A 5- to 21-Year Follow-up and Analysis of 250 Patients with Rectal Adenocarcinoma

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A total of 250 patients with rectal adenocarcinoma were operated on at the University of Chicago Medical Center between 1965 and 1981. The operation performed was curative resection in 154 patients, palliative resection in 16 patients, diverting colostomy in 21 patients, exploratory laparotomy in 11 patients, and transanal removal in 48 patients. Of the 154 curative resections, 115 were abdomino-perineal (APR), three were total proctocolectomies, and 36 were low anterior resections (LAR). No anastomotic complications were observed in this latter group. Operative mortality was 3%. Complete follow-up was obtained in 152 patients (98.7%). Five- and 10-year actuarial survival rates were 68.8 and 59.4%, respectively, for patients with Dukes' B_1 adenocarcinoma (n = 32), 55.8 and 44.2% for Dukes' B_2 tumors (n = 52), and 42.9% and 25.4% for Dukes' C tumors (n = 63). Distant metastases developed in 59 patients (39.6%), and pelvic recurrence developed in another 18 patients (12%); 5-year survival rates were 23.6% and 22.2%, respectively. Multivariate analysis with Cox regression showed that stage (p = 0.0001), race (p = 0.03), tumor morphology (p = 0.02), and vascular and/or lymphatic microinvasion (p = 0.001) were statistically significant in their association with survival. Logistic regression analysis confirmed these results and allowed for the estimation of 5-year survival probabilities in 16 groups of patients defined by various associations of these four factors. These estimates ranged from a high of 92% in Caucasian patients with Stage B, exophytic tumors with no vascular or lymphatic microinvasion, to a low of 14% in black patients with Stage C, nonexophytic tumors and with the presence of vascular and/or lymphatic microinvasion. Univariate analysis showed that histologic type (p = 0.0006), stage (p = 0.05) and vascular and/or lymphatic microinvasion (p < 0.001) were significantly associated with the incidence of pelvic recurrence. Analysis of the extent of the operation revealed that the incidence of pelvic recurrence was reduced by the performance of a wide pelvic lymphadenectomy (9.4% *vs.* 16.4%), but the result did not reach statistical significance (p = 0.16). In conclusion, this study confirms the well-established prognostic value of the Dukes' staging classification of rectal carcinoma. Further, the analysis reveals that race, tumor morphology, and the presence or absence of lymphatic and/or vascular microinvasion significantly influence outcome. By associating these four statistically significant and independent variables, the prognosis for any individual patient can be estimated more precisely than by using Dukes' staging alone. Moreover, univariate analysis of the data pertaining to the local recurrence rate has demonstrated statistically significant associations with Dukes' staging, lymphatic and/or vascular microinvasion, and tumor histologic type.

SINCE THE ERA OF Miles and Dukes, surgeons and pathologists have sought to improve their ability to predict more accurately the outcomes for patients with rectal carcinoma. Variables representing pathologic, clinical and therapeutic characteristics have been analyzed in an attempt to identify prognostic indicators. The majority of these studies have analyzed these characteristics through the use of a univariate analysis that compares and contrasts one therapy or characteristic of that therapy with patient survival. In the treatment of any cancer, however, many factors influence survival. Therefore, in an effort to refine the present predictive classification, this study employed multivariate regression analysis to identify several clinically important variables and assess their combined impact on patient survival.

Materials and Methods

Between 1965 and 1981, 250 patients with rectal adenocarcinomas underwent surgical treatment at the Uni-

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versity of Chicago Medical Center. All 25 patients who had a transanal removal of a Dukes' A adenocarcinoma survived for 5 years. Seventy-one patients recognized as having Dukes' D, either pre- or intraoperatively, underwent a palliative resection in 16 instances; a diverting colostomy in 21; exploratory laparotomy in eleven; and transanal removal in 23. Their 5-year survival rate was only 2.8%. The remaining 154 potentially curable patients form the basis of this retrospective review.

The clinical records of all these patients were reviewed, and in 152 cases (98.7%), complete follow-up to December 1986 was obtained through the Registry of Neoplastic Diseases of the University of Chicago. Data on age, sex, race, distance of distal tumor margin from anal verge, tumor morphology and size, type of operation, length of resected distal margin, extent of pelvic lymph node dissection, mortality, and evidence of local recurrence or distant metastasis were specifically sought in each instance. Length of resected distal margin, tumor morphology and size were extracted from pathology reports. 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. Local recurrence was defined as recurrence in the pelvis, perineum, anastomosis, or perineal scar.

Histologic slides and archival paraffin blocks were retrieved for confirmation of diagnosis, determination of histologic type, stage, tumor differentiation, vascular and/or lymphatic microinvasion, by one pathologist who was unaware of the patients' 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 lined space was surrounded by a smooth muscle layer. Tumors were staged according to the Astler-Coller modification of Dukes' classification.[1]

In 137 cases, data concerning the extent of pelvic lymphadenectomy were obtained from operative reports. Wide pelvic lymphadenectomy was defined as a lymphadenectomy, including lymph nodes distal to the aortocaval bifurcation along the common and internal iliac vessels. In 136 cases, vascular and/or lymphatic microinvasion was directly assessed on review of existing slides or those obtained from archival paraffin blocks. The search for all other parameters of interest was successful in at least 146 patients.

