Regression Analysis of Prognostic Factors in Colorectal Cancer after Curative Resections

THEO WIGGERS, M.D., PH.D.,* JAN W. ARENDS, M.D., PH.D.,† ALEX VOLOVICS, PH.D.‡

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The clinical, laboratory, and pathologic data of 310 patients who had curative resections were prospectively collected and analyzed in a multiple stepwise regression model. Although several factors (*i.e.*, venous invasion) were of importance in univariate analysis, the following conclusions reflect the outcome and relative importance of the regression analysis only. Blood loss as an initial symptom and duration of symptoms were associated with a better prognosis. Location of the primary tumor, age, and sex did not appear to have prognostic value. Observations during operation such as palpable lymph nodes, fixity to adjacent organs, and tumor spill were related to a diminished tumor-free survival. Laboratory data (hemoglobin, leukocytes, ESR, GGTP, SGOT, SGPT, LDH, total protein, CEA) were tested for their potential prognostic values. Only a preoperative low protein level or an elevated CEA level were associated with an increased risk of death due to recurrent tumor. The histopathologic features (stage and grade), with the exception of venous invasion, were of relative importance in the determination of prognosis. The aforementioned variables can be included in a prognostic index on the base of which high-risk groups suitable for adjuvant studies can be identified. [Key words: Colorectal cancer; Prognostic factors; Regression analysis]

PROGNOSTIC FACTORS, derived from clinical, laboratory, and pathologic data of colorectal cancer patients are important for the determination of high-risk groups for recurrent disease.[1] Not only disease-related death, but also the first site of relapse should be considered in order to make a proper choice between surgical, radiotherapeutic, and chemotherapeutic modalities.

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Address correspondence to Dr. T. Wiggers: The Dr. Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.

From the Department of Surgery, The Dr. Daniel den Hoed Cancer Center, Rotterdam, the Department of Pathology, University Hospital Maastricht, Maastricht,† and the Department of Statistics, University of Limburg, Maastricht, The Netherlands‡*

Many studies have been published about the prognostic value of parameters determined by univariate analyses, but the availability of a stepwise regression model[2] has made it possible to establish the contribution and relative importance of a certain parameter. Since no single factor, or marker, is capable of determining the possibility of growth of residual disease after "curative" resections, a set of parameters included in a prognostic index may be used for this purpose.

It is the aim of this study to analyze the prospectively collected data of 310 patients in whom the primary tumors of the colon or rectum could be curatively resected. For this purpose, preoperative symptoms, laboratory data, operative details, pathologic findings, and postoperative complications are included in a multivariate analysis.

Materials and Methods

Patients: Between 1979 and 1981, 310 patients with histologic diagnoses of adenocarcinoma of the colon and rectum were entered in the study. These patients underwent potential curative resections and were part of a prospective multicenter study.[3] Follow-up was standardized, with an average duration of 58 months (range, 48-60 months). Survival data were available on all patients. For

this analysis, death due to recurrent disease, excluding mortality within 30 days, was used.

History: At admission a standard form was used to record the first presenting symptoms (blood loss, change of bowel habits, abdominal discomfort, tumor found by chance) and bowel movements at the time of diagnosis (regular blood loss, change in frequency or quality, unchanged). Patients were divided into four groups according to duration of symptoms: less than one week, one week to two months, two to six months, and over six months. Age was classified in two groups: below or above 65 years.

Laboratory: Hemoglobin, leukocyte count, erythrocyte sedimentation rate (ESR), blood group, gamma-glutamyl transpeptidase (GGTP), serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), serum protein, and carcinoembryonic antigen (CEA) were routinely determined. Due to change and variety of methods in determination, alkaline phosphatase could not be included in the final analysis.

Operation: During laparotomy, site of the primary tumor, extent of resection, clinical impression of lymph-node metastases, fixity to adjacent organs, and complications (over 1 liter of blood loss, tumor spill) were recorded.

Location: Tumors of the cecum and ascending colon were classified as right-sided tumors. Tumors of both flexures were included in the transverse colon. Left-sided tumors compromised the descending colon and the pelvic sigmoid. Below the sacral promontory up to the peritoneal reflection, tumors were classified as rectosigmoid. Distal extraperitoneal tumors were called rectal.

