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Determinants of Prognosis in Advanced Colorectal Cancer

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The relations between patient characteristics and prognosis were examined in 340 patients with advanced colorectal cancer treated with chemotherapy. Variables were tested for relation to survival and responses in univariate and multivariate analyses. Performance status ($P < 0.001$), number of symptoms ($P < 0.001$) and haemoglobin level ($P < 0.001$) were the most important variables for survival in univariate analyses. In the multivariate analyses of survival, haemoglobin level ($P < 0.001$) and disease-free interval ($P < 0.01$) were the most influential variables. In addition, number of symptoms ($P < 0.01$), performance status ($P < 0.05$) and treatment of the primary tumour ($P < 0.05$) were independently related to survival. The main independent determinant of response was haemoglobin level ($P < 0.01$). Besides these pretreatment characteristics, type of chemotherapy regimen influenced both response rate and survival in multivariate analyses ($P < 0.001$). We conclude that haemoglobin level, disease-free interval, symptoms and performance status are important prognostic factors in advanced colorectal cancer. The distribution of these variables may influence the results of clinical trials.
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INTRODUCTION

PATIENT CHARACTERISTICS influence prognosis in advanced colorectal cancer [1–10]. Performance status, lactic dehydrogenase level and white blood cell count have emerged as major prognostic factors in patients with various metastatic sites [1–4]. The extent of liver involvement, lymph-node metastases in liver hilum and several liver function tests were related to survival in patients with hepatic metastases [5–11].

Age, sex, location of the primary tumour, performance status, and number and location of metastatic sites are commonly stated in clinical trial reports. It is not known if additional variables are necessary to describe patients from a prognostic viewpoint. For instance, information about the influence of tumour-related symptoms is scarce. This question is important since the proportion of symptomatic patients often varies between trials due to differing indications for chemotherapy.

The primary aim of this study was to identify common clinical variables with a strong relationship to survival in patients with advanced colorectal cancer treated with chemotherapy. A secondary aim was to assess variables with influence on responses.

PATIENTS AND METHODS

340 patients with advanced colorectal cancer included in three chemotherapy trials were examined. The first trial (trial 1) was a phase II study where 56 patients were treated with methotrexate/5-fluorouracil/leucovorin (MFL) between November 1982 and August 1984 [12]. Trial 2 was a randomised multicentre phase III study, where 233 patients received either MFL or single therapy with 5-fluorouracil (5-FU) between January 1985 and March 1987 [13]. Trial 3 was also a multicentre study recruiting 182 patients between February 1985 and February 1990. 92 patients were randomised to MFL in this closed and evaluated but yet unpublished trial (the remaining 90 patients, randomised to primary expectancy, were not included in the present study). Trial 1 included both symptomatic and asymptomatic patients, trial 2 consisted only of symptomatic patients whereas all patients in trial 3 were asymptomatic (Table 1). The schedules and doses of chemotherapy have previously been described [13].

The trials had the following inclusion criteria in common: metastatic or locally recurrent/inextirpable colorectal cancer, age 75 or younger, Karnofsky performance status (KPS) 50 or higher, serum creatinine < 125 mmol/l, S-bilirubin < 40 mmol/l and no signs of pleural effusion or ascites. Besides symptoms, inclusion criteria differed in two respects: 8 patients in trial 1 were previously treated with chemotherapy while such patients were ineligible in trials 2 and 3; and patients with non-measurable disease could be included in trial 3 but not in trials 1 and 2. Therefore, 8 patients from trial 1 with previous chemotherapy were excluded from the present analysis. 16 patients from trial 3 with non-measurable disease were only studied for influence on survival. In addition, 33 patients from trial 3 were not included; 10 did not receive any chemotherapy and 23 because of short follow-up. The study population then comprised 340 patients for analysis of survival and 324 patients for analysis of responses (Table 1). Survival was measured from on protocol time to death of any cause. 22 patients were alive at the time of analysis with a median follow-up of 18 months (range 10–72). No patient was lost to follow-up.