Data regarding the occurrence of distant metastases, the incidence of local recurrence, and the presence of tumor extension through the bowel wall were analyzed by the Kruskal-Wallis analysis of variance (ANOVA)[2] considering each independent variable individually. Long-term survival was analyzed both by logistic regression analysis[3] and by proportional hazards technique.[4] The parameters of the logistic regression and proportional hazards models were estimated through the use of SAS maximum likelihood procedures written by Professor F. E. Harrell of Duke University.[5] The assumptions of the latter model were confirmed through the use of the method of Schoenfield.[6]

The dependent variables for the long-term survival analyses were survival time in months for the multivariate proportional hazards regression and the 5-year survival for the multivariate logistic regression. The following independent variables were entered into both regressions: age (both as a continuous variable and dichotomized at the age 40), sex, race, the operation performed (low anterior resection (LAR) *vs.* abdominal perineal resection (APR)), distance of tumor from anal verge (both as a continuous variable and analyzed as low, middle, and high rectum), length of distal margin in LAR, extent of pelvic lymph node dissection, tumor size, differentiation degree, histologic type, Dukes' stage, tumor morphology (exophytic *vs.* nonexophytic) and presence of vascular and/or lymphatic microinvasion. For dichotomized variables, coefficients were estimated by coding the variable as "0/1." For example, the following variables were coded: race = 0/1 for Caucasians/blacks, Dukes' stage = 0.1 for Stage B/Stage C, microinvasion = 0/1 for absence/presence, and morphology = 0/1 for exophytic/nonexophytic.

The two different long-term survival analyses were performed to validate the results. Both analyses involved different assumptions, and therefore yielded a measure of statistical authenticity to any conclusions that were arrived at by both methods. In addition, the proportional hazards model makes more complete use of the data, resulting in higher significance levels, and the logistic model allows estimates of 5-year survival rates.

Results

The 154 rectal adenocarcinomas were evenly distributed over the entire length of the rectum. Sixty-one were located in the low rectum (below 6 cm); 40 were located in the midrectum (between 6 and 10 cm); and 53 were located in the upper rectum (between 10 and 16 cm). The location within the rectum had an influence on what type of operation was to be performed. Of the 115 rectal adenocarcinomas treated with APR resection, 53.0% were located in the low rectum, 25.3% were located in the middle, and 21.7% were located in the upper rectum. LAR was performed in 36 patients; the rectal cancers of 31% were located in the mid-rectum, and those of 69% were located in the upper rectum. Of these patients, 32 underwent LAR with primary anastomosis,

resulting in no anastomotic complications, and the remaining four underwent LAR with end colostomy and Hartmann pouch. In the remaining three cases, a proctocolectomy with ileostomy was performed because of the concomitant presence of ulcerative colitis. In 64 patients, the operative procedure was complemented with a wide pelvic lymphadenectomy, depending on the surgeon's preference.

Follow-up analysis revealed that five patients (3%) died in the immediate postoperative period, and two were lost to follow-up. These patients were not included in the following analysis. Of the remaining 147 with complete follow-up, 89 were men and 58 were women. The mean age at time of operation was 61.7 years, with a range from 24–93 years.

The patients' survival was analyzed by tumor stage. The two patients in whom long-term follow-up data were not available were found to have tumors with stage C_2. Of the remaining surviving 147 patients, tumor stage was B_1 in 32 cases, B_2 in 52 cases, C_1 in 5 cases, and C_2 in 58 cases. The survival rates, based on life-table analysis, at 5 and 10 years were 68.8 and 59.4%, respectively, for patients with Dukes' B_1 adenocarcinomas, 55.8 and 44.2% for Dukes' B_2 tumors, and 42.9 and 25.4% for Dukes' C tumors.

A local recurrence developed in 18 patients (12%). The local recurrence was identified as having arisen in the perineum in seven patients, and in the pelvis in the remaining eleven. The pelvic recurrence rate was 6% for Dukes' B and 20.6% for Dukes' C tumors. Four patients (22.2%) with a local recurrence survived for 5 years or longer, and one patient survived for more than 10 years. The more distal the original tumor arose, the more the incidence of local recurrence increased. For tumors of the upper third of the rectum, the incidence of local recurrence was 8.0%, but increased to 12% for middle rectal lesions, and to 14% for low rectal lesions. Half of the recurrences were clinically evident by 1 year, and 50% of the patients with local recurrences died by 20 months. Of 18 patients with a local recurrence, four also had a synchronous distant metastases. Although the difference was not statistically significant, their average survival rate was only 27 months, compared with 44.7 months for the 14 patients with local recurrence but with no distant metastasis.

Table 1 displays the association between several key variables and the incidence of local recurrence. Patients with Dukes' C tumors demonstrated a significantly greater incidence of local recurrence than patients with stage B_2 or B_1: 20.6% *versus* 9.6% *versus* 0%, respectively ($p = 0.05$, ANOVA). The presence of vascular and/or lymphatic microinvasion was associated with a significantly worse prognosis; 18 of 85 patients with microinvasion developed local recurrences, compared with none among the 51 patients who did not have evidence of microinvasion ($p < 0.001$, ANOVA). Additionally, the mucinous tumors had an increased likelihood of developing a local recurrence. Although only eleven patients had mucinous tumors, a local recurrence developed in 45.5%, as compared with 9.6% of the 135 patients with intestinal type tumors ($p = 0.0006$, ANOVA). The incidence of local recurrence in patients with exophytic tumors was slightly more than half that of patients with nonexophytic carcinomas. The incidence of local recurrence was also reduced in patients in whom a wide pelvic lymphadenectomy had been performed or in whom a distal margin of at least 5 cm was obtained. These differences did not reach statistical significance.

TABLE 1. *Variables Influencing Incidence of Local Recurrence after "Curative" Resection of Rectal Cancer*

Variable	Local Recurrence (%)	p Value*
Histologic type		
Intestinal (n = 135)	9.6	0.0006
Mucinous (n = 11)	45.5	
Vascular-lymphatic microinvasion		
Absent (n = 51)	0	<0.001
Present (n = 85)	21.2	
Dukes' stage		
B_1 (n = 32)	0	0.05
B_2 (n = 52)	9.6	
C (n = 63)	20.6	
Tumor morphology		
Exophytic (n = 76)	7.9	0.16
Nonexophytic (n = 71)	15.5	
Length of distal margin		
Less than 4.9 cm. (n = 21)	19	0.18
More than 5.0 cm (n = 14)	0	
Pelvic lymphadenectomy		
Conventional (n = 73)	16.4	0.16
Wide (n = 64)	9.4	

* Value derived from univariate Kruskal-Wallis analysis of variance.