Treatment: Patients with colon tumors were entered into a randomized trial[3] in which one group was operated on with the no-touch isolation technique of Turnbull *et al.*[4] and the second group via a conventional resection technique. Patients who could not be included in the trial for different reasons (emergency operation, age, double tumors) were classified as other patient factors. Low-lying tumors for which preoperative radiotherapy was considered were classified as distal.

Pathology: Paraffin-embedded specimens of all resected tumors were reviewed centrally by one pathologist. Size and shape of the primary tumor, distance of free margins, lymph node involvement, Dukes' classification,[4] and grade[5] were recorded.

Postoperative: The postoperative course was classified as either uneventful or as complicated by an infection directly related to the operative procedure.

Statistical Analysis: Log-rank and Cox regression[2] analyses of the parameters included were performed using the computer program BMDP2L.[6] As for most parameters included, a substantial number of missing values were present; two analyses were performed: one using patients with complete data only, and a second analysis including a separate category "missing" for each parameter with missing values. No statistically significant differences were noted between the outcome of the parameters, when dichotomized as "present" *vs.* "missing." A prognostic score (S) for an individual patient (i) can be written as: $S_i = \beta_1 \times_{i1} + \beta_2 \times_{i2} + \ldots + \beta_p \times_{ip}$ · Beta $(1-P)$ is the regression coefficient of the observed value of that particular variable ($x_{i1} \ldots X_{ip}$). A prognostic variable with two or more categories of outcome is represented by a number of values equal to the number of its categories minus one. The category not included as a value is the reference category.

Results

The outcome of the parameters included in the regression model is summarized in Table 1. Some corresponding survival curves are plotted in Figs. 1 and 2.

Patients with blood loss as a first presenting symptom had a tendency for a better disease-free survival in the univariate analysis in comparison with patients with other initial symptoms ($P = .12$). The quality of the bowel movements at the moment of admission was of no significance ($P = .27$). Very short (less than one week), or long (over six months) duration of symptoms was associated with a poorer survival in relation to patients with symptoms ranging from one week to six months, whereas intermediate duration of symptoms was correlated with a longer survival. This was not significant, however ($P = .68$). Obstruction, resulting in a diverting colostomy as a first operation, was of no significance. Location of the primary tumor was not important for disease-related survival ($P = .49$). The presence of palpable lymph nodes close to the bowel wall lead to shorter survival in comparison with the absence of palpable nodes ($P = .16$). A significantly diminished survival was present if fixity to adjacent organs was recorded ($P = .05$). Tumor spill resulted in a less favorable outcome if compared with operations without complications ($P = .05$). The opinion of the surgeon after operation was important in the prediction of the final prognosis of the patient ($P = .02$). All histopathologic data included in the univariate analyses were of significant importance in prediction of poorer survival: presence of angioinvasive growth, advance in stage, and loss of differentiation.

After correction of nondisease-related death, postoperative complications were not influencing the chance of dying as a result of recurrent tumor. Application of the no-touch isolation technique was slightly better than the use of the conventional technique ($P = .17$). The other two categories cannot be considered in this regard. Both age ($P = .89$) and sex ($P = .84$) were not associated with a difference in survival.