The examined variables in this study were obtained from the trial inclusion forms where information about sex, age, primary tumour site (colon or rectum), treatment of the primary tumour (resected vs. not resected), metastatic sites, disease-free interval, presence and type of symptoms, KPS and haemoglobin level were registered by the physicians approximately 2 weeks before start of therapy. The presence or absence of tumour-related symptoms was decisive for inclusion in two of the trials and was carefully evaluated at a personal interview in all patients. The

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Table 1. Patients' characteristics

Characteristic	Trial 1 (n = 48)	Trial 2 (n = 233)	Trial 3 (n = 59)
Mean age (range)	63 (33–75)	62 (34–75)	61 (40–75)
M:F	23:25 (48:52)	127:106 (54:46)	40:19 (68:32)
Primary			
Colon:rectum	18:30 (38:62)	146:87 (63:37)	37:22 (63:37)
Resected:			
unresected	30:18 (63:37)	165:68 (71:29)	45:14 (76:24)
Disease-free interval (days)			
<365	24 (50)	163 (70)	43 (73)
≥365	24 (50)	70 (30)	16 (27)
Performance			
100	10 (21)	0 (0)	52 (88)
90	8 (17)	49 (21)	0 (0)
70–80	22 (46)	106 (46)	6 (10)
50–60	8 (17)	78 (34)	1 (2)
Symptom			
Pain	22 (46)	166 (71)	0 (0)
Fatigue	10 (21)	131 (56)	0 (0)
Nausea	2 (4)	76 (33)	0 (0)
Bleeding	6 (12)	15 (6)	0 (0)
Other	12 (25)	59 (25)	0 (0)
Number of symptoms			
0	10 (21)	0	59 (100)
1	24 (50)	78 (34)	0
2	14 (29)	101 (43)	0
≥3	0	54 (23)	0
Metastatic site			
Liver	15 (31)	162 (70)	41 (70)
Lung	14 (29)	71 (30)	16 (27)
Nodes	1 (2)	54 (23)	15 (25)
Peritoneal	6 (12)	28 (12)	10 (17)
Local	20 (42)	84 (36)	12 (20)
Other	8 (17)	33 (14)	5 (8)
No. of metastatic sites			
1	33 (69)	91 (39)	28 (48)
2	14 (29)	92 (40)	23 (39)
≥3	1 (2)	50 (21)	8 (13)
Haemoglobin (g/l)			
≥120	30 (62)	141 (60)	44 (68)
<120	18 (38)	92 (40)	15 (32)
Treatment			
(MFL:5-FU)	48:0 (100:0)	113:120 (48:52)	59:0 (100)
Complete			
response	6 (12)	3 (1)	3 (7)
Partial response	14 (29)	20 (9)	6 (14)
Stable disease	13 (27)	74 (32)	27 (63)
Progressive			
disease	15 (31)	136 (58)	7 (16)

Percentages are given in parentheses.

physician indicated on the form whether the patient was asymptomatic or experienced pain, fatigue, nausea, secretion/bleeding or any other symptom referable to the disease. Besides routine laboratory values and chest X-ray, pretreatment staging studies were directed only towards clinically suspected metastatic sites. The evaluation of objective responses followed the UICC recommendations [14], except that the minimum duration of any response was 4 months. Criteria for response were originally less strictly applied in trial 1 compared with trials 2 and 3. Therefore, all responses in trial 1 were reassessed retrospectively. 5 patients with partial responses from trial 1 were reclassified (3 to stable disease and 2 to progressive disease). After this adjustment, criteria for response were similar in all patients.