Fifty-nine patients (39.6%) developed distant metastases and their 5-year survival rate was 23.6%. Seventy-one sites were involved: lung in 27 cases, liver in 18, peritoneum in 13, brain in eight, bone in three, and supraclavicular and inguinal lymph nodes in one each. The liver was the single organ involved in ten cases (17% of patients with metastases and 6.7% of all patients). The likelihood of developing a metastasis was found to be proportional to the stage of the original tumor: 44.0% at Stage B and 52.4% at Stage C ($p = 0.0003$, ANOVA). Vascular and/or lymphatic microinvasion was significantly associated with the development of metastases; 52.7% of patients with this characteristic developed distant metastases, as compared with 16.7% of the patients

TABLE 2. *Factors Influencing 5-year Survival after "Curative" Resection of Rectal Cancer According to the Proportional Hazards and Logistic Regression Analysis*

Variable	Proportional Hazards			Logistic Regression		
	Beta Coefficient	Standard Error	p value	Beta Coefficient	Standard Error	p value
Stage B (n = 84) C (n = 63)	−1.04	0.26	0.0001	+1.38	0.43	0.001
Race Caucasian (n = 98) Black (n = 49)	−0.56	0.25	0.03	+0.78	0.45	0.09
Tumor morphology Exophytic (n = 76) Nonexophytic (n = 71)	−0.58	0.26	0.02	+1.10	0.43	0.01
Vascular-lymphatic microinvasion Absent (n = 51) Present (n = 85)	−1.00	0.30	0.001	+1.06	0.46	0.02

without microinvasion ($p < 0.0001$, ANOVA). Tumors with a nonexophytic growth pattern also developed distant metastases significantly more frequently than did exophytic tumors (48.6% *vs.* 29.7%, respectively, $p = 0.02$, ANOVA).

There was evidence of extension through the bowel wall in 110 patients (74.8%). Our analysis revealed that the presence of vascular and/or lymphatic microinvasion was associated with a significantly greater incidence of such tumor extension, 85.9% of patients with microinvasion exhibited such evidence, compared with the 55.6% of patients without microinvasion ($p < 0.05$, ANOVA). Moreover, a significantly larger percentage of patients with nonexophytic tumors experienced invasion through the bowel wall, compared with those with exophytic tumors (85.9% *vs.* 63.5%, $p = 0.002$, ANOVA).

Multivariate logistic regression and proportional hazards analysis were performed to evaluate significant relationships between clinicopathologic features and patient survival. The patient outcome variables evaluated were 5-year survival rates in the logistic regression and the survival time in months in the proportional hazards analysis. The independent variables entered into both analyses are outlined in the "Methods" section. Table 2 summarizes the results of the analysis for those variables found to have statistically significant coefficients in the multivariate analyses. As described in the "Methods" section, the proportional hazards analysis makes more complete use of the data, resulting in more precise significance levels. Of the four variables found to be statistically significant in their association with patient survival, only race (Caucasians compared with blacks) was statistically significant in the proportional hazards analysis alone, and approached significance ($p = 0.09$) in the logistic regression. The other three variables, Dukes stage (B compared with C), tumor morphology (exophytic compared with nonexophytic) and the absence or presence of vascular and/or lymphatic microinvasion were found significant for survival by both methods of analyses.

In order to present our results in a more clinically useful manner, demonstrating the magnitude of the difference in outcome observed with each significant variable in our study population, 20-year survival rates based on life table analyses[7] were calculated for each of the four variables. Figures 1–4 graphically display these results.

The differences in 5- and 10-year survival rates based on Dukes' staging is depicted in Figure 1. It is noteworthy that five patients with Dukes' B tumors and two with Dukes' C died of recurrent disease, more than 10 years after their curative procedure. Additionally, the presence of vascular and/or lymphatic microinvasion was associated with worse long-term survival; 41.8% of patients with this histological characteristic survived for 5 years, compared with 71.4% of patients without such microinvasion (Fig. 2). Patient outcome was also found to differ significantly with respect to tumor morphology. Patients with tumors having a nonexophytic growth pattern experienced a worse long-term prognosis than patients with tumors having an exophytic growth pattern—that is, 36.6% survival at 5 years *versus* 69.3% respectively (Fig. 3). Finally, blacks were found to have a poorer survival than Caucasians; 42.9% of blacks survived to 5 years, compared with 58.2% of Caucasians (Fig. 4).

Although these life-table results make the differences in outcome associated with a specific variable readily apparent, they do not take into account the multifactorial association with outcome incorporated in the multivariate regression analysis. This difference is clearly seen