TABLE 1. *Summary of Variables Entered in Regression Model*

Variable	Categories	Number of Observations	Number of Disease-related Death (%)	*P*-value of Log rank Test
First presenting symptom	Blood loss	108	21 (19.4)	0.12
	Change in bowel habits	80	23 (28.8)	
	Abdominal pain	72	26 (36.1)	
	Other	50	16 (32.0)	
Bowel movements at admission	Blood loss	63	12 (19.0)	0.27
	Changed	149	44 (29.5)	
	Unchanged	98	30 (30.6)	
Duration of symptoms	< 1 week	28	10 (35.7)	0.68
	1 week–2 months	93	24 (25.8)	0.61*
	2–6 months	102	26 (25.5)	
	> 6 months	80	24 (30.0)	
Diverting colostomy prior to resection	No	255	65 (25.5)	0.07
	Yes	20	9 (45.0)	0.09*
Location	Right	64	18 (28.1)	0.49
	Transverse	34	14 (41.2)	
	Left	98	24 (24.5)	
	Rectosigmoid	66	16 (24.2)	
	Rectum	48	15 (31.3)	
Palpable lymph nodes during laparotomy	Close to bowel wall	43	15 (34.9)	0.16
	proximal/distal nodes	53	16 (30.2)	0.19*
	No nodes palpable	205	53 (25.9)	
Fixity to adjacent organs	No	249	66 (26.5)	0.05
	Yes	59	20 (33.9)	0.00*
Complications during surgery	No	252	64 (25.4)	0.05
	Blood loss > 1 liter	29	11 (37.9)	0.11*
	Spill (tumor)	25	11 (44.0)	
Surgical opinion	Curative resection	260	68 (26.2)	0.02
	Palliative resection	44	16 (36.4)	0.02*
Angioinvasive growth	Absent	226	52 (23.0)	0.00
	Present	77	32 (41.6)	0.00
Stage (Dukes)	A	78	7 (9.0)	0.00
	B	133	35 (26.3)	
	C	99	45 (45.5)	
Grade	Well differentiated	33	6 (18.2)	0.00
	Moderately differentiated	235	61 (26.0)	0.00*
	Poorly or undifferentiated	32	16 (50.0)	
Postoperative complications	None	244	66 (27.0)	0.11
	Infectious	63	20 (31.7)	0.20*
Treatment	No-touch isolation colon	117	28 (23.9)	0.17
	Conventional colon	119	35 (29.4)	
	Other location (distal)	38	11 (28.9)	
	Other patient factors	36	13 (36.1)	
Sex	Male	149	42 (28.2)	0.84
	Female	161	45 (28.0)	
Age (years)	≤ 65	132	40 (30.3)	0.89
	> 65	178	47 (26.4)	

*Log rank test including missing values.

The laboratory data are summarized in Table 2 and some are shown in Fig. 3. Only a low protein level ($P = .02$) and a high CEA level ($P = .05$) were related to a diminished chance of longer survival, whereas all other

