adenocarcinoma patients were the only four variables significantly associated with outcome for colonic adenocarcinoma patients. These results confirmed the validity of our staging system and extended its applicability to colon carcinoma.

In addition, in an effort to determine if the site (colon *versus* rectum) influenced outcome, we 'predicted' the outcome for the colon patients based on the rectal model. Presumably, if rectal carcinoma had a uniformly worse prognosis than colon carcinoma, the rectal model would have predicted lower survival rates than that actually observed with the colon patients. In contrast to the results based on Dukes' staging alone, in which we found that rectal patients with stage B or C had worse 5-year outcomes than colon carcinoma patients with the corre-

TABLE 5. *Factors Influencing 5-year Survival Rates After 'Curative' Resection of Colorectal Adenocarcinoma According to the Logistic Regression Analysis*

Variable	Beta Coefficient	Standard Error	p Value
Stage			
B (n = 264)	+1.38	0.22	<0.00001
C (n = 215)			
Race			
Caucasian (n = 277)	+0.6	0.22	<0.007
Black (n = 202)			
Tumor morphology			
Exophytic (n = 289)	+0.79	0.22	<0.0004
Nonexophytic (n = 190)			
Vascular–lymphatic microinvasion			
Absent (n = 295)	+1.02	0.23	<0.00001
Present (n = 184)			

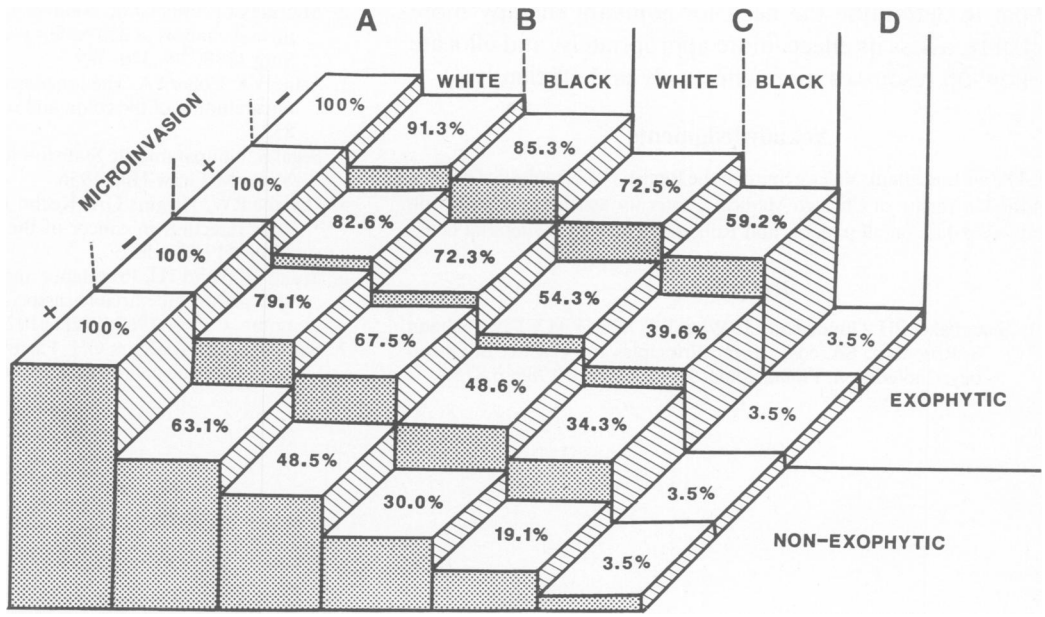

FIG. 5. Estimates of 5-year survival probabilities for colorectal adenocarcinoma. For each of the 16 Dukes' stages B and C subgroups, the estimate is based on the four coefficients obtained from the statistical analysis described in Materials and Methods. The respective 5-year survival rates of colon and rectal patients were averaged to provide probability estimates for Dukes' A and D patients.

sponding stage, our rectal staging system yielded a high degree of correlation in 15 of 16 subgroups of colon patients. The only subgroup with an observed 5-year survival rate significantly higher than the predicted rate was the subgroup with the worse prognosis: blacks with stage C, nonexophytic adenocarcinoma with microinvasion. For that group, the observed value was 36% compared to 14% based on the rectal patients. This finding suggests that rectal carcinoma, characterized by these more severe features, may have a more dismal prognosis than a similarly described colon carcinoma.

Our finding that rectal and colon carcinoma, when stratified by clinical and pathologic characteristics, have a similar prognosis, differs from that reported previously in the literature. Past reports have suggested that survival, based on the original or modified Dukes' classification, after a potentially curable resection for rectal carcinoma, is poorer than that after a similar operation for intra-abdominal colon cancer. Dwight et al.,[5] reporting on 1064 cases of colorectal cancer, found that stage, site of origin, and technical complications independently (using a multivariate analysis) influenced 5-year survival. Specifically their 5-year survival rate after curative resection of colon carcinoma was 61% compared to 43% for rectal carcinoma; while their rates for Dukes' B and C were 65% and less than 37%, respectively. Other authors,[6,7] using univariate analysis, have agreed with Dwight in asserting that site exerts a negative influence in long-term survival.

We believe that the difference in conclusions is due to the multifactorial nature of colorectal adenocarcinoma, and that once certain features are identified and incorporated into the analysis, the issue of the site of the lesion loses its influence on 5-year survival. This hypothesis is supported by the fact that our results, grouped by Dukes' stage, indicate a better prognosis for colon patients than for rectal patients, but when grouped into more homogenous subgroups, the apparent difference disappears. The discrepancy probably reflects the finding that rectal cancers more frequently than colon cancers have characteristics associated with a worse outcome (*i.e.*, more advanced stage, nonexophytic lesions, and presence of vascular and/or lymphatic microinvasion).

Therefore, to generate a more accurate clinical pathologic staging system for colorectal adenocarcinoma, we combined the data from the rectal patients and colon patients. The staging system is divided into 18 subgroups. The first subgroup, stage A, is identical to the stage A of the Astler-Coller modification of Dukes' classification.[3] The last subgroup, stage D, identifies tumors with distant metastases (carcinomatosis, liver, lung, and so on). The prognosis at 5 years in these two groups is so well defined that other clinicopathologic variables have little to contribute in terms of better prognostic accuracy. The remaining patients fall into the 16 subgroups derived from combining the four significant variables described above. Figure 5 graphically displays this new clinicopathologic staging system for colorectal adenocarcinoma, indicating the 5-year survival rate for each subgroup.

We believe that an improved prognostic capability will enable surgeons not only to advise their patients more accurately as to their prognosis but also to identify subgroups of high-risk or low-risk patients. This will allow

them to determine the need for adjuvant therapy more reliably, assess its effects more appropriately, and allocate follow-up resources more effectively and efficiently.

Acknowledgments

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