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Prognostic Factors of Advanced Colorectal Cancer Patients

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Abstract—*The cooperative oncology group for Chemotherapy of Gastrointestinal Tumors (CGT) retrospectively examined 139 patients with metastatic colorectal cancer for prognostic factors. Clinical characteristics, tumor parameters, and blood parameters were investigated for prognostic explanation of survival from the start of chemotherapy for the advanced disease. A combination of a univariate regression and a multivariate step down procedure with Cox's regression model led to the identification of performance status, sex, white blood count and, to a lesser degree, blood sedimentation rate and albumin as important prognostic factors. Based on these variables an individual risk score was calculated for each patient.*

INTRODUCTION

COLORECTAL cancer (large bowel carcinoma) is among the leading causes of morbidity and mortality in developed countries. It ranks second in both West Germany and the U.S.A. to lung cancer in males and breast cancer in females. Of reported colorectal cancers, 30–70% encountered surgically have already metastasized to regional lymph nodes [1]. Cure is rarely achieved for locally unresectable or recurrent disease and almost never in metastatic disease. Improvement of survival by chemotherapy has been moderate in the past ten years, and there is enormous variability in the results reported in the literature [2–5]. While there is good information about prognostic variables in the primary treatment of colorectal cancer from surgical literature, detailed investigations for prognostic factors in the secondary treatment of advanced and/or metastatic disease are rare.

The CGT Study Group, having conducted a series of clinical trials on the effect of polychemotherapy [6, 7] for patients with metastatic colorectal cancer, raised the question of the existence of important prognostic factors for this advanced disease. An appropriate definition of risk groups was believed to help in the planning of controlled clinical trials as well as in obtaining guidelines for the clinical management of cancer patients. Therefore, we decided to submit the well documented data of the CGT studies to a multivariate analysis in order to extract the most essential factors predicting survival.

PATIENTS AND METHODS

139 patients with histologically proven residual, recurrent or metastatic adenocarcinoma of the colon, sigmoid, or rectum, which was inoperable or beyond surgical or radiotherapeutical cure, were examined retrospectively for factors prognosing survival with the advanced disease. All patients had been recruited for Phase II and Phase III trials with different chemotherapy regimes between 1977 and 1982 by members of the CGT Study Group [6–8]. The analysis was based on 33 characteristics surveyed or measured at the start of chemotherapy including 15 parameters from laboratory assays.

Performance status (PS) was classified according

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The following members of the Chemotherapy of Gastrointestinal Tumors Study Group (CGT) participated in this study: Queisser W.; Heim M.E.; Schnitzler G.; Flechtner H. (Oncological Center Mannheim, University of Heidelberg); Koenig H.J. (Medical Clinic, University of Erlangen); Fritze D.; Herrmann R. (Ludolf-Krehl Clinic, University of Heidelberg); Arnold H.; Henss H. (Medical Clinical, University of Freiburg); Katz R. (Medical Clinic, Darmstadt); Trux F.A. (Comm. Hospital, Schweinfurth); Bloch R.; Keymling M. (Clinic, Bad Hersfeld); Kabelitz K. (University Hospital, Bad Homburg); Wolkewitz K.D.; Penzkofer F. (Hospital Ev. Diak., Karlsruhe); Fritsch H. (Comm. Hospital, Weinheim); Hanisch I.; Mantel W. (Elisabethenstift, Darmstadt); Brumen L. (Comm. Hospital, Neunkirchen/Saar); Pretner M. (Clinic Worms); Edler L. (German Cancer Research Center, Heidelberg).