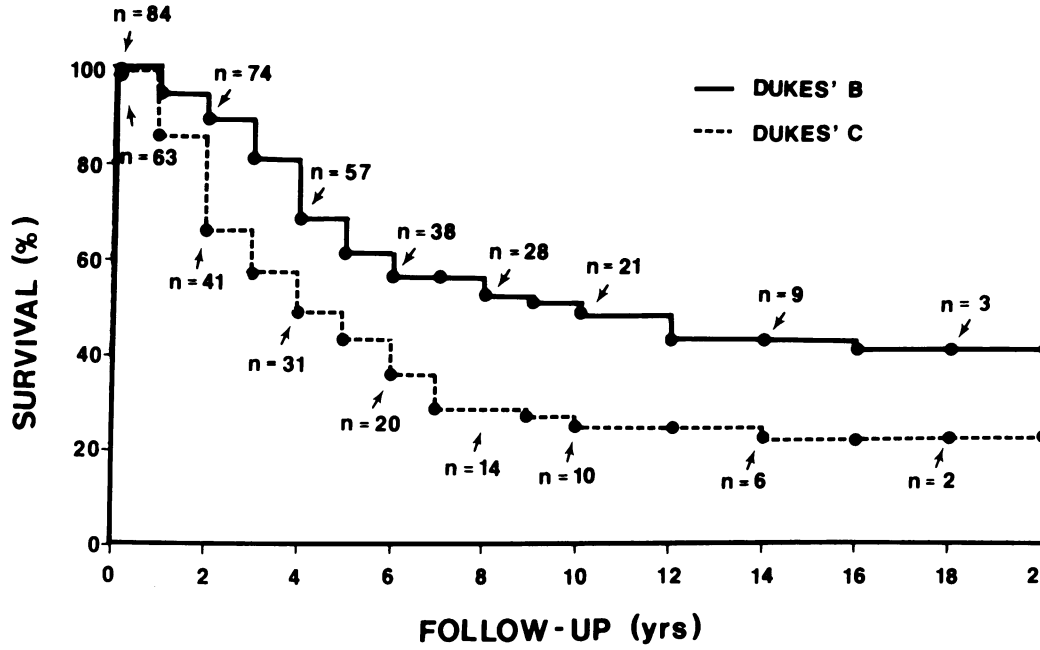

FIG. 1. Factors influencing survival after curative resection of rectal adenocarcinoma: Dukes' stage. 20-year survival rates based on life-table analysis calculated for patients after curative resection of Dukes' B and Dukes' C adenocarcinoma. Patients who died of intercurrent disease were censored at the time of the last known follow-up.

when one compares the 5-year survival rates based on life-table analysis to the estimated 5-year survival probabilities calculated from the multivariate logistic regression for the variables, presented in Figure 5. For example, the 5-year life-table survival rates classified by Dukes' stages B and C are 60.7% and 42.9%, respectively. By comparison, the estimated probabilities for 5-year survival in our population, based on the Dukes' stage coefficient generated by the logistic regression, are 73% and 41%, respectively.[1] This difference is due to the logistic regression's separating out the influence of the other significant variables and generating a coefficient that reflects the risk associated with Duke's stage B or C apart from the risk associated with the other significant variables.

Thus, in order to evaluate the influence of all four variables considered simultaneously on outcome, estimates of 5-year survival probabilities were based on the four coefficients obtained from the logistic regression, and were calculated for 16 different groups of patients. The groups were divided on the basis of those factors thought to have a significant effect on mortality (stage,

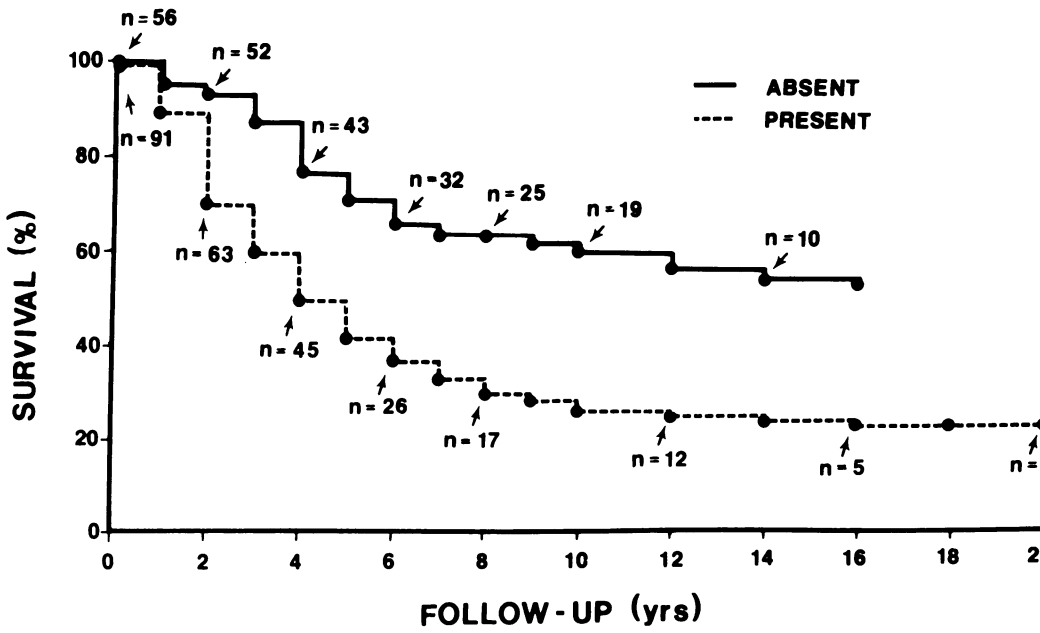

FIG. 2. Factors influencing survival after curative resection of rectal adenocarcinoma: lymphatic and/or vascular microinvasion. 20-year survival rate based on life-table analysis calculated for patients after curative resection of a rectal adenocarcinoma with or without lymphatic and/or vascular microinvasion. With this analysis, patients who died of intercurrent disease were censored at the time of last known follow-up.