Statistical methods

Survival analyses were performed with the Cox proportional hazards model [15] and in univariate survival analyses also with the logrank and Breslow–Gehan tests. The proportionality assumption connected with the Cox analyses was investigated and models where this assumption was relaxed were also estimated. In order to obtain more precise estimates of the parameters of important variables for survival, a stepwise selection procedure was employed. Here, variables were entered in order of importance until the $P = 0.05$ level. The Walker–Duncan generalisation of the logistic regression model was used in analyses involving response [16]. Except for chemotherapy regimen and response categories, all variables in Table 1 were tested in univariate analyses. The same variables were tested in multivariate analyses but the number of symptoms and metastatic sites replaced the specific symptoms and metastatic sites. Chemotherapy regimen was also tested in the multivariate analyses. The results are presented as relative hazards (RH) in analyses of survival and odds ratios (OR) in analyses of response with 95% confidence limits within parenthesis. For a categorical variable, the RH or OR is given relative a reference category. For a continuous variable, the RH and OR shows the effect associated with a one unit increase of the variable. Survival curves were constructed according to Peto *et al.* [17].

RESULTS

Survival

In the univariate analyses, performance status, number of symptoms, haemoglobin level and trial number had the strongest relationships to survival ($P < 0.001$) (Fig. 1a–d). Hepatic ($P < 0.001$) and peritoneal ($P = 0.001$) metastases implied a short survival, as did the symptoms fatigue ($P < 0.001$) and pain ($P = 0.001$). In addition, the number of metastatic sites ($P < 0.001$) and treatment of the primary tumour ($P < 0.001$) influenced survival. Survival was more favourable when the primary tumour was a rectal cancer as compared with a colonic cancer ($P = 0.02$) (Table 2). When all variables were tested together in the multivariate analysis, haemoglobin level and chemotherapy regimen were the most important variables

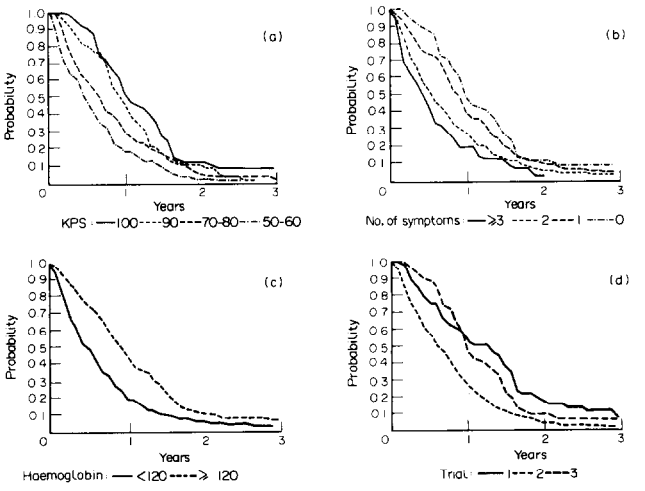

Fig. 1. Patient survival according to (a) performance status, (b) number of symptoms, (c) haemoglobin level (g/l) and (d) trial number.

Table 2. The relations between clinical variables and survival in univariate and multivariate analyses

Characteristic	Relative hazard	
	Univariate	Multivariate
Trial 1	0.5 (0.4–0.7)‡	0.8 (0.5–1.2)
Trial 3	0.5 (0.4–0.6)‡	0.7 (0.4–1.5)
Primary rectum	0.8 (0.6–1.0)*	1.0 (0.8–1.3)
Primary unresected	1.5 (1.2–2.0)‡	1.4 (1.0–1.8)*
Disease-free interval ≥365	0.7 (0.5–0.9)†	0.7 (0.5–0.9)†
Performance		
90	1.5 (1.0–2.2)*	0.8 (0.4–1.7)
70–80	1.8 (1.3–2.6)‡	0.9 (0.5–1.7)
50–60	3.0 (2.1–4.3)‡	1.2 (0.6–2.6)
Symptoms (no.)	1.4 (1.2–1.5)‡	1.1 (0.9–1.3)
Metastatic sites (no.)	1.3 (1.1–1.5)‡	1.1 (0.9–1.3)
Pain	1.5 (1.2–1.9)†	—
Fatigue	1.5 (1.2–1.9)‡	—
Nausea	1.4 (1.1–1.9)*	—
Hepatic metastases	1.7 (1.3–2.2)‡	—
Peritoneal metastases	1.7 (1.3–2.5)‡	—
Haemoglobin (g/l)	0.98 (0.97–0.99)‡	0.98 (0.96–0.99)‡
MFL	—	0.5 (0.4–0.7)‡