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Table 1. Results of the univariate Cox-regression

Factor/covariate	Units/categories	Median/percentages	Regression coefficient β (S.E. of β)	*P*-value	Relative risk
Sex	*female	51.8	—	0.05	—
	male	48.2	−0.38		0.68
Age	years	55.4(53.7–57.4)	0.004(0.01)	0.67	
Time since operation	days	295(196–396)	0.0002(0.0002)	0.30	
Site of primary tumor	*rectum	51.9	—	0.03	—
	sigma	26.0	0.25(0.23)		1.28
	colon/coecum	21.4	0.66(0.26)		1.93
Grade of differentiation	*high	29.6	—	0.80	—
	median	27.3	−0.22(0.44)		0.80
	low	40.9	−0.25(0.40)		0.76
	(undefined	2.3)			
Size of tumor	cm	5.0(4.5–5.0)	0.29(0.08)	0.0002	1.34
Extent of operation	*palliative	42.9	—	0.04	—
	possibly curative	10.0	0.96(0.38)		2.6
	curative	47.3	0.25(0.26)		1.3
Type of operation	*colon resect.	37.0	—	0.54	—
	rectum extirp.	33.6	0.21(0.24)		0.814
	anus praeter	5.9	−0.34(0.15)		0.71
	others	20.2	−0.29(0.09)		0.75
	none	3.4	0.52(0.53)		1.69
TNM					
	T_2	9.1	—	0.30	—
	T_3	42.9	0.12(0.45)		1.13
	T_4	48.0	−0.01(0.45)		0.99
	N_0	32.0	—	0.01	—
	N_1	58.7	0.28		1.32
	N_{2-4}	9.3	1.34(0.44)		3.82
	M_0	61.5	-	0.27	—
	M_1	38.5	0.29(0.26)		1.33
Location of metastases	*local	13.7	—	0.12	—
	intra-abdominal	5.8	0.80(0.50)		2.22
	liver	28.1	0.14(0.33)		1.16
	lung/bone	7.9	0.26(0.42)		1.30
	multiple+liver	30.9	0.65(0.32)		1.91
	others	13.7	0.73(0.37)		2.08
Body mass index	weight/height^2 ×100(kg/cm^2)	2.34(2.29–2.42)	−0.85(0.39)	0.03	0.43
Loss of weight in last 3 months	kg	3.0(1.0–4.0)	0.08(0.03)	0.004	1.08

to criteria of the Swiss oncology group SAKK which are similar to those of the ECOG [9]: normal activity (= 0), patient is able to live at home with tolerable tumor manifestations (= 1), patient has disabling tumor manifestations, but is less than 50% of time in bed (= 2), patient is severely disabled and more than 50% in bed (= 3), patient is very sick and bedridden (= 4).

Chemotherapy had been given at the following dosages: 5-fluorouracil(5-FU) at 10 mg/kg/day 5 days i.v., Ftorafur at 30 mg/kg/day 5 days i.v. or 2 g/m^2/day 5 days i.v. in 500 ml 5% glucose for 1–2 hr. Carmustine (BCNU) at 40 mg/m^2/day 5 days in 250 ml 5% glucose over 30 min i.v., vincristine at 1 mg/m^2 on day 1 i.v., and mitomycin C at 10 mg/m^2 i.v. on day 1. Each cycle of chemotherapy was repeated every 6 weeks until tumor progression and, if necessary, dose schedules were modified [6–8]. The distribution of the patients according to different regimes was as follows: 5-FU (4%), 5-FU+BCNU (16%), Ftorafur + BCNU (5%), 5-FU+BCNU+mitomycin C (43%), 5-FU+BCNU+vincristine (16%), Ftorafur + BCNU+vincristine (11%) and others (5%).