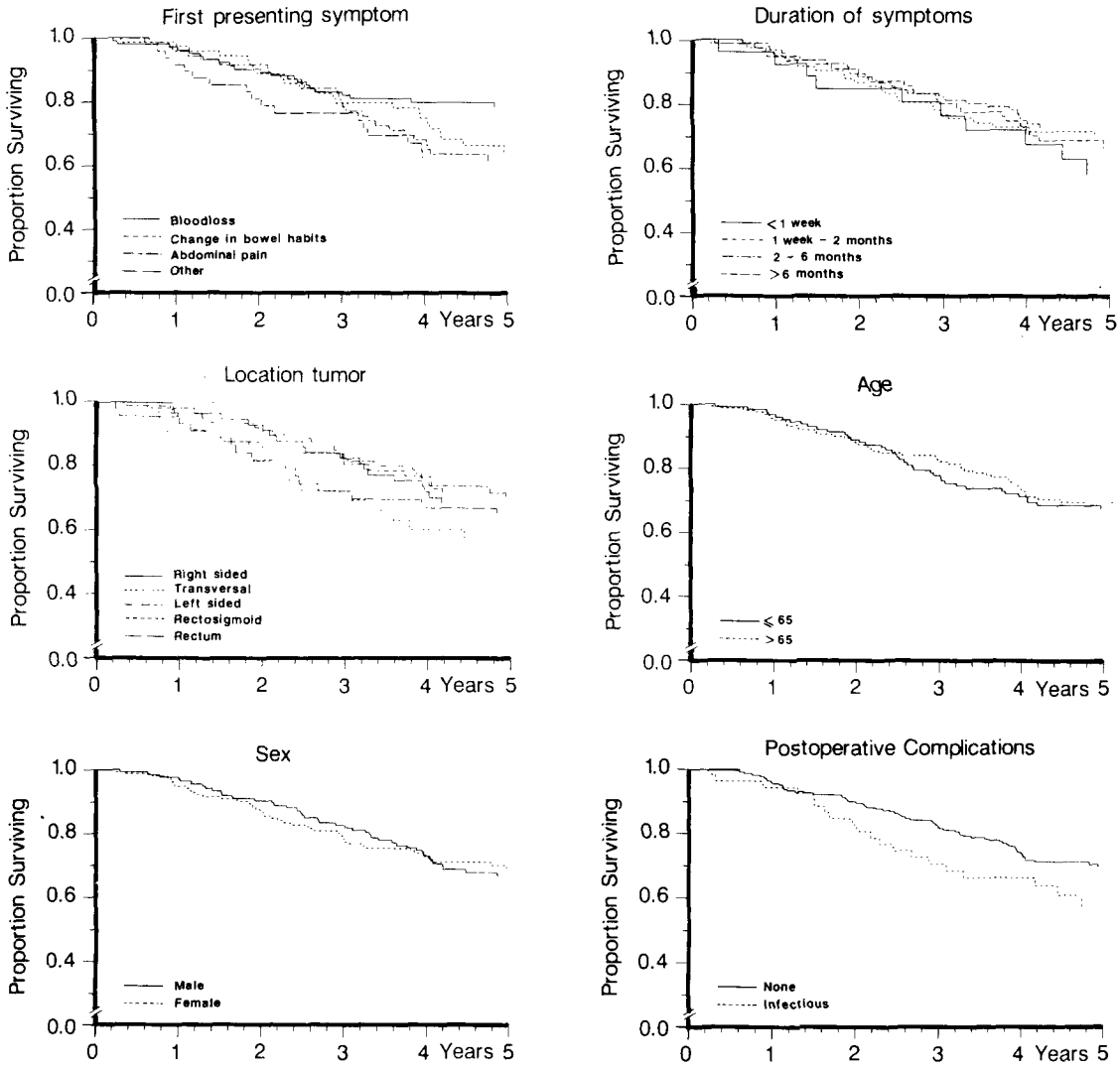

FIG. 1. Disease-related survival by patient characteristics.

hematologic and liver function data were of no interest in the univariate analyses.

Multiple Regression Analysis: The parameters derived from the multivariate analysis are listed in Table 3. Backward elimination, using Wald and likelihood ratio test, resulted in parsimonious models including a limited number of variables. The model providing the best prediction for the determination of prognosis included the following parameters: first presenting and duration of symptoms, palpation of lymph nodes during laparotomy, fixity to adjacent organs, complications during surgery, stage, grade, type of treatment, leukocyte count, total protein, and preoperative CEA level.

Discussion

The aim of this study was to select parameters of interest in the determination of the risk of dying due to recurrent disease, after curative resections. In most series patients with distant metastases or local residual disease at first admission are included in the analysis. Since these patients have a poor prognosis, irrespective of other factors, they were omitted from this analysis. The significance of a relatively good prognosis for patients with rectal bleeding as a presenting symptom has been reported, quite uniformly, in univariate studies by other authors.[7-10] After correction for stage and localization, this effect disappears[8,9] or becomes less important.[10] In the present