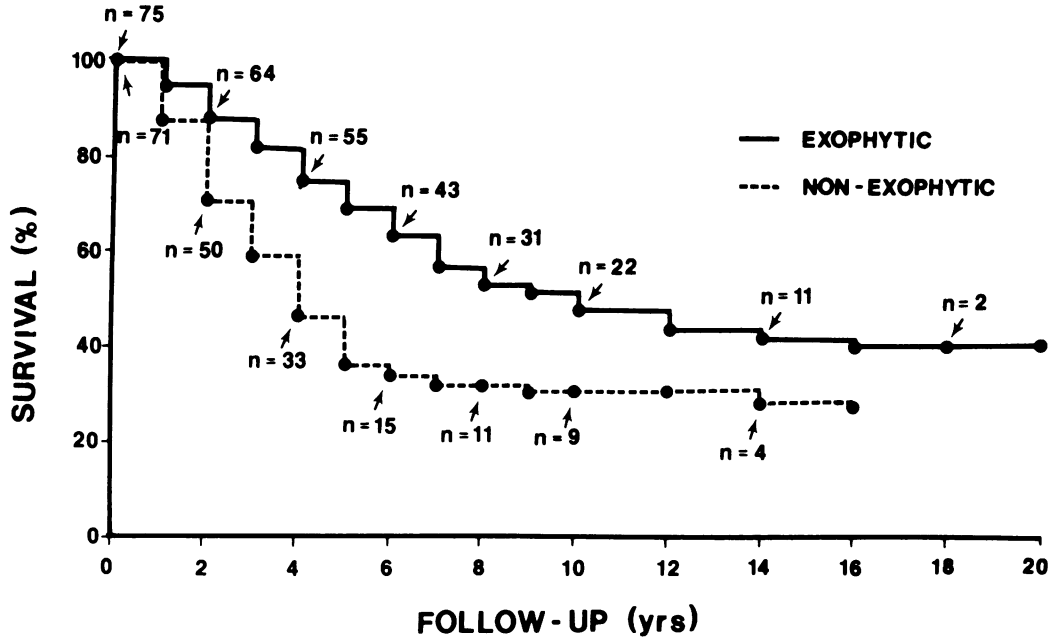

FIG. 3. Factors influencing survival after curative resection of rectal adenocarcinoma: tumor morphology. 20-year survival rates based on life-table analysis for patients after curative resection of an exophytic or nonexophytic rectal adenocarcinoma. With this analysis, patients who died of intercurrent disease were censored at the time of last known follow-up.

microinvasion, tumor type, and race). Figure 5 summarizes these findings. The survival estimates of patients for which all four attributes are known are cited at the bottom of the figure and can be generalized to accommodate other populations with the same characteristics.* The probability of surviving for 5 years ranged from a high of 92% in Caucasian patients with Stage B, exophytic tumors and absence of vascular and/or lymphatic microinvasion, to a low of 14% in black patients with Stage C, nonexophytic tumors and the presence of vascular and/or lymphatic microinvasion. It is important to note that some subpopulations with Dukes' stage C tumors have higher estimated probabilities of survival than others with Dukes' stage B. In particular, Caucasian patients with stage C, exophytic tumors and no vascular or lymphatic microinvasion had an estimated 5-year survival rate of 75%, compared with black patients with stage B, nonexophytic tumors and vascular and/or lymphatic microinvasion, who had an estimated survival rate of only 40%.

* The survival estimates in the higher levels of Figure 5, where one or more attributes are not known, were calculated by weighing the estimated probabilities in the constituent groups by those group's frequencies in the sample analyzed. Thus, these estimates are specific to samples of approximately the same composition as the sample considered here. Only the survival estimates given at the bottom are generalizable to populations with other properties.

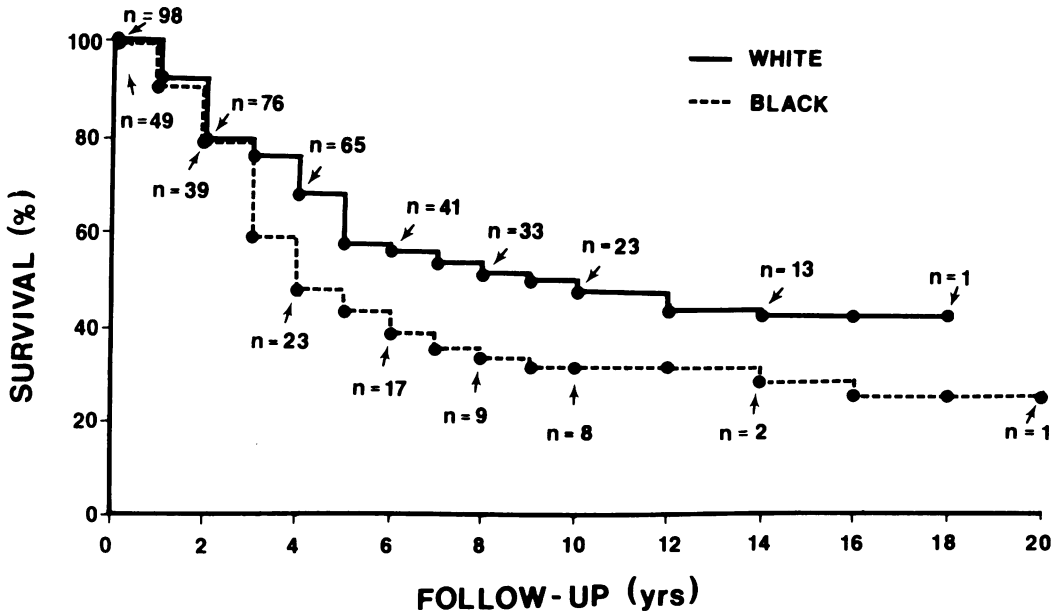

FIG. 4. Factors influencing survival after curative resection of rectal adenocarcinoma: race. 20-year survival rates based on life-table analysis calculated for Caucasian and black patients after curative resection of rectal adenocarcinoma. With this analysis, patients who died of intercurrent disease were censored at the time of the last known follow-up.