Statistical analysis

Survival time was measured from start of chemotherapy until death or loss of follow-up. At the time of analysis 109 deaths and 30 censored cases were evaluable. All factors shown in Table 1 were examined for prognostic relevance by Cox's

Table 1. *contd*

Factor/covariate	Units/categories	Median/percentages	Regression coefficient β (S.E. of β)	*P*-value	Relative risk
Performance	*normal	25.6	—	0.00001	—
ECOG criteria	restricted	44.6	1.14(0.30)		3.13
	in bed less than 50%	23.1	1.58(0.33)		4.85
	in bed more than 50%	6.6	3.05(0.47)		21.11
CEA (log)	μg/l	67(39–141)	0.10(0.05)	0.07	1.10
LDH (log)	units/l	273(231–370)	0.50(0.21)	0.02	1.66
Alkaline phosphatase	units/l	233(191–280)	0.0012(0.0003)	0.001	
SGOT	units/l	12(10–15)	0.0082(0.005)	0.10	
SGPT	units/l	15(12–17)	−0.002(0.008)	0.8	
Bilirubin	mg/0.1l	0.6(0.5–0.7)	0.003(0.03)	0.9	
Protein	g/l	70(69–71)	0.03(0.01)	0.09	
Albumin	% of proteine	49.7(47.9–51.5)	−0.06(0.01)	0.00003	
Creatinin	mg/0.1l	0.9(0.8–1.0)	0.55(0.21)	0.01	
Urea	mg/0.1l	26(24–30)	−0.004(0.009)	0.65	
WBC (log)	counts/mm^3	8100(7700–8700)	0.82(0.26)	0.002	2.26
Granulocytes (log)	counts/mm^3	5890(5600–6300)	0.68(0.21)	0.01	1.98
Lymphocytes	counts/mm^3	1716(1540–1925)	−0.13(0.18)	0.49	0.88
Hemoglobin	g/0.1l	12.6(12.1–13.1)	−0.20(0.05)	0.0002	0.82
Platelets (log)	1000 counts/mm^3	334(302–350)	0.18(0.27)	0.5	1.20
Blood sedimentation	mm	43(38–52)	0.013(0.002)	0.00002	
Chemotherapy					
	5-FU+BCNU	15.8	0.30(0.45)	0.58	1.35
	5-FU+BCNU+ Mitomycin C	43.2	0.50(0.40)		1.64
	5-FU+BCNU+VCR	15.8	0.15(0.47)		1.16
	Ftorafur+BCNU	5.4	0.66(0.54)		1.93
	Ftorafur+BCNU+ VCR	11.5	0.68(0.49)		1.98
	*others	8.6	—		—
Additional therapy	*none	75.0	—	0.8	—
	given	25.0	−0.06(0.22)		0.95

For each factor surveyed we give units of measurement or possible categories, medians (95% confidence intervals) or percentages, estimates of the regression coefficients β (standard errors: S.E.), *P*-values obtained by Wald's test based on β/S.E. of β, and—if reasonable—exp(β) as estimates of the relative risk referring to the category with * or the unit of measurement. Some factors were logarithmically transformed before they were calculated in the Cox-model. This is indicated by (log) in the first column. Relative risks were calculated for all qualitative factors.

regression model [11] for censored survival data. We denoted by V_0 this basic set of factors. At first the influence of each factor v from V_0 on survival time was examined separately by univariate regression with the proportional hazards model: $\lambda(t,z)=\lambda_0(t)\exp(\beta z)$ where β denotes the unknown regression parameter having the same dimension as z which represents v. $\lambda_0(t)$ is the baseline hazard function describing the instantaneous risk of dying at time t, for a patient with covariate $z = 0$. An estimate of β was obtained by the partial likelihood method [11]. For each covariate we calculated the *P*-value of the test of $\beta = 0$, and we defined basically the set V_2 of factors of strong prognostic influence ($P < 0.01$) and the set V_1 of factors of some prognostic influence ($0.01 \leq P < 0.1$). The simultaneous influence on survival of a set of factors with covariates $z = (z_1, \ldots z_p)$ was modelled by the multivariate proportional hazards model $\lambda(t,z) = \lambda_0(t)\exp(\beta z)$, where $\beta = (\beta_1, \ldots, \beta_p)$ denotes the vector of regression coefficients corresponding to z. Based on the maximum partial likelihood we eliminated in a step down procedure covariates with minor influence analogously to multiple linear regression [12]. The influence of a single patient P on the estimate $\hat{\beta}$ was calculated directly as $J(P) = \hat{\beta} - \hat{\beta}(-P)$, where $\hat{\beta}(-P)$ is the estimate of the regression coefficients based on the sample without P [13]. $J(P)$ was calculated for all P and plotted vs. P for each regression coefficient. That P with the highest absolute value of $J(P)$ was identified, and excluded from the data. The final