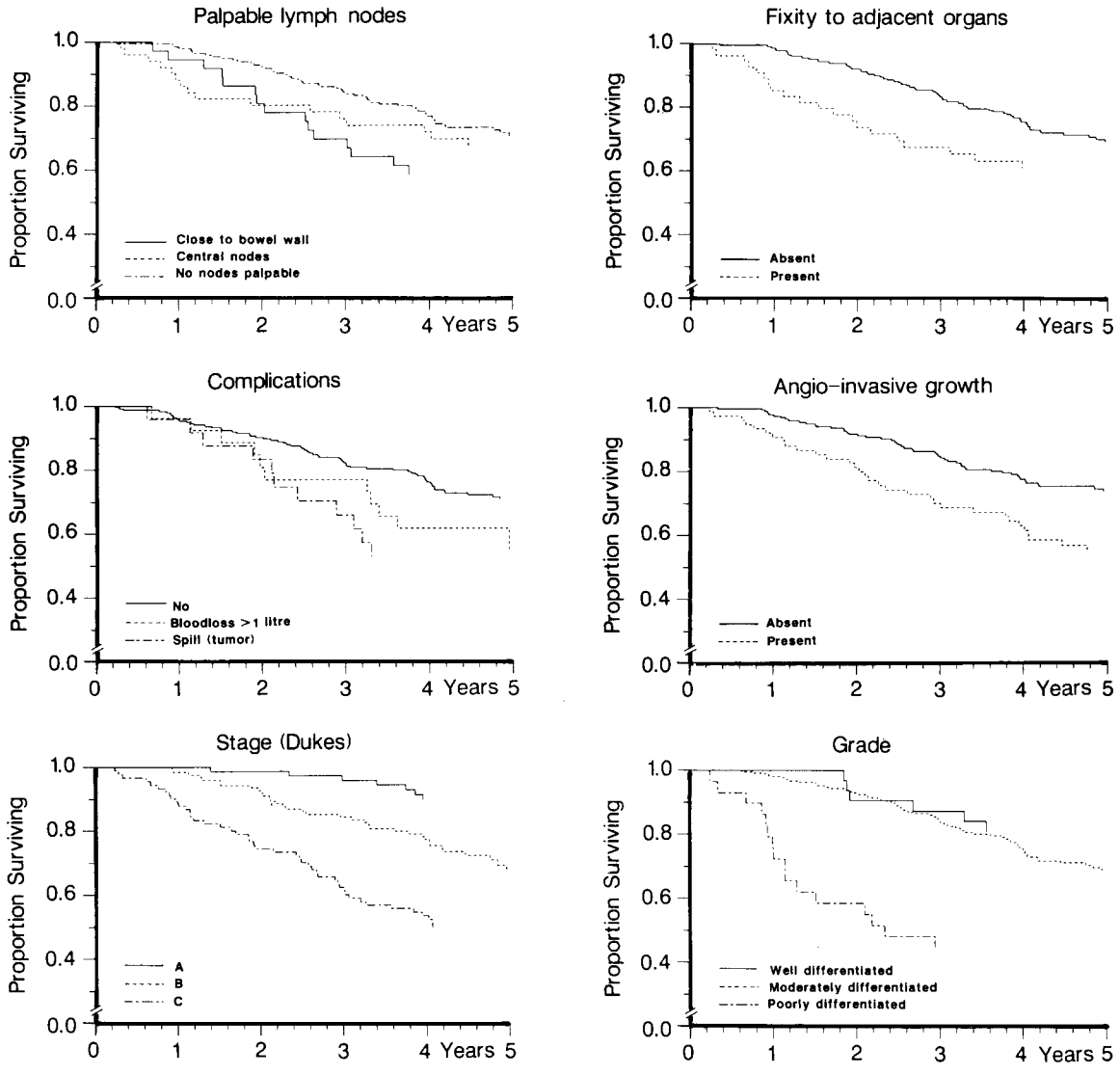

FIG. 2. Disease-related survival by operative findings and pathologic features.

analysis, altered bowel habits and abdominal pains were associated with poorer survival. These features are most likely related to an increased intraluminal pressure and may be (partly) classified in other series as obstructive carcinomas with a known poor prognosis.[9-11]

Symptom duration and survival have been the subject of many studies. In most reports short duration of symptoms is associated with a poorer[12-14] or equal survival[15,16] in comparison with long-lasting symptoms. After correction for stage, this effect sometimes disappears.[9] Since many patients with Dukes' D stage have short duration of symptoms,[14] this may explain the inverse relation in those series and why, in this study, short duration of symptoms, determined by a multivariate analysis, is associated with a better survival. It seems that for patients with the possibility of curative resections, prevention of delay in diagnosis and appropriate action on early symptoms, such as bleeding, are worthwhile. The favorable prognosis of asymptomatic patients supports this assumption.

Age and sex were of no prognostic significance for death due to recurrent disease. In the multivariate analysis of Chapuis *et al.*,[9] young patients and females had good prognoses. However, survival data in most studies[9,17] were for death from any cause. It is, however, important to realize that both age and sex are influenced by death from other causes.

TABLE 2. *Summary of Laboratory Data Entered in Regression Model*

Variable	Cut Point	Number of Observations	Number of Disease-related Death (%)	*P*-value of Log rank Test
Hemoglobin	≤ M9, ≤ F8	166	42 (25.3)	0.36
(mmol/L)	> M9, > F8	141	44 (31.2)	0.63*
Leukocytes	≤ 7.5	147	38 (25.9)	0.11
(10^9/L)	> 7.5	147	47 (31.9)	0.12*
ESR	≤ 10	73	23 (31.5)	0.66
(mm/1 hr)	> 10	225	60 (26.7)	0.62*
Blood group	A	117	32 (27.4)	0.95
	B (incl. AB)	34	11 (32.6)	0.78*
	0	124	37 (29.8)	
GGTP	≤ 20	190	50 (26.3)	0.59
(U/L)	> 20	103	30 (29.1)	0.35*
SGOT	≤ 20	214	59 (27.6)	0.78
(U/L)	> 20	79	22 (27.8)	0.72*
SGPT	≤ 20	239	66 (27.6)	0.62
(U/L)	> 20	52	13 (25.0)	0.32*
LDH	≤ 300	103	31 (30.1)	0.34
(U/L)	> 300	169	42 (24.9)	0.28*
Protein (total)	≤ 65	85	31 (36.5)	0.02
(Gm/L)	> 65	199	49 (24.6)	0.07*
CEA	≤ 5	137	31 (22.6)	0.05
(ng/ml)	> 5	83	26 (31.3)	0.04*

M = male; F = female.
*Log rank test including the missing values.