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.
95% confidence limits are given in parentheses.
–Variable not analysed.
Reference categories: trial 2, primary colon, primary resected, disease-free interval < 365, performance 100 and 5-FU. Variables without statistically significant relationship to survival: age, sex, bleeding, other symptoms, metastatic sites except hepatic and peritoneal ($P > 0.05$).

($P < 0.001$) followed by disease-free interval ($P = 0.009$) and treatment of the primary tumour ($P = 0.02$) (Table 2). The results of the stepwise selection procedure were very similar to the aforementioned analysis except that number of symptoms ($P = 0.007$) and performance status ($P = 0.02$) also appeared as significant variables (Table 3).

The variables emerging from the stepwise selection procedure were used to calculate a survival "score". The score (Y) was calculated as follows: $Y = 0.1738$ (number of symptoms) − 0.0177 haemoglobin level −0.5872 (MFL) − 0.3838 (disease-free interval ≥ 365) + 0.3576 (performance ≤ 60) + 0.2795 (primary unresected).

Based on the quartiles of this score, the population was

Table 3. Variables with significant relation to survival in the model accepted after the stepwise selection procedure

Characteristics	Relative hazard (95% CL)
MFL	0.6 (0.4–0.7)‡
Haemoglobin	0.98 (0.97–0.99)‡
Disease-free interval ≥365	0.7 (0.5–0.9)†
No. of symptoms	1.2 (1.1–1.4)†
Performance ≤60	1.4 (1.1–1.9)*
Primary unresected	1.3 (1.0–1.8)*

* $P < 0.05$, † $P < 0.01$, ‡ P 0.001.
CL = confidence limits.

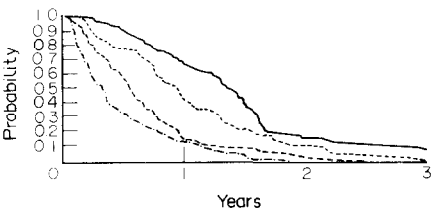

Fig. 2. Patient survival in four groups according to prognostic index: $y = 0.1738$ (number of symptoms) − 0.0177 (haemoglobin level) − 0.5872 (MFL) − 0.3838 (disease-free interval ≥ 365) + 0.3576 (performance ≤ 60) + 0.2795 (primary unresected). —— −2.74, ···· −2.74 to −2.30, ---- −2.29 to −1.785, -·-·-> −1.785.

divided into four groups. Probabilities for 6 months survival were 0.32, 0.56, 0.77 and 0.92 in these groups (Fig. 2).

Response

In the univariate analyses, haemoglobin level, trial number, performance status and number of symptoms had a strong relationship to response ($P < 0.001$). Hepatic metastases ($P = 0.001$), the symptoms pain ($P = 0.001$) and fatigue ($P = 0.005$) decreased the probability for a response (Table 4). When all variables were tested together for influence on response it was seen that chemotherapy regimen was the most important variable ($P < 0.001$) followed by haemoglobin level ($P = 0.004$) and trial number ($P = 0.008$).