estimate of $\beta = (\beta_1, \ldots, \beta_r)$ was used to calculate an individual risk score for each patient, i.e. a prognostic index [14], $l(P) = \hat{\beta}_1 z_1(P) + \ldots + \beta_r z_r(P)$, where $z(P)$ were patient's P covariates. For each factor survival curves were calculated by life-table methods [15] and empirical log–(-log)-plots and a test for acceleration [16] in the case of pairs of curves were used to check the proportional hazards assumption. All logarithms were taken to the base e. A detailed description of the statistical methods is available from the authors.

RESULTS

All 33 characteristics considered for prognostic relevance were characterized by median values (with 95% confidence intervals) in the case of quantitative and by percentages in the case of categorial covariates. Body height and body weight at time of metastatic disease were not included because of their strong association with sex (chi-square: $P < 0.001$). A body mass index defined as weight divided by the square of the height was included, instead, and it appeared to be uncorrelated with sex (chi-square $P = 0.8$). Patient's performance was found to be strongly correlated with loss of weight ($P < 0.001$) as well as with the blood sedimentation rate ($P < 0.0009$), albumin, and WBC ($P = 0.01$), and also to some extent with alkaline phosphatase and lymph node involvement of the primary tumor ($P < 0.1$).

Univariate analysis

Each factor listed in Table 1 was analyzed separately for its influence on survival by a univariate Cox-regression and the resulting P-values were used to assess prognostic importance. Strong prognostic impact of survival ($P < 0.01$) was shared by the size of the primary tumor, loss of weight, performance status, alkaline phosphatase, albumin, white blood cell count (WBC), granulocyte count, hemoglobin, and blood sedimentation rate (BSR). They generated the set of factors V_2. Performance status exhibited the highest signficance level. Patients with PS 1 or 2 showed an about 3–5 times larger risk of death than those with normal performance; those with bad performance (PS 3 or 4) had an even about 20 times larger risk. Risk of death was increasing with increasing loss of weight, alkaline phosphatase, WBC, granulocyte count, or BSR values and with decreasing hemoglobin or albumin values.

WBC and granulocyte count were highly correlated. Only WBC was included in the set V_2 of factors used in a multivariate analysis. There was some concern about the role of sex, which showed only mild influence ($P = 0.05$) in the univariate regression but which was associated with factors of high influence such as hemoglobin or loss of weight. Since preliminary analyses had revealed a larger influence of sex and since it represents a basic anamnestic variable undoubtedly important to record, we included sex into V_2. Size of the primary tumor could not be included because of a large number of missing values.

We obtained another 7 factors with some influence on survival ($0.01 \leq P < 0.1$) generating V_1: Site of primary tumor, lymph node involvement, CEA, LDH, protein, creatinine and extent of operation. Additionally SGOT($P = 0.10$) and location of metastases ($P = 0.12$) with borderline P-values were included in V_1. Chemotherapy and additional therapy both showed no influence on survival ($P > 0.5$).

Multivariate analysis

All 8 factors from V_2 were put into a multivariate regression model. Performance status 3 or 4 was combined with patients of performance status 2 into one category of nonambulatory patients (PS $\geq$ 2). Because of the strong association between performance status and blood sedimentation rate two interaction terms were considered: P1: PS = 1 and BSR > 30 and P2: PS $\geq$ 2 and BSR > 30. P2 showed a large influence on survival explaining most of the influence of BSR whereas P1 was not significnat. Introduction of interaction terms defined by performance and albumin, alkaline phosphatase, or WBC led to no substantial improvement. An addition of P_2 to V_2, however, improved substantially (likelihood ratio test: $P = 0.01$) our ability to predict survival in the presence of the other variables of V_2.