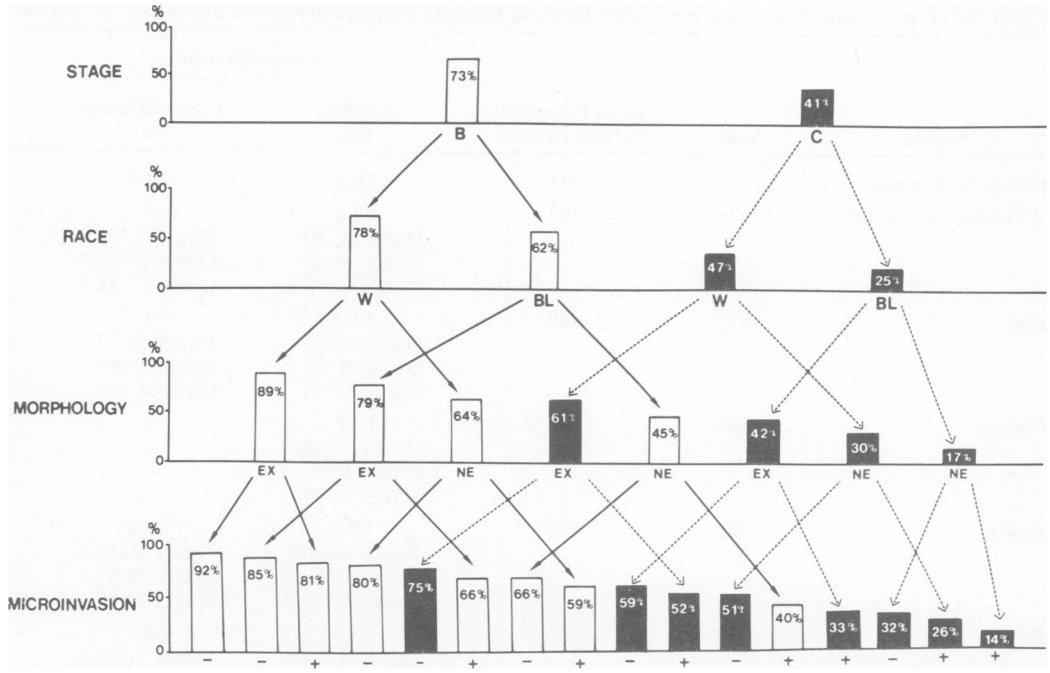

FIG. 5. Refinement of prognostic value of Dukes' classification in estimating 5-year survival probabilities. Estimates of 5-year survival probabilities, obtained from logistic regression, are shown for 16 different groups of patients. The groups were divided on the basis of those factors (stage, microinvasion,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

Discussion

The primary purpose of this study was to identify clinical or pathological characteristics that influence the prognosis of patients with rectal carcinoma in order to be able to predict more accurately their long-term prognosis. The ability to predict the long-term prognosis of an individual patient with colorectal carcinoma has been the aim of many studies since the introduction of Dukes' classification.[8] An improved prognostic capability would enable surgeons to identify subgroups at high or low risk, could conceivably help determine the type of operative procedures that should be performed and help determine the need for adjuvant therapy. Furthermore, a more precise prognostication would also be helpful in evaluating the results of different therapies and different series, as well as to allocate follow-up resources more effectively and efficiently.

A host of clinical and pathologic features have been previously analyzed by univariate analysis in an attempt to identify prognostic indicators. Little emphasis has been given to the relative contribution and importance of each of the parameters evaluated. Chapius et al.[9] analyzed 709 patients with colon or rectal adenocarcinoma, using Cox multiple regression. They found that clinicopathologic stage was the major determinat of prognosis, but also identified several other significant independent variables, including age, histologic grade and venous invasion. However, they did not group the significant variables to assess their combined impact on estimated long-term survival, nor did they try to refine the staging method. The multivariate analysis performed by us had identified the importance of four independent factors in the long-term prognosis of patients with rectal carcinoma after curative resection: Dukes' stage (B compared with C), race (Caucasians compared with blacks), tumor morphology (exophytic compared with nonexophytic), and the absence or presence of lymphatic and/or vascular microinvasion. By considering all four variables simultaneously and calculating the predicted 5-year survival for the 16 different subgroups, the Dukes' staging has been refined in a clinically useful manner. For example, some patients with a Dukes' stage C tumor have higher estimated probabilities of survival than others with a Stage B tumor. For the sixteen subgroups, the probability of surviving for 5-years ranged from a high of 92%, predicted for Caucasian patients with Stage B, exophytic tumors and no evidence of vascular or lymphatic microinvasion, to a low of 14%, predicted for black patients with Stage C, nonexophytic tumors with microinvasion. By comparison, using Dukes' staging alone, the predicted 5-year survival rate for our population was much less precise: 73% for those with Stage B tumors and 41% for those with Stage C. Since all four characteristics are readily known after surgery, our more specific classification can be used to inform the patient as to his long-term prognosis and to identify subgroups of patients who might benefit from adjuvant therapy and more intense follow-up.

Patient outcome characteristics of our population are similar to other large series of patients with rectal adenocarcinoma that were reported in the literature.[10-15]

TABLE 3. *5-Year Survival Rate, Local Recurrence Rate and Hospital Mortality in Recent Large Series on Surgical Treatment of Rectal Carcinoma*