The standard liver function tests (GGTP, SGOT, SGPT, LDH) were not able to predict the presence of occult liver metastases in peroperative palpatory normal livers. The same observation was reported for alkaline phosphatase: in patients with preoperatively elevated levels and normal livers at laparotomy, no greater risk was observed of developing metastases during follow-up in comparison with patients with normal preoperative levels.[18] Levels of hemoglobin and ESR were of no significance and the negative effect of leukocytosis observed in

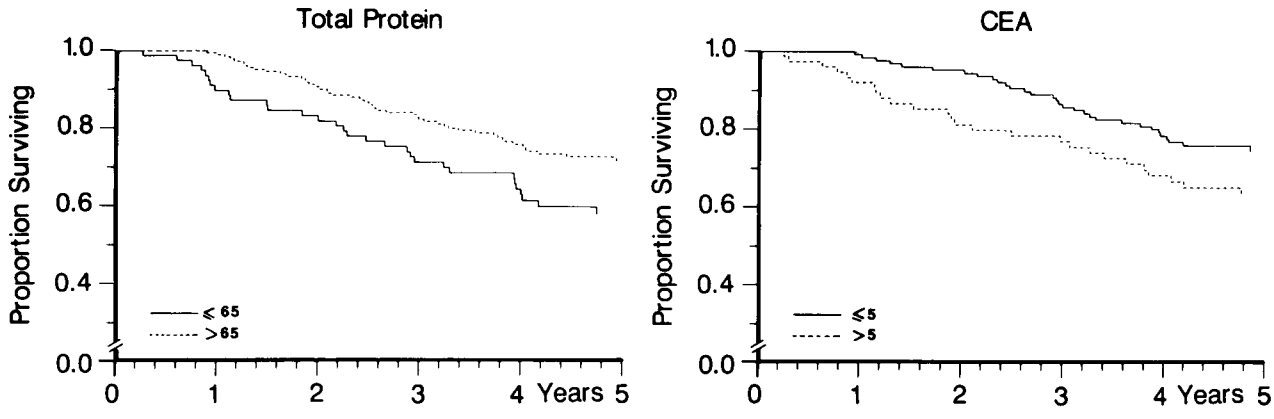

FIG. 3. Disease-related survival by laboratory data.

TABLE 3. *Proportional Hazards Regression Model Based on Patients with Complete Data Records*

Variable	Category	Coefficient	Standard Error	Hazard Ratio
First presenting symptom	Change in bowel habits	0.73	0.49	2.07
	Abdominal pain	1.16	0.55	3.18
	Other	−0.20	0.62	0.82
Duration of symptoms	1 week–2 months	0.30	0.69	1.35
	2–6 months	0.89	0.64	2.44
	> 6 months	1.49	0.67	4.42
Palpable lymph nodes during laparotomy	Proximal/distal nodes	−1.84	0.66	0.16
	No palpable nodes	−0.41	0.52	0.67
Fixity to adjacent organs	Yes	1.18	2.71	3.26
Complications during surgery	Blood loss > 1 liter	−0.57	0.81	0.57
	Spill	1.64	3.46	5.15
Stage	B	1.24	0.66	3.46
	C	2.83	0.68	16.86
Grade	Moderately differentiated	1.99	0.71	7.29
	Poorly differentiated	2.59	0.84	13.40
Treatment	Conventional colon	0.58	0.41	1.78
	Other location (distal)	1.09	0.62	2.97
	Other patient factors	1.86	0.64	6.45
Leukocyte count	> 7,5. 10^9/L	0.73	0.40	2.08
Total protein	> 65 Gm/L	−1.17	0.38	0.31
CEA	> 5 ng/ml	0.69	1.83	1.99

this analysis is not easily explained.