In a step down procedure loss of weight during the last 3 months, alkaline phosphatase, hemoglobin, and blood sedimentation rate exhibited no significant regression coefficients ($P > 0.4$) and their deletion in a subsequent model resulted in a non-significant reduction of the deviance ($P = 0.2$). The remaining four factors and P2 were all significant at the 0.05 level and a further deletion of any one of them resulted in a significant reduction of the deviance of the regression model ($P < 0.05$) and, therefore, they were designated as Model 1. The results are given in Table 2. Albumin was responsible for 25 missing values in Model 1. Therefore we used in Model 2 only the three factors sex, performance, WBC, and the interaction term P2 and so obained an active sample of size 108 patients. Compared to Model 1 there was a minor loss of information (deviance: $P = 0.03$) which was compensated by a larger sample size. Qualitatively there was no change compared to Model 1.

When factors of V_1 were added one by one to

Table 2. Results of the multivariate regression by Cox's proportional hazards model applied to the factors V_2 of strong prognostic value

Covariate	Model 1		Model 2		Model 2*	
	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Sex	−0.79	0.004	−0.69	0.004	−1.01	0.00007
Performance (1)	1.08	0.009	1.29	0.0005	1.86	0.00001
Performance (≥ 2)	0.72		0.80		0.96	
PS ≥ 2 × BSR > 30	1.70	0.003	1.89	0.0001	2.39	0.0003
Albumin	−0.04	0.03	—	—	—	—
Log WBC	0.76	0.02	0.88	0.002	1.31	0.0002
Sample size	81		108		103	

We give the estimate of the regression coefficient β (BETA) and its p-value of the two last steps with those factors remaining finally significant. Model 2* gives the fit of the model without the five most influencing cases.

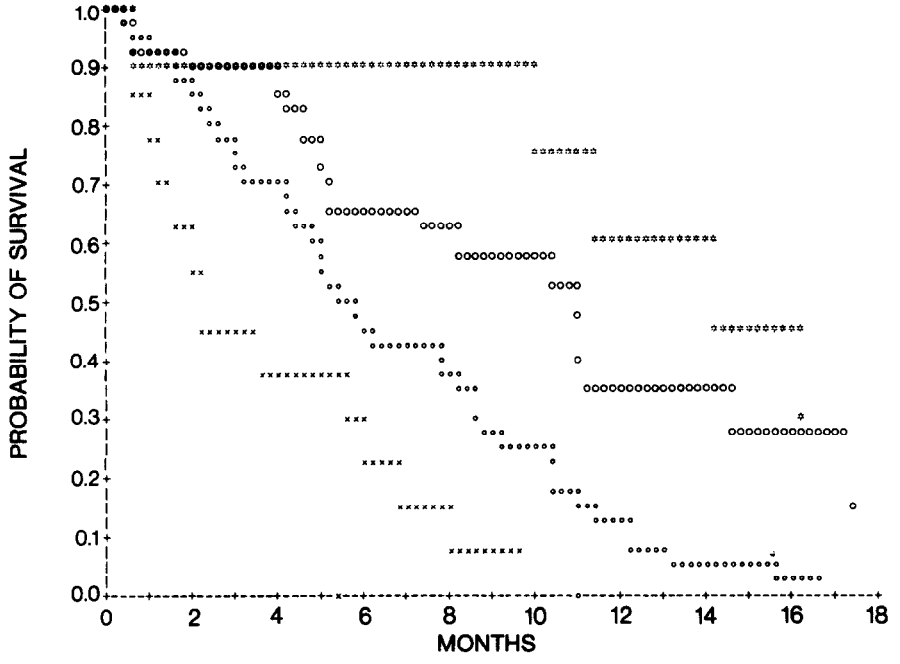

Fig. 1. Survival of all patients whose prognostic index I was evaluable subdivided according to the prognostic index. < 11.5 (*), 11.5–13 (O), 13–14.5 (o), > 14.5 (x).

those of Model 2 only site of the primary tumor, extent of operation and lymph node status from the TNM were significant ($0.01 < P < 0.1$), but their influence was smaller than that of the factors of Model 2 ($P > 0.01$).