DISCUSSION

This study was designed to determine prognostic factors in advanced colorectal cancer. We utilised information from 340 patients included in three chemotherapy trials, 1982–1990. All studied variables were prospectively registered according to the protocols, thereby ensuring good quality of the data. Despite

Table 4. Relationship to response in multivariate and univariate analyses

Characteristic	Odds ratio	
	Univariate	Multivariate
Trial 1	0.2 (0.1–0.4)‡	0.4 (0.2–0.8)†
Trial 3	0.2 (0.1–0.4)‡	0.4 (0.1–1.5)
Primary unresected	1.8 (1.1–2.9)*	1.7 (1.0–3.0)
Disease-free interval ≥365	0.6 (0.4–1.0)*	0.8 (0.5–1.4)
Performance		
90	2.0 (1.0–4.0)*	0.5 (0.1–1.5)
70–80	3.6 (1.9–6.7)‡	0.7 (0.2–2.1)
50–60	4.9 (2.5–9.7)‡	0.8 (0.2–2.7)
Symptoms (no.)	1.7 (1.4–2.2)‡	1.2 (0.8–1.6)
Metastatic sites (no.)	1.3 (1.0–1.7)*	1.1 (0.8–1.4)
Pain	2.1 (1.3–2.2)†	—
Fatigue	2.0 (1.2–3.1)†	—
Hepatic metastases	2.3 (1.4–3.6)‡	—
Haemoglobin (g/l)	0.98 (0.96–0.99)‡	0.98 (0.96–0.99)†
MFL therapy	—	0.2 (0.1–0.4)‡

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.
95% confidence limits are given in parentheses.
Reference categories and abbreviations: see Table 2.
Variables without statistically significant relation to response: age, sex, location of primary, symptoms other than pain and fatigue, and metastatic sites except hepatic ($P > 0.05$).

the adjustments to make the trials comparable, small differences between the trials may persist. Therefore, initial univariate and multivariate analyses were performed including only patients from trial 2. These analyses gave essentially similar results (data not shown).

The selection of variables in the analyses deserves to be commented. It was judged inappropriate to analyse chemotherapy regimen in univariate analysis because of the association between this variable and number of symptoms due to the inclusion criteria of the trials. However, this interrelation was accounted for in the multivariate analyses allowing the independent influence of therapy to be assessed. The variable "trial" is a marker for differences between the trials that are not reflected through the other studied variables, i.e. subtle differences in patient selection and clinical care e.g. multicentre vs. one department. Trial is thus to be distinguished from therapy. It was clear from preliminary analyses that multivariate analysis of number of symptoms and number of metastatic sites was more informative than specific symptoms and metastatic sites.

The prognostic importance of performance status in advanced colorectal cancer [1–5] was confirmed in this study. However, three additional prognostic factors of at least the same magnitude were identified. The haemoglobin level had a strong relation to survival and also response rate. Considering the great simplicity of this test, its low cost and that it is readily available, it might be of value in prediction of prognosis. Disease-free interval has been rejected as a prognostic determinant by previous investigators [2, 3, 5–8, 10]. In contrast, the present study indicated that disease-free interval is an important prognostic factor. The number of symptoms referable to the disease and registered before start of therapy was inversely related to survival. Inclusion of symptomatic patients in trials is therefore likely to shorten median survival time. Performance classification is rather arbitrary and these variables might add further information to provide a more reliable prognostic description.

In agreement with previous studies [2, 3], we found patients with advanced colorectal cancer to be heterogeneous with entirely different survival prospects after inclusion in a chemotherapy trial. Our prognostic model was able to distinguish four groups with 6-month survival ranging from 32 to 92%. This discrimination is of the same magnitude as was achieved with an earlier described model [3].

The Cox model assumes proportional hazards but for several of the important variables it was found that this assumption was not completely fulfilled. A general pattern observed for these variables (number of symptoms, disease-free interval, performance and treatment of the primary tumour) was that the difference in hazard was largest in the early part of the follow-up period and diminished over time. The convergence of the survival curves illustrates this effect. The parameters estimated in the Cox analysis can be viewed as an "average" for the whole period and thereby summarise the results. A similar time dependent effect of prognostic determinants has been observed in patients subjected to surgery with curative intent for rectal cancer [18].