Author	Year	No. of Potentially Curable Patients	5-year Survival		Local Recurrance Rate (%)	Hospital Mortality (%)
			Absolute (%)	Cancer Relative (%)		
Lockhart-Mummery	1976	1931	56.6	68.4	—	21.–7.0
Whittaker and Goligher	1976	407	48.8	56	—	9.6
			Dukes' A: 80	Dukes' A: 91.9	—	
			Dukes' B: 62	Dukes' B: 71.3	—	
			Dukes' C: 32.8	Dukes' C: 37.7	—	
Patel	1977	435	54	59	24	2.5
			Dukes' A: 65	Dukes' A: 77	Dukes' A: 13	
			Dukes' B: 63	Dukes' B: 65	Dukes' B: 17	
			Dukes' C: 30	Dukes' C: 33	Dukes' C: 37	
Localio	1983	646	60.6	—		2.2
			Dukes' A: 88.6	—	Dukes' A: 2.6	
			Dukes' B: 57	—	Dukes' B: 13.3	
			Dukes' C: 36	—	Dukes' C: 25.2	
Enker	1986	412	54.2	58.8	27.5	1.9
			Dukes' A: 80.5	Dukes' A: 84.4	Dukes' A: 13.5	
			Dukes' B: 47.7	Dukes' B: 57.6	Dukes' B: 29.7	
			Dukes' C: 35.9	Dukes' C: 37.1	Dukes' C: 41.3	
Davis	1987	235	41.9	54.9	—	3.0
			Dukes' A: 74.8	Dukes' A: 97.8	—	
			Dukes' B: 55.2	Dukes' B: 72.2	—	
			Dukes' C: 31.4	Dukes' C: 40.1	—	
Present series	1988	154	52.6	53.1	12.0	3.0
			Dukes' B: 59.5	Dukes' B: 60.7	Dukes' B_1: 0	
			Dukes' C: 42.9	Dukes' C: 42.9	Dukes' B_2: 9.6	
					Dukes' C: 20.6	

Table 3 gives a comparison of the major features of each study. Although definitions of stages and survival rates differ, our survival rates lie within the range of results reported, and therefore the prognostic classification derived from our results should be widely applicable. Moreover, the identification of the four statistically significant prognostic variables is consistent with earlier work in this field. Most series have reported a decrease in the survival rate and an increase in local recurrence associated with a Dukes' C tumors.[12–14] The influence of race has been analyzed recently by the SEER program of the National Cancer Institute.[16] According to these data, the 5-year survival rate for rectal adenocarcinoma was 50% for Caucasian patients and 37% for black patients during the last period analyzed (1977–1983). A better survival rate for Caucasians has been observed in all periods analyzed since 1960.

Rankin was the first to observe that patients with exophytic tumors had a better 5-year survival rate than patients with nonexophytic tumors.[17] This finding has subsequently been confirmed several times,[18–21] and again by our present findings of a statistically significant greater 5-year survival rate for patients with exophytic tumors, compared with that of patients with nonexophytic tumors. In an effort to explain the difference in long-term prognosis between exophytic and nonexophytic tumors, Cohen recently reported that exophytic tumors had a 34% incidence of bowel wall penetration, compared with a 77% incidence for nonexophytic tumors.[14] Cohen concluded that exophytic tumors tend to grow toward the lumen, in contrast with nonexophytic tumors, which tend to grow into the bowel wall. Our conclusion that a significantly smaller percentage of patients with exophytic tumors exhibited evidence of extension through the bowel wall, compared with patients having nonexophytic tumors, provides further support to Cohen's conclusion. Moreover, we have found that a significantly higher percentage of patients with nonexophytic tumors eventually develop distant metastases, as compared with patients with exophytic tumors.

Many reports have dealt with the influence of vascular invasion by colon and rectal cancers on the development of distant metastases and survival[22–31]; some have pursued this investigation to its influence on local recurrence.[24] Minsky has recently examined the influence of lymphatic invasion on survival.[32] Dionne, in an analysis of 1376 rectal carcinomas, observed that microscopic venous invasion was associated with a 47% incidence of blood-born metastases, in comparison with a 27% incidence in the absence of venous invasion.[33] Sunderland was the first to correlate vascular invasion with poorer long-term survival,[22] a finding later confirmed by Swinton[30] and Talbot.[23] This was also the conclusion reached by Rich, who was the first to highlight the increased rate

of local recurrence in tumors with vascular invasion.[24] Recently, Minsky has found that lymphatic vessel invasion is statistically significant as a prognostic variable having a negative influence on 5-year survival.[32] In our series, the overall incidence of vascular and/or lymphatic invasion is 61%, and parallels the experience of Minsky, who found a 48% incidence of vascular invasion and a 9.5% incidence of lymphatic invasion. Moreover, in concert with the above reports, we have found that the presence of vascular and/or lymphatic invasion is associated with a statistically significantly decreased long-term survival, as well as with a significantly increased likelihood of developing a local recurrence. The more aggressive nature of rectal adenocarcinomas with vascular and/or lymphatic microinvasion is supported further by the finding that, in our sample, a significantly greater percentage of these tumors extended through the bowel wall and eventually developed distant metastases.

Because of the small number of our patients who developed a local recurrence (n = 18), we were unable to perform a similar multivariate analysis on these data. Univariate analysis of the incidence of local recurrence revealed statistically significant associations with Duke's staging, lymphatic and/or vascular microinvasion, and histologic cell type. The mucinous type of rectal adenocarcinoma had a statistically significantly higher incidence of pelvic recurrence than the intestinal type adenocarcinoma (45.5% *vs.* 9.6%, respectively). This is in agreement with Moossa, who calculated a 28% local recurrence rate in 25 "colloid type" adenocarcinomas, compared with a 19% rate for 127 "intestinal type" adenocarcinomas.[34] We suggest that this analysis may be used in selecting patients for postoperative radiation therapy.

In conclusion, the results of our study confirm the well-established prognostic value of the Duke' staging classification for carcinoma of the rectum. Further, the analysis reveals that race, tumor morphology and the presence or absence of lymphatic and/or vascular microinvasion influence outcome significantly. By associating these four statistically significant and independent variables, the prognosis for any individual patient or groups of patients can be estimated more precisely than by Dukes' staging alone (Fig. 5). Moreover, univariate analysis of the data pertaining to the local recurrence rate has demonstrated statistically significant associations with Dukes' staging, lymphatic and/or vascular microinvasion, and histologic cell type.