Five cases with highest influence on the estimates of the regression coefficients were identified: one female with PS = 1 surviving longest (30 months); one male surviving 5 months and one female surviving 7 months with PS = 2; there was a male surviving 11 months with PS = 1 but with an extreme WBC of 24 800, and finally, one male surviving 12 months with PS = 2, BSR = 15, and WBC = 8000. Table 2 gives the regression coefficients calculated without those 5 cases in Model 2*.

For the identification of risk groups we calculated a prognostic index based on the regression coefficients from Model 2* as

$$l(\mathrm{P}) = -1.06 \times \mathrm{sex(P)} + 1.86 \times (\mathrm{PS}=1)(\mathrm{P}) + 0.96 \times (\mathrm{PS}\geq 2)(\mathrm{P}) + 2.39 \times \mathrm{P2(P)} + 1.31 \times \mathrm{logWBC(P)}$$

for each of the $n = 103$ cases used in Model 2*.

For an explicit calculation of $l(\mathrm{P})$, the values of the covariates of each patient P were used as follows: sex(P) = 1 if P was male and sex(P) = 0 if P was female; (PS=1) (P) = 1 if PS=1 and (PS=1)(P) = 0 otherwise; (PS ≥ 2)(P) = 1 if PS ≥ 2 and (PS ≥ 2)(P) = 0 otherwise; P2(P) = 1 if PS ≥ 2 and BSR > 30 and P2(P) = 0 if PS<2 or BSR ≤ 30.

After examining the distribution of l we subdivided the sample into the following four groups

(I)			l(P)	$\leqslant$	11.5	(n=9)
(II)	11.5	<	l(P)	$\leqslant$	13.0	(n=28)
(III)	13.0	<	l(P)	$\leqslant$	14.5	(n=53)
(IV)			l(P)	>	14.5	(n=13)

The number of cases are given in parentheses. The survival curves of the four groups of patients so defined show the prognostic power of the index l, see Fig. 1. Similar results are obtained if the index is calculated on the basis of Model 1 or Model 2.

DISCUSSION

The purpose of the analyses reported above was, firstly, to determine a comprehensive but minimal set of prognostic factors for advanced colorectal cancer and, secondly, to define risk groups for the present sample on the basis of these factors. The retrospective investigation of 139 patients with histologically proven metastatic adeno-carcinoma of the colon and the rectum discovered a number of patient's characteristics influencing survival from the start of treatment of the metastatic disease. In order to adjust for associations between the covariates and to define a minimal set of factors explaining most of the survival differences, a multivariate analysis with specific modifications was applied. Thereby we obtained performance status, sex, and white blood cell count as prognostic factors and also to some extent albumin and blood sedimentation rate.

Further investigation is needed to clarify the role of albumin as well as that of BSR, the latter which leads to a significant gain in explanation of differences in survival for the subgroup of patients with worse performance (PS $\geqslant$ 2). The risk of dying was 2.7 times higher for females than for males, when adjusted for other covariates. This is in contrast to findings of Refs. [17] and [18], who observed better survival among women. However, it has to be mentioned that in our sample sex was correlated to some degree with BSR and WBC (P = 0.06) and, to a lesser degree, with albumin and performance ($P > 0.1$), and that a higher proportion of females was found in the categories of worse prognosis. The relative risk of patients with PS = 1 to patients with PS = 0 was 6.4. Patients with PS > 1 but without elevated BSR showed an increase by the factor 2.6 whereas those with PS $\geqslant$ 2 and elevated BSR did worse with a risk 11.0 times larger than those with PS = 0. Thus, the role of performance status as an important prognostic factor was reassured by this study. But we also conclude that an inclusion of characteristics of the protein metabolism can improve the prediction of survival.