An interesting finding was the negative effect on disease-related survival of low preoperative protein levels since postoperative mortality was excluded from the analysis. The same effect has been reported previously by Spratt and Spjut.[1] Further investigations are necessary to find out if this parameter is a nonspecific indicator for a depressed immune status of the patient and, in this regard, related to the risk of recurrence.

The significant relation between preoperatively elevated CEA levels and survival was in accordance with other series.[19–21] Although it was strongly interrelated with stage, this effect was maintained in the regression model. The present limitations of this test are due mainly to the impossibility of distinguishing between production in the primary tumor and undetectable micrometastases. In fact, postoperatively determined levels should be better in this regard because the primary tumor, as a source of production, is eliminated.

Although, rectal and cecal tumors generally are known for their higher chance of local recurrence[22] and poorer prognosis, this effect disappears in this and other multivariate analyses.[7,9,10] Adjustment for stage and the limited effect on survival of local recurrence must be responsible for this observation.

No definite answer concerning the importance of obstruction can be drawn from the present data since this feature was only indirectly recorded as diverting colostomy preceding a resection. Several institutions performed two-stage procedures, with primary resection, instead of three-stage procedures under these circumstances. All regression analyses are clear about the fact that if this finding is present, however, this is a grave prognostic sign.[7,9,10]

Palpation of lymph nodes with suspicion for metastatic disease during an operation was included in the analysis. Lack of agreement with the final pathologic report and an unexplained good prognosis for patients with palpable nodes, both central and close to the bowel wall, made this observation of no value. Biopsy of suspected lymph nodes is the only way to confirm metastatic disease.

In fixed tumors, the high risk of a local recurrence as a first site of relapse in combination with a poor survival, has been reported in univariate[1,23–25] and multivariate analyses.[9] Microscopic invasion of adjacent organs, not

detected by histopathologic examination, must be responsible for this feature since patients with known residual disease were excluded from the study.

Tumor spill during the operation, either from the extraluminal or intraluminal sites, had, independent of stage or fixity, a deleterious effect on survival and this is in agreement with other studies[23,26,27] Increased intraluminal pressure, but especially, exfoliation of tumor cells, may be responsible for this effect. The paramount importance of clinicopathologic staging, with the most distinguishing hazard ratios in this analysis, has also been reported in other regression models.[9,28,29] Grade was shown to have a significant effect on survival, whereas angioinvasive growth, although important in the univariate analysis, was not independent and strongly interrelated to stage.

Postoperative infectious complications were included finally since, in one study, postoperative fever was the most unfavorable prognostic factor.[30] Although in this material, crude survival was worse for patients with infections, this is most likely a result of death due to other causes since exclusion of the last category obscured the significance of this factor.

The procedure of surgical treatment (no-touch isolation or conventional) for colon tumors had to be incorporated as a variable since most patients were randomized and part of a multicenter study comparing both techniques.[3] The remaining categories, out of trial patient factors and out of trial location factors, had a diminished survival that is not surprising and is a result of patient selection. It was reassuring that the relatively better prognosis of the no-touch isolation technique was maintained in the multivariate analysis.

The regression analysis resulted in a model including the following variables: surgical procedure, first presenting symptom, duration of symptoms, protein level, CEA, fixity at operation, preoperative complications, stage, and grade. These factors can be included in a prognostic index, with hazard ratios derived from Table 3, on the base of which an accurate prediction of individual prognosis can be given. The clinicopathologic stage is still the major determinant for prognosis and represents, in the best way, the balance between tumor and host. Close collaboration between pathologist and surgeon can increase the value of this factor.

It is attractive to try to modulate some factors from the index in the hope of improving prognosis. Further investigations are necessary to determine if appropriate action in rectal bleeding, prevention of delay in diagnosis, improvement of nutritional status, and aggressive local therapy (with application of measurements to prevent spill to liver or abdominal cavity) will improve survival substantially.

It is remarkable that regression analyses from other countries (Australia,[9] U.S.,[10] U.K.,[11]) reveal, depending on the factors included, the same prognostic variables. Standardization of pathologic examinations and uniform recording of history and operative details could result in a widely accepted prognostic index. This would enable comparison of the results of different centers and allow multicenter studies of adjuvant therapy for high-risk groups.

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