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Discussion

DR. RICHARD E. WILSON (Boston, Massachusetts): I congratulate Dr. Michelassi and Dr. Block for this comprehensive retrospective review of rectal cancer treated between 1955 and 1981. The manuscript, which I enjoyed reviewing, extensively correlates biologic variables with prognosis for regional and distant recurrence and survival.

I generally concur with their observations. A similar review of patients with rectal cancer operated on at the Brigham Hospital confirmed that stage of disease was the most important indicator for recurrence and survival. The low rectal cancers recurred uniquely in the region of the disease rather than distantly, and this occurred also in this study. The data from this study showed the dangerous effect of endophytic lesions, and vascular and lymphatic invasion which are important risk factors. It must be stressed, however, that there are serious defects in the Dukes' staging system because the tumor size, extent of tumor involving the circumference of the bowel, and the site and number of involved lymph nodes are not a part of that staging system, and therefore there is a broad group of patients within each stage.

I was struck by the continued worse prognosis for black patients in this study. One could not help wondering whether or not with black patients generally having less appropriate medical care in this central city, that the stage of the disease, although the same, was at the much worse end of the spectrum for these disadvantaged patients.

The same was true for breast cancer in the American College of Surgeons study that we carried out, where the black patients had a continual significant worsening of prognosis without any definite stage or type differential.

Hopefully, newer studies using DNA analysis and histochemical classification, which are both available by biopsy before operation in rectal disease, might affect plans for surgery. I wonder if the authors have used this approach more recently?

However, my main comments relate to the potential for adjuvant chemoradiotherapy, especially with a cancer showing an important incidence of regional disease. Significant improvement in disease-free survival and overall survival was seen in the multicenter GITSG study where postoperative chemoradiotherapy showed significant differences from surgery alone, chemotherapy alone, and radiation therapy alone for both survival and disease-free survival in rectal cancer. The GI consortium is continuing with these trials as a prospective randomized approach to determine more effectively the interaction of chemotherapy and radiotherapy in rectal cancer.

These types of approaches will be necessary to alter the outcome for this disease, as I doubt that there is any difference in those life table survival curves in the past 30 or 40 years.

DR. CLAUDE WELCH (Boston, Massachusetts): I congratulate the authors on this article and I rise to support many of their conclusions, but I also have one of the same worries as Dr. Wilson has.

I want to touch primarily on the question of the pelvic lymph node dissection. Many years ago with a long experience by Dr. Meigs with this dissection for cancer of the female pelvic organs, particularly the cervix, the conclusion was reached that if this operation were done widely it would work well if nodes were not involved. However, if the nodes were involved, the patients had a tendency to die.

We as surgeons are much taken with these beautiful pictures of the lymph node dissection, but I believe we have to recognize that there is a great deal of further operating time and difficulty involved in the lymph node resection.

I would like to ask the authors how many of their patients who did turn out to have positive lymph nodes survived the 5-year period?

I also want to call attention to the alternative method suggested by Dr. Wilson. Our series at the Massachusetts General Hospital has been following this particular line because we have been using postoperative radiation therapy for selected patients, with B-2 and C lesions, rather than wide lymph node resection. Our cases, of course, have been matched with historic controls. There have been no prospective studies that have been worthwhile so far, but they now are in prospect.

I ask the authors whether or not they believe that this might be a reasonable or even better alternative to their widespread lymph node dissection, and perhaps we could solve this problem which has been a rather burning controversy among colon and rectal surgeons for a long time.

DR. A. R. MOOSSA (San Diego, California): It is always an honor to discuss a paper from my former alma mater. The authors have set the gold standard for the surgical treatment of rectal cancer by reviewing their experience with patients treated between 1965 and 1981. The results are especially impressive for Dukes' C tumors. If my memory serves me right, George Block left the Astler-Coller scene at Michigan to join the University of Chicago around 1965. Hence, these superlative results are largely due to his personal efforts. A 3% operative mortality rate in 154 curative resections with no anastomotic leak is indeed impressive.

For the patient with rectal cancer, the end result is judged by two parameters: survival and pelvic–perineal recurrence. Dr. Block and his colleagues have used sophisticated multivariate regression analysis to identify factors that impact on patient outcome. They have confirmed our previous experience that Dukes' staging, vascular–lymphatic microinvasion, and histologic type are important prognostic factors. In addition, they have demonstrated that tumor morphology and race are two independent variables that also affect the end result.

I share Dr. Block's belief that the length of distal margin and pelvic lymphadenectomy are important but, unfortunately, due to relatively small numbers, the authors could not demonstrate statistical significance. I have three questions for the authors.

Is there any difference in outcome between male and female patients in this series, either in terms of survival or local recurrence?

Having delineated the prognostic factors after proctectomy, do they routinely give the high-risk patients postoperative adjuvant radiotherapy and/or chemotherapy?

Have they attempted to stage the patient before operation using CT scan of the pelvis or pre-rectal ultrasonography with a view toward giving preoperative radiotherapy to the most unfavorable lesions?

DR. JEROME J. DECOSSE (New York, New York): I do not believe that we have previously seen the presentation of the cells in relationship to prognosis. It is the best illustration I know of the interaction of prognostic factors and the cumulative effect of those not only for prognosis but also potentially serving as the basis for treatment selection of other adjuvant therapies. I congratulate the authors on this added contribution.

DR. GEORGE E. BLOCK (Closing discussion): Dr. Michelassi and I thank the discussants for their questions and for their kind remarks.

Dr. DeCosse, we are most appreciative of your generous comments about the cells that illustrated our findings. We believe that these conclusions are the major contributions of our work. I had asked Dr. Moossa to say the same thing, but he refused to do so. (Laughter)

Dr. Moossa, in answer to your question, we were surprised that there