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REFERENCES

1. Depeyster FA, Gilchrist RK. Pathology and manifestations of cancer of the colon and rectum. In: Turrel R, ed. *Diseases of the Colon and Anorectum.* Philadelphia, Saunders, 1969, 428–452.
2. Moertel CG, Reitemeier RJ. *Advanced Gastrointestinal Cancer/Clinical Management and Chemotherapy.* New York, Harper & Row, 1969.
3. David HL Jr, von Hoff DD, Rozencweig M, Handelsman H, Soper WT and Muggia FM. Gastrointestinal cancer: esophagus, stomach, small bowel, colorectum, pancreas, liver, gallbladder, and extrahepatic ducts. In: Staquet MJ, ed. *Randomized Trials: A Critical Review by Sites.* New York, Raven Press, 1978, 147–230.
4. Carter SK, Friedman M: Integration of chemotherapy into combined mortality treatment of solid tumors. *Cancer Treat Rep* 1979, **1,** 111–129.
5. Queisser W, Heim ME. Chemotherapy in alimentary tract malignomas: State of the art. *Hepato-Gastroenterology* 1981, **28,** 276–283.
6. Queisser W, Schnitzler G, Heim ME *et al.* Phase III evaluation of Ftorafur within combination chemotherapy of advanced gastric and colorectal carcinoma. In: Perevodchikova *et al.*, eds. *Tegafur/Ftorafur. Preclinical and Clinical Experiences.* Basel, Karger, 1983, 64–76.
7. Heim ME, Roemer W, Edler L, Queisser W. Combination chemotherapy of advanced colorectal cancer with 5-fluorouracil, carmustine and mitomycin C. *Tumor Diagnostic Therapy* 1983, **4,** 122–125.
8. Queisser W, Schaefer J, Arnold H *et al.* Prospektive kontrollierte Studie bei metastasierten gastrointestinalen Tumoren. Vergleich zwischen 5-Fluorouracil-Carmustin und Ftorafur-Carmustin. *Dtsch med Wschr* 1979, **104,** 1231–1236.
9. Douglass HO, Lavin PJ, Woll I. Chemotherapy of advanced measurable colon and rectal carcinoma. *Cancer* 1978, **48,** 2538–2545.
10. Cox DR. Regression models and life tables (with discussion). *J Roy Statist Soc B* 1972, **34,** 187–202.
11. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data.* New York, Wiley, 1980.

12. Byar, DP. Analysis of survival data: Cox and Weibull models with covariates. In: Mike V, Stanley KE, eds. *Statistics in Medical Research. Methods and Issues, with Applications in Cancer Research.* New York, Wiley, 1982, 365–401.
13. Storer BE, Crowley J. A diagnostic for Cox regression and general conditional likelihoods. *J Am Statist Assoc* 1985, **80,** 139–147.
14. Andersen PK, Christensen E, Fauerholt L, Schlichting P. Evaluating prognosis based on the proportional hazards model. *Scand J Statist* 1983, **10,** 141–144.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958, **53,** 457–481.
16. Breslow NE, Edler L, Berger J. A two-sample censored-data rank test for acceleration. *Biometrics* 1984, **40,** 1049–1062.
17. Buroker T, Kim PN, Groppe C *et al.* 5-FU infusion with mitomycin-C vs.5-FU infusion with methyl-CCNU in the treatment of advanced colon cancer. A Southwest Oncology Group Study. *Cancer* 1978, **42,** 1228–1233.
18. Greenspan EM, Ratner LH. Gastrointestinal cancer chemotherapy. In: Greenspan EM, ed. *Clinical Interpretation and Practice of Cancer Chemotherapy.* New York, Raven Press, 1982, 195–241.