Is an exact patient description necessary to correctly interpret the results of clinical trials? The randomisation process in large trials should even out differences between the treatment arms, making comparisons within the trial valid. However, a more detailed patient description is useful when results between different trials are compared. Combinations of 5-FU and leucovorin have been compared with 5-FU alone in several randomised trials [19–22]. Response rates and median survival in the combination arms ranged between 19–43% and 10.5–12.5 months, and in the 5-FU arms between 7–17% and 8–11 months, respectively. In the trial comparing MFL with 5-FU (trial 2) response rates and median survival were lower, both in the MFL arm (17% and 8.5 months) and in the 5-FU arm (2% and 6 months) [13]. A higher proportion of patients in trial 2 had low performance compared with the trials evaluating 5-FU/leucovorin [19–22]. The proportion of symptomatic patients was only mentioned in one of these studies where 80% were symptomatic [20], whereas all patients were symptomatic in trial 2. These differences are reasonable explanations for the shorter survival and lower response rates in trial 2.

According to this study, performance status alone may not be enough to characterise patients with advanced colorectal cancer from a prognostic viewpoint. Haemoglobin level, disease-free interval and proportion of symptomatic patients may also affect the results of a clinical trial and a possible effect of these variables may wrongly be attributed to therapy.

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Prognostic Factors in Multiple Myeloma: a New Staging System Based on Clinical and Morphological Features

Paolo Pasqualetti, Raffaele Casale, Antonio Collacciani and Domenico Colantonio

A new staging system for multiple myeloma based on clinical and morphological features has been developed on the analysis of 190 patients. A score of "1" was assigned to each of the following clinical data, referred at the time of diagnosis, and selected by multivariate analysis: bone marrow plasma cells more than 30%, haemoglobin less than 110 g/l, lytic bone lesions of degree 2 or 3, serum β_2-microglobulin levels higher than 678 nmol/l, and presence of Bence–Jones proteinuria. Therefore, the score for each patient ranged from 0 to 5, and three clinical stages were provided: I = 0 or 1, II = 2 or 3 and III = 4 or 5. Substratification into A and B for each clinical stage was performed using multiple myeloma cellular score, calculated by the formula: total bone marrow myeloma cells per 500 cells × 0.752 + bone marrow plasmablasts per 500 cells × 0.709. Substage A corresponded to multiple myeloma cellular score value lower than 0.300, and substage B to a value greater than 0.300. Significant differences were found in median survivals ($P < 0.0001$), in survival curves ($P < 0.0001$), and in responses to treatment ($P < 0.0001$) among the six staged groups. The use of this staging system for multiple myeloma could offer new prognostic information and could better quantify the picture of the disease in each patient. The substaging according to morphological criteria seems very useful in diminishing or eliminating the great prognostic variability observed within the same clinical stage. Confirmatory studies are required to validate this new staging system for multiple myeloma.
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INTRODUCTION

STAGING IS a fundamental prerequisite to optimise therapeutic approach, and to estimate survival in various neoplasias. This is particularly true for some malignant diseases, such as multiple myeloma (MM), that presents a very heterogeneous clinical and biological course, survival ranging from less than 1 month to more than 10 years, and clinical course ranging from the relatively "indolent" form to aggressive neoplasia [1].

In the last years, several staging systems, based on clinical features [2–11] or on morphological criteria [12–17] have been proposed for MM, in order to facilitate the prognostic categorisation of patients, to improve treatment and to evaluate the effects of different therapeutic protocols. However, a great variability in survival of patients allocated to the same clinical or morphological stage has been observed [1, 8–10, 18, 19]. These findings have suggested the need to search for new parameters that will allow better individual control and evaluation of each patient.

The aim of the present study was to develop a staging system for MM that considered both clinical and morphological data, and to verify whether morphological subclassification could be useful in separating groups of clinically staged MM patients.

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